CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: **205437/0**

Submission Date(s): **March 21, 2013**

Applicant: **Celgene Corporation**

Product: **apremilast (OTEZLA)**

Reviewer: **Keith M Hull, MD, PhD**

Date of Review: **February 4, 2014**

Covered Clinical Studies : **PsA-001, PsA-002, PsA-003, PsA-004, PSOR-005, PSOR-005-E, PSOR-005-LTE**

Was a list of clinical investigators provided:	Yes **X**	No ☐ (Request list from applicant)
Total number of investigators identified: **1287**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

The applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454 stating that none of the 1,287 investigators had a financial agreement with the sponsor or financial interest in the company.

[1] See [web address].

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

/s/

KEITH M HULL
02/06/2014

CLINICAL REVIEW

Application Type	NDA
Application Number	205437 s0000
Priority or Standard	Standard
Submit Date(s)	March 21, 2013
Received Date(s)	March 21, 2013
PDUFA Goal Date	April 21, 2014
Division / Office	DPARP/ODE 2
Reviewer Name	Keith M Hull, MD, PhD
Review Completion Date	TBD
Established Name	Apremilast
(Proposed) Trade Name	OTEZLA
Therapeutic Class	Phosphodiesterase-4 inhibitor
Applicant	Celgene Corporation
Formulation(s)	Immediate release tablet 10 mg, 20 mg, 30 mg
Dosing Regimen	30 mg twice daily
Indication(s)	Treatment of patients with active psoriatic arthritis
Intended Population(s)	Patients ages ≥18 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I mends approval for this new drug application for apremilast (OTEZLA) as a treatment of adult patients with active psoriatic arthritis (PsA). The data submitted in the current application are sufficient to support the findings of safety and efficacy of orally administered apremilast using an initial dose titration schedule over 5 days until the target dose of 30 mg twice daily is achieved.

1.2 Risk Benefit Assessment

Studies PSA-002, -003, and -004 were highly similar in design and provided the primary data used for assessing the safety and efficacy of apremilast in subjects with active PsA. The studies were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies. Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). Efficacy analyses demonstrated a statistically and clinically meaningful improvement in patients' treated with apremilast; however, the overall treatment effect size was modest compared to that observed with the TNF-antagonists (e.g., etanercept, adalimumab, infliximab). Secondary endpoints and sensitivity analyses were generally supportive of the primary endpoint.

The most commonly occurring adverse events (AEs) associated with apremilast were diarrhea, nausea, vomiting, headache, and URI. These AEs were dose-dependent and 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 the drug. Treatment with apremilast was also associated with weight loss, with approximately 10% of apremilast-treated subjects losing between 5%-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. The overall risk associated with apremilast in the targeted patient population appears to be acceptable given the potential clinical benefits.

There was sufficient data submitted in the current application to allow for adequate labeling and directions for use of apremilast 30 mg BID, including the proposed titration schedule

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are being recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division of Biopharmaceutics is requesting one postmarketing commitment for the sponsor 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.

The Division of Pulmonary, Allergy, and Rheumatology Products is requesting one postmarketing requirement regarding 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 embrio-fetal exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group. The primary concerns are based on:

- Animal data suggesting that apremilast
    - Increases the incidence of abortions and embryo-fetal death in both mice and monkeys in a dose-dependent manner
    - Reduces fetal weight in a dose-dependent manner in mice
    - Increases the incidence of skeletal variations in both mice and monkeys
- Teratogenic effect of apremilast could not be adequately assessed in monkeys due to high incidence of pregnancy loss and limited examination of the lost fetuses
- Limited pre-marketing embryo-fetal apremilast exposure data in humans.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor is proposing to use orally administered apremilast (OTEZLA) 30 mg BID for the treatment of adult patients with active psoriatic arthritis. The sponsor is also recommending the initial dosing of apremilast be titrated to limit the incidence of gastrointestinal adverse effects. The proposed dose titration is outlined in Table 1:

Table 1. Proposed Apremilast Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 +	
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

Apremilast tablets are diamond shaped and film coated and supplied 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) when the storage conditions are ≤30^{o}C.

2.2 Currently Available Treatments for Proposed Indications

The first-line therapy for the treatment of psoriatic arthritis is typically the off-labeled use of small molecular immunomodulators (commonly referred to as disease modifying anti-rheumatic drugs [DMARDs]), e.g., methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF). Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are also frequently used to help control the pain and inflammation associated with the synovitis. Despite the efficaciousness of these drugs, a significant proportion of subjects will require additional treatment, most commonly a biologic response modifier.

Currently, six biologic drugs are approved for the treatment of adult patients with active psoriatic arthritis: etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab (CIMZIA), and ustekinumab (STELARA). These drugs have been shown to be efficacious and to have an acceptable safety profile.

Apremilast will represent the first small molecular drug approved for the treatment of adult patients with active psoriatic arthritis.

2.3 Availability of Proposed Active Ingredient in the United States

Apremilast is a new molecular entity that is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The PDE4-inhibitor, roflumilast (DALIRESP), was approved in 2011 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Included in the WARNINGS AND PRECAUTIONS section of the product label is an increased frequency of psychiatric adverse reactions and significant loss of body weight. Psychiatric adverse reactions included insomnia, anxiety, and depression, all of which were reported at higher rates in roflumilast-treated subjects versus placebo-treated subjects. Instances of suicidal ideation and behavior, including completed suicide were observed during clinical trials and in the post-marketing setting in patients treated with roflumilast. Moderate weight loss, defined as a decrease of 5-10% of body weight, was a common adverse reaction that occurred in roflumilast-treated subjects during the clinical trials. Commonly reported adverse reactions listed in the product label included diarrhea, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An End of Phase 2 meeting was held on March 25, 2010 between the Division of Anesthesia, Analgesia, and Rheumatologic Products to discuss the design and conduct of the PsA Phase 3 clinical program. Agreement was reached on the overall study designs including the enrollment of subjects with active PsA and the Week 24 assessment of the ACR20 as the primary endpoint and improvement in the HAQ-DI score as the major secondary efficacy endpoint.

On February 28, 2012 the sponsor submitted questions to IND 101761 regarding several aspects of the ongoing PsA Phase 3 studies including the modification of the timing of endpoints, the anticipated size of the safety database, and strategies for pooling efficacy and safety data. On June 29, 2012 the Division of Pulmonary, Allergy, and Rheumatology Products provided written responses addressing the sponsor's queries including the agreement to the sponsor's proposal to modify the timing of the primary and secondary endpoints from Week 24 to Week 16.

A pre-NDA meeting was held on December 19, 2012. The Division agreed that the sponsor's overall proposed package was sufficient to constitute an NDA submission for apremilast in the treatment of adult patients with active PsA. The Division also discussed the type of additional safety tables and safety analyses required for the planned NDA to include duration of treatment period for initially-treated and as-treated populations.

The sponsor submitted the current NDA application on March 21, 2013.

2.6 Other Relevant Background Information

All relevant background information regarding the clinical use of apremilast is included in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy. Issues regarding data quality and integrity of the studies are described below.

Each of the pivotal Phase 3 studies reported protocol violations and protocol deviations. A protocol violation was defined as any departures from the approved protocol that impacted the safety, rights, and/or welfare of the subject, negatively impacted the quality or completeness of the data, or made the informed consent process inaccurate. A protocol deviation was defined as any unplanned diversions from the approved protocol that did not result in harm to the study subjects or did not significantly affect the scientific value of study data.

During study PSA-002, 61 out of 504 (12%) subjects reported ≥1 protocol violation resulting in 15 (3%) subjects being excluded from the Per-Protocol population. The most commonly cited protocol violations included missing post-baseline data, lack of early termination assessments, and poor compliance. A total of 168 (35%) subjects had ≥1 protocol deviation with the most frequently reason related to informed consent issues, omission of a scheduled study procedure/assessment, or study visits performed out of window.

During study PSA-003, 126 out of 484 (26%) subjects reported ≥1 protocol violation resulting in 20 (4%) subjects being excluded from the Per-Protocol population. The most common protocol violations included issues with informed consent, omission of a scheduled study procedure or assessment, and subjects taking excluded concomitant medications. A total of 258 (51%) subjects had ≥1 protocol deviation with the most frequently reason related to informed consent issues, omission of a scheduled study procedure/assessment and study visits performed out of window.

During study PSA-004, 75 out of 505 (15%) subjects reported ≥1 protocol violation resulting in 15 (3%) subjects being excluded from the Per-Protocol population. The most common protocol violations included issues with omission of a scheduled study procedure or assessment, and subjects taking excluded concomitant medications. A total of 193 (38%) subjects had ≥1 protocol deviation with the most frequently reason related to stratification errors and omission of a scheduled study procedure/assessment.

Overall, the total number of subjects from each group with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between

treatments arms. Subjects with protocol violations were included in the Full Analysis Set and are not expected to adversely affect the conclusions drawn from these studies.

3.2 Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. Review of the submitted form "*Certification: Financial Interests and Arrangements of Clinical Investigators"* does not raise concerns regarding the integrity of the submitted data to the current application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Controls (CMC) reviewer recommends approval of apremilast pending overall acceptable recommendations from the Office of Compliance, microbiology, and resolution of outstanding CMC information requested comments sent to the sponsor. From the reviewer's perspective, the sponsor has provided adequate information regarding the manufacturing of the drug substance and drug product; however, clarifications are needed for several manufacturing process parameters and analytical methods.

The Chemistry, Manufacturing, and Controls (CMC) review notes that the drug substance is formulated with compendia grade excipients to form immediate release 10, 20 and 30 mg tablets. (b) (4) and the tablets are prepared by (b) (4) The tablets are coated with (b) (4)

The reader is referred to the CMC review of apremilast by Ciby Abraham, PhD for a detailed analysis of the CMC aspects related to this application.

4.2 Clinical Microbiology

This section of the review is not applicable to this product.

4.3 Non-clinical Pharmacology/Toxicology

Emphasis on the non-clinical toxicology findings that directly relate to human safety (e.g., genotoxicity, carcinogenicity, and reproductive toxicology) are briefly discussed here. The reader is referred to the Pharmacology/Toxicology review by Lawrence S. Leshin, PhD for a detailed analysis of the non-clinical pharmacology and toxicology aspects related to this application.

Results from the standard series of genetic toxicology assays were negative for apremilast and the identified process impurity (b) (4) Similarly, there were no definitive apremilast-related malignancies in the two-year oral dosing studies in mice or rats.

Reproductive and developmental toxicology GLP studies were conducted using mouse and monkey models. Apremilast treatment in mice found no effect on sperm motility or sperm counts and no effect on mating parameters or resultant pregnancies and embryo-

fetal survival. Fertility studies in apremilast-treated females showed a prolonged estrous cycle due to an increase in the diestrus period that resulted in a longer time until mating. Additionally, apremilast treatment resulted in an increase of early resorptions, and a reduction in fetal body weights.

Pregnant mice administered apremilast demonstrated a reduction of body weight gain as a result of lower uterine weights. Reductions in the number of litters and litter size were observed and attributed to postimplantation losses in all apremilast dose groups. Fetal weight was also reduced in a dose -dependent manner in both sexes. There was no dose-related effect on malformations, although skeletal variations were increased.

In the monkey studies, dose-related fetal losses, mostly occurring during weeks 3 and 4 of gestation were observed. The teratogenic effects of apremilast in the monkey were not adequately evaluated due to the high incidence of fetal abortions, which was dose-related, coupled with the absence of examination of these fetuses. There was an increased incidence of skeletal variations that were mostly related to a reduced number of ossification sites and misaligned tail vertebrae.

Studies evaluating pre- and post-natal development demonstrated difficulty regarding offspring delivery in the apremilast high-dose group and resulted in the death of one dam. The high-dose group also had reduced maternal body weight. Apremilast had no effect on late pregnancy, pregnancy duration or the number of dams that delivered. Postnatal pup mortality was increased in the F_1 generation and reduced pup weights of survivors until Day 21 of lactation were noted. There were no effects on the F_1 generation following apremilast treatment of the F_0 animals regarding clinical or necropsy observations post-weaning; body, testes or epididymis weights; sexual maturation; passive avoidance; motor activity; mating; fertility or F2 embryo-fetal parameters. Apremilast was detected in the milk of lactating mice at levels approximately 1.5-times that of simultaneously collected blood plasma samples at 1 and 6 hours. Apremilast levels were non-detectable in either milk or plasma 24 hours after drug administration.

4.4 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review of apremilast by Sheetal Agarwal, PhD for a detailed analysis of the pharmacokinetic and pharmacodynamic aspects related to this application.

4.4.1 Mechanism of Action

3,5'-Cyclic adenosine monophosphate (cAMP) serves as a second messenger system for a diverse number of by G-protein-linked receptor systems, including many of those found in immunocompetent cells. The breakdown of cAMP by the enzyme, phosphodiesterase 4 (PDE4), has been shown to cause immune cell activation and

release of proinflammatory cytokines including TNF-α, IL-17, IL-22, and IFN-$_{Y}$, therefore, inhibition of the enzyme would be expected to decrease PDE4-mediatied inflammation.

Apremilast is a new, orally available, small molecular inhibitor of PDE4 being developed for the treatment of psoriasis, psoriatic arthritis, and other chronic inflammatory diseases. The current application is submitted for the potential indication of the treatment of adults with active psoriatic arthritis.

4.4.2 Pharmacodynamics

The sponsor has conducted pharmacodynamic studies assessing the effects of apremilast on the inflammation associated with psoriasis and psoriatic arthritis. In psoriasis studies, apremilast treatment was associated with decreased dendritic cell and T cell infiltration within the epidermis and dermis of psoriatic skin lesions, decreased lesional skin epidermal thickness, and decreased whole blood TNF-α production following bacterial endotoxin challenge. Psoriatic arthritis subject treated with apremilast demonstrated decreased plasma concentrations of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, TNF-α, MMP-3, and ferritin, and an increase in von Willebrand Factor; however, the clinical relevancy of these findings are uncertain.

4.4.3 Pharmacokinetics

The clinical pharmacology studies determined apremilast to have a Cmax of 2.5 hours, $t_{1/2}$ of approximately 5-7 hours, and an average bioavailability of 70%. There was linear pharmacokinetics up to 50 mg BID or 80 mg QD with no accumulation of up to the 40 mg QD dosing. There was no food effect on absorption and the plasma protein binding was 68%.

Apremilast undergoes approximately 50% metabolism and is primarily eliminated as metabolites formed by CYP-mediated oxidative metabolism (CYP3A4>>CYP1A2/CYP2A6) with subsequent glucuronidation. The mean total urinary and fecal recovery of radioactive apremilast was 97% with mean contributions of 58% and 39% from urine and feces, respectively.

Apremilast did not inhibit CYP enzymes in vitro, suggesting that it is unlikely to inhibit metabolism of co-administrated CYP substrates. In vitro studies showed that apremilast did not induce the activity of CYP1A2, CP2C9, or CYPC19. Similarly, lower concentrations (1 and 10 µM) of apremilast had no effect on the enzyme activity of CYP3A4 and CYP2B6; however, at the highest concentration (100 µM) of apremilast tested, CYP3A4 and CYP2B6 enzymatic activity was increased by approximately 4- and 2- fold, respectively. This concentration of apremilast is greater than 100-fold higher than the steady state Cmax of an apremilast 30 mg BID dose, thus, it is unlikely that the

coadministration of apremilast will result in clinically significant decreases in the exposure of CYP1A2, CYP2C9, CYP2C19, CYP3A4, or CYP2B6 substrates.

In vivo observation from animals and humans suggest that P-glycoprotein does not limit the oral absorption of apremilast, although in vitro data suggest that apremilast is a substrate and weak inhibitor of P-glycoprotein (IC50>50 µM). Furthermore, since apremilast is minimally excreted in unchanged form, P-glycoprotein does not appear to mediate an important role in apremilast excretion. Therefore, clinical drug-drug interactions are unlikely when apremilast is coadministered with a P-glycoprotein inhibitor.

The sponsor proposed an alternative apremilast-dosing regimen of 30 mg QD for patients with severe renal impairment based on PK data from apremilast-treated subjects with renal impairment and subsequent PK simulations. The Division of Clinical Pharmacology agreed with the sponsor's proposed dosing regimen and recommended a modified titration scheme for patients with severe renal impairment, which can be found in Dr. Agarwal's review. Pharmacokinetic studies in apremilast-treated subjects with mild, moderate, and severe hepatic impairment determined that no dose adjustment is need in the group of patients.

5 Sources of Clinical Data

To date, there have been a total of 30 clinical studies conducted with apremilast: 16 Clinical Pharmacology studies and 14 Phase 2/3 studies.

Clinical Pharmacology Studies

The 16 Clinical Pharmacology studies conducted with apremilast were as follows:

- Nine, single-dose studies in healthy subjects evaluating PK, bioavailability, food effect, drug-drug interaction with ketoconazole and rifampin, and the effective of age, sex, and race
- Two single-dose studies were conducted in non-healthy subjects evaluating the effect of renal or hepatic impairment on PK
- Four multiple-dose studies in healthy subjects were conducted assessing PK, drug-drug interaction with oral contraceptives, and potential QTc prolongation
- A single multiple-dose study in subjects with PsA or RA was conducted to evaluate the potential for drug-drug interaction with MTX

The reader is referred to the Clinical Pharmacology review, by Sheetal Agarwal PhD, for an in depth analyses of the Clinical Pharmacology studies. All AEs reported from these studies are included in the overall apremilast safety database.

Clinical Phase 2/3 Studies

Of the 14 Phase 2/3 studies conducted with apremilast, 5 studies enrolled subjects with active PsA, 6 studies enrolled subjects with active psoriasis, and one study each was conducted in subjects with active RA, Behçet's disease, and asthma. Three Phase 3 studies are ongoing and remain blinded including one study in PsA (CC-10004-PSA-005) and two Phase 3 studies in psoriasis (PSOR-008, -009), consequently, data from these studies are not included in the overall safety assessment of apremilast except for reported deaths and expedited SAEs. As discussed below in Section 5.2, only four of the clinical trials enrolling subjects with PsA will be discussed and used in the assessment of efficacy for the proposed indication.

5.1 Tables of Studies/Clinical Trials

Table 2. Clinical Studies Used in the Efficacy Assessment of Apremilast

Study	Centers (n)	Subjects Enrolled (n)	Dosing[a]	Study Design	Primary Endpoint
Phase 2 Study					
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
Phase 3 Studies-Completed					
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
Phase 3 Study-Ongoing					
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

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; ACR20: American College of Rheumatology 20% response; Wk: week.

Table 3. Clinical Studies Used in the Safety Assessment for Apremilast

Data Pool	Studies Included in Data Pool
PsA Phase 3 Data Pool	PsA: PSA-002, PSA-003, PSA-004
Apremilast Unblinded Data Pool	PsA: PSA-001, -002, -003, -004 RA: RA-002 PSOR: PSOR-001, -003, -004, -005LTE
Separate Apremilast Studies	Behcet's: BCT-001 Asthma: ASTH-001

5.2 Review Strategy

The sponsor has conducted a total of five studies with apremilast in subjects with PsA (Table 2). Assessment of the safety and efficacy of apremilast for treating patients with active PsA is primarily based on the data derived from three nearly identically designed placebo-controlled Phase 3 studies: CC-10004-PSA-002 (PSA-002), CC-10004-PSA-003 (PSA-003), and CC-10004-PSA-004 (PSA-004; Table 2). These studies each enrolled approximately 500 subjects with active PsA who had an inadequate clinical response to DMARDs and/or biologic therapy. The individual designs of the studies are discussed in Section 5.3 and the overall efficacy and safety analyses of apremilast are discussed in Sections 6 and 7, respectively.

The Phase 2 study CC-10004-PSA-001 (PSA-001) was designed to assess the tolerability and efficacy of apremilast as either a single 40 mg daily dose or as a 20 mg dose given twice daily. The sponsor utilized the results from this study to select the dosing regimen used in their subsequent Phase 3 studies; however, since study PSA-001 did not assess the proposed apremilast dose of 30 mg twice daily, data from the study will not be used for the efficacy analysis but are included in the overall safety analysis.

Study CC-10004-PSA-005 (PSA-005) is an ongoing Phase 3 study that currently remains blinded. Consequently, data from this study are not included in the overall assessment of the efficacy and safety of apremilast except for inclusion of deaths and expedited SAEs.

Sources of data used for the safety review of apremilast are discussed in greater detail in Section 7.1.1, but in general, included all safety data from the sponsor's apremilast clinical development program with emphasis on the studies enrolling subjects with PsA and placebo-controlled studies enrolling patients with RA and psoriasis (Table 3).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Studies Included in the Assessment of Efficacy

5.3.1.1 PSA-001

Study PSA-001 was designed to assess the efficacy and tolerability of APR20 mg BID vs. APR 40 mg QD in subjects with active PsA; however, the proposed apremilast dose of 30 mg BID was not assessed and consequently data from the study were not used for the efficacy analysis but were included in the overall safety analysis and in the sponsor's justification for dose selection in the subsequent Phase 3 studies. For that reason, the design and results of study PSA-001 will be discussed briefly here.

PSA-001 was a Phase 2, randomized, placebo-controlled, double-blind study designed to assess the tolerability and efficacy of apremilast as either a single 40 mg daily dose or as a 20 mg dose given twice daily in patients with active PsA. A total of 204 subjects with active PsA were randomized in a 1:1:1 ratio to receive PBO, APR20 BID, or APR 40 QD for 12 weeks. All subjects were subsequently treated for an additional 12 weeks with either APR20 BID or APR 40 QD in a blinded manner. The primary efficacy endpoint was prespecified as the proportion of subjects achieving and ACR20 response at Day85. A greater proportion of APR 40 mg QD- and APR20 mg BID-treated subjects achieved an ACR20 response at Day 85 compared to placebo-treated subjects, 36% and 44% vs. 12%, respectively. Assessment of the ACR 50 response demonstrated statistical significance for only the APR20 mg BID dose versus the placebo treatment arm, 17% vs. 3%, respectively, although the clinical significance was minimal. Safety analyses were most notable for nausea, diarrhea, and headache, which were more common in subjects treated with the single APR 40 mg dose compared to the APR20 mg twice-daily dose. The sponsor concluded from the data that the APR20 mg BID represented the minimally effective dose for the treatment of PsA and that splitting the apremilast dose to twice daily was more advantageous compared to a single daily dose regarding gastrointestinal tolerability.

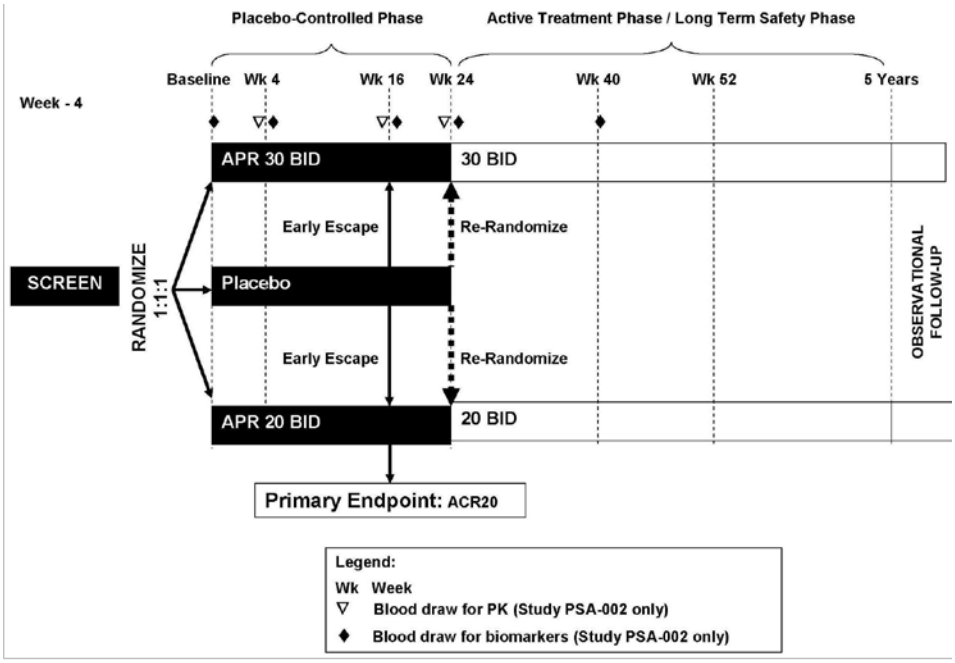
5.3.1.2 PSA-002, -003, -004

Results from studies PSA-002, -003, and -004 provided the primary data used for assessing the efficacy of apremilast in subjects with active PsA. The three studies were highly similar in design except for the difference 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 ≥3% body surface area (BSA). All studies were multicenter and enrolled patients from North America, Europe, Asia, and South Africa. Study PSA-002 began enrolling subjects on June 2, 2010 and the last subject completed the Week 24 visit on March 26, 2012. Study PSA-003 began enrolling subjects on September 27, 2010 and the last subject completed the Week 24 visit on July 4, 2012. Study PSA-004 began enrolling subjects on October 11, 2011 and the last subject completed the Week 24 visit on July 9, 2012. Final database locks occurred on June 21, 2012, July 26, 2012, and August 2012, respectively.

Studies PSA-002, -003, and -004 were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies (Figure 1). Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). To limit the gastrointestinal adverse reactions associated with PDE-4 inhibitors, apremilast dosing was dose-titrated in 10 mg/day increments over the first week of treatment, consequently, subjects in the APR20 and APR30 treatment groups reached their

targeted dose on Study Days 4 and 6, respectively. Apremilast blinding was maintained by providing doses in a blister card containing identical appearing tablets.

Figure 1. Overview of Studies PSA-002, -003, and -004



*Adapted from sponsor's Apremilast Integrated Summary of Efficacy, page 20, Figure 1.

Eligible subjects were required to meet the Classification Criteria for Psoriatic Arthritis (CASPAR) and were allowed to continue baseline DMARDs (MTX, LEF, SSZ) during the placebo-controlled portion of the study. Enrollment of subjects who had failed previous treatment with a TNF inhibitor was limited to ≤10% of the total subjects enrolled. Treatment assignments were stratified based on DMARD use at baseline with ≥25 subjects in each study taking either LEF or SSZ. Specifically for study PSA-004, all subjects had to have ≥1 qualifying psoriasis lesion ≥2 cm in addition to active PsA and ≥60% of subjects enrolled in the study were to have ≥3% BSA involved with psoriasis at baseline. All studies required eligible subjects to have met the following major inclusion and exclusion criteria as follows:

5.3.1.2.1 Major Inclusion Criteria

- Males or females ≥18 years of age
- Documented diagnosis of PsA ≥6 months
- Met the Classification Criteria for Psoriatic Arthritis (CASPAR)
- ≥3 swollen AND ≥tender joints
- History of inadequate response to prior/current therapy with DMARDS including:
  - Therapeutic failure
  - Loss of insurance
  - Intolerance
  - Adverse effects
  - "Other" reasons
- Subjects taking MTX (≤25 mg/week), LEF (≤20 mg/day), or SSZ (≤2 g/day), had to have been treated with the DMARD for ≥16 weeks and on stable doses for ≥4 weeks prior to screening and through Week 24
- Stable doses of oral corticosteroids (prednisone ≤10 mg/day or equivalent) were permitted if started ≥4 weeks prior to screening
- Subjects with active psoriasis were permitted to use low potency topical corticosteroids, coal tar shampoo, and non medicated skin emollient as background therapy. Subjects must not have used these treatments ≤24 hours prior to clinic visit.
- Stable NSAID or narcotic analgesics were permitted if started ≥2 weeks prior to screening and continued through Week 24
- Met following laboratory criteria:
  - WBC ≥3 x 10^9/L and <14 x 10^9/L
  - Platelet count ≥100 x 10^9/L
  - Serum creatinine ≤1.5 mg/dL
  - AST and ALT ≤2x ULN
  - Total bilirubin ≤2 mg/dL
  - Hemoglobin ≥9 g/dL
  - Hemoglobin A1c ≤9%
- Male and female patients were required to use acceptable contraception method(s)

5.3.1.2.2 Major Exclusion Criteria

- History of clinically significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease
- Any condition, including the presence of laboratory abnormalities that placed the subject at unacceptable risk or confounded the ability to interpret data from the study
- Abnormal ECG at screening
- Pregnant or breastfeeding female

- History of chronic infection including patients with hepatitis B, hepatitis C, HIV, or history of incompletely treated tuberculosis
- Ongoing bacterial, viral, or fungal infection ≤4 weeks prior to screening
- Abnormal chest radiograph
- History of malignancy
- Major surgery ≤8 weeks prior to screening
- Erythrodermic, guttate, or generalized pustular psoriasis
- Topical therapy for psoriasis except as noted in the inclusion criteria above
- Rheumatic/autoimmune disease other than PsA
- Use of calcineurin inhibitors, corticosteroids, small molecular DMARDS (other than those listed in the inclusion criteria), oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, tacrolimus, azathioprine, fumaric acid esters
- Use of adalimumab, etanercept, golimumab, infliximab, certolizumab, or tocilizumab ≤12 weeks of randomization
- Use of alefacept or ustekinumab ≤24 weeks of randomization
- Therapeutic failure of >3 agents for PsA, or >1 biologic TNF inhibitor

At Week 16, all subjects whose tender and swollen joint counts had not improved by ≥20% were required to enter early escape. Placebo-treated subjects were re-randomized 1:1 to receive blinded treatment with either APR20 or APR30 utilizing the dose-titration schedule until the target dose was achieved. Apremilast-treated patients entering early escape were continued in a blinded manner to continue receiving the same dosage of apremilast to which they were originally randomized. All subjects who entered early escape received identical appearing blister cards of study drug.

At Week 24, all subjects originally assigned to the placebo group were re-randomized 1:1 to either APR20 or APR30 treatment arms. All subjects who were originally assigned to an apremilast treatment arm remained in their assigned dose groups. All subjects were continued on their assigned dose of apremilast as a long-term extension study, which remains ongoing.

A total of 14,937 subjects were randomized across studies PSA-002 (n=504), PSA-003 (n=484), and PSA-004 (n=505). The full analysis set (FAS) included 493 subjects as four subjects from study PSA-003 were randomized in error but were not treated; consequently they were not included in the FAS. In general the baseline demographics and disease characteristics were similar between treatment arms and between studies. Similarly, subject disposition during the placebo-controlled periods was comparable across the three studies and across treatment groups regarding the proportion of subjects completing through Week 16.

The primary efficacy endpoint used for all three studies was the proportion of subjects achieving a ≥20% improvement of the American College of Rheumatology (ACR)

response criteria at Week 16. The ACR20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all the three studies was the assessment of apremilast on physical function as measured by the change from baseline in HAQ-DI score at Week 16.

Statistical analyses, using a two-sided 0.05 level of significance, were conducted on all randomized subjects using Cochran-Mantel-Haenszel (CMH) tests for categorical endpoints and analysis of covariance (ANCOVA) for continuous endpoints. The ANCOVA included baseline reading as a covariate, and both the CMH and ANCOVA tests controlled for baseline DMARD usage. Additionally, the statistical analyses for study PSA-004 controlled for ≥ 3% body surface area with psoriasis at baseline.
Control of Type I error within each endpoint was maintained using the 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. Of note, the use of LOCF for missing continuous data contradicts the Agency's pre-submission communications stating that LOCF should not be applied as the primary missing data imputation for continuous variables.

While analyses of the primary and major secondary endpoints were statistically valid, a large number of proposed claims were based on (b) (4)

Claims of effectiveness for secondary endpoints at Week 24 were further weakened due to the majority of patients in each study having discontinued their originally assigned treatment group after Week 16. In fact, the majority of subjects randomized to the placebo treatment arm had entered early escape at Week 16 and by Week 24 approximately 15% of subjects had withdrawn from each randomized treatment arm. Additionally, as discussed above, (b) (4)

(b) (4)

The reader is referred to the Biometrics review by Dr. Abugov for further details regarding the statistical analyses of the PsA Phase 3 studies.

5.3.2 Clinical Studies used for the Assessment of Safety

The emphasis for the safety assessment of apremilast is primarily focused on the three PsA Phase 3 trials (PSA-002, -003, and -004). Additional safety data is provided by pooled data from all Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, or RA (Table 3). With the exception of studies PSOR-001 and PSOR-04, the Phase 2/3 clinical trials were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast compared to placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. In contrast, data from the clinical pharmacology studies and the clinical studies for Behçet's disease and asthma were not included in the safety analysis given the differences in the subject population and underlying disease pathogenesis; however, any deaths and/or reported SAEs from these studies were reviewed and are included in the overall analysis of the risk-benefit assessment of apremilast. As discussed in greater detail in Section 7, safety data from studies PSA-002, -003, and -004 were analyzed separately as well as being included in the overall placebo-controlled data that included the aforementioned nine clinical studies.

The safety population included all subjects who were randomized and received ≥1 dose of study drug. These subjects were included in the treatment group corresponding to the study dose they actually received. Apremilast-treated subjects who received two different doses of apremilast were included in the apremilast dose group based on the dose first received. The reader is referred to the statistical review by Robert Abugov, PhD of the Division of Bioinformatics for a detailed statistical analysis of the submission's efficacy data.

Safety analyses included deaths, SAEs, AEs, laboratory data, vital signs, and ECG evaluation. Adverse events were coded according to MedDRA, and were deemed a treatment-related AE if it occurred on or after the date of the first dose of study drug and ≤28 days after the last dose of study drug.

6 Review of Efficacy

Efficacy Summary

Studies PSA-002, -003, and -004 were highly similar in design and provided the primary data used for assessing the efficacy of apremilast in subjects with active PsA. The studies were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies. Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). The sponsor is only seeking approval of the apremilast 30 mg BID dosing. The primary efficacy endpoint used by all three studies was the proportion of subjects achieving a ≥20% improvement of the American College of Rheumatology (ACR) response criteria at Week 16. The ACR20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all the three studies was the assessment of apremilast on physical function as measured by the change from baseline in HAQ-DI score at Week 16.

Analysis of the primary endpoint for studies PSA-002, -003, and -004 demonstrated a statistically significant greater proportion of APR30-treated subjects (38%, 32%, and 41%, respectively) achieved an ACR20 response compared to placebo-treated subjects (19%, 19%, and 18%, respectively). Additionally, APR30-treated subjects demonstrated a greater change in HAQ-DI from baseline vs. placebo-treated subjects for studies PSA-002, -003, and -004 (-0.24 vs. -0.09; -0.19 vs. -0.05; and -0.19 vs. -0.07, respectively). Secondary endpoints were supportive of the primary endpoint and major secondary endpoint analyses.

Efficacy results generally supported a greater numerical advantage for the APR30 treatment arm compared to the APR20 treatment arm but there were limited statistically significant analyses to support the conclusion that APR30 was superior to APR20. In light of the safety analyses demonstrating that both doses of apremilast were relatively well-tolerated with similar adverse event profiles, approval of the higher dose, apremilast 30 mg BID, is reasonable.

Overall, the data support the claim that apremilast 30 mg BID therapy effectively treats adult patients with active PsA including patients who were currently, or previously, treated with small molecular and/or biologic disease modifying drugs.

6.1 Indication

The sponsor has proposed the use of apremilast 30 mg BID for the treatment of adult patients with active PsA.

6.1.1 Methods

As discussed in Section 5.3, data from studies PSA-002, -003, and -004 were used to assess the efficacy of apremilast for treating patients with active PsA. The three well-controlled studies were highly similar in design and were adequately conducted to provide sufficient evidence to

demonstrate a clinically meaningful benefit of apremilast in subjects with active PsA who had an inadequate response to standard therapy.

6.1.2 Demographics

As shown in Table 4, subjects' baseline demographics were similar between treatment arms and individual studies. Almost equal proportions of male and female subjects were enrolled with an average age of 50 years and BMI of approximately 30. The majority of subjects (≥90%) were classified as White and participated at study centers located in North America and Europe.

Table 4. Baseline Demographics for Subjects Enrolled 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
Age (mean years ± SD)	51 ± 12	49 ± 11	51 ± 12	51 ± 11	51 ± 12	51 ± 11	50 ± 12	50 ± 12	50 ± 11
18 to < 40 years; n (%)	30 (18)	34 (20)	30 (18)	22 (14)	30 (18)	30 (19)	36 (21)	35 (21)	30 (18)
40 to < 65 years; n (%)	119 (71)	123 (73)	116 (69)	121 (76)	119 (73)	114 (70)	119 (70)	117 (69)	122 (73)
≥ 65 years; n (%)	19 (11)	11 (7)	22 (13)	16 9100	14 99)	18 (11)	14 (8)	17 (10)	15 (9)
Sex (female); n (%)	80 (48)	83 (49)	92 (55)	85 (54)	95 (58)	95 (59)	91 (54)	90 (53)	88 (53)
Race; n (%)									
White	153 (91)	150 (89)	152 (91)	152 (96)	151 (93)	157 (97)	158 (94)	161 (95)	163 (98)
Asian	8 (5)	8 (5)	8 (5)	3 (2)	9 (6)	1 (1)	7 (4)	6 (4)	2 (1)
Black	0	2 (1)	0	2 (1)	1 (1)	1 (1)	2 (1)	0	0
Other	7 (4)	8 (5)	8 (5)	1 (1)	2 91)	3 (2)	1 (1)	2 91)	2 (1)
Geographic Region; n (%)									
North America	81 (48)	73 (44)	69 (41)	35 (22)	38 (23)	43 (27)	48 (28)	58 (34)	58 (35)
USA	48 (29)	44 (26)	43 (26)	18 (11)	27 (17)	30 (19)	40 (24)	48 (28)	42 (25)
Europe	39 (23)	41 (24)	42 (25)	106 (67)	103 (63)	101 (62)	75 (44)	32 (19)	31 (19)
Rest of World	48 (29)	52 (32)	57 (34)	18 (11)	22 (14)	18 (11)	46 (27)	32 (19)	31 (19)
Weight (mean kg ± SD)	90 ± 22	89 ± 21	87 ± 20	85 ± 20	83 ± 22	83 ± 19	84 ± 20	86 ± 20	84 ± 20
BMI Category; n (%)									
Mean kg/m^2 ± SD	31 ± 7	31 ± 7	31 ± 6	30 ± 6	29 ± 7	29 ± 6	30 ± 6	30 ± 6	29 ± 6
<25 kg/m^2	30 (18)	27 (16)	28 (17)	41 (26)	46 (28)	45 (28)	41 (24)	38 (23)	43 (26)
25 to < 30 kg/m^2	47 (28)	67 (40)	57 (34)	45 (28)	54 (33)	55 (34)	60 (36)	53 931)	58 (35)
30 to < 35 kg/m^2	49 (29)	35 (21)	41 (24)	43 (27)	35 (22)	36 (22)	33 (20)	43 (25)	36 (22)
35 to < 40 kg/m^2	24 (14)	21 (13)	32 (19)	20 (13)	15 (9)	17 (11)	22 (13)	27 (16)	20 (12)
≥40 kg/m^2	18 (11)	18 (11)	10 (6)	10 (6)	12 (7)	9 (6)	12 (7)	8 (50	10 (6)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; BMI: body mass index. Table adapted from NDA 205437 Integrated Summary of Efficacy, page 38, Table 6.

Overall, subjects' baseline disease characteristics and background PsA-related therapy were similar between individual treatment arms and studies (Table 4 and Table 5, respectively). On average, subjects who entered the study reported approximately seven years of active PsA with

9 swollen joints, 16 tender joints, and an average HAQ-DI score of 1.2u. Not surprisingly, almost all subjects carried a diagnosis of psoriasis with an approximately equal proportion of subjects having <3% or ≥3% involvement of body surface area.

Table 5. Baseline Disease Characteristics for Subjects Enrolled 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
Duration of PsA; mean years ± SD	7 ± 7	7 ± 7	8 ± 8	8 ± 8	8 ± 9	7 ± 8	7 ± 6	8 ± 8	8 ± 8
PsA Subtype; n (%)									
Symmetric Polyarthritis	104 (62)	106 (63)	110 (66)	101 (64)	109 (67)	101 (62)	93 (55)	104 (62	98 (59)
Asymmetrical Polyarthritis	45 (27)	41 (24)	45 (27	49 (31)	43 (26)	42 (26)	44 (26)	43 (25)	49 (29)
DIP Involvement	14 (8)	14 (8)	11 (7)	4 (3)	7 (4)	7 (4)	16 (10)	10 (6)	10 (6)
Arthritis Mutilans	2 (1)	4 (2)	1 (1)	3 (2)	2 (1)	7 (4)	13 (8)	4 (2)	4 (2)
Predominant Spondylitis	3 (2)	3 (2)	1 (1)	1 (1)	2 (1)	5 (3)	3 (2)	8 (5)	6 (4)
Psoriasis (+); n (%)	168 (100)	167 (99)	166 (99)	157 (99)	163 (100)	159 (98)	169 (100)	169 (100)	167 (100)
Extent of Psoriasis; n (%)									
<3% BSA involvement	100 (60)	91 (54)	86 (49)	85 (54)	83 (51)	85 (53)	80 (47)	78 (46)	77 (46)
≥3% BSA involvement	68 (40)	77 (46)	82 (51)	74 (46)	80 (49)	77 (47)	89 (53)	91 (54)	90 (54)
Baseline PASI score; mean ± SD	9.1 ± 9.5	7.4 ± 8.7	9.2 ± 9.7	8.6 ± 10	7.4 ± 6.5	7.8 ± 7.3	7.6 ± 7.2	7.6 ± 5.2	7.9 ± 6.2
Tender Joint Count; median (range)	20 (3-78)	17 (3-70)	20 (3-78)	13 (3-66)	15 (3-78)	16 (3-78)	13 (3-78)	15 (3-78)	18 (3-76)
Swollen Joint Count; median (range)	10 (3-56)	9 (3-58)	12 (3-47)	7 (3-41)	8 (3-56)	8 (3-55)	8 (3-48)	8 (3-52)	9 (3-47)
Patient PA (VAS) ; median (range)	64 (5-99)	58 (0-99)	59 (3-100)	56 (13-100)	61 (4-99)	60 (0-98)	57 (7-99)	57 (3-99)	60 (1-99)
Patient's GA; median (range)	62 (6-100)	58 (1-100)	57 (1-98)	55 (3-99)	59 (6-100)	57 (1-98)	56 (3-99)	55 (5-99)	60 (0-100)
Physician's GA; median (range)	57 (6-95)	57 (0-97)	57 (10-96)	54 (14-92)	54 (7-93)	55 (15-97)	51 (11-100)	57 (3-98)	58 (19-95)
HAQ-DI score; median (range)	1.3 (0-2.8)	1.1 (0-2.9)	1.3 (0-2.8)	1.3 (0-2.5)	1.1 (0-2.6)	1.3 (0-2.8)	1.3 (0-2.6)	1.1 (0-2.6)	1.1 (0-2.9)
CRP (mg/dL); median (range)	0.5 (0-8.1)	0.5 (0-13.8)	0.5 (0-7.9)	0.6 (0-11.5)	0.4 (0-24)	0.4 (0-6.6)	0.4 (0-7.1)	0.4 (0-8.7)	0.4 (0-13.2)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; PASI: psoriasis area severity index; HAQ-DI: health assessment questionnaire-disability index; CRP: c-reactive protein. Table adapted from NDA 205437 Integrated Summary of Efficacy, page 44, Table 8.

Greater than 80% of all enrolled subjects had a history of treatment with MTX and approximately 20% of patients had been treated with a TNF inhibitor. At study baseline, an estimated 70% of subjects were receiving standard doses of background DMARDs (MTX 15 mg/week, LEF 20 mg/day, or SSZ 2 g/day) and NSAIDs (Table 6). A slightly higher percentage of subjects randomized to the APR20 treatment arms in all three studies were receiving oral corticosteroids compared to subjects randomized to the placebo or APR30 treatment arms; however, this difference is unlikely to affect the overall results or interpretability of the data.

Table 6. Concomitant Medications of Subjects Enrolled 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
Any Prior DMARDs used[a]; n (%)	161 (96)	166 (99)	165 (98)	158 (99)	163 (100)	157 (97)	169 (100)	168 (99)	167 (100)
DMARDs used[a]; n (%)									
Methotrexate	140 (83)	141 (84)	140 (83)	138 (87)	141 (87)	137 (85)	151 (89)	139 (82)	142 (85)
Sulfasalazine	43 (26)	51 (30)	43 (26)	62 (39)	62 (38)	47 (29)	39 (23)	30 (18)	46 (28)
Leflunomide	22 (13)	23 (14)	26 (16)	33 (21)	32 (20)	34 (21)	20 (12)	27 (16)	20 (12)
Other[b]	57 (34)	52 931)	59 (35)	31 (20)	44 (27)	47 (29)	62 (37)	68 (40)	56 (34)
Prior Biologic Use[a]; n (%)	41 (24)	37 (22)	41 (24)	23 (15)	28 (17)	23 (14)	48 (28)	50 (30)	43 (26)
Biologic used[a]; n (%)									
TNFi	39 (23)	33 (20)	37 (22)	20 (13)	27 (17)	22 (14)	45 (27)	48 (28)	39 (23)
non-TNFi	9 (5)	9 (5)	8 (5)	4 (3)	6 (4)	7 (4)	8 (5)	11 97)	7 (4)
Prior Biologic Failure; n (%)	19 (11)	14 (8)	14 (8)	8 (5)	10 (6)	7 (4)	12 (7)	18 (11)	14 (8)
Concomitant PsA Treatment at Baseline									
DMARD use; n (%)	110 (66)	111 (66)	106 (63)	113 (71)	114 (70)	113 (70)	101 (60)	104 (62)	101 (61)
Oral Corticosteroids; n (%)	12 (7)	25 (15)	16 (10)	20 (13)	36 (22)	25 (15)	16 (10)	34 (20)	23 (14)
NSAIDs; n (%)	118 (70)	123 (73)	120 (71)	108 (68)	115 (71)	114 (70)	115 (68)	121 (72)	121 (73)
Opioids/Analgesics; n (%)	27 (16)	32 (19)	25 (15)	22 (14)	22 914)	22 (14)	18 (11)	20 (12)	24 (14)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitor DMARD: disease modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug. Table adapted from NDA 205437 Integrated Summary of Efficacy, page 59, Table14.

In summary, the baseline demographics and disease characteristics of the enrolled subjects are well balanced between treatment arms and individual studies, and in general, are representative a typical US patient with PsA.

6.1.3 Subject Disposition

Approximately equal numbers of subjects were enrolled in the three studies with similar proportions of subject disposition within treatment arms. A greater number of placebo-treated subjects entered early escape at Week 16 compared to APR-treated subjects (Table 7). Within the same time period, a slightly higher number of APR30-treated subjects in studies PSA-002 and -003 discontinued the study due to an AE compared to subjects randomized to the APR20 or placebo treatment arms. Discontinuation due to lack of efficacy was similar among treatment arms. One subject randomized to the APR20 treatment arm died during study PSA-002.

Table 7. Subject Disposition at Week 16 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 16	10 (6)	10 (6)	14 (8)	11 (7)	12 (7)	13 (8)	13 (8)	12 (7)	11 (7)
Reason for Discontinuation									
Adverse event	5 (3)	5 (3)	9 (5)	3 (2)	4 (3)	11 (7)	6 (4)	6 (4)	5 (3)
Lack of efficacy	3 (2)	2 (1)	2 (1)	2 (1)	2 (1)	0	2 (1)	3 (2)	2 (1)
Noncompliance	0	0	1 (1)	0	0	0	0	0	0
Subject-initiated withdrawal	1 (1)	1 (1)	2 (1)	5 (3)	5 (3)	1 (1)	2 (1)	3 (2)	1 (1)
Death	0	1 (1)	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1 (1)	0	0	0	0	1 (1)
Protocol violation	1 (1)	0	0	0	0	1 (1)	0	0	1 (1)
Other reason	0	1 (1)	0	0	1 (1)	0	3 (2)	0	1 (1)
Entered Early Escaped at Week 16	107 (64)	78 (46)	58 (35)	88 (55)	59 (36)	64 (40)	97 (57)	76 (45)	53 (32)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Integrated Summary of Efficacy, page 34, Table 4.

Subject disposition at Week 24 was similar in proportion to that observed at Week 16 with a slightly higher number of APR30-treated subjects in studies PSA-002 and -003 discontinuing the study due to an AE compared to subjects randomized to the APR20 or placebo treatment arms (Table 8). Discontinuation due to lack of efficacy remained similar between treatment arms.

Table 8. 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	18 (11)	22 (13)	20 (12)	16 (10)	20 (12)	120 (12)	23 (14)	22 (13)	122 (13)
Reason for Discontinuation									
Adverse event	11 (7)	8 (5)	10 (6)	4 (3)	5 (3)	12 (7)	10 (6)	12 (7)	8 (5)
Lack of efficacy	4 (2)	5 (3)	4 (2)	3 (2)	2 (1)	2 (1)	6 (4)	5 (3)	7 (4)
Noncompliance	0	1 (1)	2 (1)	0	0	0	0	0	0
Subject-initiated withdrawal	2 (1)	5 (3)	3 (2)	7 (4)	9 (6)	3 (2)	3 (2)	4 (2)	1 (1)
Death	0	1 (1)	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1 (1)	1 (1)	2 (1)	1 (1)	0	3 (2)
Protocol violation	1 (1)	0	0	0	1 (1)	1 (1)	0	0	1 (1)
Other reason	0	2 (1)	1 (1)	1 (1)	1 (1)	0	3 (2)	1 (1)	2 (1)
Entered Early Escaped at Week 16	107 (64)	78 (46)	58 (35)	88 (55)	59 (36)	64 (40)	97 (57)	76 (45)	53 (32)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Integrated Summary of Efficacy, page 34, Table 4.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 General Discussion of Choice of Major Endpoints

Psoriatic arthritis is a systemic, chronic, inflammatory autoimmune disease that primarily involves the synovium of both the appendicular and axial skeleton. The inflammation of the synovium results in joint pain and swelling, and in a significant proportion of subjects, bone erosions within the joint resulting in further joint dysfunction and malformation. Together these processes lead to a decreased physical functioning in the patient and a decrease in the health related quality of life. Consequently, endpoints for a clinical trial should be chosen that assess these clinical issues associated with PsA. Given the chronicity of PsA, an endpoint that captures a change in the signs and symptoms should be evaluated for a minimum of 12 weeks to demonstrate durability of the drug effect. Lastly, it is important that a sponsor also demonstrate evidence of improved functional ability/quality of life based on the study data.

The proportion of subjects achieving an ACR20 at Week 16 was used as the primary endpoint for improvement in signs and symptoms. The ACR core data set was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts. The modified ACR response criteria consists of 7 components:

- Swollen joint count (76 joints)
- Tender joint count (78 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (AS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3/5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR20 occurred at Week 16 in all studies.

The change from baseline in the disability index of the Health Assessment Questionnaire (HAQ-DI) at Week 16 was used as a major secondary endpoint for the assessment of improvement in physical function. The HAQ is a standardized disability questionnaire developed for use in RA and PsA with a scoring range between 0 and 3. A high HAQ score has been shown to be a strong predictor of morbidity and mortality in RA, and low HAQ scores are predictive of better outcomes.

Both study endpoints have been validated and used in previous approvals of other drugs indicated for patients with active PsA and are generally accepted by the Agency. The ACR criteria used for assessing disease improvement include several subjective

measurements that are susceptible to investigator bias and therefore blinding of assessors to treatment assignment was instituted in the design of the apremilast PsA studies. Overall, these endpoints provide a reasonable assessment of meaningful clinical efficacy.

6.1.4.2 Primary Endpoint Analysis for Studies PSA-002, -003, -004

All three PsA Phase 3 studies demonstrated a statistically significant difference between placebo and the individual apremilast treatment arms, i.e., APR20 and APR30 (Table 9). The average treatment effect sizes for the APR20 and APR30 treatment arms were 13% and 18%, respectively.

Table 9. Primary Efficacy Analysis: Proportion of Subjects Achieving ACR20 at Week 16 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
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 Effect Size[a], %	-	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

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Efficacy, page 71, Table 18

Although both apremilast treatment arms demonstrated a significant improvement in signs and symptoms compared to placebo, the sponsor is proposing approval for only the apremilast 30 mg BID dosing. As detailed in the Biometrics review by Robert Abugov, PhD, there was not a clear advantage of the apremilast 30 mg BID dose over the apremilast 20 mg BID dose as only study PSA-004 demonstrated a statistically significant advantage of APR30 compared to APR20. In fact, study PSA-003 actually demonstrated a numerical advantage of the APR20 treatment arm compared to APR30.

These analyses demonstrate a clinical benefit in the improvement of the signs and symptoms of subjects with active PsA who are treated with apremilast compared to subjects treated with placebo. Additionally, apremilast-treated subjects demonstrated greater improvements in all ACR components compared to placebo-treated subjects at Week 16 (data not shown), lending further support of the efficacy of apremilast in inducing ACR20 responses in subjects with active PsA. While there appears to be a small numerical advantage of the apremilast 30 mg BID dose, the data are not so robust that this dose is clearly superior, statistically or clinically, to apremilast 20 mg BID; however, given the overall safety profile of apremilast (Section 7), the higher 30 mg BID dose appears to be acceptable.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Major Secondary Endpoint: Mean Change in HAQ-DI from Baseline at Week 16

All three PsA Phase 3 studies demonstrated a statistically significant difference between APR30-treated subjects compared to placebo-treated subjects for change from baseline HAQ-DI at Week 16 (Table 10). While only studies PSA-002 and -003 demonstrated a statistically significant difference for APR20-treated subjects compared to placebo-treated subjects. Although not statistically different, the APR30 treatment arm demonstrated larger numerical differences in all three studies compared to the APR20 treatment arm. The clinical significance of these data is unclear because minimal clinically important difference (MCID) for patients with PsA has not been established; however, an MCID of 0.25 units has been validated for patients with RA. Applying this value (threshold of ≥0.3 units) to the PsA studies demonstrated a statistically significant difference between placebo and APR30 in studies PSA-002 and PSA-003 (data not shown) lending further support of an improvement of physical function in apremilast-treated patients.

Table 10. 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	-0.09	-0.2	-0.24	-0.05	-0.16	-0.19	-0.07	-0.13	-0.19
Treatment Effect Size[a]	-	-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

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Statistical Review, page 23, Table 11

6.1.5.2 Clinically Important Secondary Endpoints

(b) (4)

(b) (4)

Despite these shortcomings, this review will include the sponsor's analyses of the clinically relative secondary endpoints in support of the primary endpoint, which was statistically valid and clinically meaningful. The reader is referred to the statistical review by Dr. Abugov of the Division of Bioinformatics for a detailed statistical analysis of the submission's efficacy data.

Clinically relevant secondary endpoints that will be included in this review include ACR20/50/70 responses at Weeks 16 and 24, ACR component scores, change from baseline HAQ-DI at Week 24, SF-36 components. Review of the PASI-75 response, MASES reduction, DAS28, and dactylitis are not reviewed here but are discussed extensively in Dr Abugov's statistical review.

6.1.5.2.1 ACR Responses and Components

Table 11 summarizes the proportion of subjects achieving an ACR20/50/70 response for the three treatment groups at Weeks 16 and 24 for the pooled analysis from the three PsA studies. After carrying forward early escape failures at week 16, the ACR20/50/70 response rates a Weeks 16 and 24 for the comparison of APR30 placebo were statistically significant in all three studies. The average difference between A30 and placebo was 16%. In general, these data support the primary endpoint by demonstrating a treatment-effect in a greater proportion of apremilast-treated subjects compared to placebo-treated subjects at Weeks 16 and 24 for ACR20/50/70 responses.

Table 11. Proportion of Subjects Achieving an ACR20/50/70 at Weeks 16 and 24 for the Pooled Analysis for PsA Phase 3 Studies

Endpoint Visit	PBO N=496 Response n (%)	APR20 BID N=500 Response n (%)	APR30 BID N=497 Response n (%)
ACR20			
Week 16	93 (19)	160 (32)	184 (37)
Week 24	73 (15)	139 (28)	151 (30)
ACR 50			
Week 16	32 (7)	71 (14)	69 (14)
Week 24	34 (7)	70 (14)	78 (16)
ACR 70			
Week 16	7 (1)	24 (5)	15 (3)
Week 24	12 (2)	25 (5)	30 (6)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Statistical Review, pages 24, 33, 34, Tables 13, 22, 33

Figure 2 and Figure 3 illustrate the median percent change from baseline in ACR component scores at Weeks 15 and 24, respectively. These data demonstrate a treatment and overall dose effect for all ACR components. Importantly, these figures demonstrate that the data used for analyzing the proportion of ACR20 responders was not driven by any single component and that apremilast's was broadly effective across all ACR components.

Figure 2. Median Percent Change from Baseline in ACR Component Scores at Weeks 16 for the Pooled Analysis for PsA Phase 3 Studies

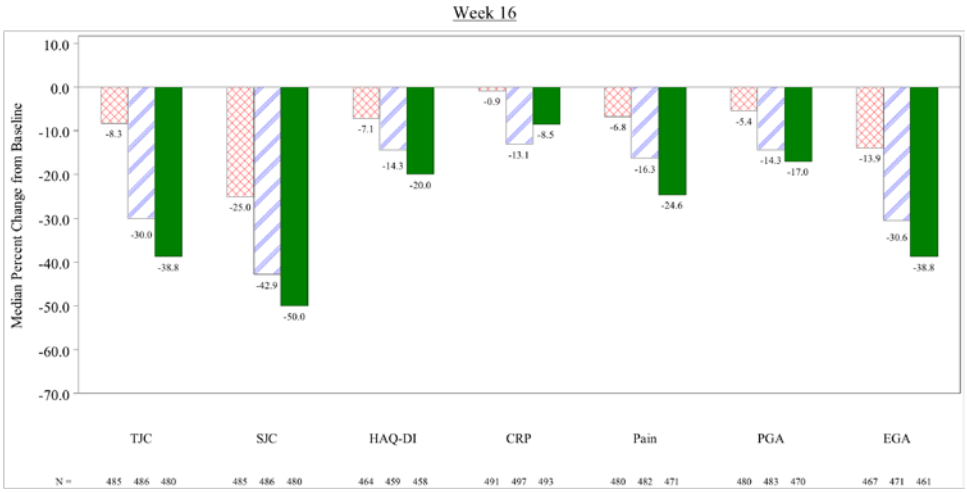


Figure adapted from NDA 205437 Integrated Summary of Efficacy, page 140, Figure 10.

Figure 3. Median Percent Change from Baseline in ACR Component Scores at Weeks 24 for the Pooled Analysis for PsA Phase 3 Studies

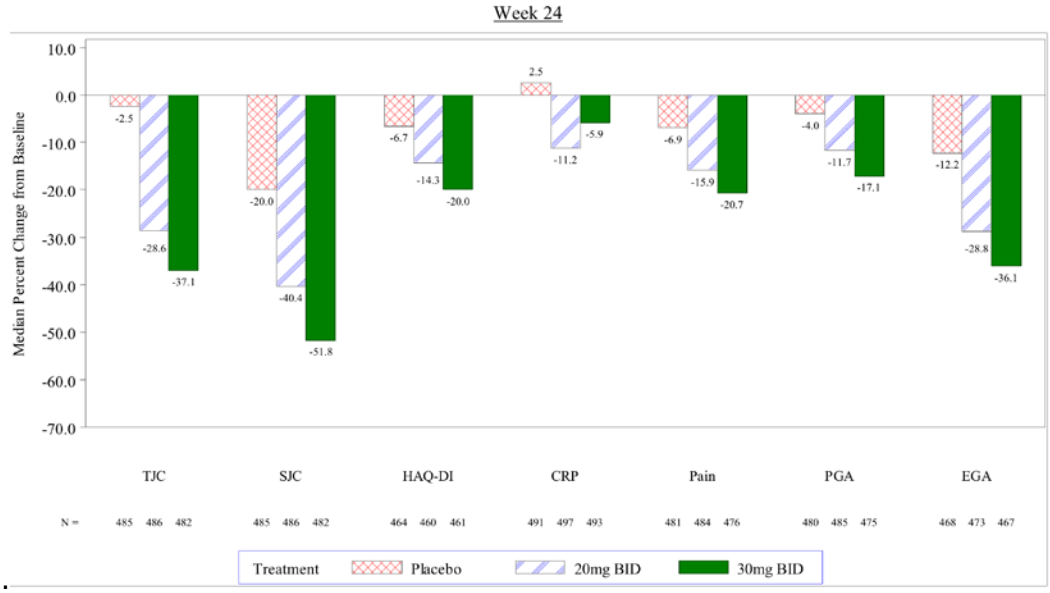


Figure adapted from NDA 205437 Integrated Summary of Efficacy, page 140, Figure 10.

6.1.5.2.2 Change from Baseline in HAQ-DI at Week 24

Statistical analyses for testing the change from baseline in HAQ-DI at week 24 were conducted on observed data rather than LOCF data (Table 12). The differences between the APR30 and placebo groups were statistically significant in one out of three studies

Table 12. Change in HAQ-DI at Week 24 for PsA Phase 3 Studies

Study	Percent Response		
	PBO	APR20	APR30
PSA-002 change, (n)	-0.2 (154)	-0.3 (147)	-0.3 (146)*
PSA-003 change, (n)	-0.2 (142)	-0.3 (145)	-0.2 (141)
PSA-004 change, (n)	-0.2 (146)	-0.2 (146)	-0.3 (147)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Statistical Review, page 27, Table 17

6.1.6 Other Endpoints

The reader is referred to Dr. Abugov's statistical review for a detailed analysis of additional endpoints.

6.1.6.1 ACR20 Response at Week 24 for Individual Studies

As discussed earlier, approximately 55-60% of placebo-treated subjects, 32% of APR20-treated subjects, and 46% of APR30-treated subjects entered early escape at Week 16. These subjects, and subjects who discontinued treatment, were considered non-responders for Week 16 and Week 24 analyses. As shown in Table 13, a higher proportion of subjects treated with APR30 and APR20 achieved an ACR20 at Week 24 compared to subjects treated with placebo.

Table 13. Proportion of Subjects Achieving an ACR20 at Week 24

	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 24; n (%)	22 (13)	43 (26)	59 (35)	25 (16)	51 (31)	40 (25)	26 (15)	46 (27)	52 (31)
Treatment Effect Size[a], %	-	13	22	-	16	9	-	12	16
p-value APR dose vs. PBO	-	0.004	<.0001	-	0.0009	0.04	-	0.01	0.0007

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Statistical Review, page 24, Table 13

Table 14 shows the proportion of subjects who had an ACR20 response at Week 16 and Week 24. Compared to placebo, a higher proportion of subjects treated with APR30 or APR20 achieved an ACR20.

Table 14. Proportion of Subjects Achieving an ACR20 at Week 16 AND Week 24

	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 Weeks 16 AND 24; n/N (%)	22/168 (13)	43/168 (26)	59/168 (35)	25/159 (16)	51/163 (31)	40/162 (25)	26/169 (15)	45/169 (27)	52/167 (31)
Treatment Effect Size[a], %	-	12	22	-	16	9	-	11	16
p-value APR dose vs. PBO	-	0.004	<0.0001	-	0.0009	0.04	-	0.01	0.0007

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Efficacy, page 80, Table 21

6.1.6.2 SF-36 Change from Baseline at Week 16

The sponsor examined SF-36 domain and component scores at Week 16. Mean change from baseline among patients randomized to APR30 differed significantly from placebo in all studies for the physical function domain and physical component score (Table 15). The average difference between APR30 and placebo was 2.3. The claim for improved physical function is reinforced by nominally significant improvements associated with APR30 compared to placebo of physical component score, physical function, role physical, and bodily pain component score, physical component score in all three studies and for general health in one of three studies (Table 15).

Statistically significant differences between the APR30 and placebo groups for the mental component score were only seen in study PSA-003 (Table 16), where statistically significant differences were seen for mental health and vitality, but not for social functioning or role emotional.

Table 15. SF-36 Physical. Mean Change from Baseline, Week 16

Metric	Study	Change from Baseline			Treatment Difference			P-Value
		P	A20	A30	A20-P	A30-P	A30-20	A30 – P
PCS	2	2.4 (168)	3.5 (168)	4.6 (168)	1.1	2.2	1.1	0.0097
	3	2 (159)	3.2 (163)	3.7 (162)	1.3	1.7	0.5	0.0335
	4	1.3 (169)	3.2 (169)	3.4 (167)	2	2.1	0.1	0.006
PF	2	1.8 (168)	3.5 (168)	4.2 (168)	1.7	2.4	0.7	0.0056
	3	0.8 (159)	2.2 (163)	2.9 (162)	1.4	2.1	0.7	0.0237
	4	1.1 (169)	2.3 (169)	3.5 (167)	1.1	2.3	1.2	0.0053
RP	2	2 (168)	2.8 (168)	4.2 (168)	0.9	2.2	1.3	0.0218
	3	1.4 (159)	1.3 (163)	3.5 (162)	-0.1	2.1	2.2	0.0247
	4	0.8 (169)	2.9 (169)	3.2 (167)	2.2	2.4	0.3	0.0049
BP	2	2 (168)	3.9 (168)	4.3 (168)	1.8	2.2	0.4	0.0083
	3	2 (159)	3.5 (163)	3.8 (162)	1.5	1.8	0.3	0.0337
	4	1.1 (169)	2.7 (169)	3.5 (167)	1.6	2.4	0.8	0.0027
GH	2	1.5 (168)	1.7 (168)	2.5 (168)	0.2	1	0.8	0.2435
	3	1.1 (159)	2.5 (163)	2.7 (162)	1.4	1.6	0.2	0.0473
	4	1 (169)	1.9 (169)	1.6 (167)	0.9	0.6	-0.3	0.4024

source: mainline.sas

PCS Physical Component Score, PF Physical Function, RP Role Physical, BP Bodily Pain, GH General Health

Table adapted from NDA 205437 Statistical Review, page 29, Table 18

Table 16. SF-36. Mental. Mean Change from Baseline, Week 16

Metric	Study	Change from Baseline			Treatment Difference			P-Value
		P	A20	A30	A20-P	A30-P	A30-20	A30 - P
MCS	2	0.1 (168)	0.4 (168)	0.7 (168)	0.3	0.6	0.3	0.4932
	3	-1 (159)	-1 (163)	0.9 (162)	0	1.9	1.9	0.0326
	4	0.2 (169)	-0.3 (169)	1.2 (167)	-0.5	1	1.5	0.1989
MH	2	1.1 (168)	1.5 (168)	1.9 (168)	0.4	0.8	0.4	0.436
	3	-0.8 (159)	-0.3 (163)	1.5 (162)	0.5	2.3	1.8	0.0369
	4	0.4 (169)	0.4 (169)	2.3 (167)	0	1.9	1.8	0.0396
VT	2	2 (168)	1.7 (168)	3.5 (168)	-0.3	1.5	1.8	0.1451
	3	0.7 (159)	1.2 (163)	3 (162)	0.5	2.3	1.8	0.0136
	4	0.8 (169)	1.9 (169)	2.6 (167)	1.1	1.8	0.7	0.0378
SF	2	0.7 (168)	0.5 (168)	0.3 (168)	-0.2	-0.4	-0.2	0.4227
	3	-0.2 (159)	-0.2 (163)	-0.4 (162)	0.1	-0.1	-0.2	0.7999
	4	0.5 (169)	0.9 (169)	1.2 (167)	0.3	0.7	0.4	0.2281
RE	2	-0.4 (168)	1.6 (168)	1.6 (168)	2	2	0.0	0.0647
	3	-0.3 (159)	-0.2 (163)	2.7 (162)	0	2.9	2.9	0.0071
	4	0.2 (169)	0 (169)	1.7 (167)	-0.2	1.5	1.7	0.1277

source: mainline.sas
MCS Mental Component Score, MH Mental Health , VT Vitality, SF Social Functioning, RE Role Emotional

Table adapted from NDA 205437 Statistical Review, page 30, Table 19

6.1.7 Subpopulations

No significant subgroup effects on efficacy were seen for race, age, or geographic region. A nominally significant effect of baseline DMARD usage on treatment effect was seen in study PSA-002 but not the other two PsA studies. Subjects not taking DMARDs at baseline demonstrated a numerically higher response to APR30 compared to

placebo in studies PSA-002 and -004 but not PSA-003. No significant differences were seen between in subjects treated with APR20 or placebo regarding baseline DMARD use. The reader is referred to Dr. Abugov's statistical review for a detailed analysis of these endpoints.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed earlier, evidence for additional efficacy benefits of apremilast 30 mg over apremilast 20 mg are suggestive but not conclusive, or even consistent, with effects of apremilast 20 mg compared to placebo. Approval of apremilast 30 mg appears to be acceptable given the suggestion of better efficacy and similar safety profile compared to apremilast 20 mg.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The reader is referred to Dr. Abugov's statistical review for a discussion of persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

The reader is referred to Dr. Abugov's statistical review for a detailed discussion of additional efficacy issues and analyses.

7 Review of Safety

Safety Summary

A total of 2401 subjects have received apremilast in Phase 2 and 3 clinical studies for the treatment of PsA, PSOR, and RA in doses ranging from 10 mg BID to 30 mg BID. A total of 672 subjects included in the Apremilast Unblinded Data Pool have received apremilast 30 mg BID, the proposed dose, for at least 24 weeks, and 269 subjects have received apremilast 30 mg BID for at least 48 weeks.

At total of 721 subjects enrolled in the PsA studies received apremilast 30 mg BID with 527 subjects treated for at least 24 weeks and 183 subjects treated for at least 48 weeks. Review of the baseline demographic and disease characteristics demonstrated that subjects enrolled in the apremilast PsA studies were representative of patients in the general US population with the disease. The studies enrolled almost equal proportions of male and female subjects who on average were White (>90%) and middle aged (median age of 51 years). Subjects reported a mean duration of PsA since diagnosis of 7.5 years and had a history of receiving treatment with small molecular DMARDs, including 22% of subjects who had received previous therapy with a biologic agent. Comorbid conditions and concomitant medications were similar across treatment arms.

There were a total of 6 deaths reported in the broader apremilast development program with one death occurring in the PsA studies and the remaining five deaths having been reported during the psoriasis studies. Two of the deaths were apparent suicides (one subject each from the placebo and apremilast treatment arms), which was concerning since the PDE4-inhibitor roflumilast has a warning included in its product labeling concerning the potential for increased psychiatric events including depression and suicidal behavior. A thorough review of psychiatric adverse events in the apremilast program was performed including a consultation from the Division of Psychiatric Products. Review of the data concluded that the current data submitted in the application does not suggest an increased risk of suicidal behavior in patients treated with apremilast.

In the PsA Phase 3 studies, serious adverse events occurred in approximately equal frequencies between placebo-, APR20-, and APR30-treated subjects. Safety analyses did not suggest a clinically important difference in the type of overall rate of SAEs between apremilast-treated subjects and subjects treated with placebo.

The frequency of all AEs between the APR20 and APR30 treatment arms were generally comparable. The most frequently reported adverse events (AEs) were diarrhea, nausea, and headache, all of which increased in a treatment- and dose-dependent manner. The majority (>96%) of AEs were reported as mild to moderate in

severity. The highest incidence of diarrhea, nausea, and headache events occurred within the first 14 days of initiating apremilast therapy and reduced substantially after 30 days. Upper respiratory tract infections were also reported in > 5% of subjects and occurred more frequently in subjects receiving apremilast than in those receiving placebo. Most of these infections were mild to moderate in severity and self-limiting. No SAES due to URIs were reported. Diarrhea, nausea, headache, URI, vomiting, and dyspepsia should be included in the product label as adverse drug reactions.

A treatment-dependent decrease in body weight was observed in the PsA studies. A greater proportion of apremilast-treated subjects experienced a >5% weight loss compared to placebo-treated subjects. No subject had a weight decrease of >20% and only one subject discontinued due to weight decrease during the apremilast-exposure period. Potential for significant weight loss should be included in the product label.

Analyses of adjudicated events for serious infections, major adverse cardiac events, and malignancies did not indicate any imbalance between apremilast-treated subjects and placebo-treated subjects. Additional analyses assessing tuberculosis, psychiatric events, hepatobiliary, and vasculitis were performed and no safety signal was identified.

Markedly abnormal laboratory test results were infrequent and transient. In general, analyses of mild and moderate laboratory abnormalities did not show an increased risk between either APR20 or APR30. The vast majority of laboratory abnormalities were transient and did not lead to study drug discontinuation. No cases of hepatic failure, or LFT elevations meeting Hy's Law criteria, were reported. Myelosuppression was not observed based on routine laboratory testing.

Clinical pharmacology studies and analysis of the Phase 2/3 safety databases did not identify a clinically meaningful drug-drug interaction with apremilast. Apremilast has demonstrated an acceptable safety profile when used alone or in combination with the DMARD MTX, SSZ, and LEF.

In summary, the data submitted in the application was sufficient to assess the overall safety of apremilast in patients with active PsA. The most commonly occurring adverse events associated with apremilast were diarrhea, nausea, vomiting, headache, and 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%-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. The overall safety profile was comparable between the apremilast 20 mg BID dosing and 30 mg BID dosing, except. Given these data, the proposed higher dose of apremilast 30 mg BID

appears reasonable as there does not appear to be an increased risk of serious adverse reactions compared to the lower apremilast dose of 20 mg BID.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed in Section 5, the principle data used for the safety assessment of apremilast was derived from the placebo-controlled period of the three PsA Phase 3 studies, PSA-002, -003, and -004. These studies were chosen as the focus of the safety review due to their similarity in study design, enrolled subjects were the targeted patient-population for the proposed indication, large number of subjects, and 16-week placebo-controlled periods. Together, these factors allowed for the reliable pooling of data to create a larger subject database in which to assess potential safety signals related to apremilast. A greater degree of emphasis for the safety analyses were placed on the placebo-controlled periods of this data pool since the observed rates of AEs in apremilast-treated subjects could be directly compared to placebo-treated subjects.

Data from the non-placebo-controlled periods of the three PsA Phase 3 studies were used to assess potential safety signals that may occur at later time points following longer exposures to apremilast; however, this data can be difficult to interpret given the lack of an adequate comparison arm. Discussion of the safety data from this period of the studies include exposure-adjusted incident rates (EAIR) to account for the potential occurrence of time effects when assessing AEs between treatment groups. A summary of the Phase 3 PsA study designs can be found in Table 2.

Additional safety data was derived from the Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, and RA (Table 17). With the exception of studies PSOR-001 and PSOR-04, these additional studies were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast versus placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. In general, data from these studies were used to confirm the findings from the PsA studies and to assess potential safety signals from the larger combined subject population.

Table 17. Clinical Studies Used in the Safety Assessment of Apremilast

Study	Centers (n)	Subjects Enrolled (n)	Dosing[a]	Study Design	Primary Endpoint
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
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
Other					
ASTH-001	4	73	PBO APR20 QD APR20 BID	Randomized, double-blind, PBO-controlled, parallel-group, exercise-challenge study enrolling subjects with mild asthma. Subjects were randomized 1:1:1 to receive PBO, APR20 mg QD, or APR30 mg BID. Primary efficacy endpoint assessing the maximum post-exercise percentage fall index (%FI) at Day 29.	%FI @ Day 29
BCT-001	6	111	PBO APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active Behçet's disease. Subjects were randomized 1:1 to receive PB or APR30 mg BID. Primary efficacy endpoint assessing the number of oral ulcers at Day 85.	Oral Ulcers @ Day 85

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; ACR20: American College of Rheumatology 20% response; Wk: week; PASI: psoriasis area severity index

Data from the clinical pharmacology studies and the clinical studies for Behçet's disease and asthma were not included in the pooled safety analyses given the differences in the subject population and underlying disease pathogenesis; however, any deaths and/or reported SAEs from these studies were reviewed and are included in the overall analysis of the risk-benefit assessment of apremilast. Additionally, three Phase 3 studies are ongoing and remain blinded including one study in PsA (CC-10004-PSA-005) and two studies in psoriasis (PSOR-008, -009), consequently, data from these studies are not included in the overall safety assessment of apremilast except for reported deaths and expedited SAEs.

Overall, the data submitted by the sponsor appears to be of adequate quality to draw conclusions regarding the initial safety of apremilast.

7.1.2 Categorization of Adverse Events

Analysis of the safety data included deaths, serious adverse events (SAE), adverse events (AE), adverse drug reactions (ADR, laboratory data, vital signs, and electrocardiographs (ECG). All AEs were coded according to MedDRA version 14.0.

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 for subjects who completed the study or had discontinued prematurely by the time of the database lock. Additionally, the event was included if it occurred on or after the date of the first dose of study drug for subjects who were enrolled in the study at the time of the database lock.

An SAE was defined as an AE that was graded 3 or above by the investigator for studies utilizing National Cancer Institute/Common Terminology Criteria for Adverse Events (NCI/CTCAE) or indicated as severe by the investigator for studies not utilizing NCI/CTCAE.

The sponsor 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. Additional analyses included AEs related to headache, and hepatic/renal systems. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, major adverse cardiac events [MACE], and hepatobiliary and hypersensitivity AEs).

All AEs related to malignancies, serious infections, and MACE/potential MACE were adjudicated by independent, blinded, subspecialty adjudicators. For each of these groups, one independent external expert in the respective field was selected to perform the adjudication. The sponsor identified the cases for adjudication based on pre-defined criteria and provided the available information to the adjudicator who then reviewed the case and provided the assessment based on the predefined categories defined in the adjudication Charter. If the adjudicator required additional information, the sponsor contacted the investigation site to obtain available information and forwarded it to the adjudicator. An adjudication form was completed by the adjudicator and provided to the sponsor for each subject. The adjudicated results were used as the primary analyses for these safety events.

An increased potential risk for suicide and other psychiatric events have been noted with the use of the PDE4 inhibitor, roflumilast (DALIRESP). Consequently, the sponsor performed a 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. A retrospective evaluation of safety data for subjects from both completed and ongoing clinical trials was conducted on a semiannual basis. The sponsor 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. In addition, The FDA's Division of Psychiatry Products was consulted for their expert advice to help determine whether a safety signal related to suicidal behavior was present in apremilast-treated subjects. A discussion of their analysis is included in this review.

Laboratory data, ECG data, and vital signs were presented using summary statistics and markedly abnormal values. A separate QTc evaluation study was performed by the sponsor and is included in this review (Section 7.4.4).

Analyses of AEs and marked abnormalities for the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool used descriptive statistics and point estimates. Subject incidence was defined as the number of subjects reporting the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period were counted only once in the numerator. Exposure-adjusted incidence rates per 100 subject-years was defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period were only counted once in the numerator. The exposure time for a subject without the specific event was defined as the treatment duration, while the exposure time for a subject with the specific event was defined as the treatment duration up to the start date of the first occurrence of the specific event. The total exposure time in years was calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25 (days/year). The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 subject-years of exposure to the study drug. Use of exposure-adjusted rates for the placebo-controlled period is to account for the differences in exposure between placebo-treated and apremilast-treated subjects resulting from the early escape design feature in the PsA Phase 3 studies PSA-002, PSA-003, PSA-004, and RA-002.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary focus of this safety review draws from data collected in the three PsA Phase 3 studies, PSA-002, -003, and -004, referred to hereafter as the ***PsA Phase 3 Data Pool***. These studies were chosen as the focus of the safety review due to their similarity in study design, enrolled subjects were the targeted patient-population for the proposed indication, large number of subjects, and 16-week placebo-controlled periods. The nearly identical study designs allowed for the data to be pooled with reasonable reliability of study conduct, apremilast dosing, and subject population. Emphasis on the placebo-controlled periods of the PsA Phase 3 Data Pool allowed for the direct comparison of AEs between subjects receiving apremilast versus placebo in the proposed targeted patient population.

Data from the non-placebo-controlled periods of the three PsA Phase 3 studies were used to assess potential safety signals that may occur at later time points following longer exposures to apremilast; however, this data can be difficult to interpret given the lack of an adequate comparison arm. Discussion of the safety data from this period of the studies include EAIRs to account for the potential occurrence of time effects when assessing AEs between treatment groups.

Additional safety data was derived from the Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, and RA. This data pool will be referred to in this review as the ***Apremilast Unblinded Data Pool***. With the exception of studies PSOR-001 and PSOR-04, these additional studies were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast versus placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. However, one shortcoming regarding the pooling of these studies is that it includes the same data used in the PsA Phase 3 Data Pool. Thus, approximately 65% of the subjects included in the Apremilast Unblinded Data Pool consist of data from the PsA Phase 3 Data Pool.

7.1.3.1 Analysis Populations

Pooled safety analyses for the placebo-controlled period were based on the safety population defined as all subjects who were randomized and received at least one dose of study drug. Subjects were included in the treatment group corresponding to the study drug actually received. Subjects who received different doses of study drug the placebo-controlled period were handled as follows:

- Subjects whose randomization assignment was apremilast, but who initially received placebo in error, were included in the placebo group until the first apremilast dose was received. Subsequently, they were included in the apremilast-exposure period at the apremilast dose level first received.

- Subjects whose randomization assignment was placebo, but who initially received apremilast in error, were included in the apremilast dose group corresponding to the apremilast dose first received.

- Subjects who received two doses of apremilast were included in the apremilast dose group based on the dose first received.

Subjects included in the apremilast-exposure data pool were based on the apremilast subjects as treated and included all subjects who received at least one dose of apremilast. Subjects were included in the apremilast dose group corresponding to the first apremilast dose actually received. Subjects who received different doses of apremilast during the apremilast-exposure period were included in the apremilast dose group corresponding to the apremilast dose first received.

7.1.3.2 Analysis Periods

In this review, use of the term, placebo-controlled period, included all data collected in each of the studies corresponding to the time during which subjects were randomized and treated with placebo, in order to allow for a direct comparison of the safety between apremilast and placebo treatment arms. Subjects who had entered early escape at Week 16 due to an inadequate clinical response were rerandomized to either apremilast 20 mg BID or 30 mg BID in studies, PSA-002, -003, and -004, or switched to apremilast 20 mg BID in study RA-002. Apremilast-treated subjects who entered early escape continued to receive their assigned apremilast dose. At Week 24, all remaining placebo-treated subjects were rerandomized to an apremilast treatment arm. The placebo-controlled period included only the data before early escape for placebo-treated subjects who entered early escape and the data up to Week 24 for placebo-treated subjects who did not early escape. Data summarized for the apremilast treatment groups included data up to Week 24, whether or not they early escaped. Therefore, exposure to study drug is less in the placebo treatment group compared with the apremilast treatment groups.

The apremilast-exposure period includes all apremilast exposure data, irrespective of when the apremilast exposure started through the completion of the study or at the time of the safety data cutoff date. For the apremilast-exposure period, all subjects who were initially assigned to receive placebo, who either early escaped, switched therapy, or who were rerandomized or switched therapy at Week 24, were included in the apremilast dose group according to the dose they received.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 PsA Phase 3 Data Pool Exposure

Table 18 shows the overall exposure to study drug during the placebo-controlled period of the PsA Phase 3 Data Pool. Approximately 500 subjects were randomized to each of the three treatment groups with all subjects having received at least 1 dose of study drug. At week 16, 73% of placebo-treated subjects remained in the study compared to 90% and 89% of subjects randomized to the APR20 and APR30 treatment arms, respectively. The amount of available placebo-controlled data at Week 16 appears adequate to assess the relative safety of apremilast at this time point. However, there are substantially fewer placebo-treated subjects by Week 24 as a result of these subjects entering early escape at Week 16, consequently, drawing conclusions up to Week 24 is more difficult.

Table 18. PsA Phase 3 Data Pool: Extent of Study Drug Exposure During the Placebo-Controlled Period

Apremilast Exposure	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
≥1 day	495 (100)	501 (100)	497 (100)
≥4 Weeks	484 (98)	485 (97)	472 (95)
≥8 Weeks	468 (95)	471 (94)	460 (93)
≥12 Weeks	458 (93)	462 (92)	451 (91)
≥16 Weeks	363 (73)	449 (90)	444 (89)
≥20 Weeks	154 (31)	437 (87)	435 (88)
≥24 Weeks	113 (23)	292 (58)	278 (56)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 41, Table 3

The total exposure to apremilast for the PsA Phase 3 Data Pool (apremilast-exposure period), including placebo-treated subjects who switched to apremilast and those subjects initially randomized to apremilast, are shown in Table 19. Over 70% of subjects in the PsA Phase 3 Data Pool had been exposed to apremilast for at least 24 weeks and approximately 25% of subjects had been exposed to apremilast for at least 48 weeks.

Table 19. PsA Phase 3 Data Pool: Extent of Study Drug Exposure During the Apremilast-Exposure Period

Apremilast Exposure	APR20 BID (n=720) n (%)	**APR30 BID (n=721) n (%)**
≥1 day	720 (100)	721 (100)
≥4 Weeks	693 (96)	686 (95)
≥12 Weeks	630 (88)	625 (87)
≥24 Weeks	516 (72)	527 (73)
≥36 Weeks	332 (46)	340 (47)
≥48 Weeks	176 (24)	183 (250
≥60 Weeks	92 (13)	84 (12)
≥72 Weeks	35 (5)	35 (5)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 42, Table 4

7.2.1.2 Apremilast Unblinded Data Pool

Exposure to study drug during the placebo-controlled period for the Apremilast Unblinded Data Pool is shown in Table 20. A total of 817 subjects were randomized to receive PBO, 824 subjects were randomized to receive APR20, and 661 subjects were randomized to receive APR30. Different apremilast treatment groups (i.e., APR 10 BID [n=89], APR20 QD [n=87], and APR 40 QD [n=67]) were included Apremilast Unblinded Data Pool resulting in a total of 1728 subjects being randomized to receive apremilast (data not shown). All subjects received at least 1 dose of study drug. Approximately 60% of placebo-treated subjects in the Apremilast Unblinded Data Pool remained in the study at Week 16. Comparatively, approximately 70% and 84% of subjects randomized to the APR20 and APR30 treatment arms, respectively, were exposed to study drug at Week 16. The disproportionate numbers of subjects between treatment arms is largely due to differences in the individual study designs, which included different durations of placebo-controlled periods (ranged between Week 12 and Week 24) and the ability of placebo subjects to escape early at Week 16.

Table 20. Apremilast Unblinded Data Pool: Extent of Study Exposure During the Placebo-Controlled Period

Apremilast Exposure	PBO (n=817) n (%)	APR20 BID (n=824) n (%)	APR30 BID (n=661) n (%)
≥1 day	817 (100)	824 (100)	661 (100)
≥4 Weeks	788 (97)	785 (95)	627 (95)
≥8 Weeks	750 (92)	756 (92)	609 (92)
≥12 Weeks	705 (86)	716 (87)	593 (90)
≥16 Weeks	479 (59)	567 (69)	557 (84)
≥20 Weeks	197 (24)	504 (61)	496 (75)
≥24 Weeks	145 (18)	345 (42)	327 (50)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 43, Table 5

The total exposure to apremilast for the Apremilast Unblinded Data Pool (apremilast-exposure period) is shown in Table 21. Approximately 62% of subjects randomized to APR20 and 73% of subjects randomized to APR30 in the Apremilast Unblinded Data Pool had been exposed to apremilast for at least 24 weeks. Subjects in Studies PSA-001, PSOR-004, and PSOR-005-E-LTE were not required to enter the Extension Phase in these studies, consequently, the decrease in numbers shown in Table 21 do not necessarily reflect treatment discontinuations but rather reflect an aspect of the study designs.

Table 21. Apremilast Unblinded Data Pool: Extent of Study Exposure During the Apremilast-Exposure Period

Apremilast Exposure	APR20 BID (n=1198) n (%)	APR30 BID (n=921) n (%)
≥1 day	1198 (100)	921 (100)
≥4 Weeks	1143 (95)	875 (95)
≥12 Weeks	1013 (85)	794 (86)
≥24 Weeks	745 (62)	672 (73)
≥36 Weeks	462 (39)	457 (50)
≥48 Weeks	245 (21)	269 (29)
≥60 Weeks	114 (10)	106 (12)
≥72 Weeks	50 (4)	51 (6)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 43, Table 6

Apremilast exposure during the Behçet's study and the Clinical Pharmacology studies are not included in this review due to the limited role these studies played in the overall safety analyses.

Demographics PsA Phase 3 Data Pool

A summary of the baseline demographics and disease characteristics for the studies comprising the PsA Phase 3 Data Pool can be found in Table 4. Baseline demographics of the subjects included in the PsA Phase 3 Data Pool were well balanced between treatment arms. Almost equal proportions of male and female subjects were enrolled with an average age of 51 years and a median body weight of approximately 84 kg. A total of 146 out of the 1493 (10%) subjects were 65 years of age or older, including 19 subjects who were 75 years of age or older. The majority of subjects (≥90%) were classified as White and participated at study centers located in North America (34%) and Europe (45%). Similarly, baseline disease characteristics were balanced between treatment arms with a mean duration of PsA of approximately 7 years. Almost 99% of the 1493 subjects enrolled into the three PsA Phase 3 studies had received prior treatment with small-molecule or biologic DMARDs prior to entering the study. A total of 76% of subjects had been previously treated with one or more small molecular DMARDs and 22% of subjects had also received a biologic DMARD. A total of 973 of 1493 (65%) subjects were receiving small molecular DMARDs at study baseline with 55% of subjects receiving MTX 15 mg weekly.

Coexisting medical conditions at study baseline were consistent between treatments. A large percentage of subjects enrolled in the PsA Phase 3 studies had coexisting cardiovascular risk factors including hypertension (40%), hypercholesterolemia (15%), obesity (12%), hyperlipidemia (8%), and Type II diabetes mellitus (7%). Approximately 15% of subjects reported depression.

Overall, the proportions and types of prior medications used by subjects were well balanced between treatment arms (data not shown). The most common prior medications used by subjects were consistent with current standard of care of patients with PsA and included MTX (85% of subjects), SSZ, leflunomide, TNF-inhibitors, NSAIDs, and corticosteroids. Subjects also reported prior medications used to treat common comorbidities including antihypertensives drugs, lipid-modifying agents, antithrombotic agents, and anti-diabetic drugs.

In summary, the data comprising the PsA Phase 3 Data Pool appears to be adequate to draw conclusions regarding the initial safety assessment of apremilast. The studies enrolled a sufficient number of subjects with PsA and included the proposed titration regimen and dose of apremilast to be marketed, apremilast 30 mg BID. Furthermore, treatment arms were well balanced in all respects and the study enrolled subjects with similar baseline demographics, PsA disease characteristics, and prior medication use to that found in the North American population, making extrapolation of the safety data more applicable to patients in the US.

Apremilast Unblinded Data Pool

Baseline demographic characteristics of the subjects included in the Apremilast Unblinded Data Pool were generally well balanced and were similar to that observed in the PsA Phase 3 Data Pool. The majority of subjects were White (94%) with approximately equal proportions of male and female subjects. The median subject age was 50 years and a median body weight of approximately 84 kg. The majority of subjects (≥94%) were classified as White and participated at study centers located in North America (45%) and Europe (43%).

7.2.2 Explorations for Dose Response

Dose-dependent increases in the frequency of nausea, diarrhea, headache, and dizziness were observed in both the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool.

7.2.3 Special Animal and/or In Vitro Testing

Preclinical testing was adequately conducted to explore for potential adverse reactions that would have been reasonably expected to occur based on the known mechanism of action of apremilast. Results from the sponsor's Pharmacology/Toxicology program for apremilast are summarized in Section 4.1 and discussed in Dr. Leshin's Pharmacology/Toxicology review.

7.2.4 Routine Clinical Testing

Routine safety monitoring and clinical testing was performed at specified time periods as defined in the study protocols. All subjects received complete physical exams, assessment of vital signs, and manual 12-lead ECG testing. Clinical laboratory evaluations included, but were not limited to, serum chemistry, hematology, ESR, CRP, fibrinogen, urinalysis, ANA, C-ANCA, and quantitative assessment of serum immunoglobulins. Overall, the studies included in this application appear to have had adequate safety monitoring and appropriated clinical testing of subjects.

7.2.5 Metabolic, Clearance, and Interaction Workup

Discussion of the enzymatic pathways responsible for metabolism, clearance, and potential drug-drug interactions can be found in Section 4.4 and Dr. Agarwal's Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The PDE4-inhibitor, roflumilast (DALIRESP), was approved in 2011 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with

chronic bronchitis and a history of exacerbations. Included in the WARNINGS AND PRECAUTIONS section of the product label is an increased frequency of psychiatric adverse reactions and significant loss of body weight. Psychiatric adverse reactions included insomnia, anxiety, and depression, all of which were reported at higher rates in DALIRESP-treated subjects versus placebo-treated subjects. Instances of suicidal ideation and behavior, including completed suicide were observed during clinical trials and in the post-marketing setting in patients treated with DALIRESP. Moderate weight loss, defined as a decrease of 5-10% of body weight, was a common adverse reaction that occurred in DALIRESP-treated subjects during the clinical trials. Commonly reported adverse reactions listed in the product label included diarrhea, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

In light of the safety issues associated with DALIRESP, the sponsor undertook efforts to specifically detect similar adverse reactions in the apremilast development program. The sponsor 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. Evaluation of psychiatric AEs utilized the C-CASA tool. Additional analyses included AEs related to hypersensitivity, hepatic and renal systems, and headache. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, MACE, and hepatobiliary AEs).

The active monitoring, and subsequent safety analysis, for predefined AEs of special interest demonstrate that the sponsor was proactive in attempting to detect adverse reactions that may be related to apremilast's mechanism of action and possible class effects of the PDE-4 inhibitors.

7.3 Major Safety Results

7.3.1 Deaths

Overall, six deaths were reported from a total of 2401 subjects who had been exposed to apremilast by the time of the data cutoff date of July 6, 2012. One death occurred in the PsA studies (PSA-002) 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 who was randomized to the APR20 BID treatment arm and died due to multiple organ failure on Study Day 73. The subject was diagnosed with vitamin B_{12} deficiency anemia prior to receiving her first dose of apremilast. The principal investigator reported the cause of death as vitamin B_{12} deficiency attributable to the induction of MTX-induced folic acid deficiency. Given the known mechanisms of action for apremilast and MTX, the underlying vitamin B_{12}/folate deficiency appears most likely related to treatment with MTX, consequently, this reported death does not appear to be directly related to apremilast.

- **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. The investigator reported the cause of death as myocardial infarction, arrhythmia, and hypertensive changes. In light of the subject's underlying risk factors, it appears that his death was due to underlying cardiovascular heart disease rather than a direct effect of apremilast; however, since apremilast is a new molecular entity, a separate safety analysis was performed for this review assessing whether apremilast-treated subjects are at increased risk of cardiovascular-related deaths or SAEs.

- **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/m^2), 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. Although the subject's comorbidities could account for the cause of death, an association with apremilast cannot be completed ruled out. A separate safety analysis assessing whether apremilast-treated subjects are at increased risk of cardiovascular-related deaths or SAEs was performed for this review.

- **Subject PSOR-008-0251014** was a 28-year-old, White female with psoriasis who was randomized to the placebo-treatment arm and 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. Given the subject's past medical history of attempted suicide predating treatment with apremilast, this death appears to be unlikely related to the study drug.

- **Subject PSOR-009-1191012** was a 51-year-old, White female with psoriasis who died secondary to an intracranial hemorrhage. On Study Day 352 the subject complained of headache and the following day was found unresponsive at which time she was brought to the hospital and received palliative care. The subject was pronounced brain dead on Study Day 354. The subject received apremilast for 225 days followed by placebo for 112 days. Considering the temporal relationship between the onset of the intracranial hemorrhage and last dose of apremilast, the death appears to be unlikely related to apremilast.

Of the six 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 rerandomized to the placebo treatment arm during the randomized withdrawal period of study PSOR-009. An additional death related to apremilast was reported in a non-Celgene-sponsored study in RA that consisted of a single case of acute myeloid leukemia (AML) in a subject treated with apremilast 30 mg BID. The case of AML was diagnosed nearly 12 months after completion of a 3-week course of apremilast treatment. Given the short-term exposure to apremilast and the temporal relationship of the diagnosis of AML, a causal relationship does not appear to be related to the study drug.

Of note, the deaths of subjects PSOR-008-0251014 and PSOR-005-E-LTE-0421019 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. A separate analysis was performed for this review assessing whether apremilast-treated subjects are at an increased risk for the development of depression, suicidal ideations, suicide attempts, and/or completed suicides.

In summary, analysis of the individual deaths, including the temporal relationship to apremilast dosing, does not suggest a safety signal from any single type of adverse event.

7.3.2 Nonfatal Serious Adverse Events

PsA Phase 3 Data Pool

Approximately 4% of subjects in each treatment arm reported SAEs during the placebo-controlled period for the PsA Phase 3 Data Pool (Table 22). The only SAEs reported in more than two subjects were psoriatic arthropathy and cholelithiasis.

Table 22. PsA Phase 3 Data Pool: Serious Adverse Events Reported in ≥1 Subject During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
Any SAE	19 (4)	17 (3)	19 (4)
Psoriatic arthropathy	2 (<1)	1 (<1)	1 (<1)
Cholelithiasis	1 (<1)	1 (<1)	1 (<1)
Atrial fibrillation	0	0	2 (<1)
Breast cancer	0	1 (<1)	1 (<1)
Depression	0	2 (<1)	0
Acute MI	1 (<1)	1 (<1)	0
Cardiac failure, congestive	1 (<1)	1 (<1)	0
Hypertensive crisis	2 (<1)	0	0
Pancreatitis, acute	2 (<1)	0	0

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 151, Table 76

Slightly higher frequencies of SAEs (approximately 5%) were reported in the apremilast treatment arms during the apremilast-exposure period for the PsA Phase 3 Data Pool (data not shown); however, the small increased frequency of events is not unexpected given the greater duration of exposure to apremilast and the increased number of subjects receiving apremilast treatment as a result of placebo-treated subjects switching to an apremilast treatment arm after Week 24. Overall, SAEs were infrequent in both the APR20 and APR30 treatment arms with an EAIR of 7.2 events per 100-subject years and 7.5 events per 100-subject years, respectively. No single SAE occurred with an EAIR greater than 0.5 events per 100-subject years (data not shown). The types of SAEs reported were similar to those reported during the placebo-controlled period and included psoriatic arthropathy, atrial fibrillation, cholelithiasis, depression, acute myocardial infarction/ischemia, breast cancer, suicide attempt, hypertension, and osteoarthritis. Events of serious infections, suicide attempt, MACE, and malignancies were reviewed by an adjudicator and are included in the analyses of AEs of special interest.

A summary of SAEs by time period for the subjects-as-initially-treated safety population is shown in Table 23. These data demonstrated that the proportion, as well as the EAIR, of subjects reporting SAEs was similar between treatment arms and was constant over time.

Table 23. PsA Phase 3 Data Pool: Serious Adverse Events Reported in ≥1 Subject During the Apremilast-Exposure Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	22	15	19	25	16	24	35
Subjects with ≥1 SAE; n(%)	18 (4)	12 (2)	16 (3)	20 (4)	11 (2)	18 (4)	24 (5)
Exposure (subject-years)	141	144	210	340	141	206	337
EAIR per 100 subject years	12.7	8.3	7.6	5.9	7.8	8.7	7.1
95% CI	7.7, 19.6	4.4, 13.9	4.5, 12	3.7, 8.8	4.1, 13.4	5.3, 13.4	4.6, 10.4

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 152, Table 77

Overall, the proportion of subjects and type of events reported were comparable across treatment groups in the PsA Phase 3 Data Pool.

Apremilast Unblinded Data Pool

Approximately 4% of subjects reported an SAE during the placebo-controlled period for the Apremilast Unblinded Data Pool (data not shown), which was similar to the frequency of SAEs reported during the placebo period of the PsA Phase 3 studies. The types of SAEs reported during this period was similar to those reported in the PsA studies and included atrial fibrillation, cellulitis, cholelithiasis, psoriasis, psoriatic arthropathy, and nausea. Atrial fibrillation was the only SAE to be reported in more than two subjects treated with apremilast. Overall, the frequencies and types of SAEs reported during the apremilast-exposure period for the Apremilast Unblinded Data Pool were consistent with data from the placebo-controlled period of the Apremilast Unblinded Data Pool and the apremilast-exposure period of the PsA Phase 3 studies. The EAIR rate for and SAEs in the APR20 treatment arm was slightly higher than that for the APR30 treatment arm, 9.4 events per 100 subject-years and 7.8 events per 100 subject-years, respectively. No single SAE occurred with an EAIR greater than 0.5 events per 100-subject years (data not shown).

Additional Studies:

A total of 12 SAEs were reported from the three ongoing, blinded Phase 3 studies: 3 events from study PSA-005, six events from study PSOR-008, and three events from study PSOR-009. One death occurred during study PSOR-008. The narrative for subject PSOR-008-4031002 was reviewed and discussed in Section 7.3.1. SAEs reported from the Behçet's study (n=6) and the Clinical Pharmacology studies (n=1) were reviewed and considered not related to treatment with apremilast except for a single case of influenza.

Overall, these data did not suggest clinically important difference in overall SAEs between apremilast-treated subjects and subjects treated with placebo. Additional analyses of SAEs are included in Section 7.3.4, which discusses events of special

interest including serious infections, cardiovascular events, malignancies, and psychiatric events.

7.3.3 Dropouts and/or Discontinuations

PsA Phase 3 Data Pool

Table 24 shows the frequency of AEs leading to drug withdrawal during the placebo-controlled period for the PsA Phase 3 Data Pool. The most frequently reported AEs leading to drug withdrawal were nausea, diarrhea, headache, and dizziness that appeared to increase in a treatment- and dose-dependent manner.

Table 24. PsA Phase 3 Data Pool: Incidence of Adverse Events Leading to Drug Withdrawal During the Placebo-Controlled Period

MedDRA Preferred Term	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

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 174, Table 88

The most frequently reported AEs leading to drug withdrawal during the apremilast-exposure period of the PsA Phase 3 studies were similar to those observed in the

placebo-controlled period, namely, nausea, diarrhea, headache, and vomiting, all of which appeared to increase in a dose-dependent manner. The EAIR for nausea, diarrhea, headache, and vomiting appeared to increase in a dose-dependent manner (Table 25).

Table 25. PsA Phase 3 Data Pool: Incidence of Adverse Events Leading to Drug Withdrawal During the Apremilast-Exposure Period

	APR20 BID (n=501)		APR30 BID (n=497)	
MedDRA Preferred Term	**n (%)**	**EAIR**	**n (%)**	**EAIR**
Any SAE	48 (7)	10.1	51 (7)	10.8
Nausea	8 (1)	1.7	15 (2)	3.1
Diarrhea	6 (1)	1.3	13 (2)	2.7
Headache	4 (1)	0.8	9 (1)	1.9
Vomiting	1 (<1)	0.2	6 (1)	1.3
Abdominal pain, upper	4 (1)	0.8	3 (<1)	0.6
Dizziness	2 (<1)	0.4	3 (<1)	0.6
Migraine	1 (<1)	0.2	3 (<1)	0.6
Fatigue	1 (<1)	0.2	3 (<1)	0.6
Psoriatic arthropathy	1 (<1)	0.2	2 (<1)	0.4
GERD	0	0	2 (<1)	0.4
Decreased appetite	1 (<1)	0.2	1 (<1)	0.2
Anxiety	1 (<1)	0.2	1 (<1)	0.2
Depressed mood	1 (<1)	0.2	1 (<1)	0.2
Abdominal distension	1 (<1)	0.2	1 (<1)	0.2
Urticaria	1 (<1)	0.2	1 (<1)	0.2
Abdominal discomfort	1 (<1)	0.2	1 (<1)	0.2
Depression	2 (<1)	0.4	0	0
Abdominal pain	2 (<1)	0.4	0	0
Dyspepsia	2 (<1)	0.4	0	0
Hyperhidrosis	2 (<1)	0.4	0	0
Rash	2 (<1)	0.4	0	0

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 175, Table 89

Adverse events leading to drug withdrawal by time period for the subjects-as-initially treated safety population is shown in Table 26. For the placebo-controlled period (Weeks 0-16) the number of subjects with AEs leading to drug withdrawal was greater in the apremilast treatment arms compared to placebo-treated subjects. For Weeks 0-24 and Weeks 0-52, the number of subjects with AEs leading to drug withdrawal was similar between the APR20 and APR30 treatment arms. Also, the data demonstrate that greatest proportion of AEs leading to drug withdrawal occurred during Weeks 0-16 weeks of treatment.

Table 26. PsA Phase 3 Data Pool: Adverse Events Leading to Drug Withdrawal By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	34	46	54	64	60	65	75
Subjects with ≥1 SAE; n(%)	20 (4)	26 (5)	29 (6)	38 (8)	32 (60	35 (7)	43 (9)
Exposure (subject-years)	143	144	210	342	140	206	340
EAIR per 100 subject years	14	18.1	13.8	11.1	22.9	17	12.6
95% CI	8.7, 21.1	12, 26	9.4, 19.5	7.9, 15	15.9, 31.8	12, 23.3	9.2, 16.8

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 177, Table 90

Overall, the types and frequencies of AEs leading to drug withdrawal were similar between treatment arms with an apparent dose-response relationship for apremilast-treated subjects for the AEs of nausea, diarrhea, headache, and dizziness.

Apremilast Unblinded Data Pool

The frequency and types of AEs leading to drug withdrawal during the placebo-controlled and apremilast-exposure periods for the Apremilast Unblinded Data Pool were similar to that observed in the PsA Phase 3 data pool with the most frequent AEs reported as nausea, diarrhea, headache, abdominal pain, dizziness, vomiting, and psoriasis. These AEs appeared to increase in a treatment- and dose-dependent manner similar to that seen in the PsA Phase 3 Study Data Pool.

Additional Studies:
Similar results were also reported during the Behçet's and Clinical Pharmacology studies (data not shown). Adverse events leading to drug interruption from these studies mirrored the frequency and types of events leading to drug withdrawal outlined above. The most common AEs were diarrhea, nausea, vomiting, and headache.

In summary, the largest proportion of subjects dropping out from the placebo-controlled periods of the PsA studies prior to Week 16 was due AEs. The frequency of AEs leading to dropout was similar between the placebo and APR20 treatment arms but slightly higher for the APR30 group (Table 20). The data presented here suggest that apremilast has a treatment- and dose-dependent effect of increasing nausea, diarrhea, vomiting, and headache, which may lead to patients discontinuing treatment with the drug. While these types of AEs may limit the tolerability of apremilast, they are typically reversible and non-life threatening.

7.3.4 Significant Adverse Events

Significant AEs as defined in the Clinical Review Template were not identified or are covered in other sections of the Safety Review.

7.3.5 Adverse Events of Special Interest

The sponsor 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. Additional analyses included AEs related to hypersensitivity, hepatic and renal systems, and headache. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, major adverse cardiac events [MACE], and hepatobiliary and hypersensitivity AEs). Analyses for AEs of Special Interest were limited to the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool only.

7.3.5.1 Serious Infections (Adjudicated Analysis) including 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. No serious infections were reported for subjects enrolled in the APR 10 BID, APR20 QD, or APR 40 QD treatment arms.

The three cases of systemic opportunistic infections included single cases of Rothia species-related tenosynovitis following a puncture wound, Herpes Zoster with associated viral meningitis, and MRSA-related naso-facial cellulitis/abscess. Three cases of non-systemic opportunistic infections consisted of two cases of bacterial pneumonia, and a single case of Clostridium difficile infection. 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.

Ten of the 18 cases of serious infections reported in the Apremilast Unblinded Data Pool, occurred during the PsA Phase 3 studies (i.e., the PsA Phase 3 Data Pool). Serious infections were reported in two placebo-treated subjects, two subjects from the APR20 BID treatment-arm, and six subjects from the APR30 BID treatment arm. A single case of a systemic opportunistic infection was reported in a placebo-treated subject (EAIR of 0.6 events per 100 subject-year). Non-systemic opportunistic infections were reported in one subject randomized to the APR20 BID treatment arm

(EAIR of 0.2 events per 100 subject-years) and two subjects in the APR30 BID arm (EAIR of 0.4 events per 100 subject-years. Non-opportunistic serious infections were reported in one placebo-treated subject (EAIR of 0.6 events per 100 subject-years), one APR20 BID subject (EAIR of 0.2 events per 100 subject-years), and four subjects in the APR30 BID treatment arm (EAIR of 0.8 events per 100 subject-years).

Occurrences of tuberculosis (TB) were analyzed separately from serious infections and were not adjudicated; however, given their association as an opportunistic infection, the data will be reviewed here. Screening for latent TB was not required for the PsA Phase 3 studies and was left to the investigator's judgment; however, all enrolled subjects received a chest radiograph and inquiry on medical history to rule out active TB. Also, subjects with active TB, or a history of incompletely treated TB, were excluded from the studies.

A total of 20 subjects with a medical history significant for TB were included in the PsA Phase 3 Data Pool: seven placebo-treated subjects, five APR20-treated subjects, and eight APR30-treated subjects. Additionally, 12 subjects had a medical history of a positive PPD: four placebo-treated subjects, five APR20-treated subjects, and three APR30-treated subjects. No cases of TB or TB reactivation were reported in either the placebo-controlled period of during the apremilast-exposure period for the PsA Phase 3 Data Pool. Similarly, no cases of TB or TB reactivation was reported for the Apremilast Unblinded Data Pool, despite the enrollment of 23 subjects with a reported medical history of TB and 14 subjects with a medical history of positive PPD.

Overall, the results from both data pools, including EAIRs, suggest no appreciative differences between placebo and apremilast adjudicated events of serious infections (opportunistic and non-opportunistic), including cases of TB or TB reactivation. Additionally, the overall number of serious infections was relatively small in light of the underlying diseases, concomitant medications, and potential immunosuppressive effects of apremilast. These data do not demonstrate an increased risk of serious infections with apremilast therapy.

7.3.5.2 Major Adverse Cardiac Events (MACE)/Potential MACE (Adjudicated Analysis)

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 with all events being reported in the APR20 and APR30 treatment arms. Five of the

reported cases occurred in the PsA Phase 3 Data Pool. Overall, the numbers of adjudicated MACE were small and all attributed to cases of MI. The calculated EAIRs were similar across the placebo (n=0), APR20 (n=3), and APR30 (n=1) treatments arms of 0, 0.4, and 0.2 events per 100 subjects-years, respectively.

The four adjudicated cases of potential MACE were attributed to single cases of unstable angina requiring a revascularization procedure, TIA, DVT, and an embolic event. The EAIRs for potential MACE were similar across treatment arms at 0, 0.4, and 0.2 events per 100 subject-years for the placebo (n=0), APR20 (n=3), and APR30 (n=1), treatment arms, respectively.

Overall, the total number of MACE and potential MACE adjudicated cases were small, and consequently, little weight can be placed in the similar EAIRs; however, it is reassuring that the overall number of events were small and that no clear dose-response relationship was identified. Moreover, all eight subjects reporting a MACE, or potential MACE, had a medical history significant for cardiovascular risk factors. These data, although limited, do not suggest an association between apremilast therapy and significant cardiovascular adverse events.

7.3.5.3 Malignancies (Adjudicated Analysis)

A total of 18 out of 22 cases meeting criteria for adjudication were identified as adjudicated malignancy events for the Apremilast Unblinded Data Pool. Malignancy events were reported in the placebo (n=3), APR20 (n=8), APR30 (n=4), and APR40 QD (n=2) treatment arms as well as and a single event in the APR10 BID group. The EAIR per 100 subject-years were similar between treatment arms (data not shown). 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.

Non-melanoma skin cancers (squamous cell/basal cell) accounted for seven of the 18 adjudicated malignancies. Of the remaining 11 events, there were four cases of prostatic adenocarcinoma, two cases of breast cancer (both ductal carcinomas), two cases of lung cancer (one case each of small cell and bronchioloalveolar carcinomas), 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. Several of the subjects had a medical history that increased their risk of malignancy including a family history of breast cancer or tobacco use.

Overall, the total numbers of adjudicated malignancies were limited, and thus, little weight can be placed on the EAIRs. Furthermore, while the possible association between apremilast and malignancy cannot be ruled out from this data due to the small numbers of reported malignancies, it is reassuring, especially given the lack of a dose-response or temporal relationship between apremilast and the events. Taken as a

whole, these data suggest that apremilast therapy does not present an increased risk of malignancy.

7.3.5.4 Upper Respiratory Tract Infections

PsA Phase 3 Data Pool

A higher frequency of upper respiratory tract infections (URIs) were reported in apremilast-treated subjects compared to placebo-treated subjects during the placebo-controlled period (Table 27). Both apremilast treatment arms reported approximately 15% of subjects experiencing an URI with no clear dose-response relationship. The higher proportion of URI events were primarily due to reports under the preferred terms "upper respiratory tract infection" and "nasopharyngitis", which accounted for 42% and 30% of the total URI events, respectively. No other single preferred term accounted for more than one percent of events except for sinusitis (2%), which was similar across the three treatment arms. None of the AEs were reported as severe or serious and none led to drug withdrawal. There were no differences between sexes but subjects younger than 65 years of age demonstrated a slightly higher increased frequency of URIs compared to older subjects, The clinical significance of these findings are unclear but may be related to the small number of subjects included in the ≥65 year-old age group. Approximately one-third of the URI events were reported in the first 30 days of treatment across the three treatment arms with relatively equal number of events thereafter (data not shown).

Table 27. PsA Phase 3 Data Pool: URI Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any URI AE	44 (9)	79 (16)	74 (15)
Age; n/N (%)			
<65 years	42/447 (9)	75/458 (16)	67/442 (15)
≥65 years	2/48 (2)	4/43 (9)	7/55 (13)
Sex; n/N (%)			
Male	22/240 (9)	36/232 (16)	28/222 (13)
Female	22/255 (9)	43/269 (16)	46/275 (17)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 218, Table 118

A slightly higher frequency of URI AEs was reported in the APR20 group compared to the APR30 group (20% vs. 17%, respectively) during the apremilast-exposure period (Table 28). Although an increased frequency of URI AEs was observed in the APR20 treatment arm, there was no notable difference in the EAIR between the treatment arms for individual preferred terms (data not shown). One subject from each treatment group

reported a severe URI infection. Overall, the EAIR for URI AEs were relatively similar between treatment arms, age, and sex.

Table 28. PsA Phase 3 Data Pool: URI Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	**EAIR**	**n (%)**	**EAIR**
Any URI AE	144 (20)	35.7	122 (17)	29.3
Any Severe URI AE	1 (<1)	0.2	1 (<1)	0.2
Age; n/N (%)				
<65 years	134/656 (20)	36.5	107/645 (17)	28.7
≥65 years	10/64 (16)	27.6	15/76 (20)	35
Sex; n/N (%)				
Male	69/347 (20)	33.3	52/324 (16)	27.2
Female	75/373 (20)	38.2	70/397 (18)	31.1

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 221, Table 121

Adverse events related to URIs by time period for the subjects-as-initially treated safety population is shown in Table 29. For the placebo-controlled period (Weeks 0-16) the number of subjects with URI AEs increased in a treatment-dependent manner; however, a dose-response effect was not observed. For Weeks 0-24 and Weeks 0-52, the number of subjects with URI-related AEs was similar between the APR20 and APR30 treatment arms with an apparent treatment-effect with time.

Table 29. PsA Phase 3 Data Pool: URI Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	34	46	54	64	60	65	75
Subjects with ≥1 SAE; n(%)	20 (4)	26 (5)	29 (6)	38 (8)	32 (60	35 (7)	43 (9)
Exposure (subject-years)	143	144	210	342	140	206	340
EAIR per 100 subject years	14	18.1	13.8	11.1	22.9	17	12.6
95% CI	8.7, 21.1	12, 26	9.4, 19.5	7.9, 15	15.9, 31.8	12, 23.3	9.2, 16.8

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 224, Table 123

These data demonstrate an increased risk of URIs associated with apremilast therapy, albeit non-dose-dependent. Appropriate language should be included in the product labeling to reflect this increased risk.

7.3.5.5 Cardiac Failure

A total of 18 subjects were identified with AEs related to cardiac failure during the placebo-controlled period of the PsA Phase 3 Data Pool (Table 30). Of these events,

only two cases were reported as a serious AE of heart failure (one case in the PBO arm and one case in the APR20 arm). The remaining cases were reported as non-serious and included 14 cases of peripheral edema, and one case each of pulmonary congestion, and cardiac failure. Relatively few events of cardiac failure were reported as severe, serious, or leading to drug withdrawal. The overall incidence of cardiac failure was similar across treatment arms and did not vary between age or gender groups.

Table 30. PsA Phase 3 Data Pool: Cardiac Failure Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Cardiac Failure AE	7 (1)	7 (1)	4 (1)
Any Severe Cardiac Failure AE	2 (<1)	1 (<1)	0
Any Cardiac Failure AE leading to drug withdrawal	0	0	1 (<1)
Any Serious Cardiac Failure AE	1 (<1)	1 (<1)	0
Age; n/N (%)			
<65 years	5/447 (1)	6/458 (1)	4/442 (1)
≥65 years	2/48 (4)	1/43 (2)	0/55 (0)
Sex; n/N (%)			
Male	4/240 (2)	2/232 (1)	2/222 (1)
Female	3/255 (1)	5/269 (2)	2/275 (1)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 226, Table 125

A total of 20 subjects reported a Cardiac Failure AE during the apremilast-exposure period of the PsA Phase 3 Data Pool (Table 31). The incidence rates of cardiac failure AEs were similar between both apremilast treatment arms with only minor differences between age and gender subgroups.

Table 31. PsA Phase 3 Data Pool: Cardiac Failure Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any Cardiac Falure AE	10 (1)	2.1	10 (1)	2.1
Any Severe Cardiac Failure AE	1 (<1)	0.2	0	0
Any Cardiac Failure AE Leading to Withdrawal	0	0	1 (<1)	0.2
Age; n/N (%)				
<65 years	8/656 (1)	1.8	9/645 (1)	2.1
≥65 years	2/64 (3)	4.9	1/76 (1)	2
Sex; n/N (%)				
Male	3/347 (1)	1.2	3/324 (1)	1.4
Female	7/373 (2)	3	7/397 (2)	2.7

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 227, Table 126

The overall number of reported AEs related to Cardiac Failure was small making it difficult to draw firm conclusions regarding the risk of apremilast therapy and cardiac failure. However, given that there were relatively few serious cases of cardiac failure reported in the clinical studies and that the incidence of events was similar between treatment arms, specific labeling will not be necessary at the present time.

7.3.5.6 Gastrointestinal Events

PsA Phase 3 Data Pool

Gastrointestinal events are commonly associated with the use of PDE4-inhibitors and were the most commonly reported AE in the apremilast studies. As shown in Table 32, the frequency of diarrhea, nausea, and vomiting was observed to increase in a dose- and treatment-dependent manner during the placebo-controlled period of the PsA Phase 3 Data Pool. In general, there were relatively few gastrointestinal events reported as severe in nature but there was one serious case of diarrhea reported in the APR20 treatment arm and one case of serious nausea and vomiting reported in the APR30 treatment arm. The incidence rates of gastrointestinal AEs were higher in subjects aged ≥65 years compared to younger subjects; however, there were relatively small numbers of subjects ≥65 enrolled in the PsA Phase 3 studies. Additionally, females appeared to be almost twice as likely to develop gastrointestinal AEs compared to males (Table 32).

Table 32. PsA Phase 3 Data Pool: Gastrointestinal Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Diarrhea Adverse Events			
Any Diarrhea AE	14 (3)	63 (13)	88 (18)
Any Severe Diarrhea AE	1 (<1)	3 (1)	1 (<1)
Any Diarrhea AE leading to drug withdrawal	3 (1)	5 (1)	11 (2)
Any Serious Diarrhea AE	0	1 (<1)	0
Age; n/N (%)			
<65 years	13/447 (3)	51/458 (12)	82/442 (17)
≥65 years	1/48 (2)	7/43 (16)	14/55 (26)
Sex; n/N (%)			
Male	7/240 (3)	23/232 (10)	27/222 (12)
Female	7/225 (3)	40/269 (15)	61/275 (22)
Nausea and Vomiting Adverse Events			
Any Nausea/Vomiting AE	24 (5)	56 (11)	88 (18)
Any Severe Nausea/Vomiting AE	0	2 (<1)	4 (1)
Any Nausea/Vomiting AE leading to drug withdrawal	3 (1)	7 (1)	15 (3)
Any Serious Nausea/Vomiting AE	0	0	1 (<1)
Age; n/N (%)			
<65 years	21/447 (5)	51/458 (11)	82/442 (19)
≥65 years	3/48 (6)	5/43 (12)	6/55 (11)
Sex; n/N (%)			
Male	12/240 (5)	19/232 (8)	30/222 (14)
Female	12/255 (5)	37/269 (14)	58/275 (21)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 229, Table 127

The vast majority of reported cases using the preferred term of diarrhea were of mild or moderate severity with only a few cases in each treatment arm reporting severe cases of diarrhea. Three subjects in the APR20 treatment arm reported a case of severe diarrhea and only one subject from each of the placebo and APR30 treatment arms.

The majority of diarrhea events occurred during the first two weeks of treatment (Figure 4) and the majority of diarrhea events did not last more than 30 days (Figure 5). The duration of diarrhea was ≤30 days in approximately 69%, 59%, and 53% of subjects reporting a diarrheal event in the placebo, APR20, and APR30 treatment arms.

Figure 4. PsA Phase 3 Data Pool: Diarrhea Adverse Events by Onset Day During the Placebo-Controlled Period

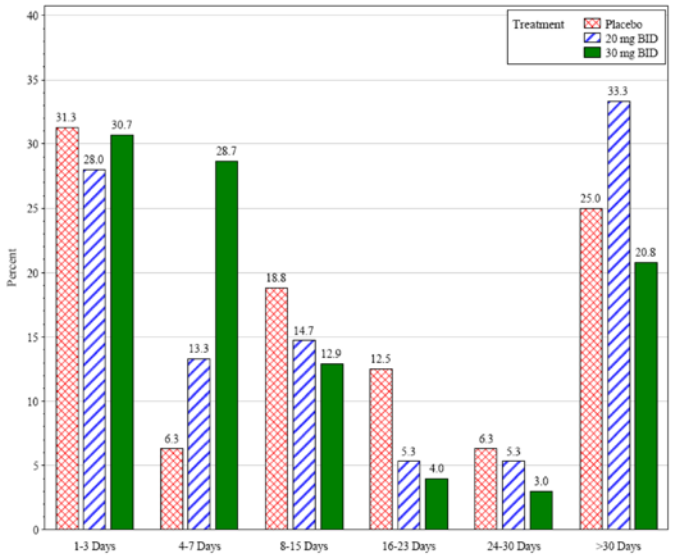


Figure adapted from NDA 205437 Integrated Summary of Safety, page 231, Figure 1.

Figure 5. PsA Phase 3 Data Pool: Diarrhea Adverse Events by Treatment Duration During the Placebo-Controlled Period

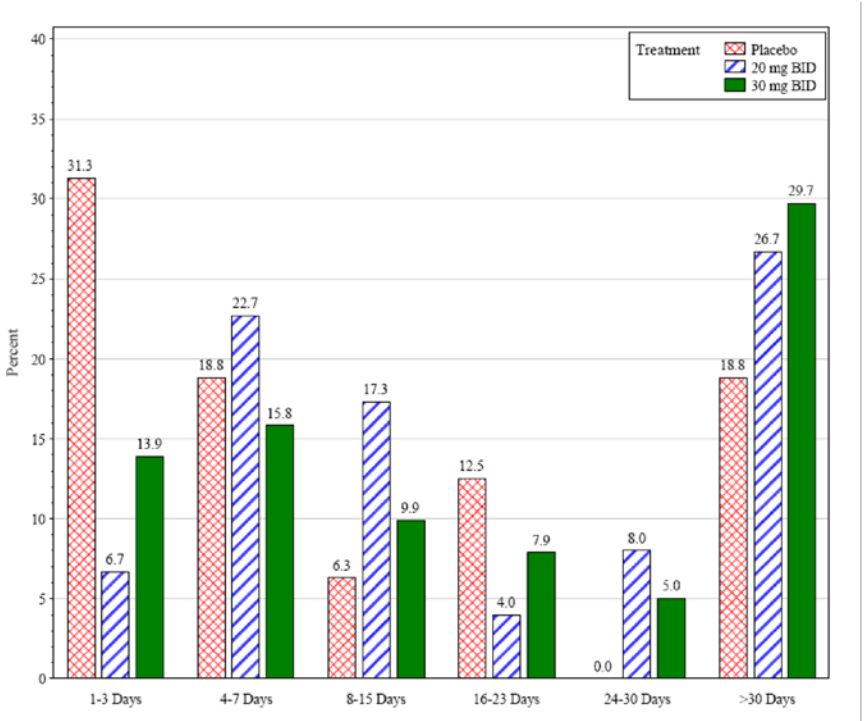


Figure adapted from NDA 205437 Integrated Summary of Safety, page 232, Figure 2.

More than two-thirds of diarrhea events occurred within the first 30 days of initiating study drug. Thereafter, the number of subjects reporting new cases diarrhea decreased over time (data not shown).

Similarly, more than two-thirds of nausea and vomiting AEs occurred during the first 30 days of treatment (Figure 6) in all treatment arms and the majority of these cases did not last greater than 30 days (Figure 7). Thereafter, the number of subjects reporting new cases nausea and vomiting decreased over time (data not shown).

Figure 6. PsA Phase 3 Data Pool: Nausea and Vomiting Adverse Events by Onset Day During the Placebo-Controlled Period

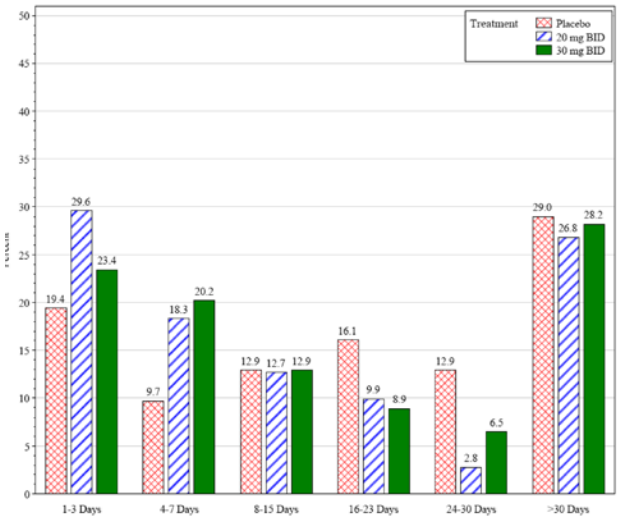


Figure adapted from NDA 205437 Integrated Summary of Safety, page 234, Figure 3.

Figure 7. PsA Phase 3 Data Pool: Nausea and Vomiting Adverse Events by Treatment Duration During the Placebo-Controlled Period

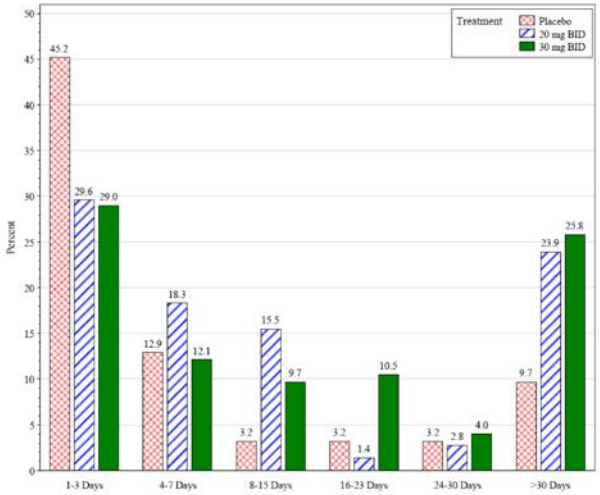


Figure adapted from NDA 205437 Integrated Summary of Safety, page 235, Figure 4.

Similar to the data from the placebo-controlled period, the EAIR of diarrhea and nausea and vomiting was observed to increase in a dose-dependent manner during the apremilast-exposure period of the PsA Phase 3 Data Pool with very few cases of diarrhea or nausea and vomiting reported as severe in intensity (data not shown). A greater number of gastrointestinal-related events were reported in females compared to males.

As shown in Table 33, the frequency of reported events for diarrhea by time periods for the subjects-as-initially-treated safety population increased in a treatment- and dose-dependent manner in the PsA Phase 3 Data Pool. Similarly, the frequency for events of nausea and vomiting increased in a treatment- and dose-dependent manner (data not shown).

Table 33. PsA Phase 3 Data Pool: Diarrhea Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
AE; n	16	66	75	84	97	101	112
Subjects with ≥1 SAE; n(%)	14 (3)	54 (11)	63 (13)	68 (14)	88 (18)	88 (18)	93 (19)
Exposure (subject-years)	141	133	192	306	123	179	294
EAIR per 100 subject years	9.9	40.7	32.9	22.2	71.8	49.2	31.7
95% CI	5.6, 16.1	30.8, 52.6	25.4, 41.7	17.4, 27.9	57.8, 87.9	39.6, 60.2	25.7, 38.6

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 240, Table 133

In summary, these data demonstrate a treatment- and dose-dependent increase in the frequency of reported cases of diarrhea and nausea and vomiting. The majority of the

cases was of mild to moderate severity and occurred in the first 30 days after starting therapy. Despite titrating the dose of apremilast in subjects initiating apremilast, a large percentage of patients experienced gastrointestinal events. While the apremilast-related gastrointestinal events may affect a patient's ability to tolerate therapy, the severity of the effects is likely to be moderate and reversible. Gastrointestinal AEs should be included in the product labeling.

7.3.5.7 Psychiatric Events

7.3.5.8.1 Depression

Higher reported cases of depression were reported in the APR20 (n=9) treatment arm compared to either placebo (n=4) or APR30 (n=5) during the placebo-controlled period of the PsA Phase 3 data Pool (Table 34). Only two subjects, both in the APR20 treatment arm, reported a serious case of depression. The incidence of depression was higher in females than in males, although the number of events was small.

Table 34. PsA Phase 3 Data Pool: Depression Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Depression AE	4 (1)	9 (2)	5 (1)
Any Severe Depression AE	0	0	0
Any Depression AE leading to drug withdrawal	0	3 (1)	1 (<1)
Any Serious Depression AE	0	2 (<1)	0
Age; n/N (%)			
<65 years	4/447 (1)	9/458 (2)	5/442 (1)
≥65 years	0/48 (0)	0/43 (0)	0/55 (0)
Sex; n/N (%)			
Male	1/240 (<1)	2/232 (1)	1/222 (1)
Female	3/255 (1)	7/269 (3)	4/275 (2)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 245, Table 137

The EAIR for depression AEs reported during the apremilast-exposure period of the PsA Phase 3 Data Pool was higher in the APR20 treatment arm compared to the APR30 treatment arm (3 events per 100 subject-years vs. 1.9 events per 100 subject-years, respectively). There were no notable differences in the incidences of serious cases of depression or depression leading to drug withdrawal between the two apremilast treatment arms (data not shown). A greater EAIR for depression was reported for subjects less than 65 years of age compared to older subjects; however, the total number of subjects over 65 years of age was small and the data may not accurately reflect the true incidence of depression in this age group in a broader population.

The PDE4-inhibitor roflumilast has been associated with increased frequencies of psychiatric events including depression and suicidal behavior. Consequently, the sponsor tried to detect a similar effect in the apremilast clinical studies. The data show that although a greater number of APR20 treated subjects reported depression in the PsA Phase 3 Data Pool, the overall number of events was small and an obvious dose-response effect was not observed as subjects in the PBO and APR30 treatment arms reported a similar number of events. Overall, these data do not suggest an increased incidence of depression in subjects treated with apremilast.

7.3.5.8.2 Suicidal Ideation and Behavior

Two subjects in the PsA Phase 3 Data Pool (both in the APR20 treatment arm) reported a suicide attempt or ideation during the placebo-controlled period or the apremilast-exposure period. Neither of these events resulted in death.

Cases of suicidal behavior in the Apremilast Unblinded Data Pool included one case of suicidal ideation in a patient with a history of bipolar disorder randomized to APR30 BID in study RA-001. A subject randomized to the APR30 treatment arm in Study PSA-003 was hospitalized for worsening depression and attempted suicide. The subject had received 14 days of apremilast therapy at the time of hospitalization. This case was included in the safety review of SAEs. Subject PSOR-008-0251014 was randomized to placebo and committed suicide via a gunshot would. This case is included in the review of deaths in Section 7.3.1. Subject PSOR-004-0020009 (randomized to APR20) and Subject PSOR-05-E-LTE-0421019 (randomized to placebo) had reported outcomes of death and suicide could not be ruled out. Lastly, the C-CASA analysis identified one additional case of attempted suicide in the ongoing, blinded study PSOR-009.

An assessment of suicidal ideation and behavior for the entire safety database was conducted using C-CASA terms. In addition to identifying two subjects with suicidal ideation, the results of the analysis demonstrated three subjects classified with suicidal behaviors: one completed suicide and two cases of attempted suicide. The completed suicide and one suicide attempt occurred in the blinded studies PSOR-008 and PSOR-009, respectively. The remaining three subjects were enrolled in study PSA-002 (suicide attempt), PSA-004 (suicidal ideation), and study RA-002 (suicidal ideation).

Taken together, the review of the data does not identify a safety signal for an increased risk of depression or suicidal behavior; however, in light of the fact that roflumilast has psychiatric events, including suicidality, listed in the WARNINGS AND PRECAUTIONS section of its label, we requested a consult from the Division of Psychiatry Products (DPP) for further review of the apremilast data.

Phillip D Kronstein, MD (DPP) independently reviewed all available data from the apremilast clinical development program, including and concluded that there did not appear to be a safety signal regarding depression, suicidal ideation, or suicidal behavior

in either the placebo-controlled period of the PsA Phase 3 Data Pool or the Apremilast Unblinded Data Pool.

Of note, Dr. Kronstein casted some doubt on the fidelity of the sponsor's C-CASA analysis based on a missed case of suicide, use of Celgene physicians for assessing cases rather than independent experts in suicide and suicide assessment, and to the lack of clarity regarding what, if any, of the many measures recommended in the C-CASA guidelines to blind the raters were followed. To avoid the problem of having to perform a complicated retrospective classification and analysis, Dr. Kronstein recommended adding a prospective assessment of suicidal ideation and behavior to future apremilast clinical trials.

7.3.5.9 Hepatobiliary Adverse Events

The frequency of hepatobiliary AEs reported during the placebo-controlled period of the PsA Phase 3 Data Pool appeared to increase in a treatment- and dose-dependent manner (Table 35). Only two subjects reported a hepatobiliary event that led to drug withdrawal. A female subject in the APR30 treatment arm developed jaundice, cholelithiasis, chronic cholecystits, and stenosis of the major duodenal palilla on Study Day 166. Apremilast dosing was discontinued temporarily and restarted following her recovery without further incident. The data also demonstrated a higher incidence of hepatobiliary AEs in females than males, although the clinical significance of this finding is unclear. Analyses of LTFs were performed separately and are reviewed in Section 7.4.2.

Table 35. PsA Phase 3 Data Pool: Hepatobiliary Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Hepatobiliary AE	5 (1)	8 (2)	11 (2)
Any Severe Hepatobiliary AE	0	0	2 (<1)
Any Hepatobiliary AE leading to drug withdrawal	1 (<1)	1 (<1)	0
Any Serious Hepatobiliary AE	1 (<1)	1 (<1)	3 (1)
Age; n/N (%)			
<65 years	5/447 (1)	7/458 (2)	11/442 (3)
≥65 years	0/48 (0)	1/43 (2)	0/55 (0)
Sex; n/N (%)			
Male	4/240 (2)	2/232 (1)	3/222 (1)
Female	1/255 (<1)	6/269 (2)	8/275 (3)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 252, Table 142

Similar rates of hepatobiliary AEs were reported for APR20 and APR30 treatment arms during the apremilast-exposure period in the PsA Phase 3 Data Pool (Table 36). The EAIR of hepatobiliary AEs was comparable between age groups and sexes.

Table 36. PsA Phase 3 Data Pool: Hepatobiliary Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any Hepatobiliary AE	26 (4)	5.6	23 (4)	5.3
Any Severe Hepatobiliary AE	0	0	2 (<1)	0.4
Any Hepatobiliary AE leading to drug withdrawal	2 (<1)	0.4	0	0
Any Serious Hepatobiliary AE	1 (<1)	0.2	4 (1)	0.8
Age; n/N (%)				
<65 years	23/656 (4)	5.4	23/645 (4)	5.5
≥65 years	3/64 (5)	7.4	2/76 (3)	4
Sex; n/N (%)				
Male	10/347 (3)	4.1	11/324 (3)	5.2
Female	16/373 (4.3)	7	14/397 (4)	5.4

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 254, Table 144

7.3.5.9 Vasculitis

PDE4-inhibitors, including apremilast, have been demonstrated to induce inflammatory perivascular histopathological changes consistent with vasculitis in animal studies. Consequently, investigators were instructed to monitor for any clinical signs and symptoms of vasculitis during the apremilast clinical program. Subjects with suspected signs or symptoms of vasculitis were to be thoroughly evaluated and followed until the signs and symptoms resolved. A thorough analysis of the PsA Phase 3 Data Pool did not identify any cases of vasculitis; however, two subjects from study RA-001 were identified reported vasculitis in the Apremilast Unblinded Data Pool: one subject with RA was randomized to the APR30 treatment arm and was diagnosed with rheumatoid vasculitis leading to study discontinuation and the second subject with RA was randomized to the placebo treatment arm and diagnosed with cutaneous vasculitis that subsequently resolved. As vasculitis is known to occur in patients with RA, and no additional cases of vasculitis were reported during the apremilast development program, the data overall do not support an association between apremilast and vasculitis.

7.3.6 Headache

PsA Phase 3 Data Pool

As shown in Table 37, the .0frequency of headache was observed to increase in a dose- and treatment-dependent manner during the placebo-controlled period of the PsA Phase 3 Data Pool. The majority of headaches were reported as mild in severity. Although less than 1% of all subjects reported severe or serious headaches, a greater number of these events were reported in the APR30 group compared to subjects in the

placebo ore APR20 groups. There were no apparent differences related to the age or gender of the subjects. Eleven cases of migraines were reported during the placebo-controlled period all of which occurred in the apremilast treatment arms (APR20, n=2; APR30, n=9).

Table 37. PsA Phase 3 Data Pool: Headache Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Headache AE	23 (5)	46 (9)	67 (14)
Any Severe Headache AE	1 (<1)	0	3 (1)
Any Headache AE leading to drug withdrawal	2 (<1)	2 (<1)	10 (2)
Any Serious Headache AE	0	0	2 (<1)
Age; n/N (%)			
<65 years	19/447 (4)	43/458 (9)	60/442 (14)
≥65 years	4/48 (8)	3/43 (7)	7/55 (13)
Sex; n/N (%)			
Male	8/240 (3)	23/232 (10)	23/222 (10)
Female	1/5255 (6)	23/269 (9)	44/275 (16)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 259, Table 147

During the placebo-controlled period, the majority of headaches occurred during the first two weeks of the treatment and did not tend to last more than two weeks. Two subjects in each of the placebo and APR20 groups, and ten subjects in the APR30 group withdrew from drug due to headache. Figure 8 and Figure 9 illustrate the reported headache events based on onset day and duration, respectively.

Figure 8. PsA Phase 3 Data Pool: Headache Adverse Events by Onset Day During the Placebo-Controlled Period

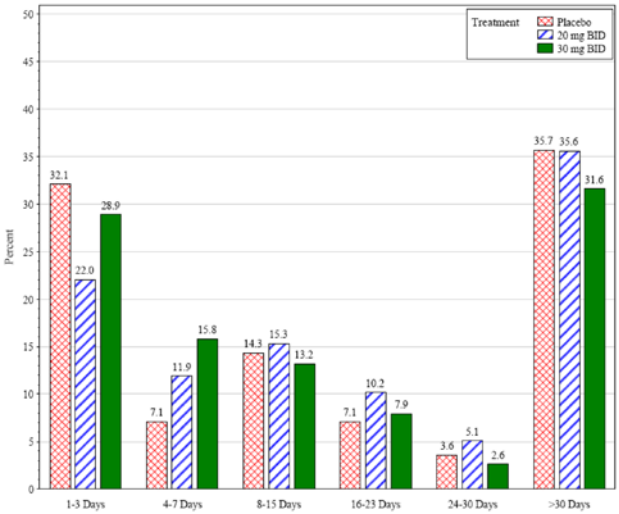


Figure adapted from NDA 205437 Integrated Summary of Safety, page 261, Figure 5.

Figure 9. PsA Phase 3 Data Pool: Headache Adverse Events by Treatment Duration During the Placebo-Controlled Period

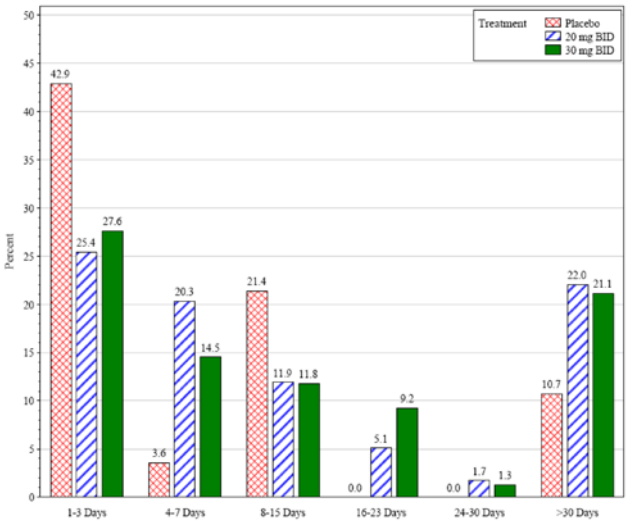


Figure adapted from NDA 205437 Integrated Summary of Safety, page 262, Figure 6.

More than two-thirds of headaches occurred within the first 30 days of initiating study drug. Thereafter, the number of subjects reporting new cases diarrhea decreased over time (data not shown).

Similar to the data from the placebo-controlled period, the EAIR of headache was observed to increase in a dose-dependent manner during the apremilast-exposure period of the PsA Phase 3 Data Pool. In general, the number of subjects reporting headaches was similar regardless of age or gender (Table 38).

Table 38. PsA Phase 3 Data Pool: Headache Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any Headache AE	66 (9)	15	86 (12)	19.8
Any Severe Headache AE	3 (<1)	0.6	5 91)	1.1
Any Headache AE leading to drug withdrawal	5 (1)	1	12 (2)	2.5
Any Serious Headache AE	1 (<1)	0.2	2 (<1)	0.4
Age; n/N (%)				
<65 years	61/656 (9)	15.2	75/645 (12)	19.3
≥65 years	5/64 (8)	13.1	11/76 (25)	23.8
Sex; n/N (%)				
Male	33/347 (10)	14.9	31/324 (10)	15.7
Female	33/373 (9)	15.1	55/397 (14)	23.2

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 264, Table 150

As shown in Table 39, the frequency of reported events for headache by time periods for the subjects-as-initially-treated safety population increased in a treatment- and dose-dependent manner in the PsA Phase 3 Data Pool.

Table 39. PsA Phase 3 Data Pool: Headache Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
AE; n	24	53	60	71	68	76	95
Subjects with ≥1 SAE; n(%)	20 (4)	42 98)	46 (9)	54 (11)	62 (13)	67 (14)	74 (15)
Exposure (subject-years)	140	135	196	315	130	190	308
EAIR per 100 subject years	14.3	31.1	23.4	17.2	47.5	35.2	24
95% CI	8.9, 21.6	22.6, 41.4	17.3, 30.9	13, 22.2	36.7, 60.4	27.5, 44.4	18.9, 29.9

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 266, Table 152

In summary, these data demonstrate a treatment- and dose-dependent increase in the frequency of reported cases of headache. The majority of the cases were of mild to moderate severity and occurred in the first 30 days after starting therapy. Despite titrating the dose of apremilast in subjects initiating apremilast, a large percentage of patients experienced headaches. While the apremilast-related headache events may

affect a patient's ability to tolerate therapy, the severity of the effects is likely to be moderate and reversible. Headache AEs should be included in the product labeling.

7.3.6.1 Weight Change

PsA Phase 3 Data Pool

During the placebo-controlled period, placebo-treated subjects had a mean weight gain of 0.09 kg compared with a mean weight loss -1.16 kg ad -0.96 kg observed in the APR20 and APR30 treatment arms, respectively. Similarly, during the apremilast-exposure period, both the APR20 and APR30 groups had a mean weight loss of -0.97 kg and -0.72 kg, respectively.

Weight loss during the placebo-controlled period was observed in 58% of subjects in the APR20 group and 57% of subjects in the APR30 group compared with 40% of placebo-treated subjects. The weight loss appeared to be treatment-dependent but not dose-dependent. Most cases of weight loss was between 0-5% of total body weight; however, 11% and 10% of APR20- and APR30-treated subjects, respectively, lost between 5-10% of body weight compared to 3% of placebo-treated subjects. At the end of the placebo-controlled period, only three subjects from the placebo arm, nine subjects from the APR20 group, and 5 subjects from the APR30 group lost greater than 10% of body weight. No subject discontinued due to weight loss.

A total of three placebo-treated subjects, 23 APR20-treated subjects, and 22 APR30-treated subjects experienced weight loss ≥10% from baseline at any time during the study. Figure 10 and Figure 11 illustrate weight loss over time in subjects in the APR20 and APR30 treatment arms, respectively.

Figure 10. PsA Phase 3 Data Pool: APR20 Subjects Reporting ≥10% Weight Loss From Baseline at Any Time

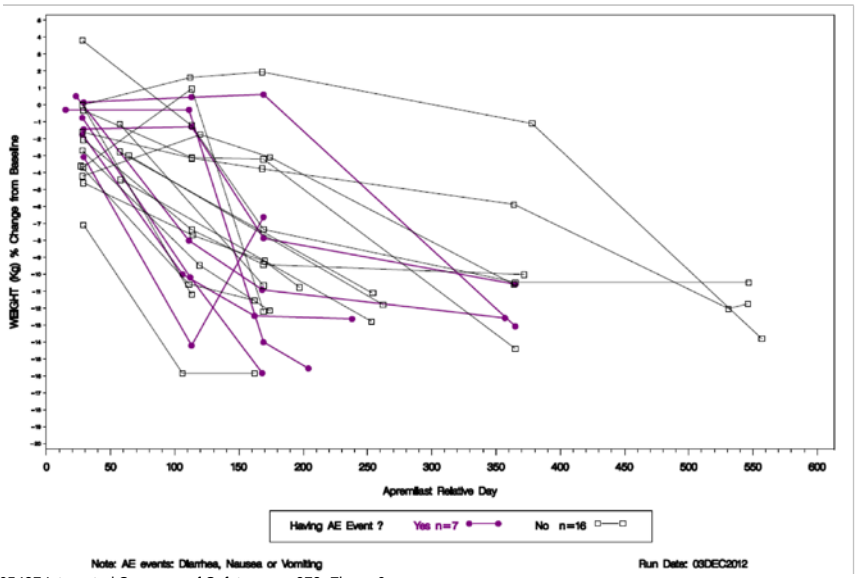


Figure adapted from NDA 205437 Integrated Summary of Safety, page 273, Figure 9.

Figure 11. PsA Phase 3 Data Pool: APR30 Subjects Reporting ≥10% Weight Loss From Baseline at Any Time

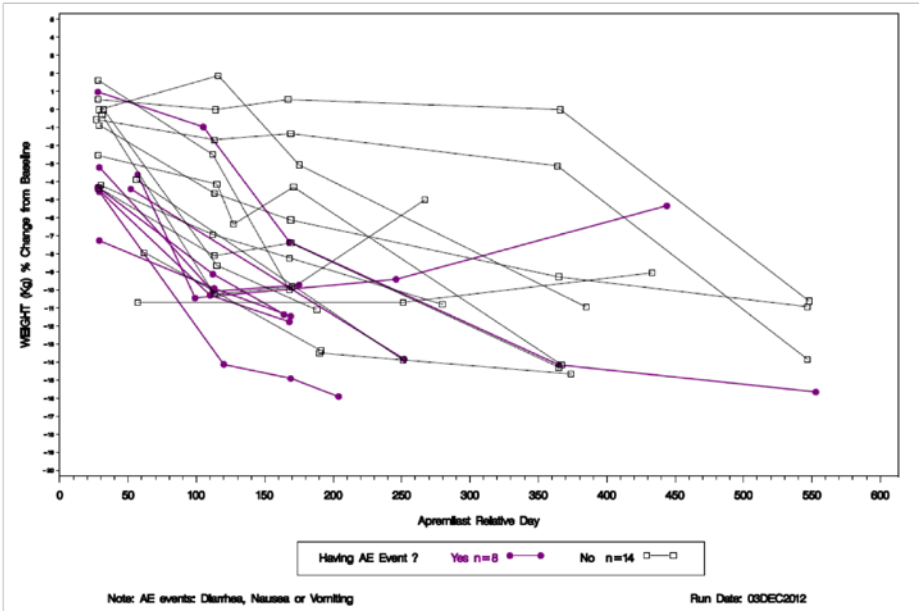


Figure adapted from NDA 205437 Integrated Summary of Safety, page 274, Figure 10.

Further analyses were conducted to determine whether a correlation existed between the incidence of weight loss in the presence of reported diarrhea or nausea and vomiting AEs; however, a definitive conclusion could not be drawn due to limited data as weight measurements did not occur at the time of the AEs.

The data presented here demonstrate a treatment-related loss of weight in subjects receiving apremilast with the majority of subjects losing between 0-5% of body weight. , The data did not suggest a dose-response relationship and no subjects had to withdraw for study drug due to weight loss. Weight loss should be included in the product label as a possible adverse reaction related to apremilast therapy.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse drug reactions (ADRs) were defined as any AEs occurring in ≥2% of apremilast-treated subjects where the incidence of events in any apremilast treatment group was ≥1% higher than the incidents of events in the placebo group. Since incidence rates for common AEs are best estimated using placebo-controlled studies, emphasis was placed on the data for subjects-as-treated safety population for Weeks 0-16 of the placebo-controlled period for the PsA Phase 3 Data Pool. Numbers of subjects in the apremilast-treatment groups exceed the number of patients enrolled during the first 16 weeks of study as the subjects-as-treated safety population for Weeks 0-16 includes data up to 16 weeks after the respective treatment start date. Data for the apremilast treatment arms include data up to 16 weeks after the apremilast start date for subjects randomized to placebo who also received apremilast. Use of this data increases the number of subjects exposed to both doses of apremilast and increases the sensitivity for detecting AEs.

Table 40 shows the ADRs for Weeks 0-16 of the PsA Phase 3 Data Pool. Diarrhea, nausea, and headache were the most frequently reported events and appeared to be dose-dependent. Events of URIs, vomiting, and dyspepsia were also more frequently reported in the apremilast treatment arms compared to placebo-treated subjects. Nasopharyngitis was reported in a higher percentage of APR20-treated subjects compared to placebo-treated subjects; however, incidence rates were similar between the APR30 and placebo treatment arms.

Table 40. PsA Phase 3 Data Pool: Adverse Drug Reactions From Weeks 0-16

Preferred Term	PBO (n=495)	APR20 BID (n=720)	APR30 BID (n=721)
Diarrhea	14 (3)	67 (9)	100 (14)
Nausea	22 (4)	52 (7)	84 (12)
Headache	20 (4)	45 (6)	61 (9)
URI	12 (2)	35 (5)	27 (4)
Nasopharyngitis	9 (2)	23 (3)	16(2)
Vomiting	4 (1)	12 (2)	24 (3)
Dyspepsia	6 (1)	13 (2)	19 (3)
Abdominal pain, upper	1 (<1)	17 (2)	13 (2)
Cough	2 (<1)	8 (1)	10 (1)
GERD	1 (<1)	6 (1)	11 (2)
Decreased appetite	1 (<1)	9 (1)	8 (1)
Rash	2 (<1)	10 (1)	4 (1)
Migraine	0	2 (<1)	11
Frequent bowel movements	0	2 (<1)	10 (1)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 190, Table 101

For the ADRs with the highest frequency, the number of the ADR events that were reported within the first 15 days from the initiation of study drug is summarized in Table 41.

Table 41. PsA Phase 3 Data Pool: Adverse Drug Reactions Reported in the First 15 Days of Apremilast Therapy

Preferred Term	PBO (n=495) n/m (%)	APR20 BID (n=720) n/m (%)	APR30 BID (n=721) n/m (%)
Any AE	44/89 (49)	137/262 (52)	216/348 (62)
Diarrhea	9/16 (56)	47/70 (60)	79/29 (73)
Nausea	10/26 (39)	41/50 (71)	68/97 (70)
Headache	15/24 (63)	31/61 (51)	42/66 (64)
Dyspepsia	3/6 (50)	8/13 (62)	10/19 (53)
Vomiting	3/4 (75)	5/14 (36)	9/20 (32)
URI	4/13 (31)	5/30 (13)	8/29 (28)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 194, Table 105

The number of these ADR events with duration of ≤15 days is summarized in Table 42. For apremilast-treated subjects, the majority of headache, URI, and vomiting events resolved within 15 days.

Table 42. PsA Phase 3 Data Pool: Adverse Drug Reactions With a Duration of ≤15 Days of Apremilast Therapy

Preferred Term	PBO (n=495) n/m (%)	APR20 BID (n=720) n/m (%)	APR30 BID (n=721) n/m (%)
Any AE	58/89 (65)	156/262 (60)	162/348 (47)
Headache	18/24 (75)	44/61 (66)	37/66 (56)
Diarrhea	9/16 (56)	37/78 (47)	38/29 (35)
Nausea	16/26 (62)	32/50 (55)	39/97 (40)
URI	10/13 (77)	34/30 (79)	24/29 (83)
Vomiting	3/4 (75)	14/14 (100)	22/29 (79)
Dyspepsia	2/3 (33)	3/13 (23)	2/19 (11)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 195, Table 106

In summary, the most common adverse events for the APR30 dosage that should be reported as ADR events in the product label include diarrhea, nausea, headache, URI, vomiting, and dyspepsia.

7.4.2 Laboratory Findings

PsA Phase 3 Data Pool

Summary statistics of observed values and changes from baseline over time were assessed for hematology and clinical chemistry parameters in the placebo-controlled and apremilast-exposure periods for the PsA Phase 3 Data Pool. Review of the data demonstrated that baseline hematology and clinical chemistry values were well balanced in all three treatment arms. In general, mean changes from baseline in hematology and clinical chemistry values were small, infrequent, and not clinically significant. Review of the data did not demonstrate a dose-response relationship.

Additional analyses were performed assessing shifts from baseline to the end of the study period in selected hematology and clinical chemistry values for the placebo-controlled and apremilast-exposure periods. Review of the data did not demonstrate any clinically meaningful differences between treatment arms.

The most frequently abnormal hematology values reported during the placebo-controlled period was decreased lymphocyte counts (<0.8 x 10^9/L) which occurred in approximately 4% of placebo-treated subjects and in 2% and 3% of subjects randomized to APR20 and APR30 treatment arms, respectively. Assessment of liver function tests (LFTs) demonstrated that two placebo-treated subjects, two subjects in the APR20 group, and seven subjects in the APR30 had reported an ALT or AST> 3 x ULN during the placebo-controlled period. Additionally, two subjects in the APR20 group and two subjects in the APR30 group had bilirubin >1.8 x ULN; however, there were no

cases of LFT elevations meeting Hy's Law. The most frequent marked abnormal clinical chemistry values reported during the placebo-controlled period included elevated triglycerides (>3.4 mmol/L) and uric acid levels (>590 µmol/L [male] or >480 µmol/L) in the PBO (10% and 3%, respectively), APR20 (9%and 3%, respectively), and APR30 (9% and 3%, respectively) treatment arms. All marked abnormalities in hematology and clinical chemistry values occurred in similar proportions of subjects in all treatment arms and no dose-response relationship was noted. Similar results were observed during the apremilast-exposure period for the PsA Phase 3 Data Pool.

Apremilast Unblinded Data Pool

A greater proportion of APR30 subjects were noted to have elevated phosphate levels >1.60 mmol/L compared with subjects in the PBO or APR20 BID groups during the placebo-controlled (1%, 1%, and 2%) and apremilast-exposure periods (not performed, 2%, and 3%, respectively). Phosphate levels were slightly higher in the PsA Phase 3 Data Pool albeit to a lesser degree. There were no correlative changes regarding other electrolytes or associated AEs from either Data Pool. The clinical significance of this finding is unclear.

Overall, analysis of hematology and clinical chemistry parameters as assessed over time, by individual subject changes, and individual clinically significant abnormalities were similar to the values observed from the placebo-controlled and apremilast-exposure periods from the PsA Phase 3 Data Pool. Marked abnormalities were infrequent and review of the data did not demonstrate any clinically meaningful differences between treatment arms or a dose-response relationship with apremilast treatment.

Given the increased frequency of gastrointestinal AEs, LFTs were analyzed separately for this review. More than 80% of subjects had normal (≤1 x ULN) ALT and AST values during both periods of the PsA Phase 3 data pool. The majority of the subjects reporting LFTs >3 x ULN had these elevations only once with resolution of the lab value while remaining on study drug. None of the subjects had an AST/ALT value >3 x ULN with an associated increase in bilirubin >1.5 x ULN. A single subject from the APR30 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. Many of the subjects were receiving concomitant medications known to be hepatotoxic including MTX or statins. No cases of LFT elevations that met Hy's Law criteria in any Data Pool.

The sponsor conducted adequate routine testing throughout the clinical studies with appropriate hematology and clinical chemistry laboratories. The most notable changes were found in the clinical chemistry laboratory values which demonstrated mild elevations of LFTs, most of which were reported as a single event and resolved while maintaining study therapy. These results are somewhat confounded due to the number

of potentially hepatotoxic concomitant medications taken by study subjects. No cases of LFT elevations met Hy's Law criteria. Elevated phosphate levels were also noted in subjects in the APR30 group.

Overall, changes in laboratory values were small, infrequent, and of minimal clinical significance. Additionally, the frequency of laboratory abnormalities was typically well balanced between treatment arms and was not correlated with clinically meaningful AEs.

7.4.3 Vital Signs

During the placebo-controlled period, the mean change from baseline to the end of period ranged among the three treatment groups between -0.2 to -1.1 mmHg for systolic BP and between -0.1 to -1.0 mmHg for diastolic BP. During the apremilast-exposure period, the mean change from baseline to the end of period ranged between the two apremilast treatment groups between -0.9 to -1.1 mmHg for systolic BP and was -1.3 mmHg for diastolic BP in both groups. Mean changes from baseline for all vital signs parameters were generally consistent across treatment groups, and no dose relationships were noted. The overall mean changes from baseline to the end of period in pulse rate was 0, 0.4, and 0.6 beats per minute in the PBO, APR20, and APR30 treatment arms, respectively. Similar observations were noted when changes from baseline over time in vital signs were analyzed for the Apremilast Unblinded Data Pool. Overall, there were no clinically meaningful differences or trends.

7.4.4 Electrocardiograms (ECGs)

Study CC-10004-PK-008 was conducted to assess the QT effects of apremilast 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.

Analyses of the data demonstrated no significant QT prolongation effect of either dose of apremilast. The largest upper bounds of the two-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 minimum threshold for regulatory concern as described in the ICH E14 guidelines. Assay sensitivity was established as evidenced by the largest lower bound of the two-sided 90% CI for the ΔQTcF for moxifloxacin, which was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated. Further details of Study CC-10004-PK-008 can be found in the Clinical Pharmacology Review by Dr. Agarwal.

7.4.5 Special Safety Studies/Clinical Trials

A thorough study assessing the potential for apremilast to prolong the QT/QTc interval was conducted by the sponsor as is discussed in Section 7.4.4.

7.4.6 Immunogenicity

This section of the review is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The overall incidence of AEs during the placebo-controlled period and apremilast-exposure period for the PsA Phase 3 Data Pool were similar between the APR20 and AP30 BID treatment arms (Table 43). Additionally, the incidence of AEs by System Organ Class (SOC) was similar in both treatment arms except for AEs occurring under the SOCs of Gastrointestinal Disorders and Nervous System Disorders. As discussed in Sections 7.3.5.6 and 7.3.6.0, the proportion of subjects reporting diarrhea, nausea, and headache appeared to increase in a treatment- and dose-dependent manner in both the placebo-controlled and the apremilast-exposure period. The majority of these AEs were reported as mild to moderate in severity and occurred early in the study and resolved within the first 30 days.

Table 43. PsA Phase 3 Data Pool: Overall Incidence of Adverse Events during the Placebo-Controlled Period

System Organ Class	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
Any AE	235 (48)	308 (62)	302 (61)
Gastrointestinal disorders	64 (13)	128 (26)	181 (36)
Infections and infestations	92 (19)	120 (24)	117 (24)
Nervous system disorders	35 (7)	66 (13)	82 (17)
Musculoskeletal and connective tissue disorders	36 (7)	39 (8)	42 (9)
Respiratory, thoracic, and mediastinal disorders	18 (4)	32 (6)	24 (5)
General disorders and administration site conditions	22 (4)	31 (6)	24 (5)
Investigations	13 (3)	27 (5)	25 (5)
Skin and subcutaneous tissue disorders	22 (4)	29 (6)	20 (4)
Metabolism nutrition disorders	12 (2)	30 (6)	13 (3)
Injury, poisoning and procedural complications	24 (5)	19 (4)	22 (4)
Psychiatric disorders	17 (3)	22 (4)	19 (4)
Vascular disorders	18 (4)	17 (3)	19 (4)
Cardiac disorders	9 (2)	15 (3)	16 (3)
Eye disorders	10 (2)	6 (1)	8 (2)
Reproductive system in breast disorders	10 (2)	6 (1)	5 (1)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Safety, page 94, Table 36

Overall, the incidence of AEs leading to drug withdrawal during the placebo-controlled period was higher in the APR30 group than in the APR20 group (Section 7.3.3; Table 24); however, the rates were similar between the two dose groups for the apremilast-exposure period.

In summary, the frequency of SAEs was low and did not vary notably across the treatment arms in both the placebo-controlled and apremilast-exposure period (Section 7.3.2, Table 22). Analyses for AEs of special interest demonstrated the incidence of AEs were similar, if not lower, in the APR30 treatment arm compared to the APR20 treatment arm with the exception of gastrointestinal events and headaches (Sections 7.3.5.6 and 7.3.6.0, respectively).

7.5.2 Time Dependency for Adverse Events

The overall EIARs for AEs events in the APR20 and APR30 treatment arms for the time periods of Weeks 0-24 and 0-52 were 261.3 vs. 276.7 and 212.3 vs. 217.3, respectively. Further review of AEs from all periods of the PsA Phase 3 and Apremilast Unblinded Data Pools did not identify a time dependency between the occurrence and frequency of AEs versus apremilast exposure.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Age

The small numbers of subjects older than 65 years of age complicates the interpretation of the incidence of AEs according to age. In general, the frequency of AEs during the placebo-controlled period for the PsA Phase 3 Data Pool was similar between subjects <65 years of age compared to those ≥65 years of age. Higher incidences of AEs of diarrhea and headache were reported in subjects ≥65 years of age during the placebo-controlled period for the PsA Phase 3 Data Pool.

No effects of age were observed on the proportion of subjects reporting AEs in the APR20 treatment arm; however, a higher percentage of subject ≥65 years of age in the APR30 group experienced AEs compared to subjects <65 years of age, 76% vs. 65%, respectively.

7.5.3.2 Sex

A higher overall frequency of SAEs, AEs leading to drug withdrawal, and overall AEs was observed among female subjects compared to male subjects over all three treatment arms. Apremilast-treated female subjects experienced a greater frequency of diarrhea, nausea, and vomiting compared to male subjects. Similar trends were observed during the apremilast-exposure period for the PsA Phase 3 Data Pool.

7.5.3.3 Race

The vast majority of subjects included in the PsA Phase 3 Data Pool were White (94%) and the remaining 6% of subjects were Asian (3.5%), Black or African American (0.5%), and the remainder were American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other race. No meaningful conclusions can be drawn from the data due to the small number of non-White subjects.

7.5.3.3 Region

Overall, a higher proportion of subjects enrolled in North America reported AEs was compared to those enrolled in Europe or the Rest of the World, across all three treatment arms. The types and patterns of AEs were similar across regions with diarrhea, nausea, headache, and URI being the most commonly reported AEs in all regions. No consistent trend was observed for AEs analyzed by region during the apremilast-exposure period.

7.5.4 Drug-Disease Interactions

Overall, the proportion of subjects reporting AEs was similar between subjects with a medical history of coronary artery disorders, vascular hypertensive disorders, lipid metabolism disorders, and glucose metabolism disorders compared to those subjects without a medical history of the respective medical condition, regardless of treatment group. The proportion of subjects reporting AEs was higher in subjects with a medical history of depressive or anxiety disorders compared to subject without a medical history of depressive or anxiety disorders, regardless of treatment group.

Analysis of AEs for subjects with mild to moderate renal impairment demonstrated a treatment-dependent increase in AEs compared to placebo-treated subjects with comparable renal function during the placebo-controlled period for the PsA Phase 3 Data Pool. Overall, no dose adjustment is required for patients with mild to moderate renal impairment. Dosing recommendations for patients with severe renal failure were based on the PK study CC-10004-CP-019, the results of which are discussed in Section 4.4 of this review and in Dr. Agarwal's review.

Analysis of AEs for subjects with mild to moderate renal impairment demonstrated a treatment-dependent increase in AEs compared to placebo-treated subjects with comparable renal function during the placebo-controlled period for the PsA Phase 3 Data Pool. Overall, no dose adjustment is required for patients with mild to moderate renal impairment. Dosing recommendations for patients with severe renal failure were based on the PK study CC-10004-CP-019, the results of which are discussed in Section 4.4 of this review and in Dr. Agarwal's review.

Study CC-10004-CP-011 assessed the PK parameters of apremilast in subjects wit hepatic impairment, the results of which concluded that no dose adjustment is necessary for patients with hepatic impairment. The reader is referred to Dr. Agarwal's review for a more detailed discussion of the results of this study.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were evaluated in both the Clinical Pharmacology and Phase 3 clinical programs. Discussion of the results for the Clinical Pharmacology studies is found in Section 4.4 and in Dr. Agarwal's review. Potential drug-drug interactions during the Phase 3 studies were evaluated using the PsA Phase 3 Data Pool by baseline use of DMARDs, MTX, LEF, SSZ, corticosteroid, and prior biologics.

A lower frequency of AEs was reported among subjects with baseline DMARD use in each of the three treatment groups compared with subjects who were not receiving baseline DMARDs. A treatment-dependent trend was observed in the incidence of AEs independent of baseline DMARD use; however, a dose-related effect was not observed.

Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

Similar to the observation with baseline DMARD use, an overall lower frequency of AEs was observed among subjects receiving MTX at baseline compared with those who were not. A treatment-dependent trend was observed regarding the incidence of AEs, independent of baseline methotrexate use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

No differences in the frequency of reported AEs were observed between subjects who were, or were not receiving SSZ or LEF. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

In the placebo group, the type and pattern of AEs were generally similar between subjects who had baseline oral corticosteroid use and those subjects who did not use corticosteroids at baseline. A higher frequency of AEs was observed among subjects in the apremilast treatment groups who had baseline oral corticosteroid use compared with those who did not. The different incidence rates were primarily driven by the gastrointestinal-related events of diarrhea and dyspepsia, which were observed in both apremilast treatment groups to be more frequently reported by subjects who had baseline oral corticosteroid use compared with those who did not. A treatment-dependent trend was observed in the frequency of AEs, regardless of baseline oral corticosteroid use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

A higher incidence of AEs was reported among apremilast-treated subjects who had prior biologic use compared with those subjects who did not have prior biologic use. This imbalance was primarily driven by the AEs of nausea, headache, and vomiting in the APR20 BID group and diarrhea in the APR30 BID group. A treatment-dependent trend was observed in the incidence of AEs, regardless of prior biologic use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

Overall, the safety comparing the incidence of AEs from the PsA Phase 3 Data Pools demonstrate an acceptable safety profile when used alone or in combination with DMARDs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not conducted.

7.6.2 Human Reproduction and Pregnancy Data

No safety signals regarding human reproduction or pregnancy were identified. The Division will require the sponsor to conduct post-marketing surveillance regarding pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric studies have been deferred.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A total of eight subjects reported 14 AEs termed “Overdose” in the PsA Phase 3 Data Pool, all of which were without an associated AE. Some healthy adults were exposed to a maximal dose of 50 mg BID for up to 4.5 days during the Clinical Pharmacology dose-escalation studies without evidence of dose-limiting toxicities. Supportive care is advised in the event of apremilast overdose. No safety signals were identified regarding abuse potential, withdrawal, or rebound effect with apremilast.

7.7 120-Day Safety Update

The 120-day safety update report included safety data from a total of 1441 subjects who were exposed to apremilast in the PsA Phase 3 Data Pool, which included 721 subjects who received apremilast 30 mg BID, the proposed marketed dose. While the overall number of apremilast-treated subjects remained the same as that submitted to the original application, the total exposure to apremilast 30 mg BID increased from 478 subject-years to 769 subject-years. Consequently, the number of subjects in the APR30 BID group who were exposed to apremilast for at least 24-weeks increased from 527 (73%) in the original NDA to 622 (86%) in the 120-day safety update, and those who were exposed to apremilast for at least 48-weeks increased from 183 (25%) in the original NDA to 477 (66%) in the 120-day safety update. Approximately half of the APR30-treated subjects included in the 120-day safety update exposed to apremilast for at least 60-weeks.

The adverse event data for this additional time period demonstrated a similar safety profile for apremilast with that presented in the original NDA. Overall, the type and pattern of AEs and SAEs did not change. The incidences of individual AEs increased slightly compared to those observed in the original NDA but remained at less than 5%, and when adjusted for drug exposure, the EAIRs did not increase. The most frequently reported AEs in the 120-day safety update were diarrhea, nausea, headache, and URI, which are consistent with the results observed in the original NDA. The majority of AEs were reported as mild to moderate in severity. Additionally, the data confirmed that AEs of diarrhea, nausea, and headache occurred at the highest frequency during the first four weeks of dosing with apremilast and decreased thereafter.

The same analyses used to assess AEs of special interests in the original NDA were utilized in this 120-day safety update. Overall, the EAIRs of AEs of special interest observed in the updated data for both apremilast treatment arms remained comparable to those observed in the original NDA. The voerall frequency of serious infections, MACE or potential MACE, and malignancies were not increased in apremilast-treated subjects. One additional subject in the APR30 treatment arm reported a suicide attempt.

Overall, the data included in the 120-day safety update expanded the total exposure to apremilast and were consistent with the data included in the original NDA. No new safety signals were identified in the 120-day safety update despite increased exposure to apremilast and the safety profile appears comparable between the APR20 mg BID and APR30 mg BID dosing regimens.

In conclusion, the safety data included in the 120-day safety update did not identify a safety signal different from what was seen in the original NDA.

8 Postmarket Experience

This is the initial NDA application for apremilast. No postmarketing experience is available.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Labeling recommendations are pending following receipt of all outstanding consults.

9.3 Advisory Committee Meeting

Following the initial review and discussion of the application, the review team determined apremilast to be efficacious in adult patients with PsA with an acceptable safety profile and no identifiable serious safety signals or outstanding issues. Consequently, a determination was made deciding that a meeting of the FDA's Arthritis Advisory Committee would not be required.

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/s/

KEITH M HULL
01/23/2014

Consultative Review and Evaluation of Clinical Data
DPP Consult #11,411

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Subject:	Otezla (apremilast; NDA 205437)
Date Received:	December 19, 2013
Date Reviewed:	January 3, 2014

I. Background

The New Drug Application in question is for approval of apremilast (proposed trade name: Otezla), a phosphodiesterase-4 (PDE-4) inhibitor, for the treatment of adult patients with active psoriatic arthritis (PsA). Although studied in other diseases, apremilast is coming in as a new molecular entity. Previously, psychiatric adverse events and suicidality were identified as a potential safety signal with another PDE-4 inhibitor, roflumilast, in COPD patients and was included in the Warnings and Precautions section of the roflumilast labeling. DPARP requests our opinion on the assessment of psychiatric adverse events, including suicide-related AEs, in the apremilast submission.

Three large, multicenter, randomized, double-blind, placebo-controlled studies (PSA-002, PSA-003, and PSA-004) provide the primary safety and efficacy data for apremilast. Each of these studies enrolled subjects with moderate to severe active PsA. Referred to as the *PsA Phase 3 Data Pool*, the analysis period of most interest is the *placebo-controlled period*, when subjects maintained their original randomization to apremilast or placebo (before possible early escape at Week 16 and re-randomization of all remaining placebo-treated subjects to an apremilast treatment arm at Week 24). For the placebo-controlled period of the PsA Phase 3 Data Pool, the pooled treatment arms were apremilast 30mg BID (n=497), apremilast 20mg BID (n=501), or placebo (n=495). This is in contrast to the *apremilast-exposure period*, which includes all apremilast data, regardless of when apremilast-exposure started (n=1441 on either apremilast 20 or 30 BID)

In addition to the primary efficacy studies (PSA-002, PSA-003, and PSA-004), safety data was derived from all Phase 2/3 clinical studies that assessed the safety and efficacy of apremilast in the treatment of PsA, psoriasis (PSOR), and rheumatoid arthritis (RA). This is referred to as the *Apremilast Unblinded Data Pool*. Of note, approximately 65% of the data in Apremilast Unblinded Data Pool is also part of the PsA Phase 3 Data Pool. For the *placebo-controlled period* of

the Apremilast Unblinded Data Pool, the exposures were apremilast 30mg BID (n=661), apremilast 20mg BID (n=824), or placebo (n=817). For the *apremilast-exposure period* of the Apremilast Unblinded Data Pool, n=2119 on either apremilast 20 or 30 BID.

Overall, six deaths were reported from a total of 2401 subjects who had been exposed to apremilast by the time of the data cutoff date of July 6, 2012 (this pool included additional subjects from PK studies and two small studies in asthma and Behcet's disease). One death occurred in the PsA studies (PSA-002), and the remaining five deaths occurred during the psoriasis studies (PSOR-004, PSOR-005, PSOR-008, and PSOR-009). Two of the deaths in the psoriasis studies were apparent suicides: one with a self-inflicted gunshot wound and one found dead in his closed garage with a motorcycle running. However, both occurred in subjects randomized to the placebo treatment arm.

For all the subjects in the *PsA Phase 3 Data Pool*, a review of the SAE narratives revealed one apremilast-treated subject with the SAE preferred term of "*suicide attempt*" and one with the term "*suicidal ideation*." Both cases occurred during the placebo-controlled period. The two narratives are summarized below.

- **Subject PSA-002-0381009:** The subject was a 35-year old white female who attempted suicide with medications on Study Day 11. She had no known psychiatric history but a medical history including migraines, sciatica, tendonitis, diabetes mellitus type II, obesity, and back pain. On Study Day 9, she developed "anxiety and insomnia," for which she received treatment with alprazolam and flurazepam, while her acetaminophen/butalbital/caffeine was discontinued. On Study Day 11 (on apremilast 20 mg BID), the subject had an argument with her teenage son that prompted him to move out of the house. She was so upset that she took 6-8 carisoprodol 350mg, 6-8 alprazolam 2mg, and 3 flurazepam 30 mg tablets. The subject was taken by ambulance to the ER and then transferred to a psychiatric facility. The event was considered resolved three days later when she was discharged home. It is unclear what her psychiatric diagnosis was or whether she was discharged on any psychiatric medications. There was no change to study medication due to this event. However, study drug was discontinued almost two months later due to the sponsor's request in response to the event.

- **Subject PSA-004-1031011**: The subject was a 34-year old white male who developed suicidal ideation on Study Day 40. Study medication (apremilast 20 mg BID) was withdrawn permanently in response to the event. The subject's relevant medical history included "depression and bipolar disorder (no manic disorder)" and hypertension. The subject stated that "depression and bipolar disorder" were diagnosed in 1994 and coincided with the diagnosis of his psoriasis. The subject was not taking any psychiatric medications and had not taken any in the past. The

subject reported consuming between 1-14 alcoholic drinks per week and denied illicit drug use. On Study Day 40, he developed "severe suicidal ideations". He corresponded with the study physician via e-mail, stating his psoriasis was getting worse and that he was increasingly depressed as a result. The subject stated in the e-mail that he did not have a plan for suicide and agreed to speak with the physician the following day. On Study Day 41, after a phone conversation with the subject, the investigator decided that the subject was unfit to continue the study and was in need of psychiatric care; study medication was discontinued. The subject continued to deny any plan to commit suicide.

For all the subjects in the *PsA Phase 3 data pool*, three subjects had a SAE of "*depression*". A review of those narratives revealed that all three had a worsening of a long-standing history of depression. One of them did have a possible suicide attempt (although not coded as such), but it did not occur during the placebo-controlled period. The narrative is summarized below:

- **Subject PSA-003-8751014:** The subject was a 56-year old white female who experienced worsening of depression on Study Day 126. She received placebo in the placebo-controlled phase followed by apremilast 30 mg BID from Study Day 112. There was no change in study medication in response to this event. The subject's medical history included depression (since 1990) and gastritis. Additional medical history included previous drug and alcohol dependence. Concomitant medications were levomepromazine, venlafaxine, methotrexate, folic acid, diclofenac, and omeprazole. On Study Day 126 (Day 14 on active treatment), the subject fell at home secondary to a balance disorder or an overdose of a tranquilizer and was transported via ambulance to the hospital. After being stabilized medically, she was transferred to a psychiatric hospital. Follow-up information from the subject's psychiatrist indicated that she had admitted to him having taken 30 drops of her father's diazepam, levomepromazine 5 mg, valeriana 5 pills, and 1 tablet of rivotril 2 mg prior to the event. Her levomepromazine was discontinued and quetiapine was started for depression; venlafaxine was continued. Almost a month later, the subject was fully recovered from this event and was discharged from the psychiatric hospital with follow-up therapy for her depression to continue in an outpatient setting.

Expanding the search to all available SAE narratives from the *Apremilast Unblinded Data Pool*, this reviewer identified a case of "*suicidal ideation*" from the rheumatoid arthritis studies:

- **Subject RA-002-1121002:** The subject was a 23-year old white female with suicidal ideation and newly diagnosed bipolar disorder. She was treated with apremilast 30 mg BID for rheumatoid arthritis. Relevant medical history included adjustment disorder with mixed anxiety and

depressed mood, post-traumatic stress disorder, and major depressive disorder. Relevant concomitant medications were duloxetine, methotrexate, folic acid, ergocalciferol, ibuprofen, ethinyl estradiol / norgestimate, salbutamol, nabumetone, and fexofenadine. On day 112 of the study, her symptoms began. The following day, the subject presented to the investigational site for her regularly scheduled visit and reported an increase of depression, stating that she would like to kill herself. She was recommended for crisis evaluation at a mental health facility. She completed the crisis evaluation, and the event of suicidal ideation was considered resolved that same day. She continued outpatient treatment at that facility and was diagnosed with bipolar disorder a week later.

In terms of total depression adverse events, the primary clinical reviewer included the following table in his review (see Table 1)

Table 1 PsA Phase 3 Data Pool: Depression Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Depression AE	4 (1)	9 (2)	5 (1)
Any Severe Depression AE	0	0	0
Any Depression AE leading to drug withdrawal	0	3 (1)	1 (<1)
Any Serious Depression AE	0	2 (<1)	0
Age; n/N (%)			
<65 years	4/447 (1)	9/458 (2)	5/442 (1)
≥65 years	0/48 (0)	0/43 (0)	0/55 (0)
Sex; n/N (%)			
Male	1/240 (<1)	2/232 (1)	1/222 (1)
Female	3/255 (1)	7/269 (3)	4/275 (2)

Finally, the sponsor attempted to conduct a retrospective search for and classification of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) and the methods described by Posner, et al.[1] The apremilast clinical trial database for all Phase 2 and 3 completed and ongoing studies (including ASTH, BCT, RA, PSOR, and PsA studies) was searched for all data available up to July 06, 2012. The sponsor describes their methodology as the following:

> All adverse event (AE) terms were searched using the 15 C-CASA text strings. The list of AE terms identified using the string search were reviewed by Celgene physicians and classified as either "suspect" AE verbatim terms or "false positives." Additionally, there was broadening of the event term search to ensure that all potential suicide events were captured. All AE verbatim terms in the clinical trial safety database were

[1] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. 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.

reviewed by Celgene physicians to identify for inclusion all accidental injuries, overdoses, and serious adverse events, such as life-threatening events, psychiatric events (e.g. anxiety, depression, insomnia, mood changes, and psychosis), and deaths. Once the AEs from the combined list, which included those flagged by the string search and the broadened AE verbatim term search, were identified, subject profiles were constructed for each AE verbatim term using data from case report forms, recorded by investigators during the course of the trials. Since the subject profiles are currently only programmed in the studies using SDTM datasets, subject profiles were only available for subjects in the following ongoing apremilast studies: ASTH-001, BCT-001, RA-002, PSA-001, PSA-002, PSA-003, PSA-004, PSA-005, PSOR-001, PSOR-003, PSOR-004, PSOR-005, PSOR-005E, PSOR-005LTE, PSOR-008, and PSOR-009. When available, the subject profiles included demographics (including age, race, sex, height, weight, country), past medical history (including history of suicidality), concomitant medications, and adverse 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 for Industry:

A. Suicidal Behavior

    1. Completed Suicide
    2. Suicide Attempt
    3. Interrupted Attempt
    4. Aborted Attempt
    5. Preparatory Actions Toward Imminent Suicidal Behaviors

B. Suicidal Ideation (Passive or Active)

However, the sponsor's C-CASA analysis identified only one of the two apparent completed suicides (both in placebo patients in the psoriasis studies). In addition, it failed to find one of the two possible suicide attempts identified by this reviewer. Two cases of suicidal ideation were found by the analysis, but no details are given, so it is unclear whether these were the same two cases identified by this reviewer. The analysis did come up with an additional suicide attempt in a still blinded psoriasis study (PSOR-9), which may be why the sponsor unfortunately did not indicate whether this subject was on apremilast or placebo. The verbatim brief narrative is below:

> Subject 3241011 was a 66 year-old white male who participated in Study CC-10004-PSOR-009 at a site in Germany. He had a past medical history of psoriasis since 01/1999, sleep apnea since 1997, hypertension since 1997, hypercholesterolemia since 2008, deafness since 2009, knee pain since 01/26/2010. His concomitant medications included atacand plus and ibuprofen. The subject's first dose of study drug was on 08/25/2011. He

was hospitalized for attempted suicide by overdose with zopliclone on (b) (6) after an altercation with his wife and a neighbor. This event occurred (b) (6) after initiation of study medication. He recovered without event and was discharged outpatient psychiatric follow-up care. His last dose of study medication was on 12/19/2011 and he was withdrawn from the study on 12/20/2011 at the Sponsor's request. Investigator assessed this event as not suspected to study medication.

II. Response to DPARP Questions

1. **Please comment on the adequacy of the assessment of psychiatric events, including suicidality and the C-CASA assessment performed by the sponsor.**

2. **Do you agree with the conclusion that there was no association between apremilast treatment and psychiatric adverse events including suicide?**

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. However, the sponsor's C-CASA analysis found only one of the two apparent completed suicides identified by this reviewer (both in placebo patients in the psoriasis studies). One might perhaps argue that the apparent completed suicide missed by their analysis (subject found dead in his closed garage with a motorcycle running, with autopsy not establishing cause of death) could be judged either way, given the lack of information. In addition, however, the sponsor's C-CASA analysis failed to identify one of the two possible suicide attempts found by this reviewer (Subject PSA-003-8751014). Although the narrative does not explicitly state that she intended to kill herself, she had worsening of her long-standing depression and admitted taking a combination of medications that made her ataxic, causing a fall and requiring medical stabilization followed by an almost month long psychiatric hospitalization. Therefore, there is some doubt that the C-CASA analysis was conducted correctly. This doubt is increased by the fact that they used in-house raters (i.e. Celgene physicians) rather than independent experts in suicide and suicide assessment (as in the article by Posner et al.). It is also unclear what, if any, of the many measures recommended in the article to blind the raters was followed.

Although not considered to be a comprehensive review, this reviewer went through all the available SAE narratives from the Apremilast Unblinded Data Pool (n=2119 on either apremilast 20 or 30 BID) and found only two cases each of suicidal ideation and possible suicide attempts in apremilast-treated patients. The C-CASA analysis identified an additional suicide attempt in a still blinded psoriasis study, but it is not clear whether this subject was on apremilast or

placebo. Two cases of suicidal ideation were also found by the C-CASA analysis, but since no details are given, these could very well be the same cases identified by this reviewer. However, even these relatively few events did not all occur in PsA studies. For the placebo-controlled period of the PsA Phase 3 Data Pool (n=998 on either apremilast 20 or 30 BID, n=495 on placebo), there were, based on the SAE narrative review, one case each of suicidal ideation and suicide attempt in apremilast-treated patients. Of note, it is unclear whether there were any cases of suicidal ideation or behavior in placebo-treated patients, as the SAE narratives apparently only included apremilast-treated patients. It would not be surprising if there had also been one or two cases of suicidal ideation and/or behavior in placebo patients, given the characteristics of the treatment population (see below).

Putting together all this information, we would have to conclude that there does not appear to be much of a 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. This is especially the case when you consider the treatment population, which is made up in large part or completely (depending on which pool you look at) of individuals with moderate to severe psoriatic arthritis, a chronic condition that can be very painful and even debilitating. In addition, subjects entering such studies often have failed multiple other treatments and see the study as their last hope, making them very vulnerable if they experience no improvement. Therefore, this population very likely has a higher background rate of depression and suicidal ideation/behavior than the general population.

In terms of depression adverse events, as seen in Table 1 in the background section of this document, 9 (~2%) of subjects on apremilast 20 BID and 5 (1%) of subjects on apremilast 30 BID experienced any depression AEs vs. 4 subjects (~1%) on placebo. This does not constitute much of a signal either, especially considering that there were more cases at a lower dose (one might expect to see a dose-response for this like most AEs). Also, if you combine the two apremilast treatments arms, you get only 1.4% for apremilast vs. 0.8% for placebo.

Finally, to avoid the problem of having to perform such a complicated retrospective classification and analysis for any future apremilast indications as well as for all other CNS active drugs, we recommend adding a prospective assessment of suicidal ideation and behavior to clinical trials. One such instrument is the Columbia Suicide Severity Rating Scale (C-SSRS), but any validated scale for which mapping to the C-CASA algorithm has been demonstrated can be used.

Phillip D. Kronstein, M.D.
Medical Officer
CDER/ODE-1/DPP

cc: Kronstein
Borges
Mathis
Berman
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/s/

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01/17/2014

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01/21/2014

CLINICAL REVIEW

Application Type	NDA
Application Number	205437 s0000
Priority or Standard	Standard
Submit Date(s)	March 21, 2013
Received Date(s)	March 21, 2013
PDUFA Goal Date	April 21, 2014
Division / Office	DPARP/ODE 2
Reviewer Name	Keith M Hull, MD, PhD
Review Completion Date	TBD
Established Name	Apremilast
(Proposed) Trade Name	OTEZLA
Therapeutic Class	Phosphodiesterase-4 inhibitor
Applicant	Celgene Corporation
Formulation(s)	Immediate release tablet 10 mg, 20 mg, 30 mg
Dosing Regimen	30 mg twice daily
Indication(s)	Treatment of patients with active psoriatic arthritis
Intended Population(s)	Patients ages ≥18 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This new drug application is for approval of apremilast (proposed trade name: OTEZLA) for the treatment of adult patients with active psoriatic arthritis (PsA). Three large, multicenter, randomized, double-blind, placebo-controlled studies (PSA-002, PSA-003, and PSA-004) provide the primary evidence of the safety and efficacy of apremilast. Each of the studies enrolled subjects with moderately to severely active PsA. The majority of these subjects had failed one or more non-biologic or biologic DMARDs. Review of the efficacy and safety data submitted in this application demonstrates that apremilast provides a clinically meaningful benefit to patients with an acceptable safety profile.

This clinical reviewer recommends approval orally administered apremilast 30 mg BID for the treatment of adult patients with active PsA.

1.2 Risk Benefit Assessment

Studies PSA-002, -003, and -004 were highly similar in design and provided the primary data used for assessing the safety and efficacy of apremilast in subjects with active PsA. The studies were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies. Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). The sponsor is only seeking approval of the apremilast 30 mg BID dosing. The primary efficacy endpoint used by all three studies was the proportion of subjects achieving a ≥20% improvement of the American College of Rheumatology (ACR) response criteria at Week 16. The ACR 20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all the three studies was the assessment of apremilast on physical function as measured by the change from baseline in HAQ-DI score at Week 16.

Analysis of the primary endpoint for studies PSA-002, -003, and -004 demonstrated a statistically significant greater proportion of APR30-treated subjects (38%, 32%, and 41%, respectively) achieved an ACR20 response compared to placebo-treated subjects (19%, 19%, and 18%, respectively). Additionally, APR30-treated subjects demonstrated a greater change in HAQ-DI from baseline vs. placebo-treated subjects for studies PSA-002, -003, and -004 (-0.24 vs. -0.09; -0.19 vs. -0.05; and -0.19 vs. -0.07, respectively). Secondary endpoints were supportive of the primary endpoint and major secondary endpoint analyses.

Efficacy results generally supported a greater numerical advantage for the APR30 treatment arm compared to the APR20 treatment arm but there were limited statistically significant analyses to support the conclusion that APR30 was superior to APR20.

The data submitted to this application was sufficient to assess the overall safety of apremilast in patients with active PsA. The most commonly occurring adverse events associated with apremilast were diarrhea, nausea, vomiting, headache, and 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%-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. The overall safety profile was comparable between the apremilast 20 mg BID dosing and 30 mg BID dosing.

Given the data, approval of the proposed higher dose of apremilast 30 mg BID appears reasonable given its potential for greater efficacy and that there does not appear to be an increased risk of serious adverse reactions compared to the lower apremilast dose of 20 mg BID.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are being recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division of Biopharmaceutics is requesting one postmarketing commitment for the sponsor 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.

The Division of Pulmonary, Allergy, and Rheumatology Products is requesting one postmarketing requirement regarding 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 embrio-fetal exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group. The primary concerns are based on:

- Animal data suggesting that apremilast
    - Increases the incidence of abortions and embryo-fetal death in both mice and monkeys in a dose-dependent manner

  - Reduces fetal weight in a dose-dependent manner in mice
  - Increases the incidence of skeletal variations in both mice and monkeys

- Teratogenic effect of apremilast could not be adequately assessed in monkeys due to high incidence of pregnancy loss and limited examination of the lost fetuses
- Limited pre-marketing embryo-fetal apremilast exposure data in humans.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor is proposing to use orally administered apremilast (OTEZLA) 30 mg BID for the treatment of adult patients with active psoriatic arthritis. The sponsor is also recommending the initial dosing of apremilast be titrated to limit the incidence of gastrointestinal adverse effects. The proposed dose titration is outlined in Table 1:

Table 1. Proposed Apremilast Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 +	
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

Apremilast tablets are diamond shaped and film coated and supplied 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) when the storage conditions are ≤30^{o}C.

2.2 Tables of Currently Available Treatments for Proposed Indications

The first-line therapy for the treatment of psoriatic arthritis is typically the off-labeled use of small molecular immunomodulators (commonly referred to as disease modifying anti-rheumatic drugs [DMARDs]), e.g., methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF). Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are also frequently used to help control the pain and inflammation associated with the synovitis. Despite the efficaciousness of these drugs, a significant proportion of subjects will require additional treatment, most commonly a biologic response modifier.

Currently, six biologic drugs are approved for the treatment of adult patients with active psoriatic arthritis: etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab (CIMZIA), and ustekinumab (STELARA). These drugs have been shown to be efficacious and to have an acceptable safety profile.

Apremilast will represent the first small molecular drug approved for the treatment of adult patients with active psoriatic arthritis.

2.3 Availability of Proposed Active Ingredient in the United States

Apremilast is a new molecular entity that is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The PDE4-inhibitor, roflumilast (DALIRESP), was approved in 2011 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Included in the WARNINGS AND PRECAUTIONS section of the product label is an increased frequency of psychiatric adverse reactions and significant loss of body weight. Psychiatric adverse reactions included insomnia, anxiety, and depression, all of which were reported at higher rates in DALIRESP-treated subjects versus placebo-treated subjects. Instances of suicidal ideation and behavior, including completed suicide were observed during clinical trials and in the post-marketing setting in patients treated with DALIRESP. Moderate weight loss, defined as a decrease of 5-10% of body weight, was a common adverse reaction that occurred in DALIRESP-treated subjects during the clinical trials. Commonly reported adverse reactions listed in the product label included diarrhea, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

2.6 Other Relevant Background Information

All relevant background information regarding the clinical use of apremilast is included in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy. Issues regarding data quality and integrity of the studies are described below.

Each of the pivotal Phase 3 studies reported protocol violations and protocol deviations. A protocol violation was defined as any departures from the approved protocol that impacted the safety, rights, and/or welfare of the subject, negatively impacted the quality or completeness of the data, or made the informed consent process inaccurate. A protocol deviation was defined as any unplanned diversions from the approved protocol that did not result in harm to the study subjects or did not significantly affect the scientific value of study data.

During study PSA-002, 61 out of 504 (12%) subjects reported ≥1 protocol violation resulting in 15 (3%) subjects being excluded from the Per-Protocol population. The most commonly cited protocol violations included missing post-baseline data, lack of early termination assessments, and poor compliance. A total of 168 (35%) subjects had ≥1 protocol deviation with the most frequently reason related to informed consent issues, omission of a scheduled study procedure/assessment, or study visits performed out of window.

During study PSA-003, 126 out of 484 (26%) subjects reported ≥1 protocol violation resulting in 20 (4%) subjects being excluded from the Per-Protocol population. The most common protocol violations included issues with informed consent, omission of a scheduled study procedure or assessment, and subjects taking excluded concomitant medications. A total of 258 (51%) subjects had ≥1 protocol deviation with the most frequently reason related to informed consent issues, omission of a scheduled study procedure/assessment and study visits performed out of window.

During study PSA-004, 75 out of 505 (15%) subjects reported ≥1 protocol violation resulting in 15 (3%) subjects being excluded from the Per-Protocol population. The most common protocol violations included issues with omission of a scheduled study procedure or assessment, and subjects taking excluded concomitant medications. A total of 193 (38%) subjects had ≥1 protocol deviation with the most frequently reason related to stratification errors and omission of a scheduled study procedure/assessment.

Overall, the total number of subjects from each group with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between

treatments arms. Subjects with protocol violations were included in the Full Analysis Set and are not expected to adversely affect the conclusions drawn from these studies.

3.2 Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. Review of the submitted form "*Certification: Financial Interests and Arrangements of Clinical Investigators"* does not raise concerns regarding the integrity of the submitted data to the current application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Controls (CMC) reviewer recommends approval of apremilast pending overall acceptable recommendations from the Office of Compliance, microbiology, and resolution of outstanding CMC information requested comments sent to the sponsor. From the reviewer's perspective, the sponsor has provided adequate information regarding the manufacturing of the drug substance and drug product; however, clarifications are needed for several manufacturing process parameters and analytical methods.

The Chemistry, Manufacturing, and Controls (CMC) review notes that the drug substance is formulated with compendia grade excipients to form immediate release 10, 20 and 30 mg tablets. (b) (4) and the tablets are prepared by (b) (4) The tablets are coated with (b) (4)

The reader is referred to the CMC review of apremilast by Ciby Abraham, PhD for a detailed analysis of the CMC aspects related to this application.

4.2 Clinical Microbiology

This section of the review is not applicable to this product.

4.3 Non-clinical Pharmacology/Toxicology

Emphasis on the non-clinical toxicology findings that directly relate to human safety (e.g., genotoxicity, carcinogenicity, and reproductive toxicology) are briefly discussed here. The reader is referred to the Pharmacology/Toxicology review by Lawrence S. Leshin, PhD for a detailed analysis of the non-clinical pharmacology and toxicology aspects related to this application.

Results from the standard series of genetic toxicology assays were negative for apremilast and the identified process impurity (b) (4) Similarly, there were no definitive apremilast-related malignancies in the two-year oral dosing studies in mice or rats.

Reproductive and developmental toxicology GLP studies were conducted using mouse and monkey models. Apremilast treatment in mice found no effect on sperm motility or sperm counts and no effect on mating parameters or resultant pregnancies and embryo-

fetal survival. Fertility studies in apremilast-treated females showed a prolonged estrous cycle due to an increase in the diestrus period that resulted in a longer time until mating. Additionally, apremilast treatment resulted in an increase of early resorptions, and a reduction in fetal body weights.

Pregnant mice administered apremilast demonstrated a reduction of body weight gain as a result of lower uterine weights. Reductions in the number of litters and litter size were observed and attributed to postimplantation losses in all apremilast dose groups. Fetal weight was also reduced in a dose -dependent manner in both sexes. There was no dose-related effect on malformations, although skeletal variations were increased.

In the monkey studies, dose-related fetal losses, mostly occurring during weeks 3 and 4 of gestation were observed. The teratogenic effects of apremilast in the monkey were not adequately evaluated due to the high incidence of fetal abortions, which was dose-related, coupled with the absence of examination of these fetuses. There was an increased incidence of skeletal variations that were mostly related to a reduced number of ossification sites and misaligned tail vertebrae.

Studies evaluating pre- and post-natal development demonstrated difficulty regarding offspring delivery in the apremilast high-dose group and resulted in the death of one dam. The high-dose group also had reduced maternal body weight. Apremilast had no effect on late pregnancy, pregnancy duration or the number of dams that delivered. Postnatal pup mortality was increased in the F_1 generation and reduced pup weights of survivors until Day 21 of lactation were noted. There were no effects on the F_1 generation following apremilast treatment of the F_0 animals regarding clinical or necropsy observations post-weaning; body, testes or epididymis weights; sexual maturation; passive avoidance; motor activity; mating; fertility or F2 embryo-fetal parameters. Apremilast was detected in the milk of lactating mice at levels approximately 1.5-times that of simultaneously collected blood plasma samples at 1 and 6 hours. Apremilast levels were non-detectable in either milk or plasma 24 hours after drug administration.

4.4 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review of apremilast by Sheetal Agarwal, PhD for a detailed analysis of the pharmacokinetic and pharmacodynamic aspects related to this application.

4.4.1 Mechanism of Action

3,5'-Cyclic adenosine monophosphate (cAMP) serves as a second messenger system for a diverse number of by G-protein-linked receptor systems, including many of those found in immunocompetent cells. The breakdown of cAMP by the enzyme, phosphodiesterase 4 (PDE4), has been shown to cause immune cell activation and

release of proinflammatory cytokines including TNF-α, IL-17, IL-22, and IFN-$_{Y}$, therefore, inhibition of the enzyme would be expected to decrease PDE4-mediatied inflammation.

Apremilast is a new, orally available, small molecular inhibitor of PDE4 being developed for the treatment of psoriasis, psoriatic arthritis, and other chronic inflammatory diseases. The current application is submitted for the potential indication of the treatment of adults with active psoriatic arthritis.

4.4.2 Pharmacodynamics

The sponsor has conducted pharmacodynamic studies assessing the effects of apremilast on the inflammation associated with psoriasis and psoriatic arthritis. In psoriasis studies, apremilast treatment was associated with decreased dendritic cell and T cell infiltration within the epidermis and dermis of psoriatic skin lesions, decreased lesional skin epidermal thickness, and decreased whole blood TNF-α production following bacterial endotoxin challenge. Psoriatic arthritis subject treated with apremilast demonstrated decreased plasma concentrations of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, TNF-α, MMP-3, and ferritin, and an increase in von Willebrand Factor.

4.4.3 Pharmacokinetics

The clinical pharmacology studies determined apremilast to have a Cmax of 2.5 hours, $t_{1/2}$ of approximately 5-7 hours, and an average bioavailability of 70%. There was linear pharmacokinetics up to 50 mg BID or 80 mg QD with no accumulation of up to the 40 mg QD dosing. There was no food effect on absorption and the plasma protein binding was 68%.

Apremilast undergoes approximately 50% metabolism and is primarily eliminated as metabolites formed by CYP-mediated oxidative metabolism (CYP3A4>>CYP1A2/CYP2A6) with subsequent glucuronidation. The mean total urinary and fecal recovery of radioactive apremilast was 97% with mean contributions of 58% and 39% from urine and feces, respectively.

Apremilast did not inhibit CYP enzymes in vitro, suggesting that it is unlikely to inhibit metabolism of co-administrated CYP substrates. In vitro studies showed that apremilast did not induce the activity of CYP1A2, CP2C9, or CYPC19. Similarly, lower concentrations (1 and 10 µM) of apremilast had no effect on the enzyme activity of CYP3A4 and CYP2B6; however, at the highest concentration (100 µM) of apremilast tested, CYP3A4 and CYP2B6 enzymatic activity was increased by approximately 4- and 2- fold, respectively. This concentration of apremilast is greater than 100-fold higher than the steady state Cmax of an apremilast 30 mg BID dose, thus, it is unlikely that the coadministration of apremilast will result in clinically significant decreases in the exposure of CYP1A2, CYP2C9, CYP2C19, CYP3A4, or CYP2B6 substrates.

In vivo observation from animals and humans suggest that P-glycoprotein does not limit the oral absorption of apremilast, although in vitro data suggest that apremilast is a substrate and weak inhibitor of P-glycoprotein (IC50>50 μM). Furthermore, since apremilast is minimally excreted in unchanged form, P-glycoprotein does not appear to mediate an important role in apremilast excretion. Therefore, clinical drug-drug interactions are unlikely when apremilast is coadministered with a P-glycoprotein inhibitor.

The sponsor proposed an alternative apremilast dosing regimen of 30 mg QD for patients with severe renal impairment based on PK data from apremilast-treated subjects with renal impairment and subsequent PK simulations. The Division of Clinical Pharmacology agreed with the sponsor's proposed dosing regimen and recommended a modified titration scheme for patients with severe renal impairment, which can be found in Dr. Agarwal's review. Pharmacokinetic studies in apremilast-treated subjects with mild, moderate, and severe hepatic impairment determined that no dose adjustment is need in the group of patients.

5 Sources of Clinical Data

To date, there have been a total of 30 clinical studies conducted with apremilast: 16 Clinical Pharmacology studies and 14 Phase 2/3 studies.

Clinical Pharmacology Studies

The 16 Clinical Pharmacology studies conducted with apremilast were as follows:

- Nine, single-dose studies in healthy subjects evaluating PK, bioavailability, food effect, drug-drug interaction with ketoconazole and rifampin, and the effective of age, sex, and race
- Two single-dose studies were conducted in non-healthy subjects evaluating the effect of renal or hepatic impairment on PK
- Four multiple-dose studies in healthy subjects were conducted assessing PK, drug-drug interaction with oral contraceptives, and potential QTc prolongation
- A single multiple-dose study in subjects with PsA or RA was conducted to evaluate the potential for drug-drug interaction with MTX

The reader is referred to the Clinical Pharmacology review, by Sheetal Agarwal PhD, for an in depth analyses of the Clinical Pharmacology studies. All AEs reported from these studies are included in the overall apremilast safety database.

Clinical Phase 2/3 Studies

Of the 14 Phase 2/3 studies conducted with apremilast, 5 studies enrolled subjects with active PsA, 6 studies enrolled subjects with active psoriasis, and one study each was conducted in subjects with active RA, Behçet's disease, and asthma. Three Phase 3 studies are ongoing and remain blinded including one study in PsA (CC-10004-PSA-005) and two Phase 3 studies in psoriasis (PSOR-008, -009), consequently, data from these studies are not included in the overall safety assessment of apremilast except for reported deaths and expedited SAEs. As discussed below in Section 5.2, only four of the clinical trials enrolling subjects with PsA will be discussed and used in the assessment of efficacy for the proposed indication.

5.1 Tables of Studies/Clinical Trials

Table 2. Clinical Studies Used in the Efficacy Assessment of Apremilast

Study	Centers (n)	Subjects Enrolled (n)	Dosing[a]	Study Design	Primary Endpoint
Phase 2 Study					
PSA-001	38	204	PBO APR 20 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, APR 20, or APR 40. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Day 85.	ACR 20 @ Day 85
Phase 3 Studies-Completed					
PSA-002	83	504	PBO APR 20 BID APR 30 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, APR 20, or APR 30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Week 16.	ACR 20 @ Wk 16
PSA-003	84	488	PBO APR 20 BID APR 30 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, APR 20, or APR 30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Week 16.	ACR 20 @ Wk 16
PSA-004	78	505	PBO APR 20 BID APR 30 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, APR 20, or APR 30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Week 16.	ACR 20 @ Wk 16
Phase 3 Study-Ongoing					
PSA-005	96	528	PBO APR 20 BID APR 30 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, APR 20, or APR 30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Week 16.	ACR 20 @ Wk 16

Table 3. Clinical Studies Used in the Safety Assessment for Apremilast

Data Pool	Studies Included in Data Pool
PsA Phase 3 Data Pool	PsA: PSA-002, PSA-003, PSA-004
Apremilast Unblinded Data Pool	PsA: PSA-001, -002, -003, -004 RA: RA-002 PSOR: PSOR-001, -003, -004, -005LTE
Separate Apremilast Studies	Behcet's: BCT-001 Asthma: ASTH-001

5.2 Review Strategy

The sponsor has conducted a total of five studies with apremilast in subjects with PsA (Table 2). Assessment of the safety and efficacy of apremilast for treating patients with

active PsA is primarily based on the data derived from three nearly identically designed placebo-controlled Phase 3 studies: CC-10004-PSA-002 (PSA-002), CC-10004-PSA-003 (PSA-003), and CC-10004-PSA-004 (PSA-004; Table 2). These studies each enrolled approximately 500 subjects with active PsA who had an inadequate clinical response to DMARDs and/or biologic therapy. The individual designs of the studies are discussed in Section 5.3 and the overall efficacy and safety analyses of apremilast are discussed in Sections 6 and 7, respectively.

The Phase 2 study CC-10004-PSA-001 (PSA-001) was designed to assess the tolerability and efficacy of apremilast as either a single 40 mg daily dose or as a 20 mg dose given twice daily. The sponsor utilized the results from this study to select the dosing regimen used in their subsequent Phase 3 studies; however, since study PSA-001 did not assess the proposed apremilast dose of 30 mg twice daily, data from the study will not be used for the efficacy analysis but are included in the overall safety analysis.

Study CC-10004-PSA-005 (PSA-005) is an ongoing Phase 3 study that currently remains blinded. Consequently, data from this study are not included in the overall assessment of the efficacy and safety of apremilast except for inclusion of deaths and expedited SAEs.

Sources of data used for the safety review of apremilast are discussed in greater detail in Section 7.1.1, but in general, included all safety data from the sponsor's apremilast clinical development program with emphasis on the studies enrolling subjects with PsA and placebo-controlled studies enrolling patients with RA and psoriasis (Table 3).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Studies Included in the Assessment of Efficacy

5.3.1.1 PSA-001

Study PSA-001 was designed to assess the efficacy and tolerability of APR 20 mg BID vs. APR 40 mg QD in subjects with active PsA; however, the proposed apremilast dose of 30 mg BID was not assessed and consequently data from the study were not used for the efficacy analysis but were included in the overall safety analysis and in the sponsor's justification for dose selection in the subsequent Phase 3 studies. For that reason, the design and results of study PSA-001 will be discussed briefly here.

PSA-001 was a Phase 2, randomized, placebo-controlled, double-blind study designed to assess the tolerability and efficacy of apremilast as either a single 40 mg daily dose or as a 20 mg dose given twice daily in patients with active PsA. A total of 204 subjects

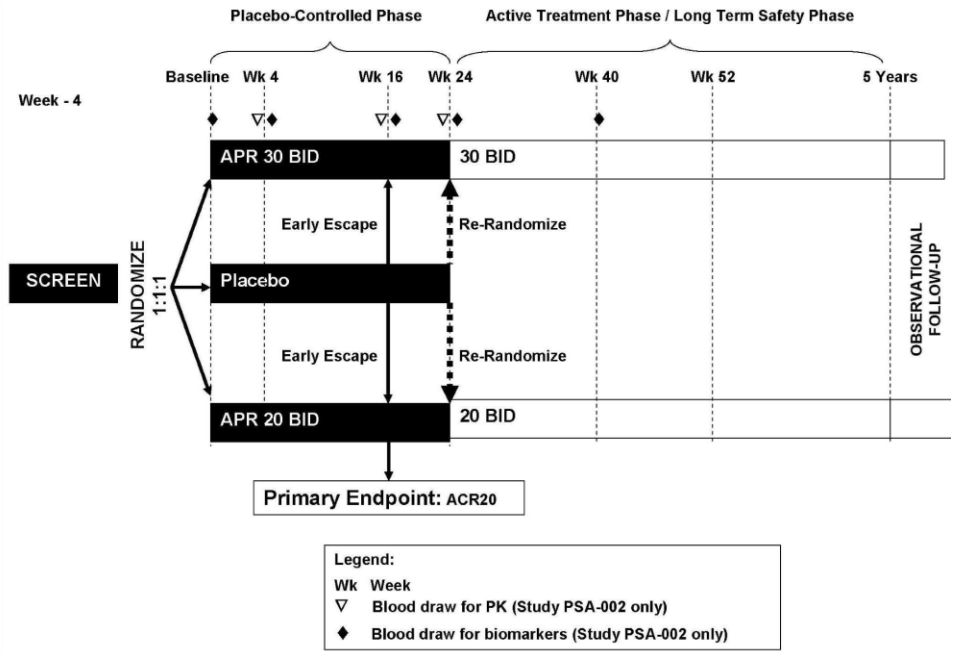
with active PsA were randomized in a 1:1:1 ratio to receive PBO, APR 20 BID, or APR 40 QD for 12 weeks. All subjects were subsequently treated for an additional 12 weeks with either APR 20 BID or APR 40 QD in a blinded manner. The primary efficacy endpoint was prespecified as the proportion of subjects achieving and ACR 20 response at Day85. A greater proportion of APR 40 mg QD- and APR 20 mg BID-treated subjects achieved an ACR 20 response at Day 85 compared to placebo-treated subjects, 36% and 44% vs. 12%, respectively. Assessment of the ACR 50 response demonstrated statistical significance for only the APR 20 mg BID dose versus the placebo treatment arm, 17% vs. 3%, respectively, although the clinical significance was minimal. Safety analyses were most notable for nausea, diarrhea, and headache, which were more common in subjects treated with the single APR 40 mg dose compared to the APR 20 mg twice-daily dose. The sponsor concluded from the data that the APR 20 mg BID represented the minimally effective dose for the treatment of PsA and that splitting the apremilast dose to twice daily was more advantageous compared to a single daily dose regarding gastrointestinal tolerability.

5.3.1.2 PSA-002, -003, -004

Results from studies PSA-002, -003, and -004 provided the primary data used for assessing the efficacy of apremilast in subjects with active PsA. The three studies were highly similar in design except for the difference 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 ≥3% body surface area (BSA). All studies were multicenter and enrolled patients from North America, Europe, Asia, and South Africa. Study PSA-002 began enrolling subjects on June 2, 2010 and the last subject completed the Week 24 visit on March 26, 2012. Study PSA-003 began enrolling subjects on September 27, 2010 and the last subject completed the Week 24 visit on July 4, 2012. Study PSA-004 began enrolling subjects on October 11, 2011 and the last subject completed the Week 24 visit on July 9, 2012. Final database locks occurred on June 21, 2012, July 26, 2012, and August 2012, respectively.

Studies PSA-002, -003, and -004 were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies (Figure 1). Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). To limit the gastrointestinal adverse reactions associated with PDE-4 inhibitors, apremilast dosing was dose-titrated in 10 mg/day increments over the first week of treatment, consequently, subjects in the APR 20 and APR30 treatment groups reached their targeted dose on Study Days 4 and 6, respectively. Apremilast blinding was maintained by providing doses in a blister card containing identical appearing tablets.

Figure 1. Overview of Studies PSA-002, -003, and -004



Eligible subjects were required to meet the Classification Criteria for Psoriatic Arthritis (CASPAR) and were allowed to continue baseline DMARDs (MTX, LEF, SSZ) during the placebo-controlled portion of the study. Enrollment of subjects who had failed previous treatment with a TNF inhibitor was limited to ≤10% of the total subjects enrolled. Treatment assignments were stratified based on DMARD use at baseline with ≥25 subjects in each study taking either LEF or SSZ. Specifically for study PSA-004, all subjects had to have ≥1 qualifying psoriasis lesion ≥2 cm in addition to active PsA and ≥60% of subjects enrolled in the study were to have ≥3% BSA involved with psoriasis at baseline. All studies required eligible subjects to have met the following major inclusion and exclusion criteria as follows:

5.3.1.2.1 Major Inclusion Criteria

- Males or females ≥18 years of age
- Documented diagnosis of PsA ≥6 months
- Met the Classification Criteria for Psoriatic Arthritis (CASPAR)
- ≥3 swollen AND ≥tender joints
- History of inadequate response to prior/current therapy with DMARDS including:
  - Therapeutic failure
  - Loss of insurance
  - Intolerance
  - Adverse effects

- "Other" reasons
- Subjects taking MTX (≤25 mg/week), LEF (≤20 mg/day), or SSZ (≤2 g/day), had to have been treated with the DMARD for ≥16 weeks and on stable doses for ≥4 weeks prior to screening and through Week 24
- Stable doses of oral corticosteroids (prednisone ≤10 mg/day or equivalent) were permitted if started ≥4 weeks prior to screening
- Subjects with active psoriasis were permitted to use low potency topical corticosteroids, coal tar shampoo, and non medicated skin emollient as background therapy. Subjects must not have used these treatments ≤24 hours prior to clinic visit.
- Stable NSAID or narcotic analgesics were permitted if started ≥2 weeks prior to screening and continued through Week 24
- Met following laboratory criteria:
  - WBC ≥3 x 10^9/L and <14 x 10^9/L
  - Platelet count ≥100 x 10^9/L
  - Serum creatinine ≤1.5 mg/dL
  - AST and ALT ≤2x ULN
  - Total bilirubin ≤2 mg/dL
  - Hemoglobin ≥9 g/dL
  - Hemoglobin A1c ≤9%
- Male and female patients were required to use acceptable contraception method(s)

5.3.1.2.2 Major Exclusion Criteria

- History of clinically significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease
- Any condition, including the presence of laboratory abnormalities that placed the subject at unacceptable risk or confounded the ability to interpret data from the study
- Abnormal ECG at screening
- Pregnant or breastfeeding female
- History of chronic infection including patients with hepatitis B, hepatitis C, HIV, or history of incompletely treated tuberculosis
- Ongoing bacterial, viral, or fungal infection ≤4 weeks prior to screening
- Abnormal chest radiograph
- History of malignancy
- Major surgery ≤8 weeks prior to screening
- Erythrodermic, guttate, or generalized pustular psoriasis
- Topical therapy for psoriasis except as noted in the inclusion criteria above
- Rheumatic/autoimmune disease other than PsA

- Use of calcineurin inhibitors, corticosteroids, small molecular DMARDS (other than those listed in the inclusion criteria), oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, tacrolimus, azathioprine, fumaric acid esters
- Use of adalimumab, etanercept, golimumab, infliximab, certolizumab, or tocilizumab ≤12 weeks of randomization
- Use of alefacept or ustekinumab ≤24 weeks of randomization
- Therapeutic failure of >3 agents for PsA, or >1 biologic TNF inhibitor

At Week 16, all subjects whose tender and swollen joint counts had not improved by ≥20% were required to enter early escape. Placebo-treated subjects were re-randomized 1:1 to receive blinded treatment with either APR20 or APR30 utilizing the dose-titration schedule until the target dose was achieved. Apremilast-treated patients entering early escape were continued in a blinded manner to continue receiving the same dosage of apremilast to which they were originally randomized. All subjects who entered early escape received identical appearing blister cards of study drug.

At Week 24, all subjects originally assigned to the placebo group were re-randomized 1:1 to either APR20 or APR30 treatment arms. All subjects who were originally assigned to an apremilast treatment arm remained in their assigned dose groups. All subjects were continued on their assigned dose of apremilast as a long-term extension study, which remains ongoing.

A total of 14,937 subjects were randomized across studies PSA-002 (n=504), PSA-003 (n=484), and PSA-004 (n=505). The full analysis set (FAS) included 493 subjects as four subjects from study PSA-003 were randomized in error but were not treated; consequently they were not included in the FAS. In general the baseline demographics and disease characteristics were similar between treatment arms and between studies. Similarly, subject disposition during the placebo-controlled periods was comparable across the three studies and across treatment groups regarding the proportion of subjects completing through Week 16.

The primary efficacy endpoint used for all three studies was the proportion of subjects achieving a ≥20% improvement of the American College of Rheumatology (ACR) response criteria at Week 16. The ACR 20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all the three studies was the assessment of apremilast on physical function as measured by the change from baseline in HAQ-DI score at Week 16.

Statistical analyses, using a two-sided 0.05 level of significance, were conducted on all randomized subjects using Cochran-Mantel-Haenszel (CMH) tests for categorical endpoints and analysis of covariance (ANCOVA) for continuous endpoints. The ANCOVA included baseline reading as a covariate, and both the CMH and ANCOVA

tests controlled for baseline DMARD usage. Additionally, the statistical analyses for study PSA-004 controlled for ≥ 3% body surface area with psoriasis at baseline.

Control of Type I error within each endpoint was maintained using the Hochberg procedure using pairwise comparisons between APR 30 vs. placebo treatment arms and between APR 20 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. Of note, the use of LOCF for missing continuous data contradicts the Agency's pre-submission communications stating that LOCF should not be applied as the primary missing data imputation for continuous variables.

While analyses of the primary and major secondary endpoints were statistically valid, a large number of proposed claims were based on (b) (4)

Claims of effectiveness for secondary endpoints at Week 24 were further weakened due to the majority of patients in each study having discontinued their originally assigned treatment group after Week 16. In fact, the majority of subjects randomized to the placebo treatment arm had entered early escape at Week 16 and by Week 24 approximately 15% of subjects had withdrawn from each randomized treatment arm. Additionally, as discussed above, (b) (4)

5.3.2 Clinical Studies used for the Assessment of Safety

The emphasis for the safety assessment of apremilast is primarily focused on the three PsA Phase 3 trials (PSA-002, -003, and -004). Additional safety data is provided by pooled data from all Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, or RA (Table 3). With the exception of studies PSOR-001 and PSOR-04, the Phase 2/3 clinical trials were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast compared to placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. In contrast, data from the clinical pharmacology studies and the clinical studies for Behçet's disease and asthma were not included in the safety analysis given the differences in the subject population and underlying disease pathogenesis; however, any deaths and/or reported SAEs from these studies were reviewed and are included in the overall analysis of the risk-benefit assessment of apremilast. As discussed in greater detail in Section 7, safety data from studies PSA-002, -003, and -004 were analyzed separately as well as being included in the overall placebo-controlled data that included the aforementioned nine clinical studies.

The safety population included all subjects who were randomized and received ≥1 dose of study drug. These subjects were included in the treatment group corresponding to the study dose they actually received. Apremilast-treated subjects who received two different doses of apremilast were included in the apremilast dose group based on the dose first received. The reader is referred to Section 7.1 for further discussion of the data pools used for safety analyses.

Safety analyses included deaths, SAEs, AEs, laboratory data, vital signs, and ECG evaluation. Adverse events were coded according to MedDRA, and were deemed a treatment-related AE if it occurred on or after the date of the first dose of study drug and ≤28 days after the last dose of study drug.

6 Review of Efficacy

Efficacy Summary

Studies PSA-002, -003, and -004 were highly similar in design and provided the primary data used for assessing the efficacy of apremilast in subjects with active PsA. The studies were designed as 24-week, randomized, placebo-controlled, double-blind, parallel group, multicenter studies. Subjects were randomized in a 1:1:1 ratio to receive oral treatment with apremilast 20 mg BID (APR20), apremilast 30 mg BID (APR30), or matching placebo (PBO). The sponsor is only seeking approval of the apremilast 30 mg BID dosing. The primary efficacy endpoint used by all three studies was the proportion of subjects achieving a ≥20% improvement of the American College of Rheumatology (ACR) response criteria at Week 16. The ACR 20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all the three studies was the assessment of apremilast on physical function as measured by the change from baseline in HAQ-DI score at Week 16.

Analysis of the primary endpoint for studies PSA-002, -003, and -004 demonstrated a statistically significant greater proportion of APR30-treated subjects (38%, 32%, and 41%, respectively) achieved an ACR20 response compared to placebo-treated subjects (19%, 19%, and 18%, respectively). Additionally, APR30-treated subjects demonstrated a greater change in HAQ-DI from baseline vs. placebo-treated subjects for studies PSA-002, -003, and -004 (-0.24 vs. -0.09; -0.19 vs. -0.05; and -0.19 vs. -0.07, respectively). Secondary endpoints were supportive of the primary endpoint and major secondary endpoint analyses.

Efficacy results generally supported a greater numerical advantage for the APR30 treatment arm compared to the APR20 treatment arm but there were limited statistically significant analyses to support the conclusion that APR30 was superior to APR20. In light of the safety analysis which demonstrated that both doses of apremilast were relatively well-tolerated and similar in their adverse event profile, approval of the higher dose, apremilast 30 mg BID, is reasonable.

Overall, the data support the claim that apremilast 30 mg BID therapy effectively treats adult patients with active PsA.

6.1 Indication

The sponsor has proposed the use of apremilast 30 mg BID for the treatment of adult patients with active PsA.

6.1.1 Methods

As discussed in Section 5.3, data from studies PSA-002, -003, and -004 were used to assess the efficacy of apremilast for treating patients with active PsA. The three well-controlled studies were highly similar in design and were adequately conducted to provide sufficient evidence to demonstrate a clinically meaningful benefit of apremilast in subjects with active PsA who had an inadequate response to standard therapy.

6.1.2 Demographics

As shown in Table 4, subjects' baseline demographics were similar between treatment arms and individual studies. Almost equal proportions of male and female subjects were enrolled with an average age of 50 years and BMI of approximately 30. The majority of subjects (≥90%) were classified as White and participated at study centers located in North America and Europe.

Table 4. Baseline Demographics for Subjects Enrolled in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Age (mean years ± SD)	51 ± 12	49 ± 11	51 ± 12	51 ± 11	51 ± 12	51 ± 11	50 ± 12	50 ± 12	50 ± 11
18 to < 40 years; n (%)	30 (18)	34 (20)	30 (18)	22 (14)	30 (18)	30 (19)	36 (21)	35 (21)	30 (18)
40 to < 65 years; n (%)	119 (71)	123 (73)	116 (69)	121 (76)	119 (73)	114 (70)	119 (70)	117 (69)	122 (73)
≥ 65 years; n (%)	19 (11)	11 (7)	22 (13)	16 9100	14 99)	18 (11)	14 (8)	17 (10)	15 (9)
Sex (female); n (%)	80 (48)	83 (49)	92 (55)	85 (54)	95 (58)	95 (59)	91 (54)	90 (53)	88 (53)
Race; n (%)									
White	153 (91)	150 (89)	152 (91)	152 (96)	151 (93)	157 (97)	158 (94)	161 (95)	163 (98)
Asian	8 (5)	8 (5)	8 (5)	3 (2)	9 (6)	1 (1)	7 (4)	6 (4)	2 (1)
Black	0	2 (1)	0	2 (1)	1 (1)	1 (1)	2 (1)	0	0
Other	7 (4)	8 (5)	8 (5)	1 (1)	2 91)	3 (2)	1 (1)	2 91)	2 (1)
Geographic Region; n (%)									
North America	81 (48)	73 (44)	69 (41)	35 (22)	38 (23)	43 (27)	48 (28)	58 (34)	58 (35)
USA	48 (29)	44 (26)	43 (26)	18 (11)	27 (17)	30 (19)	40 (24)	48 (28)	42 (25)
Europe	39 (23)	41 (24)	42 (25)	106 (67)	103 (63)	101 (62)	75 (44)	32 (19)	31 (19)
Rest of World	48 (29)	52 (32)	57 (34)	18 (11)	22 (14)	18 (11)	46 (27)	32 (19)	31 (19)
Weight (mean kg ± SD)	90 ± 22	89 ± 21	87 ± 20	85 ± 20	83 ± 22	83 ± 19	84 ± 20	86 ± 20	84 ± 20
BMI Category; n (%)									
Mean kg/m² ± SD	31 ± 7	31 ± 7	31 ± 6	30 ± 6	29 ± 7	29 ± 6	30 ± 6	30 ± 6	29 ± 6
<25 kg/m²	30 (18)	27 (16)	28 (17)	41 (26)	46 (28)	45 (28)	41 (24)	38 (23)	43 (26)
25 to < 30 kg/m²	47 (28)	67 (40)	57 (34)	45 (28)	54 (33)	55 (34)	60 (36)	53 931)	58 (35)
30 to < 35 kg/m²	49 (29)	35 (21)	41 (24)	43 (27)	35 (22)	36 (22)	33 (20)	43 (25)	36 (22)
35 to < 40 kg/m²	24 (14)	21 (13)	32 (19)	20 (13)	15 (9)	17 (11)	22 (13)	27 (16)	20 (12)
≥40 kg/m²	18 (11)	18 (11)	10 (6)	10 (6)	12 (7)	9 (6)	12 (7)	8 (50	10 (6)

Overall, subjects' baseline disease characteristics and background PsA-related therapy were similar between individual treatment arms and studies (Table 4 and Table 5, respectively). On average, subjects who entered the study reported approximately seven years of active PsA with 9 swollen joints, 16 tender joints, and an average HAQ-DI score of 1.2u. Not surprisingly, almost all subjects carried a diagnosis of psoriasis with an approximately equal proportion of subjects having <3% or ≥3% involvement of body surface area.

Table 5. Baseline Disease Characteristics for Subjects Enrolled in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Duration of PsA; mean years ± SD	7 ± 7	7 ± 7	8 ± 8	8 ± 8	8 ± 9	7 ± 8	7 ± 6	8 ± 8	8 ± 8
PsA Subtype; n (%)									
Symmetric Polyarthritis	104 (62)	106 (63)	110 (66)	101 (64)	109 (67)	101 (62)	93 (55)	104 (62	98 (59)
Asymmetrical Polyarthritis	45 (27)	41 (24)	45 (27	49 (31)	43 (26)	42 (26)	44 (26)	43 (25)	49 (29)
DIP Involvement	14 (8)	14 (8)	11 (7)	4 (3)	7 (4)	7 (4)	16 (10)	10 (6)	10 (6)
Arthritis Mutilans	2 (1)	4 (2)	1 (1)	3 (2)	2 (1)	7 (4)	13 (8)	4 (2)	4 (2)
Predominant Spondylitis	3 (2)	3 (2)	1 (1)	1 (1)	2 (1)	5 (3)	3 (2)	8 (5)	6 (4)
Psoriasis (+); n (%)	168 (100)	167 (99)	166 (99)	157 (99)	163 (100)	159 (98)	169 (100)	169 (100)	167 (100)
Extent of Psoriasis; n (%)									
<3% BSA involvement	100 (60)	91 (54)	86 (49)	85 (54)	83 (51)	85 (53)	80 (47)	78 (46)	77 (46)
≥3% BSA involvement	68 (40)	77 (46)	82 (51)	74 (46)	80 (49)	77 (47)	89 (53)	91 (54)	90 (54)
Baseline PASI score; mean ± SD	9.1 ± 9.5	7.4 ± 8.7	9.2 ± 9.7	8.6 ± 10	7.4 ± 6.5	7.8 ± 7.3	7.6 ± 7.2	7.6 ± 5.2	7.9 ± 6.2
Tender Joint Count; median (range)	20 (3-78)	17 (3-70)	20 (3-78)	13 (3-66)	15 (3-78)	16 (3-78)	13 (3-78)	15 (3-78)	18 (3-76)
Swollen Joint Count; median (range)	10 (3-56)	9 (3-58)	12 (3-47)	7 (3-41)	8 (3-56)	8 (3-55)	8 (3-48)	8 (3-52)	9 (3-47)
Patient PA (VAS) ; median (range)	64 (5-99)	58 (0-99)	59 (3-100)	56 (13-100)	61 (4-99)	60 (0-98)	57 (7-99)	57 (3-99)	60 (1-99)
Patient's GA; median (range)	62 (6-100)	58 (1-100)	57 (1-98)	55 (3-99)	59 (6-100)	57 (1-98)	56 (3-99)	55 (5-99)	60 (0-100)
Physician's GA; median (range)	57 (6-95)	57 (0-97)	57 (10-96)	54 (14-92)	54 (7-93)	55 (15-97)	51 (11-100)	57 (3-98)	58 (19-95)
HAQ-DI score; median (range)	1.3 (0-2.8)	1.1 (0-2.9)	1.3 (0-2.8)	1.3 (0-2.5)	1.1 (0-2.6)	1.3 (0-2.8)	1.3 (0-2.6)	1.1 (0-2.6)	1.1 (0-2.9)
CRP (mg/dL); median (range)	0.5 (0-8.1)	0.5 (0-13.8)	0.5 (0-7.9)	0.6 (0-11.5)	0.4 (0-24)	0.4 (0-6.6)	0.4 (0-7.1)	0.4 (0-8.7)	0.4 (0-13.2)

Greater than 80% of all enrolled subjects had a history of treatment with MTX and approximately 20% of patients had been treated with a TNF inhibitor. At study baseline, an estimated 70% of subjects were receiving standard doses of background DMARDs (MTX 15 mg/week, LEF 20 mg/day, or SSZ 2 g/day) and NSAIDs (Table 6). A slightly higher percentage of subjects randomized to the APR20 treatment arms in all three studies were receiving oral corticosteroids compared to subjects randomized to the

placebo or APR30 treatment arms; however, this difference is unlikely to affect the overall results or interpretability of the data.

Table 6. Concomitant Medications of Subjects Enrolled in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Any Prior DMARDs used[a]; n (%)	161 (96)	166 (99)	165 (98)	158 (99)	163 (100)	157 (97)	169 (100)	168 (99)	167 (100)
DMARDs used[a]; n (%)									
Methotrexate	140 (83)	141 (84)	140 (83)	138 (87)	141 (87)	137 (85)	151 (89)	139 (82)	142 (85)
Sulfasalazine	43 (26)	51 (30)	43 (26)	62 (39)	62 (38)	47 (29)	39 (23)	30 (18)	46 (28)
Leflunomide	22 (13)	23 (14)	26 (16)	33 (21)	32 (20)	34 (21)	20 (12)	27 (16)	20 (12)
Other[b]	57 (34)	52 931)	59 (35)	31 (20)	44 (27)	47 (29)	62 (37)	68 (40)	56 (34)
Prior Biologic Use[a]; n (%)	41 (24)	37 (22)	41 (24)	23 (15)	28 (17)	23 (14)	48 (28)	50 (30)	43 (26)
Biologic used[a]; n (%)									
TNFi	39 (23)	33 (20)	37 (22)	20 (13)	27 (17)	22 (14)	45 (27)	48 (28)	39 (23)
non-TNFi	9 (5)	9 (5)	8 (5)	4 (3)	6 (4)	7 (4)	8 (5)	11 97)	7 (4)
Prior Biologic Failure; n (%)	19 (11)	14 (8)	14 (8)	8 (5)	10 (6)	7 (4)	12 (7)	18 (11)	14 (8)
Concomitant PsA Treatment at Baseline									
DMARD use; n (%)	110 (66)	111 (66)	106 (63)	113 (71)	114 (70)	113 (70)	101 (60)	104 (62)	101 (61)
Oral Corticosteroids; n (%)	12 (7)	25 (15)	16 (10)	20 (13)	36 (22)	25 (15)	16 (10)	34 (20)	23 (14)
NSAIDs; n (%)	118 (70)	123 (73)	120 (71)	108 (68)	115 (71)	114 (70)	115 (68)	121 (72)	121 (73)
Opioids/Analgesics; n (%)	27 (16)	32 (19)	25 (15)	22 (14)	22 914)	22 (14)	18 (11)	20 (12)	24 (14)

In summary, the baseline demographics and disease characteristics of the enrolled subjects are well balanced between treatment arms and individual studies, and in general, are representative a typical US patient with PsA.

6.1.3 Subject Disposition

Approximately equal numbers of subjects were enrolled in the three studies with similar proportions of subject disposition within treatment arms. A greater number of placebo-treated subjects entered early escape at Week 16 compared to APR-treated subjects (Table 7). Within the same time period, a slightly higher number of APR30-treated subjects in studies PSA-002 and -003 discontinued the study due to an AE compared to subjects randomized to the APR20 or placebo treatment arms. Discontinuation due to lack of efficacy was similar among treatment arms. One subject randomized to the APR20 treatment arm died during study PSA-002.

Table 7. Subject Disposition at Week 16 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Discontinued prior to Week 16	10 (6)	10 (6)	14 (8)	11 (7)	12 (7)	13 (8)	13 (8)	12 (7)	11 (7)
Reason for Discontinuation									
Adverse event	5 (3)	5 (3)	9 (5)	3 (2)	4 (3)	11 (7)	6 (4)	6 (4)	5 (3)
Lack of efficacy	3 (2)	2 (1)	2 (1)	2 (1)	2 (1)	0	2 (1)	3 (2)	2 (1)
Noncompliance	0	0	1 (1)	0	0	0	0	0	0
Subject-initiated withdrawal	1 (1)	1 (1)	2 (1)	5 (3)	5 (3)	1 (1)	2 (1)	3 (2)	1 (1)
Death	0	1 (1)	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1 (1)	0	0	0	0	1 (1)
Protocol violation	1 (1)	0	0	0	0	1 (1)	0	0	1 (1)
Other reason	0	1 (1)	0	0	1 (1)	0	3 (2)	0	1 (1)
Entered Early Escaped at Week 16	107 (64)	78 (46)	58 (35)	88 (55)	59 (36)	64 (40)	97 (57)	76 (45)	53 (32)

Subject disposition at Week 24 was similar in proportion to that observed at Week 16 with a slightly higher number of APR30-treated subjects in studies PSA-002 and -003 discontinuing the study due to an AE compared to subjects randomized to the APR20 or placebo treatment arms (Table 8). Discontinuation due to lack of efficacy remained similar between treatment arms.

Table 8. Subject Disposition at Week 24 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Discontinued prior to Week 24	18 (11)	22 (13)	20 (12)	16 (10)	20 (12)	120 (12)	23 (14)	22 (13)	122 (13)
Reason for Discontinuation									
Adverse event	11 (7)	8 (5)	10 (6)	4 (3)	5 (3)	12 (7)	10 (6)	12 (7)	8 (5)
Lack of efficacy	4 (2)	5 (3)	4 (2)	3 (2)	2 (1)	2 (1)	6 (4)	5 (3)	7 (4)
Noncompliance	0	1 (1)	2 (1)	0	0	0	0	0	0
Subject-initiated withdrawal	2 (1)	5 (3)	3 (2)	7 (4)	9 (6)	3 (2)	3 (2)	4 (2)	1 (1)
Death	0	1 (1)	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1 (1)	1 (1)	2 (1)	1 (1)	0	3 (2)
Protocol violation	1 (1)	0	0	0	1 (1)	1 (1)	0	0	1 (1)
Other reason	0	2 (1)	1 (1)	1 (1)	1 (1)	0	3 (2)	1 (1)	2 (1)
Entered Early Escaped at Week 16	107 (64)	78 (46)	58 (35)	88 (55)	59 (36)	64 (40)	97 (57)	76 (45)	53 (32)

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 General Discussion of Choice of Major Endpoints

Psoriatic arthritis is a systemic, chronic, inflammatory autoimmune disease that primarily involves the synovium of both the appendicular and axial skeleton. The inflammation of the synovium results in joint pain and swelling, and in a significant proportion of subjects, bone erosions within the joint resulting in further joint dysfunction and malformation. Together these processes lead to a decreased physical functioning in the patient and a decrease in the health related quality of life. Consequently, endpoints for a clinical trial should be chosen that assess these clinical issues associated with PsA. Given the chronicity of PsA, an endpoint that captures a change in the signs and symptoms should be evaluated for a minimum of 12 weeks to demonstrate durability of the drug effect. Lastly, it is important that a sponsor also demonstrate evidence of improved functional ability/quality of life based on the study data.

The proportion of subjects achieving an ACR 20 at Week 16 was used as the primary endpoint for improvement in signs and symptoms. The ACR core data set was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts. The modified ACR response criteria consists of 7 components:

- Swollen joint count (76 joints)
- Tender joint count (78 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (AS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR 20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3/5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR 20 occurred at Week 16 in all studies.

The change from baseline in the disability index of the Health Assessment Questionnaire (HAQ-DI) at Week 16 was used as a major secondary endpoint for the assessment of improvement in physical function. The HAQ is a standardized disability questionnaire developed for use in RA and PsA with a scoring range between 0 and 3. A high HAQ score has been shown to be a strong predictor of morbidity and mortality in RA, and low HAQ scores are predictive of better outcomes.

Both study endpoints have been validated and used in previous approvals of other drugs indicated for patients with active PsA and are generally accepted by the Agency. The ACR criteria used for assessing disease improvement include several subjective

measurements that are susceptible to investigator bias and therefore blinding of assessors to treatment assignment was instituted in the design of the apremilast PsA studies. Overall, these endpoints provide a reasonable assessment of meaningful clinical efficacy.

6.1.4.2 Primary Endpoint Analysis for Studies PSA-002, -003, -004

All three PsA Phase 3 studies demonstrated a statistically significant difference between placebo and the individual apremilast treatment arms, i.e., APR20 and APR30 (Table 9). The average treatment effect sizes for the APR20 and APR30 treatment arms were 13% and 18%, respectively.

Table 9. Primary Efficacy Analysis: Proportion of Subjects Achieving ACR20 at Week 16 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR 20 BID N=168	APR 30 BID N=168	PBO N=159	APR 20 BID N=163	APR 30 BID N=162	PBO N=169	APR 20 BID N=169	APR 30 BID N=167
Proportion of Subjects Achieving ACR 20 at Week 16; n (%)	32 (19)	51 (30)	64 (38)	30 (19)	61 (37)	52 (32)	31 (18)	48 (28)	68 (41)
Treatment Effect Size[a], %	-	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. APR 20	-	-	0.14	-	-	0.31	-	-	0.02

Although both apremilast treatment arms demonstrated a significant improvement in signs and symptoms compared to placebo, the sponsor is proposing approval for only the apremilast 30 mg BID dosing. As detailed in the Biometrics review by Robert Abugov, PhD, there was not a clear advantage of the apremilast 30 mg BID dose over the apremilast 20 mg BID dose as only study PSA-004 demonstrated a statistically significant advantage of APR 30 compared to APR 20. In fact, study PSA-003 actually demonstrated a numerical advantage of the APR 20 treatment arm compared to APR 30.

These analyses demonstrate a clinical benefit in the improvement of the signs and symptoms of subjects with active PsA who are treated with apremilast compared to subjects treated with placebo. Additionally, apremilast-treated subjects demonstrated greater improvements in all ACR components compared to placebo-treated subjects at Week 16 (data not shown), lending further support of the efficacy of apremilast in inducing ACR20 responses in subjects with active PsA. While there appears to be a small numerical advantage of the apremilast 30 mg BID dose, the data are not so robust that this dose is clearly superior, statistically or clinically, to apremilast 20 mg BID;

however, given the overall safety profile of apremilast (Section 7), the higher 30 mg BID dose appears to be acceptable.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Major Secondary Endpoint: Mean Change in HAQ-DI from Baseline at Week 16

All three PsA Phase 3 studies demonstrated a statistically significant difference between APR30-treated subjects compared to placebo-treated subjects for change from baseline HAQ-DI at Week 16 (Table 10). While only studies PSA-002 and -003 demonstrated a statistically significant difference for APR20-treated subjects compared to placebo-treated subjects. Although not statistically different, the APR30 treatment arm demonstrated larger numerical differences in all three studies compared to the APR20 treatment arm.

Table 10. 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	APR 20 BID N=163	APR 30 BID N=159	PBO N=153	APR 20 BID N=159	APR 30 BID N=154	PBO N=163	APR 20 BID N=163	APR 30 BID N=160
Mean Change from Baseline	-0.09	-0.2	-0.24	-0.05	-0.16	-0.19	-0.07	-0.13	-0.19
Treatment Effect Size[a]	-	-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. APR 20	-	-	0.36	-	-	0.45	-	-	0.2

6.1.5.2 Clinically Important Secondary Endpoints

(b) (4)

Despite these shortcomings, this review will include the sponsor's analyses of the clinically relative secondary endpoints in support of the primary endpoint, which was statistically valid and clinically meaningful. The reader is referred to the statistical review by Robert Abugov, PhD of the Division of Bioinformatics for a detailed statistical analysis of the submission's efficacy data.

Clinically relevant secondary endpoints that will be included in this review include ACR 20/50/70 responses at Weeks 16 and 24; and change from baseline HAQ-DI at Week16. Extensive review of the secondary endpoints is discussed in Dr Abugov's statistical review.

6.1.5.2.1 ACR Responses and Components

Table 11summarizes the proportion of subjects achieving an ACR 20/50/70 response for the three treatment groups at Weeks 16 and 24 for the pooled analysis from the three PsA studies. After carrying forward early escape failures at week 16, the ACR 20/50/70 response rates a Weeks 16 and 24 for the comparison of APR30 placebo were statistically significant in all three studies. The average difference between A30 and placebo was 16%. In general, these data support the primary endpoint by demonstrating a treatment-effect in a greater proportion of apremilast-treated subjects compared to placebo-treated subjects at Weeks 16 and 24 for ACR 20/50/70 responses.

Table 11. Proportion of Subjects Achieving an ACR 20/50/70 at Weeks 16 and 24 for the Pooled Analysis for PsA Phase 3 Studies

	PBO N=496	APR20 BID N=500	APR30 BID N=497
Endpoint Visit	Response n (%)	Response n (%)	Response n (%)
ACR 20			
Week 16	93 (19)	160 (32)	184 (37)
Week 24	73 (15)	139 (28)	151 (30)
ACR 50			
Week 16	32 (7)	71 (14)	69 (14)
Week 24	34 (7)	70 (14)	78 (16)
ACR 70			
Week 16	7 (1)	24 (5)	15 (3)
Week 24	12 (2)	25 (5)	30 (6)

Figure 2 and Figure 3 illustrate the median percent change from baseline in ACR component scores at Weeks 15 and 24, respectively. These data demonstrate a treatment and overall dose effect for all ACR components. Importantly, these figures demonstrate that the data used for analyzing the proportion of ACR20 responders was

not driven by any single component and that apremilast's was broadly effective across all ACR components.

Figure 2. Median Percent Change from Baseline n ACR Component Scores at Weeks 16 for the Pooled Analysis for PsA Phase 3 Studies

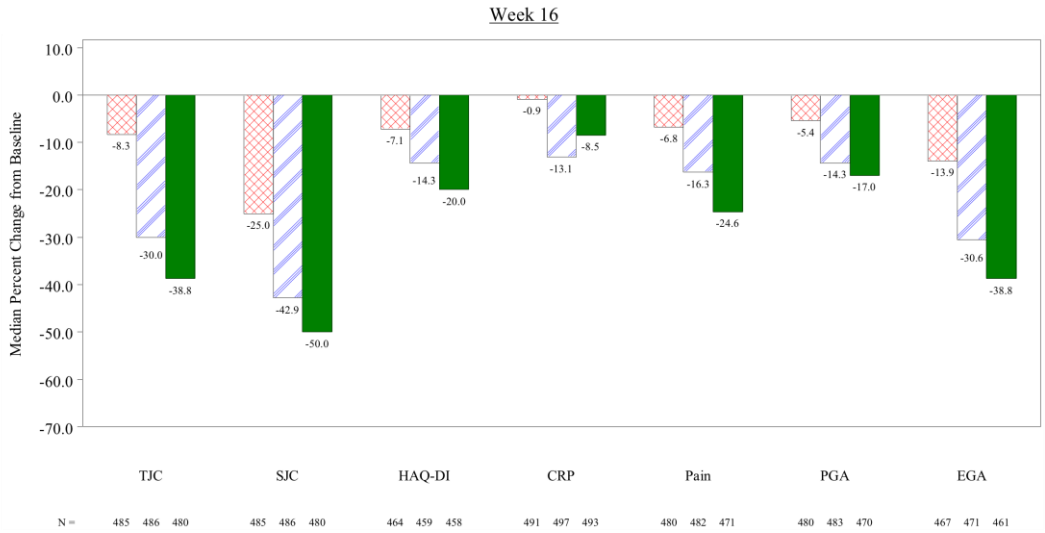
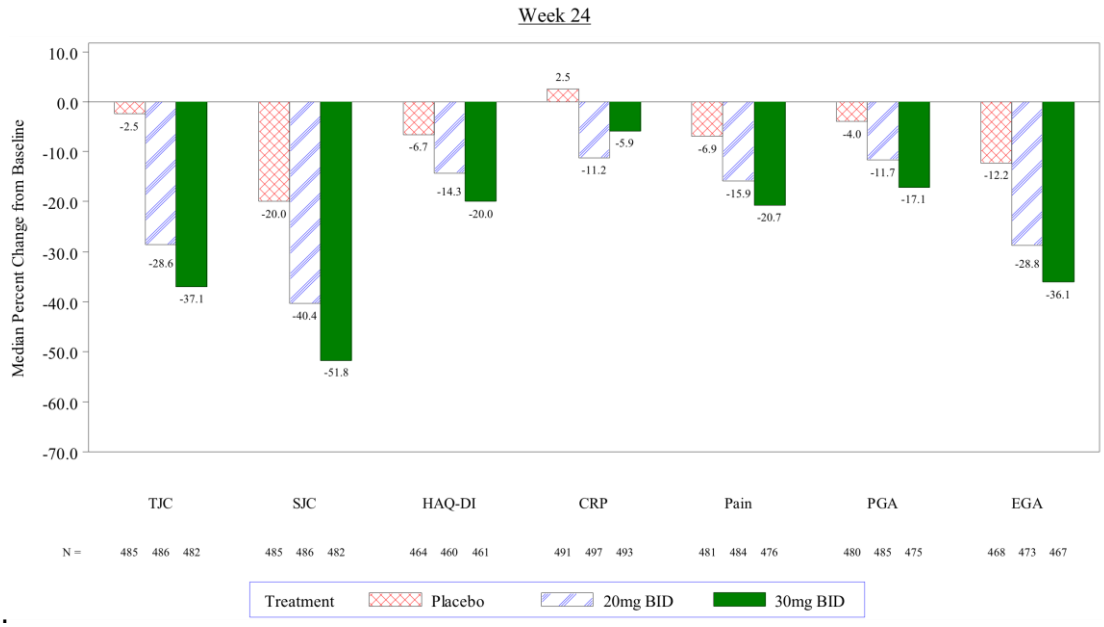


Figure 3. Median Percent Change from Baseline n ACR Component Scores at Weeks 24 for the Pooled Analysis for PsA Phase 3 Studies



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6.1.5.2.2 Change from Baseline in HAQ-DI at Week 24

Statistical analyses for testing the change from baseline in HAQ-DI at week 24 were conducted on observed data rather than LOCF data (Table 12). The differences between the APR30 and placebo groups were statistically significant in one out of three studies

Table 12. Change in HAQ-DI at Week 24 for PsA Phase 3 Studies

Study	Percent Response		
	PBO	APR20	APR30
PSA-002 change, (n)	-0.2 (154)	-0.3 (147)	-0.3 (146)*
PSA-003 change, (n)	-0.2 (142)	-0.3 (145)	-0.2 (141)
PSA-004 change, (n)	-0.2 (146)	-0.2 (146)	-0.3 (147)

6.1.6 Other Endpoints

The reader is referred to Dr. Abugov's statistical review for a detailed analysis of additional endpoints.

6.1.7 Subpopulations

The reader is referred to Dr. Abugov's statistical review for a detailed analysis of additional endpoints.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The reader is referred to Dr. Abugov's statistical review for a detailed analysis of dose selection.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The reader is referred to Dr. Abugov's statistical review for a discussion of persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

The reader is referred to Dr. Abugov's statistical review for a detailed discussion of additional efficacy issues and analyses.

7 Review of Safety

Safety Summary

A total of 2401 subjects have received apremilast in Phase 2 and 3 clinical studies for the treatment of PsA, PSOR, and RA in doses ranging from 10 mg BID to 30 mg BID. A total of 672 subjects included in the Apremilast Unblinded Data Pool have received apremilast 30 mg BID, the proposed dose, for at least 24 weeks, and 269 subjects have received apremilast 30 mg BID for at least 48 weeks.

At total of 721 subjects enrolled in the PsA studies received apremilast 30 mg BID with 527 subjects treated for at least 24 weeks and 183 subjects treated for at least 48 weeks. Review of the baseline demographic and disease characteristics demonstrated that subjects enrolled in the apremilast PsA studies were representative of patients in the general US population with the disease. The studies enrolled almost equal proportions of male and female subjects who on average were White (>90%) and middle aged (median age of 51 years). Subjects reported a mean duration of PsA since diagnosis of 7.5 years and had a history of receiving treatment with small molecular DMARDs, including 22% of subjects who had received previous therapy with a biologic agent. Comorbid conditions and concomitant medications were similar across treatment arms.

There were a total of 6 deaths reported in the broader apremilast development program with one death occurring in the PsA studies and the remaining five deaths having been reported during the psoriasis studies. Two of the deaths were apparent suicides (one subject each from the placebo and apremilast treatment arms), which was concerning since the PDE4-inhibitor roflumilast has a warning included in its product labeling concerning the potential for increased psychiatric events including depression and suicidal behavior. A thorough review of psychiatric adverse events in the apremilast program was performed including a consultation from the Division of Psychiatric Products. Review of the data concluded that the current data submitted in the application does not suggest an increased risk of suicidal behavior in patients treated with apremilast.

In the PsA Phase 3 studies, serious adverse events occurred in approximately equal frequencies between placebo-, APR20-, and APR30-treated subjects. Safety analyses did not suggest a clinically important difference in the type of overall rate of SAEs between apremilast-treated subjects and subjects treated with placebo.

The frequency of all AEs between the APR20 and APR30 treatment arms were generally comparable. The most frequently reported adverse events (AEs) were diarrhea, nausea, and headache, all of which increased in a treatment- and dose-dependent manner. The majority (>96%) of AEs were reported as mild to moderate in

severity. The highest incidence of diarrhea, nausea, and headache events occurred within the first 14 days of initiating apremilast therapy and reduced substantially after 30 days. Upper respiratory tract infections were also reported in > 5% of subjects and occurred more frequently in subjects receiving apremilast than in those receiving placebo. Most of these infections were mild to moderate in severity and self-limiting. No SAES due to URIs were reported. Diarrhea, nausea, headache, URI, vomiting, and dyspepsia should be included in the product label as adverse drug reactions.

A treatment-dependent decrease in body weight was observed in the PsA studies. A greater proportion of apremilast-treated subjects experienced a >5% weight loss compared to placebo-treated subjects. No subject had a weight decrease of >20% and only one subject discontinued due to weight decrease during the apremilast-exposure period. Potential for significant weight loss should be included in the product label.

Analyses of adjudicated events for serious infections, major adverse cardiac events, and malignancies did not indicate any imbalance between apremilast-treated subjects and placebo-treated subjects. Additional analyses assessing tuberculosis, psychiatric events, hepatobiliary, and vasculitis were performed and no safety signal was identified.

Markedly abnormal laboratory test results were infrequent and transient. In general, analyses of mild and moderate laboratory abnormalities did not show an increased risk between either APR20 or APR30. The vast majority of laboratory abnormalities was transient and did not lead to study drug discontinuation. No cases of hepatic failure, or LFT elevations meeting Hy's Law criteria, were reported. Myelosuppression was not observed based on routine laboratory testing.

Clinical pharmacology studies and analysis of the Phase 2/3 safety databases did not identify a clinically meaningful drug-drug interaction with apremilast. Apremilast has demonstrated an acceptable safety profile when used alone or in combination with the DMARD MTX, SSZ, and LEF.

In summary, the data submitted in the application was sufficient to assess the overall safety of apremilast in patients with active PsA. The most commonly occurring adverse events associated with apremilast were diarrhea, nausea, vomiting, headache, and 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%-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. The overall safety profile was comparable between the apremilast 20 mg BID dosing and 30 mg BID dosing, except. Given these data, the proposed higher dose of apremilast 30 mg BID

appears reasonable as there does not appear to be an increased risk of serious adverse reactions compared to the lower apremilast dose of 20 mg BID.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed in Section 5, the principle data used for the safety assessment of apremilast was derived from the placebo-controlled period of the three PsA Phase 3 studies, PSA-002, -003, and -004. These studies were chosen as the focus of the safety review due to their similarity in study design, enrolled subjects were the targeted patient-population for the proposed indication, large number of subjects, and 16-week placebo-controlled periods. Together, these factors allowed for the reliable pooling of data to create a larger subject database in which to assess potential safety signals related to apremilast. A greater degree of emphasis for the safety analyses were placed on the placebo-controlled periods of this data pool since the observed rates of AEs in apremilast-treated subjects could be directly compared to placebo-treated subjects.

Data from the non-placebo-controlled periods of the three PsA Phase 3 studies were used to assess potential safety signals that may occur at later time points following longer exposures to apremilast; however, this data can be difficult to interpret given the lack of an adequate comparison arm. Discussion of the safety data from this period of the studies include exposure-adjusted incident rates (EAIR) to account for the potential occurrence of time effects when assessing AEs between treatment groups. A summary of the Phase 3 PsA study designs can be found in Table 2.

Additional safety data was derived from the Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, and RA (Table 13). With the exception of studies PSOR-001 and PSOR-04, these additional studies were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast versus placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. In general, data from these studies were used to confirm the findings from the PsA studies and to assess potential safety signals from the larger combined subject population.

Table 13. Clinical Studies Used in the Safety Assessment of Apremilast

Study	Centers (n)	Subjects Enrolled (n)	Dosing[a]	Study Design	**Primary Endpoint**
RA					
RA-002	42	237	PBO APR 20 BID APR 30 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, APR 20 mg BID, or APR 30 mg BID. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR 20 was performed at Week 16.	ACR 20 @ Wk 16
Psoriasis					
PSOR-001	3	19	APR 20 QD	Open-label, single-arm, pilot study enrolling subjects with severe plaque - type psoriasis. Subjects were treated with APR 20 mg QD. Primary efficacy endpoint was improvement in the PASI score at Day 29.	PASI @ Day 29
PSOR-003	34	260	PBO APR 20 QD APR 20 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, APR 20 mg QD, or APR 20 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	APR 20 BID	Open-label, multicenter study enrolling subjects with plaque-type psoriasis. All subjects received APR 20 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 APR 20 BID APR 30 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, APR 20 mg BID, or APR 30 mg BID. Primary efficacy endpoint assessing the proportion of subjects achieving a PASI score ≥75 at Week 16.	PASI @ Wk 16
Other					
ASTH-001	4	73	PBO APR 20 QD APR 20 BID	Randomized, double-blind, PBO-controlled, parallel-group, exercise-challenge study enrolling subjects with mild asthma. Subjects were randomized 1:1:1 to receive PBO, APR 20 mg QD, or APR 30 mg BID. Primary efficacy endpoint assessing the maximum post-exercise percentage fall index (%FI) at Day 29.	%FI @ Day 29
BCT-001	6	111	PBO APR 30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active Behçet's disease. Subjects were randomized 1:1 to receive PB or APR 30 mg BID. Primary efficacy endpoint assessing the number of oral ulcers at Day 85.	Oral Ulcers @ Day 85

Data from the clinical pharmacology studies and the clinical studies for Behçet's disease and asthma were not included in the pooled safety analyses given the differences in the subject population and underlying disease pathogenesis; however, any deaths and/or reported SAEs from these studies were reviewed and are included in the overall analysis of the risk-benefit assessment of apremilast. Additionally, three Phase 3 studies are ongoing and remain blinded including one study in PsA (CC-10004-PSA-005) and two studies in psoriasis (PSOR-008, -009), consequently, data from these studies are not included in the overall safety assessment of apremilast except for reported deaths and expedited SAEs.

Overall, the data submitted by the sponsor appears to be of adequate quality to draw conclusions regarding the initial safety of apremilast.

7.1.2 Categorization of Adverse Events

Analysis of the safety data included deaths, serious adverse events (SAE), adverse events (AE), adverse drug reactions (ADR, laboratory data, vital signs, and electrocardiographs (ECG). All AEs were coded according to MedDRA version 14.0.

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 for subjects who completed the study or had discontinued prematurely by the time of the database lock. Additionally, the event was included if it occurred on or after the date of the first dose of study drug for subjects who were enrolled in the study at the time of the database lock.

An SAE was defined as an AE that was graded 3 or above by the investigator for studies utilizing National Cancer Institute/Common Terminology Criteria for Adverse Events (NCI/CTCAE) or indicated as severe by the investigator for studies not utilizing NCI/CTCAE.

The sponsor 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. Additional analyses included AEs related to headache, and hepatic/renal systems. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, major adverse cardiac events [MACE], and hepatobiliary and hypersensitivity AEs).

All AEs related to malignancies, serious infections, and MACE/potential MACE were adjudicated by independent, blinded, subspecialty adjudicators. For each of these groups, one independent external expert in the respective field was selected to perform the adjudication. The sponsor identified the cases for adjudication based on pre-defined criteria and provided the available information to the adjudicator who then reviewed the case and provided the assessment based on the predefined categories defined in the adjudication Charter. If the adjudicator required additional information, the sponsor contacted the investigation site to obtain available information and forwarded it to the adjudicator. An adjudication form was completed by the adjudicator and provided to the sponsor for each subject. The adjudicated results were used as the primary analyses for these safety events.

An increased potential risk for suicide and other psychiatric events have been noted with the use of the PDE4 inhibitor, roflumilast (DALIRESP). Consequently, the sponsor performed a 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. A retrospective evaluation of safety data for subjects from both completed and ongoing clinical trials was conducted on a semiannual basis. The sponsor 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. In addition, The FDA's Division of Psychiatry Products was consulted for their expert advice to help determine whether a safety signal related to suicidal behavior was present in apremilast-treated subjects. A discussion of their analysis is included in this review.

Laboratory data, ECG data, and vital signs were presented using summary statistics and markedly abnormal values. A separate QTc evaluation study was performed by the sponsor and is included in this review (Section 7.4.4).

Analyses of AEs and marked abnormalities for the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool used descriptive statistics and point estimates. Subject incidence was defined as the number of subjects reporting the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period were counted only once in the numerator. Exposure-adjusted incidence rates per 100 subject-years was defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period were only counted once in the numerator. The exposure time for a subject without the specific event was defined as the treatment duration, while the exposure time for a subject with the specific event was defined as the treatment duration up to the start date of the first occurrence of the specific event. The total exposure time in years was calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25 (days/year). The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 subject-years of exposure to the study drug. Use of exposure-adjusted rates for the placebo-controlled period is to account for the differences in exposure between placebo-treated and apremilast-treated subjects resulting from the early escape design feature in the PsA Phase 3 studies PSA-002, PSA-003, PSA-004, and RA-002.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary focus of this safety review draws from data collected in the three PsA Phase 3 studies, PSA-002, -003, and -004, referred to hereafter as the ***PsA Phase 3 Data Pool***. These studies were chosen as the focus of the safety review due to their similarity in study design, enrolled subjects were the targeted patient-population for the proposed indication, large number of subjects, and 16-week placebo-controlled periods. The nearly identical study designs allowed for the data to be pooled with reasonable reliability of study conduct, apremilast dosing, and subject population. Emphasis on the placebo-controlled periods of the PsA Phase 3 Data Pool allowed for the direct comparison of AEs between subjects receiving apremilast versus placebo in the proposed targeted patient population.

Data from the non-placebo-controlled periods of the three PsA Phase 3 studies were used to assess potential safety signals that may occur at later time points following longer exposures to apremilast; however, this data can be difficult to interpret given the lack of an adequate comparison arm. Discussion of the safety data from this period of the studies include EAIRs to account for the potential occurrence of time effects when assessing AEs between treatment groups.

Additional safety data was derived from the Phase 2/3 clinical studies that assessed the safety of apremilast in the treatment of PsA, psoriasis, and RA. This data pool will be referred to in this review as the ***Apremilast Unblinded Data Pool***. With the exception of studies PSOR-001 and PSOR-04, these additional studies were designed as placebo-controlled trials and provide additional data to compare the safety of apremilast versus placebo. The duration of the placebo-controlled periods varied but typically ranged between 12 to 24 weeks. Together, these nine studies used the following apremilast dosing regimens: 10 mg BID, 20 mg QD, 20 mg BID, 30 mg BID, and 40 mg QD. Pooling safety data from these studies was reasonable considering the similarity of the diseases, the doses of apremilast, and adequately long placebo-controlled periods. However, one shortcoming regarding the pooling of these studies is that it includes the same data used in the PsA Phase 3 Data Pool. Thus, approximately 65% of the subjects included in the Apremilast Unblinded Data Pool consist of data from the PsA Phase 3 Data Pool.

7.1.3.1 Analysis Populations

Pooled safety analyses for the placebo-controlled period were based on the safety population defined as all subjects who were randomized and received at least one dose of study drug. Subjects were included in the treatment group corresponding to the study drug actually received. Subjects who received different doses of study drug the placebo-controlled period were handled as follows:

- Subjects whose randomization assignment was apremilast, but who initially received placebo in error, were included in the placebo group until the first apremilast dose was received. Subsequently, they were included in the apremilast-exposure period at the apremilast dose level first received.

- Subjects whose randomization assignment was placebo, but who initially received apremilast in error, were included in the apremilast dose group corresponding to the apremilast dose first received.

- Subjects who received two doses of apremilast were included in the apremilast dose group based on the dose first received.

Subjects included in the apremilast-exposure data pool were based on the apremilast subjects as treated and included all subjects who received at least one dose of apremilast. Subjects were included in the apremilast dose group corresponding to the first apremilast dose actually received. Subjects who received different doses of apremilast during the apremilast-exposure period were included in the apremilast dose group corresponding to the apremilast dose first received.

7.1.3.2 Analysis Periods

In this review, use of the term, placebo-controlled period, included all data collected in each of the studies corresponding to the time during which subjects were randomized and treated with placebo, in order to allow for a direct comparison of the safety between apremilast and placebo treatment arms. Subjects who had entered early escape at Week 16 due to an inadequate clinical response were rerandomized to either apremilast 20 mg BID or 30 mg BID in studies, PSA-002, -003, and -004, or switched to apremilast 20 mg BID in study RA-002. Apremilast-treated subjects who entered early escape continued to receive their assigned apremilast dose. At Week 24, all remaining placebo-treated subjects were rerandomized to an apremilast treatment arm. The placebo-controlled period included only the data before early escape for placebo-treated subjects who entered early escape and the data up to Week 24 for placebo-treated subjects who did not early escape. Data summarized for the apremilast treatment groups included data up to Week 24, whether or not they early escaped. Therefore, exposure to study drug is less in the placebo treatment group compared with the apremilast treatment groups.

The apremilast-exposure period includes all apremilast exposure data, irrespective of when the apremilast exposure started through the completion of the study or at the time of the safety data cutoff date. For the apremilast-exposure period, all subjects who were initially assigned to receive placebo, who either early escaped, switched therapy, or who were rerandomized or switched therapy at Week 24, were included in the apremilast dose group according to the dose they received.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 PsA Phase 3 Data Pool Exposure

Table 14 shows the overall exposure to study drug during the placebo-controlled period of the PsA Phase 3 Data Pool. Approximately 500 subjects were randomized to each of the three treatment groups with all subjects having received at least 1 dose of study drug. At week 16, 73% of placebo-treated subjects remained in the study compared to 90% and 89% of subjects randomized to the APR20 and APR30 treatment arms, respectively. The amount of available placebo-controlled data at Week 16 appears adequate to assess the relative safety of apremilast at this time point. However, there are substantially fewer placebo-treated subjects by Week 24 as a result of these subjects entering early escape at Week 16, consequently, drawing conclusions up to Week 24 is more difficult.

Table 14. PsA Phase 3 Data Pool: Extent of Study Drug Exposure During the Placebo-Controlled Period

Apremilast Exposure	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
≥1 day	495 (100)	501 (100)	497 (100)
≥4 Weeks	484 (98)	485 (97)	472 (95)
≥8 Weeks	468 (95)	471 (94)	460 (93)
≥12 Weeks	458 (93)	462 (92)	451 (91)
≥16 Weeks	363 (73)	449 (90)	444 (89)
≥20 Weeks	154 (31)	437 (87)	435 (88)
≥24 Weeks	113 (23)	292 (58)	278 (56)

The total exposure to apremilast for the PsA Phase 3 Data Pool (apremilast-exposure period), including placebo-treated subjects who switched to apremilast and those subjects initially randomized to apremilast, are shown in Table 15. Over 70% of subjects in the PsA Phase 3 Data Pool had been exposed to apremilast for at least 24 weeks and approximately 25% of subjects had been exposed to apremilast for at least 48 weeks.

Table 15. PsA Phase 3 Data Pool: Extent of Study Drug Exposure During the Apremilast-Exposure Period

Apremilast Exposure	APR20 BID (n=720) n (%)	**APR30 BID (n=721) n (%)**
≥1 day	720 (100)	721 (100)
≥4 Weeks	693 (96)	686 (95)
≥12 Weeks	630 (88)	625 (87)
≥24 Weeks	516 (72)	527 (73)
≥36 Weeks	332 (46)	340 (47)
≥48 Weeks	176 (24)	183 (250
≥60 Weeks	92 (13)	84 (12)
≥72 Weeks	35 (5)	35 (5)

7.2.1.2 Apremilast Unblinded Data Pool

Exposure to study drug during the placebo-controlled period for the Apremilast Unblinded Data Pool is shown in Table 16. A total of 817 subjects were randomized to receive PBO, 824 subjects were randomized to receive APR20, and 661 subjects were randomized to receive APR30. Different apremilast treatment groups (i.e., APR 10 BID [n=89], APR 20 QD [n=87], and APR 40 QD [n=67]) were included Apremilast Unblinded Data Pool resulting in a total of 1728 subjects being randomized to receive apremilast (data not shown). All subjects received at least 1 dose of study drug. Approximately 60% of placebo-treated subjects in the Apremilast Unblinded Data Pool remained in the study at Week 16. Comparatively, approximately 70% and 84% of subjects randomized to the APR20 and APR30 treatment arms, respectively, were exposed to study drug at Week 16. The disproportionate numbers of subjects between treatment arms is largely due to differences in the individual study designs, which included different durations of placebo-controlled periods (ranged between Week 12 and Week 24) and the ability of placebo subjects to escape early at Week 16.

Table 16. Apremilast Unblinded Data Pool: Extent of Study Exposure During the Placebo-Controlled Period

Apremilast Exposure	**PBO (n=817) n (%)**	**APR20 BID (n=824) n (%)**	**APR30 BID (n=661) n (%)**
≥1 day	817 (100)	824 (100)	661 (100)
≥4 Weeks	788 (97)	785 (95)	627 (95)
≥8 Weeks	750 (92)	756 (92)	609 (92)

≥12 Weeks	705 (86)	716 (87)	593 (90)
≥16 Weeks	479 (59)	567 (69)	557 (84)
≥20 Weeks	197 (24)	504 (61)	496 (75)
≥24 Weeks	145 (18)	345 (42)	327 (50)

The total exposure to apremilast for the Apremilast Unblinded Data Pool (apremilast-exposure period) is shown in Table 17. Approximately 62% of subjects randomized to APR20 and 73% of subjects randomized to APR30 in the Apremilast Unblinded Data Pool had been exposed to apremilast for at least 24 weeks. Subjects in Studies PSA-001, PSOR-004, and PSOR-005-E-LTE were not required to enter the Extension Phase in these studies, consequently, the decrease in numbers shown in Table 17 do not necessarily reflect treatment discontinuations but rather reflect an aspect of the study designs.

Table 17. Apremilast Unblinded Data Pool: Extent of Study Exposure During the Apremilast-Exposure Period

Apremilast Exposure	**APR20 BID (n=1198) n (%)**	**APR30 BID (n=921) n (%)**
≥1 day	1198 (100)	921 (100)
≥4 Weeks	1143 (95)	875 (95)
≥12 Weeks	1013 (85)	794 (86)
≥24 Weeks	745 (62)	672 (73)
≥36 Weeks	462 (39)	457 (50)
≥48 Weeks	245 (21)	269 (29)
≥60 Weeks	114 (10)	106 (12)
≥72 Weeks	50 (4)	51 (6)

Apremilast exposure during the Behçet's study and the Clinical Pharmacology studies are not included in this review due to the limited role these studies played in the overall safety analyses.

Demographics PsA Phase 3 Data Pool

A summary of the baseline demographics and disease characteristics for the studies comprising the PsA Phase 3 Data Pool can be found in Table 4. Baseline demographics of the subjects included in the PsA Phase 3 Data Pool were well balanced between treatment arms. Almost equal proportions of male and female subjects were enrolled with an average age of 51 years and a median body weight of approximately 84 kg. A total of 146 out of the 1493 (10%) subjects were 65 years of age or older, including 19 subjects who were 75 years of age or older. The majority of subjects (≥90%) were classified as White and participated at study centers located in North America (34%) and Europe (45%). Similarly, baseline disease characteristics

were balanced between treatment arms with a mean duration of PsA of approximately 7 years. Almost 99% of the 1493 subjects enrolled into the three PsA Phase 3 studies had received prior treatment with small-molecule or biologic DMARDs prior to entering the study. A total of 76% of subjects had been previously treated with one or more small molecular DMARDs and 22% of subjects had also received a biologic DMARD. A total of 973 of 1493 (65%) subjects were receiving small molecular DMARDs at study baseline with 55% of subjects receiving MTX 15 mg weekly.

Coexisting medical conditions at study baseline were consistent between treatments. A large percentage of subjects enrolled in the PsA Phase 3 studies had coexisting cardiovascular risk factors including hypertension (40%), hypercholesterolemia (15%), obesity (12%), hyperlipidemia (8%), and Type II diabetes mellitus (7%). Approximately 15% of subjects reported depression.

Overall, the proportions and types of prior medications used by subjects were well balanced between treatment arms (data not shown). The most common prior medications used by subjects were consistent with current standard of care of patients with PsA and included MTX (85% of subjects), SSZ, leflunomide, TNF-inhibitors, NSAIDs, and corticosteroids. Subjects also reported prior medications used to treat common comorbidities including antihypertensives drugs, lipid-modifying agents, antithrombotic agents, and anti-diabetic drugs.

In summary, the data comprising the PsA Phase 3 Data Pool appears to be adequate to draw conclusions regarding the initial safety assessment of apremilast. The studies enrolled a sufficient number of subjects with PsA and included the proposed titration regimen and dose of apremilast to be marketed, apremilast 30 mg BID. Furthermore, treatment arms were well balanced in all respects and the study enrolled subjects with similar baseline demographics, PsA disease characteristics, and prior medication use to that found in the North American population, making extrapolation of the safety data more applicable to patients in the US.

Apremilast Unblinded Data Pool

Baseline demographic characteristics of the subjects included in the Apremilast Unblinded Data Pool were generally well balanced and were similar to that observed in the PsA Phase 3 Data Pool. The majority of subjects were White (94%) with approximately equal proportions of male and female subjects. The median subject age was 50 years and a median body weight of approximately 84 kg. The majority of subjects (≥94%) were classified as White and participated at study centers located in North America (45%) and Europe (43%).

7.2.2 Explorations for Dose Response

Dose-dependent increases in the frequency of nausea, diarrhea, headache, and dizziness were observed in both the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool.

7.2.3 Special Animal and/or In Vitro Testing

Preclinical testing was adequately conducted to explore for potential adverse reactions that would have been reasonably expected to occur based on the known mechanism of action of apremilast. Results from the sponsor's Pharmacology/Toxicology program for apremilast are summarized in Section 4.1 and discussed in Dr. Leshin's Pharmacology/Toxicology review.

7.2.4 Routine Clinical Testing

Routine safety monitoring and clinical testing was performed at specified time periods as defined in the study protocols. All subjects received complete physical exams, assessment of vital signs, and manual 12-lead ECG testing. Clinical laboratory evaluations included, but were not limited to, serum chemistry, hematology, ESR, CRP, fibrinogen, urinalysis, ANA, C-ANCA, and quantitative assessment of serum immunoglobulins. Overall, the studies included in this application appear to have had adequate safety monitoring and appropriated clinical testing of subjects.

7.2.5 Metabolic, Clearance, and Interaction Workup

Discussion of the enzymatic pathways responsible for metabolism, clearance, and potential drug-drug interactions can be found in Section 4.4 and Dr. Agarwal's Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The PDE4-inhibitor, roflumilast (DALIRESP), was approved in 2011 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Included in the WARNINGS AND PRECAUTIONS section of the product label is an increased frequency of psychiatric adverse reactions and significant loss of body weight. Psychiatric adverse reactions included insomnia, anxiety, and depression, all of which were reported at higher rates in DALIRESP-treated subjects versus placebo-treated subjects. Instances of suicidal ideation and behavior, including completed suicide were observed during clinical trials and in the post-marketing setting in patients treated with DALIRESP. Moderate weight loss, defined as a decrease of 5-10% of body weight, was a common adverse reaction that occurred in DALIRESP-treated subjects during the clinical trials. Commonly

reported adverse reactions listed in the product label included diarrhea, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

In light of the safety issues associated with DALIRESP, the sponsor undertook efforts to specifically detect similar adverse reactions in the apremilast development program. The sponsor 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. Evaluation of psychiatric AEs utilized the C-CASA tool. Additional analyses included AEs related to hypersensitivity, hepatic and renal systems, and headache. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, MACE, and hepatobiliary AEs).

The active monitoring, and subsequent safety analysis, for predefined AEs of special interest demonstrate that the sponsor was proactive in attempting to detect adverse reactions that may be related to apremilast's mechanism of action and possible class effects of the PDE-4 inhibitors.

7.3 Major Safety Results

7.3.1 Deaths

Overall, six deaths were reported from a total of 2401 subjects who had been exposed to apremilast by the time of the data cutoff date of July 6, 2012. One death occurred in the PsA studies (PSA-002) 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 who was randomized to the APR20 BID treatment arm and died due to multiple organ failure on Study Day 73. The subject was diagnosed with vitamin B_{12} deficiency anemia prior to receiving her first dose of apremilast. The principal investigator reported the cause of death as vitamin B_{12} deficiency attributable to the induction of MTX-induced folic acid deficiency. Given the known mechanisms of action for apremilast and MTX, the underlying vitamin B_{12}/folate deficiency appears most likely related to treatment with MTX, consequently, this reported death does not appear to be directly related to apremilast.

- **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. The investigator reported the cause of death as myocardial infarction, arrhythmia, and hypertensive changes. In light of the subject's underlying risk factors, it appears that his death was due to underlying cardiovascular heart disease rather than a direct effect of apremilast; however, since apremilast is a new molecular entity, a separate safety analysis was performed for this review assessing whether apremilast-treated subjects are at increased risk of cardiovascular-related deaths or SAEs (Section X).

- **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/m^2), 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. Although the subject's comorbidities could account for the cause of death, an association with apremilast cannot be completed ruled out. A separate safety analysis assessing whether apremilast-treated subjects are at increased risk of cardiovascular-related deaths or SAEs was performed for this review, the results of which can be found in Section X.

- **Subject PSOR-008-0251014** was a 28-year-old, White female with psoriasis who was randomized to the placebo-treatment arm and 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. Given the subject's past medical history of attempted suicide predating treatment with apremilast, this death appears to be unlikely related to the study drug.

- **Subject PSOR-009-1191012** was a 51-year-old, White female with psoriasis who died secondary to an intracranial hemorrhage. On Study Day 352 the subject complained of headache and the following day was found unresponsive at which

time she was brought to the hospital and received palliative care. The subject was pronounced brain dead on Study Day 354. The subject received apremilast for 225 days followed by placebo for 112 days. Considering the temporal relationship between the onset of the intracranial hemorrhage and last dose of apremilast, the death appears to be unlikely related to apremilast.

Of the six 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 rerandomized to the placebo treatment arm during the randomized withdrawal period of study PSOR-009. An additional death related to apremilast was reported in a non-Celgene-sponsored study in RA that consisted of a single case of acute myeloid leukemia (AML) in a subject treated with apremilast 30 mg BID. The case of AML was diagnosed nearly 12 months after completion of a 3-week course of apremilast treatment. Given the short-term exposure to apremilast and the temporal relationship of the diagnosis of AML, a causal relationship does not appear to be related to the study drug.

Of note, the deaths of subjects PSOR-008-0251014 and PSOR-005-E-LTE-0421019 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. A separate analysis was performed for this review assessing whether apremilast-treated subjects are at an increased risk for the development of depression, suicidal ideations, suicide attempts, and/or completed suicides (Section 7.3.5.8).

In summary, analysis of the individual deaths, including the temporal relationship to apremilast dosing, does not suggest a safety signal from any single type of adverse event.

7.3.2 Nonfatal Serious Adverse Events

PsA Phase 3 Data Pool

Approximately 4% of subjects in each treatment arm reported SAEs during the placebo-controlled period for the PsA Phase 3 Data Pool (Table 18). The only SAEs reported in more than two subjects were psoriatic arthropathy and cholelithiasis.

Table 18. PsA Phase 3 Data Pool: Serious Adverse Events Reported in ≥1 Subject During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
Any SAE	19 (4)	17 (3)	19 (4)
Psoriatic arthropathy	2 (<1)	1 (<1)	1 (<1)

Cholelithiasis	1 (<1)	1 (<1)	1 (<1)
Atrial fibrillation	0	0	2 (<1)
Breast cancer	0	1 (<1)	1 (<1)
Depression	0	2 (<1)	0
Acute MI	1 (<1)	1 (<1)	0
Cardiac failure, congestive	1 (<1)	1 (<1)	0
Hypertensive crisis	2 (<1)	0	0
Pancreatitis, acute	2 (<1)	0	0

Slightly higher frequencies of SAEs (approximately 5%) were reported in the apremilast treatment arms during the apremilast-exposure period for the PsA Phase 3 Data Pool (data not shown); however, the small increased frequency of events is not unexpected given the greater duration of exposure to apremilast and the increased number of subjects receiving apremilast treatment as a result of placebo-treated subjects switching to an apremilast treatment arm after Week 24. Overall, SAEs were infrequent in both the APR20 and APR30 treatment arms with an EAIR of 7.2 events per 100-subject years and 7.5 events per 100-subject years, respectively. No single SAE occurred with an EAIR greater than 0.5 events per 100-subject years (data not shown). The types of SAEs reported were similar to those reported during the placebo-controlled period and included psoriatic arthropathy, atrial fibrillation, cholelithiasis, depression, acute myocardial infarction/ischemia, breast cancer, suicide attempt, hypertension, and osteoarthritis. Events of serious infections, suicide attempt, MACE, and malignancies were reviewed by an adjudicator and are included in the analyses of AEs of special interest in Section 7.3.5.

A summary of SAEs by time period for the subjects-as-initially-treated safety population is shown in Table 19. These data demonstrated that the proportion, as well as the EAIR, of subjects reporting SAEs was similar between treatment arms and was constant over time.

Table 19. PsA Phase 3 Data Pool: Serious Adverse Events Reported in ≥1 Subject During the Apremilast-Exposure Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	22	15	19	25	16	24	35
Subjects with ≥1 SAE; n(%)	18 (4)	12 (2)	16 (3)	20 (4)	11 (2)	18 (4)	24 (5)
Exposure (subject-years)	141	144	210	340	141	206	337
EAIR per 100 subject years	12.7	8.3	7.6	5.9	7.8	8.7	7.1
95% CI	7.7, 19.6	4.4, 13.9	4.5, 12	3.7, 8.8	4.1, 13.4	5.3, 13.4	4.6, 10.4

Overall, the proportion of subjects and type of events reported were comparable across treatment groups in the PsA Phase 3 Data Pool.

Apremilast Unblinded Data Pool

Approximately 4% of subjects reported an SAE during the placebo-controlled period for the Apremilast Unblinded Data Pool (data not shown), which was similar to the frequency of SAEs reported during the placebo period of the PsA Phase 3 studies. The types of SAEs reported during this period was similar to those reported in the PsA studies and included atrial fibrillation, cellulitis, cholelithiasis, psoriasis, psoriatic arthropathy, and nausea. Atrial fibrillation was the only SAE to be reported in more than two subjects treated with apremilast. Overall, the frequencies and types of SAEs reported during the apremilast-exposure period for the Apremilast Unblinded Data Pool were consistent with data from the placebo-controlled period of the Apremilast Unblinded Data Pool and the apremilast-exposure period of the PsA Phase 3 studies. The EAIR rate for and SAEs in the APR20 treatment arm was slightly higher than that for the APR30 treatment arm, 9.4 events per 100 subject-years and 7.8 events per 100 subject-years, respectively. No single SAE occurred with an EAIR greater than 0.5 events per 100-subject years (data not shown).

Additional Studies:

A total of 12 SAEs were reported from the three ongoing, blinded Phase 3 studies: 3 events from study PSA-005, six events from study PSOR-008, and three events from study PSOR-009. One death occurred during study PSOR-008. The narrative for subject PSOR-008-4031002 was reviewed and discussed in Section 7.3.1. SAEs reported from the Behçet's study (n=6) and the Clinical Pharmacology studies (n=1) were reviewed and considered not related to treatment with apremilast except for a single case of influenza.

Overall, these data did not suggest clinically important difference in overall SAEs between apremilast-treated subjects and subjects treated with placebo. Additional analyses of SAEs are included in Section 7.3.4, which discusses events of special interest including serious infections, cardiovascular events, malignancies, and psychiatric events.

7.3.3 Dropouts and/or Discontinuations

PsA Phase 3 Data Pool

Table 20shows the frequency of AEs leading to drug withdrawal during the placebo-controlled period for the PsA Phase 3 Data Pool. The most frequently reported AEs leading to drug withdrawal were nausea, diarrhea, headache, and dizziness that appeared to increase in a treatment- and dose-dependent manner.

Table 20. PsA Phase 3 Data Pool: Incidence of Adverse Events Leading to Drug Withdrawal During the Placebo-Controlled Period

MedDRA Preferred Term	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

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The most frequently reported AEs leading to drug withdrawal during the apremilast-exposure period of the PsA Phase 3 studies were similar to those observed in the placebo-controlled period, namely, nausea, diarrhea, headache, and vomiting, all of which appeared to increase in a dose-dependent manner (Table X). The EAIR for nausea, diarrhea, headache, and vomiting appeared to increase in a dose-dependent manner (Table 21).

Table 21. PsA Phase 3 Data Pool: Incidence of Adverse Events Leading to Drug Withdrawal During the Apremilast-Exposure Period

	APR20 BID (n=501)		**APR30 BID (n=497)**	
MedDRA Preferred Term	n (%)	EAIR	n (%)	EAIR
Any SAE	48 (7)	10.1	51 (7)	10.8
Nausea	8 (1)	1.7	15 (2)	3.1
Diarrhea	6 (1)	1.3	13 (2)	2.7
Headache	4 (1)	0.8	9 (1)	1.9

Vomiting	1 (<1)	0.2	6 (1)	1.3
Abdominal pain, upper	4 (1)	0.8	3 (<1)	0.6
Dizziness	2 (<1)	0.4	3 (<1)	0.6
Migraine	1 (<1)	0.2	3 (<1)	0.6
Fatigue	1 (<1)	0.2	3 (<1)	0.6
Psoriatic arthropathy	1 (<1)	0.2	2 (<1)	0.4
GERD	0	0	2 (<1)	0.4
Decreased appetite	1 (<1)	0.2	1 (<1)	0.2
Anxiety	1 (<1)	0.2	1 (<1)	0.2
Depressed mood	1 (<1)	0.2	1 (<1)	0.2
Abdominal distension	1 (<1)	0.2	1 (<1)	0.2
Urticaria	1 (<1)	0.2	1 (<1)	0.2
Abdominal discomfort	1 (<1)	0.2	1 (<1)	0.2
Depression	2 (<1)	0.4	0	0
Abdominal pain	2 (<1)	0.4	0	0
Dyspepsia	2 (<1)	0.4	0	0
Hyperhidrosis	2 (<1)	0.4	0	0
Rash	2 (<1)	0.4	0	0

Adverse events leading to drug withdrawal by time period for the subjects-as-initially treated safety population is shown in Table 22. For the placebo-controlled period (Weeks 0-16) the number of subjects with AEs leading to drug withdrawal was greater in the apremilast treatment arms compared to placebo-treated subjects. For Weeks 0-24 and Weeks 0-52, the number of subjects with AEs leading to drug withdrawal was similar between the APR20 and APR30 treatment arms. Also, the data demonstrate that greatest proportion of AEs leading to drug withdrawal occurred during Weeks 0-16 weeks of treatment.

Table 22. PsA Phase 3 Data Pool: Adverse Events Leading to Drug Withdrawal By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	34	46	54	64	60	65	75
Subjects with ≥1 SAE; n(%)	20 (4)	26 (5)	29 (6)	38 (8)	32 (60	35 (7)	43 (9)
Exposure (subject-years)	143	144	210	342	140	206	340
EAIR per 100 subject years	14	18.1	13.8	11.1	22.9	17	12.6
95% CI	8.7, 21.1	12, 26	9.4, 19.5	7.9, 15	15.9, 31.8	12, 23.3	9.2, 16.8

Overall, the types and frequencies of AEs leading to drug withdrawal were similar between treatment arms with an apparent dose-response relationship for apremilast-treated subjects for the AEs of nausea, diarrhea, headache, and dizziness.

Apremilast Unblinded Data Pool

The frequency and types of AEs leading to drug withdrawal during the placebo-controlled and apremilast-exposure periods for the Apremilast Unblinded Data Pool were similar to that observed in the PsA Phase 3 data pool with the most frequent AEs reported as nausea, diarrhea, headache, abdominal pain, dizziness, vomiting, and psoriasis. These AEs appeared to increase in a treatment- and dose-dependent manner similar to that seen in the PsA Phase 3 Study Data Pool.

Additional Studies:
Similar results were also reported during the Behçet's and Clinical Pharmacology studies (data not shown). Adverse events leading to drug interruption from these studies mirrored the frequency and types of events leading to drug withdrawal outlined above. The most common AEs were diarrhea, nausea, vomiting, and headache.

In summary, the largest proportion of subjects dropping out from the placebo-controlled periods of the PsA studies prior to Week 16 was due AEs. The frequency of AEs leading to dropout was similar between the placebo and APR20 treatment arms but slightly higher for the APR30 group (Table 20). The data presented here suggest that apremilast has a treatment- and dose-dependent effect of increasing nausea, diarrhea, vomiting, and headache, which may lead to patients discontinuing treatment with the drug. While these types of AEs may limit the tolerability of apremilast, they are typically reversible and non-life threatening.

7.3.4 Significant Adverse Events

Significant AEs as defined in the Clinical Review Template were not identified or are covered in other sections of the Safety Review.

7.3.5 Adverse Events of Special Interest

The sponsor 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. Additional analyses included AEs related to hypersensitivity, hepatic and renal systems, and headache. Adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries (e.g., malignancies, cardiac failure, depression, suicide, vasculitis, acute renal failure, dyspepsia) or sponsor-created queries (e.g., nausea and vomiting, diarrhea, upper respiratory tract infection, major adverse cardiac events [MACE], and hepatobiliary and hypersensitivity AEs). Analyses for AEs of Special Interest were limited to the PsA Phase 3 Data Pool and the Apremilast Unblinded Data Pool only.

7.3.5.1 Serious Infections (Adjudicated Analysis) including 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. No serious infections were reported for subjects enrolled in the APR 10 BID, APR 20 QD, or APR 40 QD treatment arms.

The three cases of systemic opportunistic infections included single cases of Rothia species-related tenosynovitis following a puncture wound, Herpes Zoster with associated viral meningitis, and MRSA-related naso-facial cellulitis/abscess. Three cases of non-systemic opportunistic infections consisted of two cases of bacterial pneumonia, and a single case of Clostridium difficile infection. 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.

Ten of the 18 cases of serious infections reported in the Apremilast Unblinded Data Pool, occurred during the PsA Phase 3 studies (i.e., the PsA Phase 3 Data Pool). Serious infections were reported in two placebo-treated subjects, two subjects from the APR20 BID treatment-arm, and six subjects from the APR30 BID treatment arm. A single case of a systemic opportunistic infection was reported in a placebo-treated subject (EAIR of 0.6 events per 100 subject-year). Non-systemic opportunistic infections were reported in one subject randomized to the APR20 BID treatment arm (EAIR of 0.2 events per 100 subject-years) and two subjects in the APR30 BID arm (EAIR of 0.4 events per 100 subject-years. Non-opportunistic serious infections were reported in one placebo-treated subject (EAIR of 0.6 events per 100 subject-years), one APR20 BID subject (EAIR of 0.2 events per 100 subject-years), and four subjects in the APR30 BID treatment arm (EAIR of 0.8 events per 100 subject-years).

Occurrences of tuberculosis (TB) were analyzed separately from serious infections and were not adjudicated; however, given their association as an opportunistic infection, the data will be reviewed here. Screening for latent TB was not required for the PsA Phase 3 studies and was left to the investigator's judgment; however, all enrolled subjects received a chest radiograph and inquiry on medical history to rule out active TB. Also, subjects with active TB, or a history of incompletely treated TB, were excluded from the studies.

A total of 20 subjects with a medical history significant for TB were included in the PsA Phase 3 Data Pool: seven placebo-treated subjects, five APR20-treated subjects, and eight APR30-treated subjects. Additionally, 12 subjects had a medical history of a positive PPD: four placebo-treated subjects, five APR20-treated subjects, and three APR30-treated subjects. No cases of TB or TB reactivation were reported in either the

placebo-controlled period of during the apremilast-exposure period for the PsA Phase 3 Data Pool. Similarly, no cases of TB or TB reactivation was reported for the Apremilast Unblinded Data Pool, despite the enrollment of 23 subjects with a reported medical history of TB and 14 subjects with a medical history of positive PPD.

Overall, the results from both data pools, including EAIRs, suggest no appreciative differences between placebo and apremilast adjudicated events of serious infections (opportunistic and non-opportunistic), including cases of TB or TB reactivation. Additionally, the overall number of serious infections was relatively small in light of the underlying diseases, concomitant medications, and potential immunosuppressive effects of apremilast. These data do not demonstrate an increased risk of serious infections with apremilast therapy.

7.3.5.2 Major Adverse Cardiac Events (MACE)/Potential MACE (Adjudicated Analysis)

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 with all events being reported in the APR20 and APR30 treatment arms. Five of the reported cases occurred in the PsA Phase 3 Data Pool. Overall, the numbers of adjudicated MACE were small and all attributed to cases of MI. The calculated EAIRs were similar across the placebo (n=0), APR20 (n=3), and APR30 (n=1) treatments arms of 0, 0.4, and 0.2 events per 100 subjects-years, respectively.

The four adjudicated cases of potential MACE were attributed to single cases of unstable angina requiring a revascularization procedure, TIA, DVT, and an embolic event. The EAIRs for potential MACE were similar across treatment arms at 0, 0.4, and 0.2 events per 100 subject-years for the placebo (n=0), APR20 (n=3), and APR30 (n=1), treatment arms, respectively.

Overall, the total number of MACE and potential MACE adjudicated cases were small, and consequently, little weight can be placed in the similar EAIRs; however, it is reassuring that the overall number of events were small and that no clear dose-response relationship was identified. Moreover, all eight subjects reporting a MACE, or potential MACE, had a medical history significant for cardiovascular risk factors. These data, although limited, do not suggest an association between apremilast therapy and significant cardiovascular adverse events.

7.3.5.3 Malignancies (Adjudicated Analysis)

A total of 18 out of 22 cases meeting criteria for adjudication were identified as adjudicated malignancy events for the Apremilast Unblinded Data Pool. Malignancy events were reported in the placebo (n=3), APR20 (n=8), APR30 (n=4), and APR40 QD (n=2) treatment arms as well as and a single event in the APR10 BID group. The EAIR per 100 subject-years were similar between treatment arms (data not shown). 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.

Non-melanoma skin cancers (squamous cell/basal cell) accounted for seven of the 18 adjudicated malignancies. Of the remaining 11 events, there were four cases of prostatic adenocarcinoma, two cases of breast cancer (both ductal carcinomas), two cases of lung cancer (one case each of small cell and bronchioloalveolar carcinomas), 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. Several of the subjects had a medical history that increased their risk of malignancy including a family history of breast cancer or tobacco use.

Overall, the total numbers of adjudicated malignancies were limited, and thus, little weight can be placed on the EAIRs. Furthermore, while the possible association between apremilast and malignancy cannot be ruled out from this data due to the small numbers of reported malignancies, it is reassuring, especially given the lack of a dose-response or temporal relationship between apremilast and the events. Taken as a whole, these data suggest that apremilast therapy does not present an increased risk of malignancy.

7.3.5.4 Upper Respiratory Tract Infections

PsA Phase 3 Data Pool

A higher frequency of upper respiratory tract infections (URIs) were reported in apremilast-treated subjects compared to placebo-treated subjects during the placebo-controlled period (Table 23). Both apremilast treatment arms reported approximately 15% of subjects experiencing an URI with no clear dose-response relationship. The higher proportion of URI events were primarily due to reports under the preferred terms “upper respiratory tract infection” and “nasopharyngitis”, which accounted for 42% and 30% of the total URI events, respectively. No other single preferred term accounted for more than one percent of events except for sinusitis (2%), which was similar across the three treatment arms. None of the AEs were reported as severe or serious and none led to drug withdrawal. There were no differences between sexes but subjects younger than 65 years of age demonstrated a slightly higher increased frequency of URIs compared to older subjects, The clinical significance of these findings are unclear but

may be related to the small number of subjects included in the ≥65 year-old age group. Approximately one-third of the URI events were reported in the first 30 days of treatment across the three treatment arms with relatively equal number of events thereafter (data not shown).

Table 23. PsA Phase 3 Data Pool: URI Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any URI AE	44 (9)	79 (16)	74 (15)
Age; n/N (%)			
<65 years	42/447 (9)	75/458 (16)	67/442 (15)
≥65 years	2/48 (2)	4/43 (9)	7/55 (13)
Sex; n/N (%)			
Male	22/240 (9)	36/232 (16)	28/222 (13)
Female	22/255 (9)	43/269 (16)	46/275 (17)

A slightly higher frequency of URI AEs was reported in the APR20 group compared to the APR30 group (20% vs. 17%, respectively) during the apremilast-exposure period (Table 24). Although an increased frequency of URI AEs was observed in the APR20 treatment arm, there was no notable difference in the EAIR between the treatment arms for individual preferred terms (data not shown). One subject from each treatment group reported a severe URI infection. Overall, the EAIR for URI AEs were relatively similar between treatment arms, age, and sex.

Table 24. PsA Phase 3 Data Pool: URI Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any URI AE	144 (20)	35.7	122 (17)	29.3
Any Severe URI AE	1 (<1)	0.2	1 (<1)	0.2
Age; n/N (%)				
<65 years	134/656 (20)	36.5	107/645 (17)	28.7
≥65 years	10/64 (16)	27.6	15/76 (20)	35
Sex; n/N (%)				
Male	69/347 (20)	33.3	52/324 (16)	27.2
Female	75/373 (20)	38.2	70/397 (18)	31.1

Adverse events related to URIs by time period for the subjects-as-initially treated safety population is shown in **Error! Reference source not found.**. For the placebo-controlled period (Weeks 0-16) the number of subjects with URI AEs increased in a treatment-dependent manner; however, a dose-response effect was not observed. For

Weeks 0-24 and Weeks 0-52, the number of subjects with URI-related AEs was similar between the APR20 and APR30 treatment arms with an apparent treatment-effect with time.

Table 25. PsA Phase 3 Data Pool: URI Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
SAE; n	34	46	54	64	60	65	75
Subjects with ≥1 SAE; n(%)	20 (4)	26 (5)	29 (6)	38 (8)	32 (60	35 (7)	43 (9)
Exposure (subject-years)	143	144	210	342	140	206	340
EAIR per 100 subject years	14	18.1	13.8	11.1	22.9	17	12.6
95% CI	8.7, 21.1	12, 26	9.4, 19.5	7.9, 15	15.9, 31.8	12, 23.3	9.2, 16.8

These data demonstrate an increased risk of URIs associated with apremilast therapy, albeit non-dose-dependent. Appropriate language should be included in the product labeling to reflect this increased risk.

7.3.5.5 Cardiac Failure

A total of 18 subjects were identified with AEs related to cardiac failure during the placebo-controlled period of the PsA Phase 3 Data Pool (Table 26). Of these events, only two cases were reported as a serious AE of heart failure (one case in the PBO arm and one case in the APR20 arm). The remaining cases were reported as non-serious and included 14 cases of peripheral edema, and one case each of pulmonary congestion, and cardiac failure. Relatively few events of cardiac failure were reported as severe, serious, or leading to drug withdrawal. The overall incidence of cardiac failure was similar across treatment arms and did not vary between age or gender groups.

Table 26. PsA Phase 3 Data Pool: Cardiac Failure Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Cardiac Failure AE	7 (1)	7 (1)	4 (1)
Any Severe Cardiac Failure AE	2 (<1)	1 (<1)	0
Any Cardiac Failure AE leading to drug withdrawal	0	0	1 (<1)
Any Serious Cardiac Failure AE	1 (<1)	1 (<1)	0
Age; n/N (%)			
<65 years	5/447 (1)	6/458 (1)	4/442 (1)
≥65 years	2/48 (4)	1/43 (2)	0/55 (0)
Sex; n/N (%)			
Male	4/240 (2)	2/232 (1)	2/222 (1)

Female	3/255 (1)	5/269 (2)	2/275 (1)

A total of 20 subjects reported a Cardiac Failure AE during the apremilast-exposure period of the PsA Phase 3 Data Pool (Table 27). The incidence rates of cardiac failure AEs were similar between both apremilast treatment arms with only minor differences between age and gender subgroups.

Table 27. PsA Phase 3 Data Pool: Cardiac Failure Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	**EAIR**	**n (%)**	**EAIR**
Any Cardiac Falure AE	10 (1)	2.1	10 (1)	2.1
Any Severe Cardiac Failure AE	1 (<1)	0.2	0	0
Any Cardiac Failure AE Leading to Withdrawal	0	0	1 (<1)	0.2
Age; n/N (%)				
<65 years	8/656 (1)	1.8	9/645 (1)	2.1
≥65 years	2/64 (3)	4.9	1/76 (1)	2
Sex; n/N (%)				
Male	3/347 (1)	1.2	3/324 (1)	1.4
Female	7/373 (2)	3	7/397 (2)	2.7

The overall number of reported AEs related to Cardiac Failure was small making it difficult to draw firm conclusions regarding the risk of apremilast therapy and cardiac failure. However, given that there were relatively few serious cases of cardiac failure reported in the clinical studies and that the incidence of events was similar between treatment arms, specific labeling will not be necessary at the present time.

7.3.5.6 Gastrointestinal Events

PsA Phase 3 Data Pool

Gastrointestinal events are commonly associated with the use of PDE4-inhibitors and were the most commonly reported AE in the apremilast studies. As shown in Table X, the frequency of diarrhea, nausea, and vomiting was observed to increase in a dose- and treatment-dependent manner during the placebo-controlled period of the PsA Phase 3 Data Pool. In general, there were relatively few gastrointestinal events reported as severe in nature but there was one serious case of diarrhea reported in the APR20 treatment arm and one case of serious nausea and vomiting reported in the APR30 treatment arm. The incidence rates of gastrointestinal AEs were higher in subjects aged ≥65 years compared to younger subjects; however, there were relatively small numbers of subjects ≥65 enrolled in the PsA Phase 3 studies. Additionally, females

appeared to be almost twice as likely to develop gastrointestinal AEs compared to males (Table 28).

Table 28. PsA Phase 3 Data Pool: Gastrointestinal Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Diarrhea Adverse Events			
Any Diarrhea AE	14 (3)	63 (13)	88 (18)
Any Severe Diarrhea AE	1 (<1)	3 (1)	1 (<1)
Any Diarrhea AE leading to drug withdrawal	3 (1)	5 (1)	11 (2)
Any Serious Diarrhea AE	0	1 (<1)	0
Age; n/N (%)			
<65 years	13/447 (3)	51/458 (12)	82/442 (17)
≥65 years	1/48 (2)	7/43 (16)	14/55 (26)
Sex; n/N (%)			
Male	7/240 (3)	23/232 (10)	27/222 (12)
Female	7/225 (3)	40/269 (15)	61/275 (22)
Nausea and Vomiting Adverse Events			
Any Nausea/Vomiting AE	24 (5)	56 (11)	88 (18)
Any Severe Nausea/Vomiting AE	0	2 (<1)	4 (1)
Any Nausea/Vomiting AE leading to drug withdrawal	3 (1)	7 (1)	15 (3)
Any Serious Nausea/Vomiting AE	0	0	1 (<1)
Age; n/N (%)			
<65 years	21/447 (5)	51/458 (11)	82/442 (19)
≥65 years	3/48 (6)	5/43 (12)	6/55 (11)
Sex; n/N (%)			
Male	12/240 (5)	19/232 (8)	30/222 (14)
Female	12/255 (5)	37/269 (14)	58/275 (21)

The vast majority of reported cases using the preferred term of diarrhea were of mild or moderate severity with only a few cases in each treatment arm reporting severe cases of diarrhea. Three subjects in the APR20 treatment arm reported a case of severe diarrhea and only one subject from each of the placebo and APR30 treatment arms.

The majority of diarrhea events occurred during the first two weeks of treatment (Figure 4) and the majority of diarrhea events did not last more than 30 days (Figure 5). The duration of diarrhea was ≤30 days in approximately 69%, 59%, and 53% of subjects reporting a diarrheal event in the placebo, APR20, and APR30 treatment arms.

Figure 4. PsA Phase 3 Data Pool: Diarrhea Adverse Events by Onset Day During the Placebo-Controlled Period

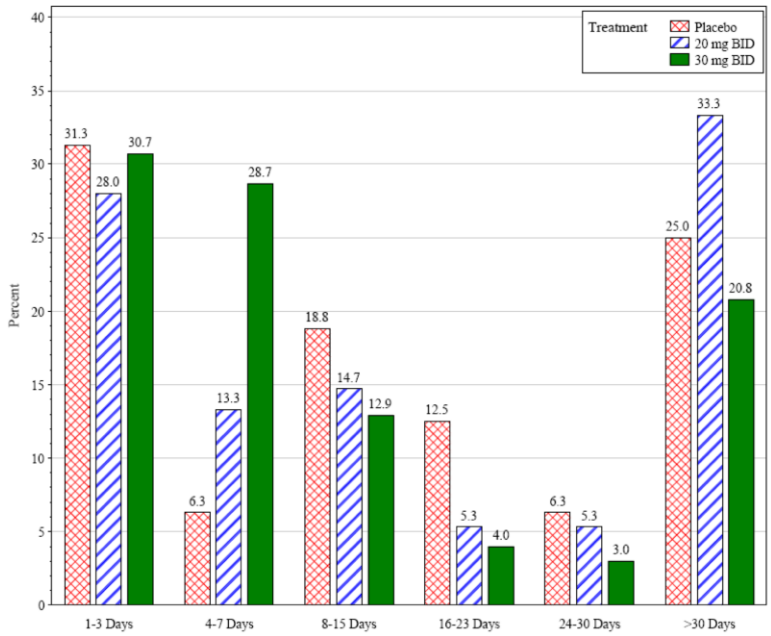
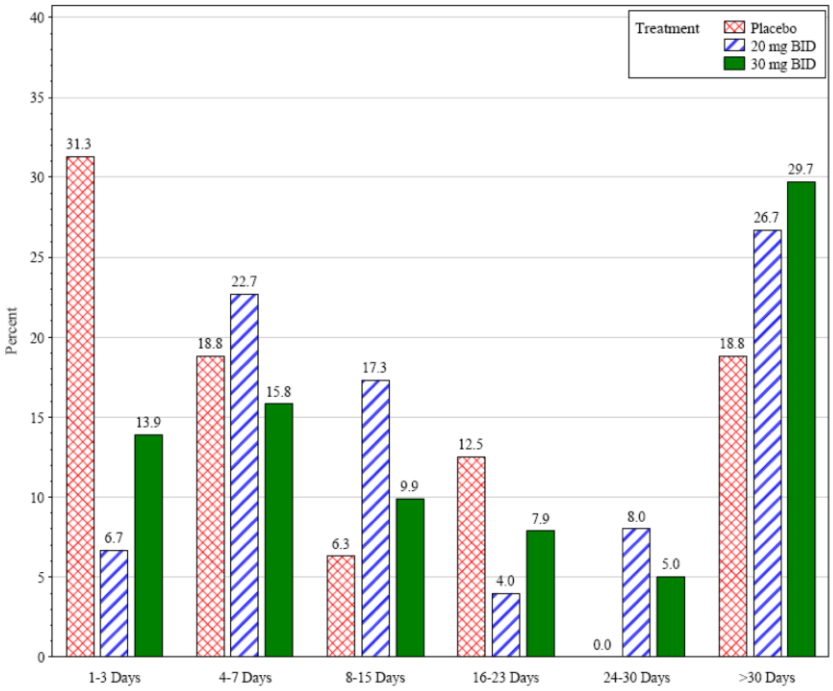


Figure 5. PsA Phase 3 Data Pool: Diarrhea Adverse Events by Treatment Duration During the Placebo-Controlled Period



More than two-thirds of diarrhea events occurred within the first 30 days of initiating study drug. Thereafter, the number of subjects reporting new cases diarrhea decreased over time (data not shown).

Similarly, more than two-thirds of nausea and vomiting AEs occurred during the first 30 days of treatment (Figure 6) in all treatment arms and the majority of these cases did not last greater than 30 days (Figure 7). Thereafter, the number of subjects reporting new cases nausea and vomiting decreased over time (data not shown).

Figure 6. PsA Phase 3 Data Pool: Nausea and Vomiting Adverse Events by Onset Day During the Placebo-Controlled Period

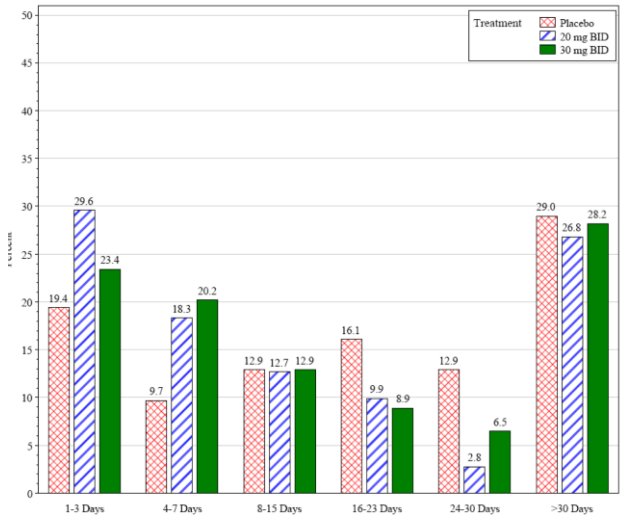
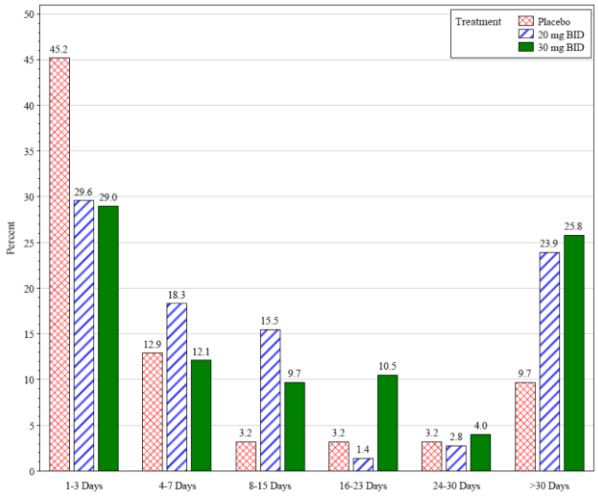


Figure 7. PsA Phase 3 Data Pool: Nausea and Vomiting Adverse Events by Treatment Duration During the Placebo-Controlled Period



Similar to the data from the placebo-controlled period, the EAIR of diarrhea and nausea and vomiting was observed to increase in a dose-dependent manner during the apremilast-exposure period of the PsA Phase 3 Data Pool with very few cases of diarrhea or nausea and vomiting reported as severe in intensity (data not shown). A greater number of gastrointestinal-related events were reported in females compared to males.

As shown in Table 29, the frequency of reported events for diarrhea by time periods for the subjects-as-initially-treated safety population increased in a treatment- and dose-dependent manner in the PsA Phase 3 Data Pool. Similarly, the frequency for events of nausea and vomiting increased in a treatment- and dose-dependent manner (data not shown).

Table 29. PsA Phase 3 Data Pool: Diarrhea Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
AE; n	16	66	75	84	97	101	112
Subjects with ≥1 SAE; n(%)	14 (3)	54 (11)	63 (13)	68 (14)	88 (18)	88 (18)	93 (19)
Exposure (subject-years)	141	133	192	306	123	179	294
EAIR per 100 subject years	9.9	40.7	32.9	22.2	71.8	49.2	31.7
95% CI	5.6, 16.1	30.8, 52.6	25.4, 41.7	17.4, 27.9	57.8, 87.9	39.6, 60.2	25.7, 38.6

In summary, these data demonstrate a treatment- and dose-dependent increase in the frequency of reported cases of diarrhea and nausea and vomiting. The majority of the cases was of mild to moderate severity and occurred in the first 30 days after starting therapy. Despite titrating the dose of apremilast in subjects initiating apremilast, a large percentage of patients experienced gastrointestinal events. While the apremilast-related gastrointestinal events may affect a patient's ability to tolerate therapy, the severity of the effects is likely to be moderate and reversible. Gastrointestinal AEs should be included in the product labeling.

7.3.5.7 Psychiatric Events

7.3.5.8.1 Depression

Higher reported cases of depression were reported in the APR20 (n=9) treatment arm compared to either placebo (n=4) or APR 30 (n=5) during the placebo-controlled period of the PsA Phase 3 data Pool (Table 30). Only two subjects, both in the APR20 treatment arm, reported a serious case of depression. The incidence depression was higher in females than in males, although the incidence of events was small.

Table 30. PsA Phase 3 Data Pool: Depression Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Depression AE	4 (1)	9 (2)	5 (1)
Any Severe Depression AE	0	0	0
Any Depression AE leading to drug withdrawal	0	3 (1)	1 (<1)
Any Serious Depression AE	0	2 (<1)	0
Age; n/N (%)			
<65 years	4/447 (1)	9/458 (2)	5/442 (1)
≥65 years	0/48 (0)	0/43 (0)	0/55 (0)
Sex; n/N (%)			
Male	1/240 (<1)	2/232 (1)	1/222 (1)
Female	3/255 (1)	7/269 (3)	4/275 (2)

The EAIR for depression AEs reported during the apremilast-exposure period of the PsA Phase 3 Data Pool was higher in the APR20 treatment arm compared to the APR30 treatment arm (3 events per 100 subject-years vs. 1.9 events per 100 subject-years, respectively). There were no notable differences in the incidences of serious cases of depression or depression leading to drug withdrawal between the two apremilast treatment arms (data not shown). A greater EAIR for depression was reported for subjects less than 65 years of age compared to older subjects; however, the total number of subjects over 65 years of age was small and the data may not accurately reflect the true incidence of depression in this age group in a broader population.

The PDE4-inhibitor roflumilast has been associated with increased frequencies of psychiatric events including depression and suicidal behavior. Consequently, the sponsor tried to detect a similar effect in the apremilast clinical studies. The data show that although a greater number of APR20 treated subjects reported depression in the PsA Phase 3 Data Pool, the overall number of events was small and an obvious dose-response effect was not observed as subjects in the PBO and APR30 treatment arms reported a similar number of events. Overall, these data do not suggest an increased incidence of depression in subjects treated with apremilast.

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7.3.5.8.2 Suicidal Ideation and Behavior

Two subjects in the PsA Phase 3 Data Pool (both in the APR20 treatment arm) reported a suicide attempt or ideation during the placebo-controlled period or the apremilast-exposure period. Neither of these events resulted in death.

Cases of suicidal behavior in the Apremilast Unblinded Data Pool included one case of suicidal ideation in a patient with a history of bipolar disorder randomized to APR30 BID in study RA-001. A subject randomized to the APR30 treatment arm in Study PSA-003 was hospitalized for worsening depression and attempted suicide. The subject had received 14 days of apremilast therapy at the time of hospitalization. This case was included in the safety review of SAEs in Section 7.3.X. Subject PSOR-008-0251014 was randomized to placebo and committed suicide via a gunshot would. This case is included in the review of deaths in Section 7.3.1. Subject PSOR-004-0020009 (randomized to APR20) and Subject PSOR-05-E-LTE-0421019 (randomized to placebo) had reported outcomes of death and suicide could not be ruled out. These cases are reviewed in Section 7.3.1. Lastly, the C-CASA analysis identified one additional case of attempted suicide in the ongoing, blinded study PSOR-009.

An assessment of suicidal ideation and behavior for the entire safety database was conducted using C-CASA terms. In addition to identifying two subjects with suicidal ideation, the results of the analysis demonstrated three subjects classified with suicidal behaviors: one completed suicide and two cases of attempted suicide. The completed suicide and one suicide attempt occurred in the blinded studies PSOR-008 and PSOR-009, respectively. The remaining three subjects were enrolled in study PSA-002 (suicide attempt), PSA-004 (suicidal ideation), and study RA-002 (suicidal ideation).

Taken together, the data do not identify a safety signal for suicidal behavior.

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7.3.5.9 Hepatobiliary Adverse Events

The frequency of hepatobiliary AEs reported during the placebo-controlled period of the PsA Phase 3 Data Pool appeared to increase in a treatment- and dose-dependent manner (Table 31). Only two subjects reported a hepatobiliary event that led to drug withdrawal. A female subject in the APR30 treatment arm developed jaundice, cholelithiasis, chronic cholecystits, and stenosis of the major duodenal palilla on Study Day 166. Apremilast dosing was discontinued temporarily and restarted following her recovery without further incident. The data also demonstrated a higher incidence of hepatobiliary AEs in females than males, although the clinical significance of this finding is unclear. Analysis of LTFs were performed separately and are reviewed in Section 7.4.2.

Table 31. PsA Phase 3 Data Pool: Hepatobiliary Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Hepatobiliary AE	5 (1)	8 (2)	11 (2)

Any Severe Hepatobiliary AE	0	0	2 (<1)
Any Hepatobiliary AE leading to drug withdrawal	1 (<1)	1 (<1)	0
Any Serious Hepatobiliary AE	1 (<1)	1 (<1)	3 (1)
Age; n/N (%)			
<65 years	5/447 (1)	7/458 (2)	11/442 (3)
≥65 years	0/48 (0)	1/43 (2)	0/55 (0)
Sex; n/N (%)			
Male	4/240 (2)	2/232 (1)	3/222 (1)
Female	1/255 (<1)	6/269 (2)	8/275 (3)

Similar rates of hepatobiliary AEs were reported for APR20 and APR30 treatment arms during the apremilast-exposure period in the PsA Phase 3 Data Pool (Table 32). The EAIR of hepatobiliary AEs was comparable between age groups and sexes.

Table 32. PsA Phase 3 Data Pool: Hepatobiliary Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any Hepatobiliary AE	26 (4)	5.6	23 (4)	5.3
Any Severe Hepatobiliary AE	0	0	2 (<1)	0.4
Any Hepatobiliary AE leading to drug withdrawal	2 (<1)	0.4	0	0
Any Serious Hepatobiliary AE	1 (<1)	0.2	4 (1)	0.8
Age; n/N (%)				
<65 years	23/656 (4)	5.4	23/645 (4)	5.5
≥65 years	3/64 (5)	7.4	2/76 (3)	4
Sex; n/N (%)				
Male	10/347 (3)	4.1	11/324 (3)	5.2
Female	16/373 (4.3)	7	14/397 (4)	5.4

7.3.5.9 Vasculitis

PDE4-inhibitors, including apremilast, have been demonstrated to induce inflammatory perivascular histopathological changes consistent with vasculitis in animal studies. Consequently, investigators were instructed to monitor for any clinical signs and symptoms of vasculitis during the apremilast clinical program. Subjects with suspected signs or symptoms of vasculitis were to be thoroughly evaluated and followed until the signs and symptoms resolved. A thorough analysis of the PsA Phase 3 Data Pool did not identify any cases of vasculitis; however, two subjects from study RA-001 were identified reported vasculitis in the Apremilast Unblinded Data Pool: one subject with RA was randomized to the APR30 treatment arm and was diagnosed with rheumatoid

vasculitis leading to study discontinuation and the second subject with RA was randomized to the placebo treatment arm and diagnosed with cutaneous vasculitis that subsequently resolved. As vasculitis is known to occur in patients with RA, and no additional cases of vasculitis were reported during the apremilast development program, the data overall do not support an association between apremilast and vasculitis.

7.3.6.0 Headache

PsA Phase 3 Data Pool

As shown in Table 33, the frequency of headache was observed to increase in a dose- and treatment-dependent manner during the placebo-controlled period of the PsA Phase 3 Data Pool. The majority of headaches were reported as mild in severity. Although less than 1% of all subjects reported severe or serious headaches, a greater number of these events were reported in the APR30 group compared to subjects in the placebo ore APR20 groups. There were no apparent differences related to the age or gender of the subjects. Eleven cases of migraines were reported during the placebo-controlled period all of which occurred in the apremilast treatment arms (APR20, n=2; APR30, n=9).

Table 33. PsA Phase 3 Data Pool: Headache Adverse Events During the Placebo-Controlled Period

MedDRA Preferred Term	PBO (n=495)	APR20 BID (n=501)	APR30 BID (n=497)
Any Headache AE	23 (5)	46 (9)	67 (14)
Any Severe Headache AE	1 (<1)	0	3 (1)
Any Headache AE leading to drug withdrawal	2 (<1)	2 (<1)	10 (2)
Any Serious Headache AE	0	0	2 (<1)
Age; n/N (%)			
<65 years	19/447 (4)	43/458 (9)	60/442 (14)
≥65 years	4/48 (8)	3/43 (7)	7/55 (13)
Sex; n/N (%)			
Male	8/240 (3)	23/232 (10)	23/222 (10)
Female	1/5255 (6)	23/269 (9)	44/275 (16)

During the placebo-controlled period, the majority of headaches occurred during the first two weeks of the treatment and did not tend to last more than two weeks. Two subjects in each of the placebo and APR20 groups, and ten subjects in the APR30 group withdrew from drug due to headache. Figure 8 and Figure 9 illustrate the reported headache events based on onset day and duration, respectively.

Figure 8. PsA Phase 3 Data Pool: Headache Adverse Events by Onset Day During the Placebo-Controlled Period

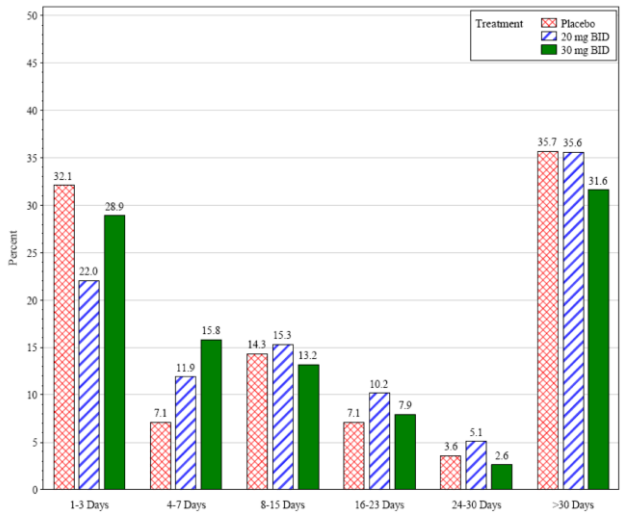
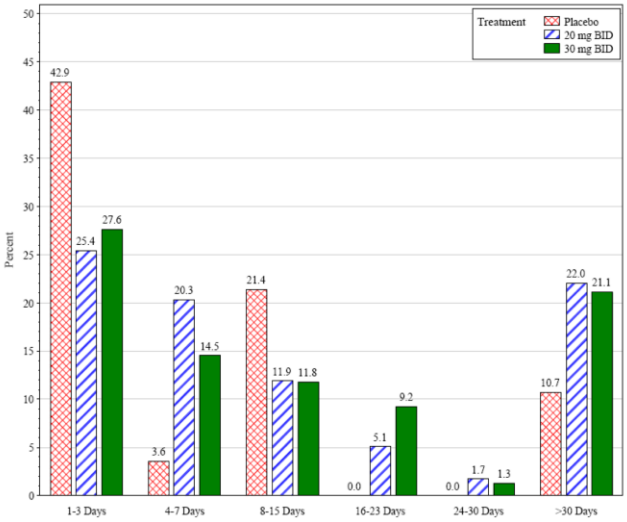


Figure 9. PsA Phase 3 Data Pool: Headache Adverse Events by Treatment Duration During the Placebo-Controlled Period



More than two-thirds of headaches occurred within the first 30 days of initiating study drug. Thereafter, the number of subjects reporting new cases diarrhea decreased over time (data not shown).

Similar to the data from the placebo-controlled period, the EAIR of headache was observed to increase in a dose-dependent manner during the apremilast-exposure

period of the PsA Phase 3 Data Pool. In general, the number of subjects reporting headaches was similar regardless of age or gender (Table 34

Table 34. PsA Phase 3 Data Pool: Headache Adverse Events During the Apremilast-Exposure Period

	APR20 BID (n=720)		APR30 BID (n=721)	
	n (%)	EAIR	n (%)	EAIR
Any Headache AE	66 (9)	15	86 (12)	19.8
Any Severe Headache AE	3 (<1)	0.6	5 91)	1.1
Any Headache AE leading to drug withdrawal	5 (1)	1	12 (2)	2.5
Any Serious Headache AE	1 (<1)	0.2	2 (<1)	0.4
Age; n/N (%)				
<65 years	61/656 (9)	15.2	75/645 (12)	19.3
≥65 years	5/64 (8)	13.1	11/76 (25)	23.8
Sex; n/N (%)				
Male	33/347 (10)	14.9	31/324 (10)	15.7
Female	33/373 (9)	15.1	55/397 (14)	23.2

As shown in Table 35, the frequency of reported events for headache by time periods for the subjects-as-initially-treated safety population increased in a treatment- and dose-dependent manner in the PsA Phase 3 Data Pool.

Table 35. PsA Phase 3 Data Pool: Headache Adverse Events By Time Period

	PBO (n=495)	APR20 BID (n=501)			APR30 BID (n=497)		
	0-16 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks	0-16 Weeks	0-24 Weeks	0-52 Weeks
AE; n	24	53	60	71	68	76	95
Subjects with ≥1 SAE; n(%)	20 (4)	42 98)	46 (9)	54 (11)	62 (13)	67 (14)	74 (15)
Exposure (subject-years)	140	135	196	315	130	190	308
EAIR per 100 subject years	14.3	31.1	23.4	17.2	47.5	35.2	24
95% CI	8.9, 21.6	22.6, 41.4	17.3, 30.9	13, 22.2	36.7, 60.4	27.5, 44.4	18.9, 29.9

In summary, these data demonstrate a treatment- and dose-dependent increase in the frequency of reported cases of headache. The majority of the cases were of mild to moderate severity and occurred in the first 30 days after starting therapy. Despite titrating the dose of apremilast in subjects initiating apremilast, a large percentage of patients experienced headaches. While the apremilast-related headache events may affect a patient's ability to tolerate therapy, the severity of the effects is likely to be moderate and reversible. Headache AEs should be included in the product labeling.

7.3.6.1 Weight Change

PsA Phase 3 Data Pool

During the placebo-controlled period, placebo-treated subjects had a mean weight gain of 0.09 kg compared with a mean weight loss -1.16 kg ad -0.96 kg observed in the APR20 and APR30 treatment arms, respectively. Similarly, during the apremilast-exposure period, both the APR20 and APR30 groups had a mean weight loss of -0.97 kg and -0.72 kg, respectively.

Weight loss during the placebo-controlled period was observed in 58% of subjects in the APR20 group and 57% of subjects in the APR30 group compared with 40% of placebo-treated subjects. The weight loss appeared to be treatment-dependent but not dose-dependent. Most cases of weight loss was between 0-5% of total body weight; however, 11% and 10% of APR20- and APR30-treated subjects, respectively, lost between 5-10% of body weight compared to 3% of placebo-treated subjects. At the end of the placebo-controlled period, only three subjects from the placebo arm, nine subjects from the APR20 group, and 5 subjects from the APR30 group lost greater than 10% of body weight. No subject discontinued due to weight loss.

A total of three placebo-treated subjects, 23 APR20-treated subjects, and 22 APR30-treated subjects experienced weight loss ≥10% from baseline at any time during the study. Figure 10 and Figure 11 illustrate weight loss over time in subjects in the APR20 and APR30 treatment arms, respectively.

Figure 10. PsA Phase 3 Data Pool: APR20 Subjects Reporting ≥10% Weight Loss From Baseline at Any Time

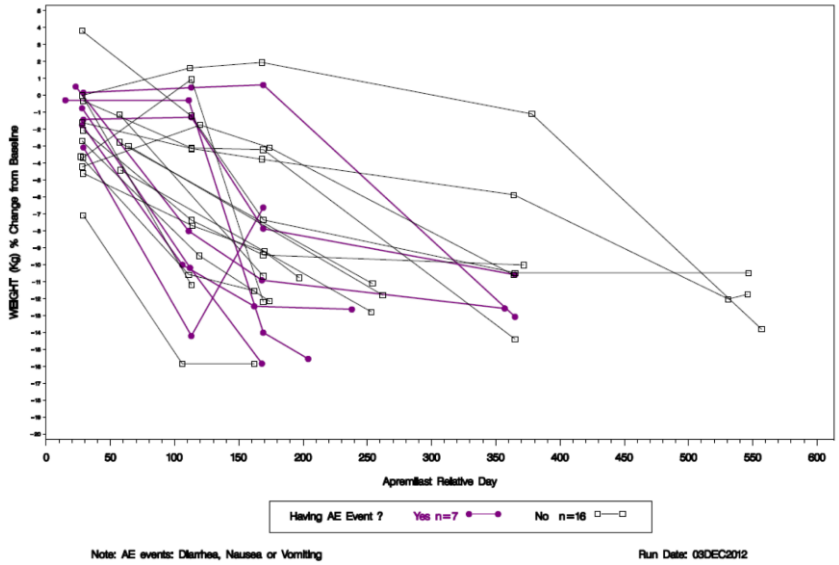
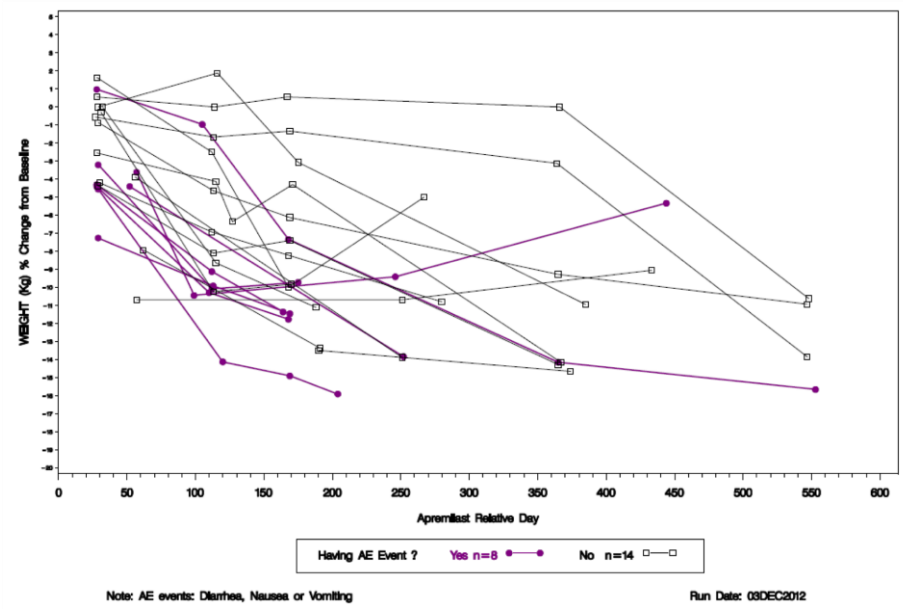


Figure 11. PsA Phase 3 Data Pool: APR30 Subjects Reporting ≥10% Weight Loss From Baseline at Any Time



Further analyses were conducted to determine whether a correlation existed between the incidence of weight loss in the presence of reported diarrhea or nausea and vomiting AEs; however, a definitive conclusion could not be drawn due to limited data as weight measurements did not occur at the time of the AEs.

The data presented here demonstrate a treatment-related loss of weight in subjects receiving apremilast with the majority of subjects losing between 0-5% of body weight. , The data did not suggest a dose-response relationship and no subjects had to withdraw for study drug due to weight loss. Weight loss should be included in the product label as a possible adverse reaction related to apremilast therapy.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse drug reactions (ADRs) were defined as any AEs occurring in ≥2% of apremilast-treated subjects where the incidence of events in any apremilast treatment group was ≥1% higher than the incidents of events in the placebo group. Since incidence rates for common AEs are best estimated using placebo-controlled studies, emphasis was placed on the data for subjects-as-treated safety population for Weeks 0-16 of the placebo-controlled period for the PsA Phase 3 Data Pool. Numbers of subjects in the apremilast-treatment groups exceed the number of patients enrolled during the first 16 weeks of study as the subjects-as-treated safety population for Weeks 0-16 includes data up to 16 weeks after the respective treatment start date. Data for the apremilast treatment arms include data up to 16 weeks after the apremilast start date for subjects randomized to placebo who also received apremilast. Use of this data increases the number of subjects exposed to both doses of apremilast and increases the sensitivity for detecting AEs.

Table 36shows the ADRs for Weeks 0-16 of the PsA Phase 3 Data Pool. Diarrhea, nausea, and headache were the most frequently reported events and appeared to be dose-dependent. Events of URIs, vomiting, and dyspepsia were also more frequently reported in the apremilast treatment arms compared to placebo-treated subjects. Nasopharyngitis was reported in a higher percentage of APR20-treated subjects compared to placebo-treated subjects; however, incidence rates were similar between the APR30 and placebo treatment arms.

Table 36. PsA Phase 3 Data Pool: Adverse Drug Reactions From Weeks 0-16

Preferred Term	PBO (n=495)	APR20 BID (n=720)	APR30 BID (n=721)
Diarrhea	14 (3)	67 (9)	100 (14)
Nausea	22 (4)	52 (7)	84 (12)
Headache	20 (4)	45 (6)	61 (9)
URI	12 (2)	35 (5)	27 (4)
Nasopharyngitis	9 (2)	23 (3)	16(2)
Vomiting	4 (1)	12 (2)	24 (3)
Dyspepsia	6 (1)	13 (2)	19 (3)
Abdominal pain, upper	1 (<1)	17 (2)	13 (2)
Cough	2 (<1)	8 (1)	10 (1)
GERD	1 (<1)	6 (1)	11 (2)
Decreased appetite	1 (<1)	9 (1)	8 (1)
Rash	2 (<1)	10 (1)	4 (1)
Migraine	0	2 (<1)	11

Frequent bowel movements	0	2 (<1)	10 (1)

For the ADRs with the highest frequency, the number of the ADR events that were reported within the first 15 days from the initiation of study drug is summarized in Table 37.

Table 37. PsA Phase 3 Data Pool: Adverse Drug Reactions Reported in the First 15 Days of Apremilast Therapy

Preferred Term	PBO (n=495) n/m (%)	APR20 BID (n=720) n/m (%)	APR30 BID (n=721) n/m (%)
Any AE	44/89 (49)	137/262 (52)	216/348 (62)
Diarrhea	9/16 (56)	47/70 (60)	79/29 (73)
Nausea	10/26 (39)	41/50 (71)	68/97 (70)
Headache	15/24 (63)	31/61 (51)	42/66 (64)
Dyspepsia	3/6 (50)	8/13 (62)	10/19 (53)
Vomiting	3/4 (75)	5/14 (36)	9/20 (32)
URI	4/13 (31)	5/30 (13)	8/29 (28)

The number of these ADR events with duration of ≤15 days is summarized in Table 38. For apremilast-treated subjects, the majority of headache, URI, and vomiting events resolved within 15 days.

Table 38. PsA Phase 3 Data Pool: Adverse Drug Reactions With a Duration of ≤15 Days of Apremilast Therapy

Preferred Term	PBO (n=495) n/m (%)	APR20 BID (n=720) n/m (%)	APR30 BID (n=721) n/m (%)
Any AE	58/89 (65)	156/262 (60)	162/348 (47)
Headache	18/24 (75)	44/61 (66)	37/66 (56)
Diarrhea	9/16 (56)	37/78 (47)	38/29 (35)
Nausea	16/26 (62)	32/50 (55)	39/97 (40)
URI	10/13 (77)	34/30 (79)	24/29 (83)
Vomiting	3/4 (75)	14/14 (100)	22/29 (79)
Dyspepsia	2/3 (33)	3/13 (23)	2/19 (11)

In summary, the most common adverse events for the APR30 dosage that should be reported as ADR events in the product label include diarrhea, nausea, headache, URI, vomiting, and dyspepsia.

7.4.2 Laboratory Findings

PsA Phase 3 Data Pool

Summary statistics of observed values and changes from baseline over time were assessed for hematology and clinical chemistry parameters in the placebo-controlled and apremilast-exposure periods for the PsA Phase 3 Data Pool. Review of the data demonstrated that baseline hematology and clinical chemistry values were well balanced in all three treatment arms. In general, mean changes from baseline in hematology and clinical chemistry values were small, infrequent, and not clinically significant. Review of the data did not demonstrate a dose-response relationship.

Additional analyses were performed assessing shifts from baseline to the end of the study period in selected hematology and clinical chemistry values for the placebo-controlled and apremilast-exposure periods. Review of the data did not demonstrate any clinically meaningful differences between treatment arms.

The most frequently abnormal hematology values reported during the placebo-controlled period was decreased lymphocyte counts (<0.8 x 10^9/L) which occurred in approximately 4% of placebo-treated subjects and in 2% and 3% of subjects randomized to APR20 and APR30 treatment arms, respectively. Assessment of liver function tests (LFTs) demonstrated that two placebo-treated subjects, two subjects in the APR20 group, and seven subjects in the APR 30 had reported an ALT or AST> 3 x ULN during the placebo-controlled period. Additionally, two subjects in the APR20 group and two subjects in the APR30 group had bilirubin >1.8 x ULN; however, there were no cases of LFT elevations meeting Hy‘s Law. The most frequent marked abnormal clinical chemistry values reported during the placebo-controlled period included elevated triglycerides (>3.4 mmol/L) and uric acid levels (>590 µmol/L [male] or >480 µmol/L) in the PBO (10% and 3%, respectively), APR20 (9%and 3%, respectively), and APR30 (9% and 3%, respectively) treatment arms. All marked abnormalities in hematology and clinical chemistry values occurred in similar proportions of subjects in all treatment arms and no dose-response relationship was noted. Similar results were observed during the apremilast-exposure period for the PsA Phase 3 Data Pool.

Apremilast Unblinded Data Pool

A greater proportion of APR30 subjects were noted to have elevated phosphate levels >1.60 mmol/L compared with subjects in the PBO or APR 20 BID groups during the placebo-controlled (1%, 1%, and 2%) and apremilast-exposure periods (not performed, 2%, and 3%, respectively). Phosphate levels were slightly higher in the PsA Phase 3 Data Pool albeit to a lesser degree. There were no correlative changes regarding other electrolytes or associated AEs from either Data Pool. The clinical significance of this finding is unclear.

Overall, analysis of hematology and clinical chemistry parameters as assessed over time, by individual subject changes, and individual clinically significant abnormalities were similar to the values observed from the placebo-controlled and apremilast-exposure periods from the PsA Phase 3 Data Pool. Marked abnormalities were infrequent and review of the data did not demonstrate any clinically meaningful differences between treatment arms or a dose-response relationship with apremilast treatment.

Given the increased frequency of gastrointestinal AEs, LFTs were analyzed separately for this review. More than 80% of subjects had normal (≤1 x ULN) ALT and AST values during both periods of the PsA Phase 3 data pool. The majority of the subjects reporting LFTs >3 x ULN had these elevations only once with resolution of the lab value while remaining on study drug. None of the subjects had an AST/ALT value >3 x ULN with an associated increase in bilirubin >1.5 x ULN. A single subject from the APR30 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. Many of the subjects were receiving concomitant medications known to be hepatotoxic including MTX or statins. No cases of LFT elevations that met Hy's Law criteria in any Data Pool.

The sponsor conducted adequate routine testing throughout the clinical studies with appropriate hematology and clinical chemistry laboratories. The most notable changes were found in the clinical chemistry laboratory values which demonstrated mild elevations of LFTs, most of which were reported as a single event and resolved while maintaining study therapy. These results are somewhat confounded due to the number of potentially hepatotoxic concomitant medications taken by study subjects. No cases of LFT elevations met Hy's Law criteria. Elevated phosphate levels were also noted in subjects in the APR30 group.

Overall, changes in laboratory values were small, infrequent, and of minimal clinical significance. Additionally, the frequency of laboratory abnormalities was typically well balanced between treatment arms and was not correlated with clinically meaningful AEs.

7.4.3 Vital Signs

During the placebo-controlled period, the mean change from baseline to the end of period ranged among the three treatment groups between -0.2 to -1.1 mmHg for systolic BP and between -0.1 to -1.0 mmHg for diastolic BP. During the apremilast-exposure period, the mean change from baseline to the end of period ranged between the two apremilast treatment groups between -0.9 to -1.1 mmHg for systolic BP and was -1.3 mmHg for diastolic BP in both groups. Mean changes from baseline for all vital signs parameters were generally consistent across treatment groups, and no

dose relationships were noted. The overall mean changes from baseline to the end of period in pulse rate was 0, 0.4, and 0.6 beats per minute in the PBO, APR20, and APR 30 treatment arms, respectively. Similar observations were noted when changes from baseline over time in vital signs were analyzed for the Apremilast Unblinded Data Pool. Overall, there were no clinically meaningful differences or trends.

7.4.4 Electrocardiograms (ECGs)

Study CC-10004-PK-008 was conducted to assess the QT effects of apremilast 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.

Analyses of the data demonstrated no significant QT prolongation effect of either dose of apremilast. The largest upper bounds of the two-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 minimum threshold for regulatory concern as described in the ICH E14 guidelines. Assay sensitivity was established as evidenced by the largest lower bound of the two-sided 90% CI for the ΔQTcF for moxifloxacin, which was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated. Further details of Study CC-10004-PK-008 can be found in the Clinical Pharmacology Review by Dr. Agarwal.

7.4.5 Special Safety Studies/Clinical Trials

A thorough study assessing the potential for apremilast to prolong the QT/QTc interval was conducted by the sponsor as is discussed in Section 7.4.4.

7.4.6 Immunogenicity

This section of the review is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The overall incidence of AEs during the placebo-controlled period and apremilast-exposure period for the PsA Phase 3 Data Pool were similar between the APR20 and AP30 BID treatment arms (Table 39). Additionally, the incidence of AEs by System Organ Class (SOC) was similar in both treatment arms except for AEs occurring under the SOCs of Gastrointestinal Disorders and Nervous System Disorders. As discussed in Sections 7.3.5.6 and 7.3.6.0, the proportion of subjects reporting diarrhea, nausea, and

headache appeared to increase in a treatment- and dose-dependent manner in both the placebo-controlled and the apremilast-exposure period. The majority of these AEs were reported as mild to moderate in severity and occurred early in the study and resolved within the first 30 days.

Table 39. PsA Phase 3 Data Pool: Overall Incidence of Adverse Events during the Placebo-Controlled Period

System Organ Class	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
Any AE	235 (48)	308 (62)	302 (61)
Gastrointestinal disorders	64 (13)	128 (26)	181 (36)
Infections and infestations	92 (19)	120 (24)	117 (24)
Nervous system disorders	35 (7)	66 (13)	82 (17)
Musculoskeletal and connective tissue disorders	36 (7)	39 (8)	42 (9)
Respiratory, thoracic, and mediastinal disorders	18 (4)	32 (6)	24 (5)
General disorders and administration site conditions	22 (4)	31 (6)	24 (5)
Investigations	13 (3)	27 (5)	25 (5)
Skin and subcutaneous tissue disorders	22 (4)	29 (6)	20 (4)
Metabolism nutrition disorders	12 (2)	30 (6)	13 (3)
Injury, poisoning and procedural complications	24 (5)	19 (4)	22 (4)
Psychiatric disorders	17 (3)	22 (4)	19 (4)
Vascular disorders	18 (4)	17 (3)	19 (4)
Cardiac disorders	9 (2)	15 (3)	16 (3)
Eye disorders	10 (2)	6 (1)	8 (2)
Reproductive system in breast disorders	10 (2)	6 (1)	5 (1)

Overall, the incidence of AEs leading to drug withdrawal during the placebo-controlled period was higher in the APR30 group than in the APR20 group (Section 7.3.3; Table X); however, the rates were similar between the two dose groups for the apremilast-exposure period.

In summary, the frequency of SAEs was low and did not vary notably across the treatment arms in both the placebo-controlled and apremilast-exposure period (Section 7.3.2, Table X). Analyses for AEs of special interest demonstrated the incidence of AEs were similar, if not lower, in the APR30 treatment arm compared to the APR20 treatment arm with the exception of gastrointestinal events and headaches (Sections 7.3.5.6 and 7.3.6.0, respectively).

7.5.2 Time Dependency for Adverse Events

The overall EIARs for AEs events in the APR20 and APR30 treatment arms for the time periods of Weeks 0-24 and 0-52 were 261.3 vs. 276.7 and 212.3 vs. 217.3, respectively. Further review of AEs from all periods of the PsA Phase 3 and Apremilast Unblinded Data Pools did not identify a time dependency between the occurrence and frequency of AEs versus apremilast exposure.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Age

The small numbers of subjects older than 65 years of age complicates the interpretation of the incidence of AEs according to age. In general, the frequency of AEs during the placebo-controlled period for the PsA Phase 3 Data Pool was similar between subjects <65 years of age compared to those ≥65 years of age. Higher incidences of AEs of diarrhea and headache were reported in subjects ≥65 years of age during the placebo-controlled period for the PsA Phase 3 Data Pool.

No effects of age were observed on the proportion of subjects reporting AEs in the APR20 treatment arm; however, a higher percentage of subject ≥65 years of age in the APR30 group experienced AEs compared to subjects <65 years of age, 76% vs. 65%, respectively.

7.5.3.2 Sex

A higher overall frequency of SAEs, AEs leading to drug withdrawal, and overall AEs was observed among female subjects compared to male subjects over all three treatment arms. Apremilast-treated female subjects experienced a greater frequency of diarrhea, nausea, and vomiting compared to male subjects. Similar trends were observed during the apremilast-exposure period for the PsA Phase 3 Data Pool.

7.5.3.3 Race

The vast majority of subjects included in the PsA Phase 3 Data Pool were White (94%) and the remaining 6% of subjects were Asian (3.5%), Black or African American (0.5%), and the remainder were American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other race. No meaningful conclusions can be drawn from the data due to the small number of non-White subjects.

7.5.3.3 Region

Overall, a higher proportion of subjects enrolled in North America reported AEs was compared to those enrolled in Europe or the Rest of the World, across all three treatment arms. The types and patterns of AEs were similar across regions with diarrhea, nausea, headache, and URI being the most commonly reported AEs in all regions. No consistent trend was observed for AEs analyzed by region during the apremilast-exposure period.

7.5.4 Drug-Disease Interactions

Overall, the proportion of subjects reporting AEs was similar between subjects with a medical history of coronary artery disorders, vascular hypertensive disorders, lipid metabolism disorders, and glucose metabolism disorders compared to those subjects without a medical history of the respective medical condition, regardless of treatment group. The proportion of subjects reporting AEs was higher in subjects with a medical history of depressive or anxiety disorders compared to subject without a medical history of depressive or anxiety disorders, regardless of treatment group.

Analysis of AEs for subjects with mild to moderate renal impairment demonstrated a treatment-dependent increase in AEs compared to placebo-treated subjects with comparable renal function during the placebo-controlled period for the PsA Phase 3 Data Pool. Overall, no dose adjustment is required for patients with mild to moderate renal impairment. Dosing recommendations for patients with severe renal failure were based on the PK study CC-10004-CP-019, the results of which are discussed in Section 4.4 of this review and in Dr. Agarwal's review.

Analysis of AEs for subjects with mild to moderate renal impairment demonstrated a treatment-dependent increase in AEs compared to placebo-treated subjects with comparable renal function during the placebo-controlled period for the PsA Phase 3 Data Pool. Overall, no dose adjustment is required for patients with mild to moderate renal impairment. Dosing recommendations for patients with severe renal failure were based on the PK study CC-10004-CP-019, the results of which are discussed in Section 4.4 of this review and in Dr. Agarwal's review.

Study CC-10004-CP-011 assessed the PK parameters of apremilast in subjects wit hepatic impairment, the results of which concluded that no dose adjustment is necessary for patients with hepatic impairment. The reader is referred to Dr. Agarwal's review for a more detailed discussion of the results of this study.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were evaluated in both the Clinical Pharmacology and Phase 3 clinical programs. Discussion of the results for the Clinical Pharmacology studies is found in Section 4.4 and in Dr. Agarwal's review. Potential drug-drug interactions during the Phase 3 studies were evaluated using the PsA Phase 3 Data Pool by baseline use of DMARDs, MTX, LEF, SSZ, corticosteroid, and prior biologics.

A lower frequency of AEs was reported among subjects with baseline DMARD use in each of the three treatment groups compared with subjects who were not receiving baseline DMARDs. A treatment-dependent trend was observed in the incidence of AEs independent of baseline DMARD use; however, a dose-related effect was not observed.

Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

Similar to the observation with baseline DMARD use, an overall lower frequency of AEs was observed among subjects receiving MTX at baseline compared with those who were not. A treatment-dependent trend was observed regarding the incidence of AEs, independent of baseline methotrexate use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

No differences in the frequency of reported AEs were observed between subjects who were, or were not receiving SSZ or LEF. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

In the placebo group, the type and pattern of AEs were generally similar between subjects who had baseline oral corticosteroid use and those subjects who did not use corticosteroids at baseline. A higher frequency of AEs was observed among subjects in the apremilast treatment groups who had baseline oral corticosteroid use compared with those who did not. The different incidence rates were primarily driven by the gastrointestinal-related events of diarrhea and dyspepsia, which were observed in both apremilast treatment groups to be more frequently reported by subjects who had baseline oral corticosteroid use compared with those who did not. A treatment-dependent trend was observed in the frequency of AEs, regardless of baseline oral corticosteroid use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

A higher incidence of AEs was reported among apremilast-treated subjects who had prior biologic use compared with those subjects who did not have prior biologic use. This imbalance was primarily driven by the AEs of nausea, headache, and vomiting in the APR 20 BID group and diarrhea in the APR 30 BID group. A treatment-dependent trend was observed in the incidence of AEs, regardless of prior biologic use; however, a dose-related effect was not observed. Similar findings were observed during the placebo-controlled and apremilast-exposure periods.

Overall, the safety comparing the incidence of AEs from the PsA Phase 3 Data Pools demonstrate an acceptable safety profile when used alone or in combination with DMARDs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not conducted.

7.6.2 Human Reproduction and Pregnancy Data

MATERNAL HEALTH CONSULT PENDING

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric studies have been deferred.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A total of eight subjects reported 14 AEs termed “Overdose” in the PsA Phase 3 Data Pool, all of which were without an associated AE. Some healthy adults were exposed to a maximal dose of 50 mg BID for up to 4.5 days during the Clinical Pharmacology dose-escalation studies without evidence of dose-limiting toxicities. Supportive care is advised in the event of apremilast overdose. No safety signals were identified regarding abuse potential, withdrawal, or rebound effect with apremilast.

7.7 120-Day Safety Update

The 120-day safety update report included safety data from a total of 1441 subjects who were exposed to apremilast in the PsA Phase 3 Data Pool, which included 721 subjects who received apremilast 30 mg BID, the proposed marketed dose. While the overall number of apremilast-treated subjects remained the same as that submitted to the original application, the total exposure to apremilast 30 mg BID increased from 478 subject-years to 769 subject-years. Consequently, the number of subjects in the APR 30 BID group who were exposed to apremilast for at least 24-weeks increased from 527 (73%) in the original NDA to 622 (86%) in the 120-day safety update, and those who were exposed to apremilast for at least 48-weeks increased from 183 (25%) in the original NDA to 477 (66%) in the 120-day safety update. Approximately half of the APR30-treated subjects included in the 120-day safety update exposed to apremilast for at least 60-weeks.

The adverse event data for this additional time period demonstrated a similar safety profile for apremilast with that presented in the original NDA. Overall, the type and pattern of AEs and SAEs did not change. The incidences of individual AEs increased slightly compared to those observed in the original NDA but remained at less than 5%, and when adjusted for drug exposure, the EAIRs did not increase. The most frequently

reported AEs in the 120-day safety update were diarrhea, nausea, headache, and URI, which are consistent with the results observed in the original NDA. The majority of AEs were reported as mild to moderate in severity. Additionally, the data confirmed that AEs of diarrhea, nausea, and headache occurred at the highest frequency during the first four weeks of dosing with apremilast and decreased thereafter.

The same analyses used to assess AEs of special interests in the original NDA were utilized in this 120-day safety update. Overall, the EAIRs of AEs of special interest observed in the updated data for both apremilast treatment arms remained comparable to those observed in the original NDA. The voerall frequency of serious infections, MACE or potential MACE, and malignancies were not increased in apremilast-treated subjects. One additional subject in the APR30 treatment arm reported a suicide attempt.

Overall, the data included in the 120-day safety update expanded the total exposure to apremilast and were consistent with the data included in the original NDA. No new safety signals were identified in the 120-day safety update despite increased exposure to apremilast and the safety profile appears comparable between the APR 20 mg BID and APR 30 mg BID dosing regimens.

In conclusion, the safety data included in the 120-day safety update did not identify a safety signal different from what was seen in the original NDA.

8 Postmarket Experience

This is the initial NDA application for apremilast. No postmarketing experience is available.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Labeling recommendations are pending following receipt of all outstanding consults.

9.3 Advisory Committee Meeting

Following the initial review and discussion of the application, the review team determined apremilast to be efficacious in adult patients with PsA with an acceptable safety profile and no identifiable serious safety signals or outstanding issues. Consequently, a determination was made deciding that a meeting of the FDA's Arthritis Advisory Committee would not be required.

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/s/

KEITH M HULL

11/20/2013

NOTE: This primary review is a late draft. Several consultations are still pending, the results of which will be required to complete the final conclusions of efficacy, safety, and labeling recommendations. An updated version of this review will be entered as soon as the required data is available and reviewed.