CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206088Orig1s000

MEDICAL REVIEW(S)

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Food and Drug Administration
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Memorandum

DATE: June 2, 2014

FROM: Shari L. Targum, M.D., Team Leader
Division of Cardiovascular and Renal Products

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products

TO: Dawn Williams, Regulatory Project Manager, Division of Dermatology and Dental Products
Snezana Trajkovic, M.D., Medical Officer, Division of Dermatology and Dental Products

SUBJECT: NDA #206088
NAME OF PRODUCT: Apremilast
TRADE NAME: Otezla
FORMULATION: oral tablets

RELATED APPLICATIONS: NDA # 205 437, IND #070270
APPROVED INDICATIONS: Psoriatic arthritis
SPONSOR: Celgene Corporation

DOCUMENTS AVAILABLE FOR REVIEW: NDA submission, electronic document room; package insert, Otezla; package insert, roflumilast (Daliresp)
DATE CONSULT RECEIVED: 4/29/2014
REQUESTED COMPLETION DATE: 5/5/2014, amended to 5/31/2014
DATE CONSULT COMPLETED: 5/30/2014

INTRODUCTION:

Apremilast is a phosphodiesterase 4 (PDE 4) inhibitor; PDE 4 is the predominant form of phosphodiesterase in inflammatory cells. NDA 206088 is intended to support the approval of apremilast for the treatment of moderate to severe psoriasis. Subjects with stable cardiovascular risk factors were not excluded from clinical trials, and the applicant has provided an analysis of cardiovascular events. During the review of this application by the Division of Dermatology and Dental Products (DDDP), an imbalance in major adverse cardiac events (MACE) was noted, with higher frequency in apremilast-treated subjects compared to those on placebo; however, this imbalance reverses when adjusted for the difference in exposure.

DDDP has requested that the Division of Cardiovascular and Renal Products provide an assessment of cardiovascular safety and advice on whether to include language in labeling or additional data/analysis to assess cardiovascular safety.

BACKGROUND:

Apremilast was approved, in doses up to 30 mg BID, for the treatment of adult patients with active psoriatic arthritis. The apremilast label reports exposures up to 16 weeks in 493 patients; listed under "Warnings and Precautions," are depression and weight decrease, (b) (4)

The pharmacokinetics of apremilast in healthy subjects are characterized by a median time to maximum plasma concentration (Tmax) of 1 to 4 hours postdose; (steady-state plasma concentrations achieved by 24 hours after the start of multiple dosing) and mean apparent elimination half-life of 5-7 hours. The systemic exposure appears to be increased in a dose-proportional manner, with slight accumulation following multiple twice-daily dosing at 40 mg and 50 mg. Apremilast is extensively metabolized, with a glucuronide conjugate of O-demethylated apremilast (M12) as the major circulating metabolite (urinary excretion 34% of the total administered dose). According to the thorough QT study report, the plasma elimination half-life for M12 was 12 hours and for M14 (a second metabolite) about 19 hours.

Another marketed PDE4 inhibitor, roflumilast (Daliresp), was approved in February, 2011 to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD. Labeling for Daliresp contains Warnings and Precautions language for acute bronchospasm, psychiatric events and drug interactions.

The thorough QT study results revealed an upper bound of the placebo-subtracted change in QTc I under 10 msec, with assay sensitivity demonstrated with single-dose moxifloxacin. No changes in vital signs were reported. There were dose-related increases in the frequency of headache and nausea (no such events in placebo). However, this study has not been formally reviewed by the interdisciplinary QT review team.

The apremilast NDA submission included 6 phase 2/3 trials: two open-label Phase 2 trials (PSOR-001 and PSOR-004), two randomized, double-blind Phase 2 trials (PSOR-003 and PSOR-005-E-LTE) and two Phase 3 pivotal trials (PSOR-008 and PSOR-009). PSOR-005, PSOR-008 and PSOR-009 include ongoing open-label extension phases.

Table 1. Apremilast Phase 2/3 clinical trials

Study number	N	Treatments	Design/ duration
PSOR-001	19 enrolled	APR 20 mg QD	Open-label, single-arm, pilot/ 29 day duration
PSOR-003	260 randomized	Placebo, APR 20 mg QD, APR 20 mg BID	Randomized, double-blind, placebo-controlled, APR 20 mg QD vs. BID/ 12 week duration
PSOR-004	31 enrolled	APR 20 mg BID; APR 30 mg BID	Open-label, 12 weeks, with 12 week extension (nonresponders up-titrated to 30 mg BID)/ 24 weeks total duration
PSOR-005	352 randomized	Placebo, APR 10 mg BID, 20 mg BID, 30 mg BID	Randomized, double-blind, placebo-controlled (16 weeks) followed by randomized, double-blind, active-controlled, dose-ranging/ up to 4 year total treatment duration
PSOR-008*	844 randomized (562 APR,	Placebo, APR 30 mg BID	Placebo-controlled, randomized (2:1 ratio) x 16 weeks (Weeks 0-16), followed by 16 week maintenance phase (placebo subjects switched to APR 30 mg BID (Weeks

	282 placebo)		16-32), followed by 20 week randomized withdrawal (placebo, APR 30 mg BID) (Weeks 32-52), followed by long-term extension (208 weeks, Weeks 52-260/ total study duration of 5 years
PSOR-009*	413 randomized (275 APR, 138 placebo)	Identical design to PSOR-008	

Source: NDA 206088 clinical overview, Table 1. *Pivotal Phase 3 efficacy trial.

PSOR-003, PSOR-005, PSOR-008 and PSOR-009 contained double-blind, placebo-controlled phases. PSOR-008 and PSOR-009, the pivotal efficacy studies, were designed with 2:1 randomization, active drug: placebo for a maximum duration of 16 weeks prior to active therapy.

About twice as many subjects were exposed to apremilast 30 mg BID at Week 0 compared to those exposed to placebo. In addition, subjects were exposed to apremilast for a longer duration. These imbalances in exposure should be considered when evaluating absolute numbers of events.

Table 2. Psoriasis Phase 3 data pool: extent of study drug exposure

Exposure Category[a]	Subjects as Initially Treated at Week 0		Apremilast Subjects as Treated[b]
	Placebo (N=418) n (%)	APR 30 BID (N=832) n (%)	APR 30 BID (N=1184) n (%)
≥ 1 Day	418 (100.0)	832 (100.0)	1184 (100.0)
≥ 4 Weeks	397 (95.0)	792 (95.2)	1137 (96.0)
≥ 8 Weeks	377 (90.2)	766 (92.1)	1101 (93.0)
≥ 12 Weeks	363 (86.8)	752 (90.4)	1072 (90.5)
≥ 24 Weeks	0	687 (82.6)	968 (81.8)
≥ 32 Weeks	0	598 (71.9)	854 (72.1)
≥ 52 Weeks	0	431 (51.8)	564 (47.6)
≥ 78 Weeks	0	165 (19.8)	197 (16.6)
≥ 91 Weeks	0	66 (7.9)	72 (6.1)
≥ 104 Weeks	0	24 (2.9)	24 (2.0)

APR = apremilast; BID = twice daily.

[a] Exposure is based on each subject's total exposure to investigational product which is defined as the time interval between the date of the first dose of investigational product and the date of the last dose of investigational product in the period, inclusive. For the randomized withdrawal phase, the time interval while subjects are exposed to placebo is excluded from exposure.

[b] Apremilast Subjects as Treated includes all subjects exposed to apremilast regardless when apremilast began.

Source: Sponsor's summary of clinical safety

Demographics and study population characteristics:

The majority of enrolled subjects were white (91%) and male (68%); the overall median age was 46 years (range 18-83 years, with 108 subjects ≥ 65 years). About 31% had a history of hypertension, 10% type 2 diabetes mellitus, 15% obesity, 13% hyperlipidemia, and only 5% with a history of coronary

artery disorders (e.g., coronary artery disease, myocardial infarction, angina pectoris). No imbalances are observed between treatment groups.

Safety results:
In the pooled Phase 3 pivotal trials, a higher percentage of subjects discontinued from placebo than active treatment.

Table 3. Subject disposition (PSOR Phase 3 pool, subjects initially treated at Week 0)

Disposition	Placebo (N=418)	APR 30 mg BID (N=832)
Safety population (%)	418 (100)	832 (100)
Completed	352 (84)	723 (87)
Discontinued	58 (14)	95 (11)
Primary Reason for discontinuation		
Adverse event	14 (3)	36 (4)
Lack of efficacy	9 (2)	5 (0.6)
Noncompliance with study drug	0	7 (0.8)
Withdrawal by subject	16 (4)	20 (2)
Death	1 (0.2)	0
Lost to follow-up	15 (4)	17 (2)
Protocol violation	1 (0.2)	2 (0.2)
Other	2 (0.5)	2 (0.2)
Missing	0	0

Source: Table 1.3.1. Studies PSOR-008 and PSOR-009 included.

When adjusted for exposure, more APR-treated subjects, compared to placebo, experienced an adverse event that led to therapy discontinuation. No imbalances are reported in exposure-adjusted incidence of serious adverse events.

Table 4. Overview of treatment-emergent adverse events during the treatment duration period Weeks 0 to 16 (PSOR Phase 3 data pool).

	Subjects as Initially Treated at Week 0				Apremilast Subjects as Treated	
	Placebo (N=418)		APR 30 BID (N=832)		APR 30 BID (N=1184)	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
Any TEAE	239 (57.2)	**350.3**	573 (68.9)	**536.4**	793 (67.0)	**483.8**
Any severe TEAE	15 (3.6)	**13.0**	32 (3.8)	**13.7**	40 (3.4)	**12.0**
Any serious TEAE	11 (2.6)	**9.5**	17 (2.0)	**7.2**	22 (1.9)	**6.5**
Any TEAE leading to drug withdrawal	16 (3.8)	**13.8**	45 (5.4)	**19.2**	57 (4.8)	**17.0**

APR 30 BID = apremilast 30 mg twice daily; EAIR = exposure-adjusted incidence rate; TEAE = Treatment-emergent adverse event.
Note: For Subjects as Initially Treated at Week 0 data up to the Week 16 visit are included. For Apremilast Subjects as Treated, data for the first 16 weeks of exposure are included regardless of when apremilast exposure started, ie, for subjects treated with apremilast at Week 0, data from study Weeks 0-16 are included, whereas for subjects who are first treated with apremilast at Week 16, data from study weeks 16 to 32 are included.
The EAIR per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event)

Treatment-emergent adverse events (TEAE):

The most common TEAEs with a significantly higher incidence in APR-treated subjects (vs. placebo) were diarrhea, nausea, tension headache, and frequent bowel movements.

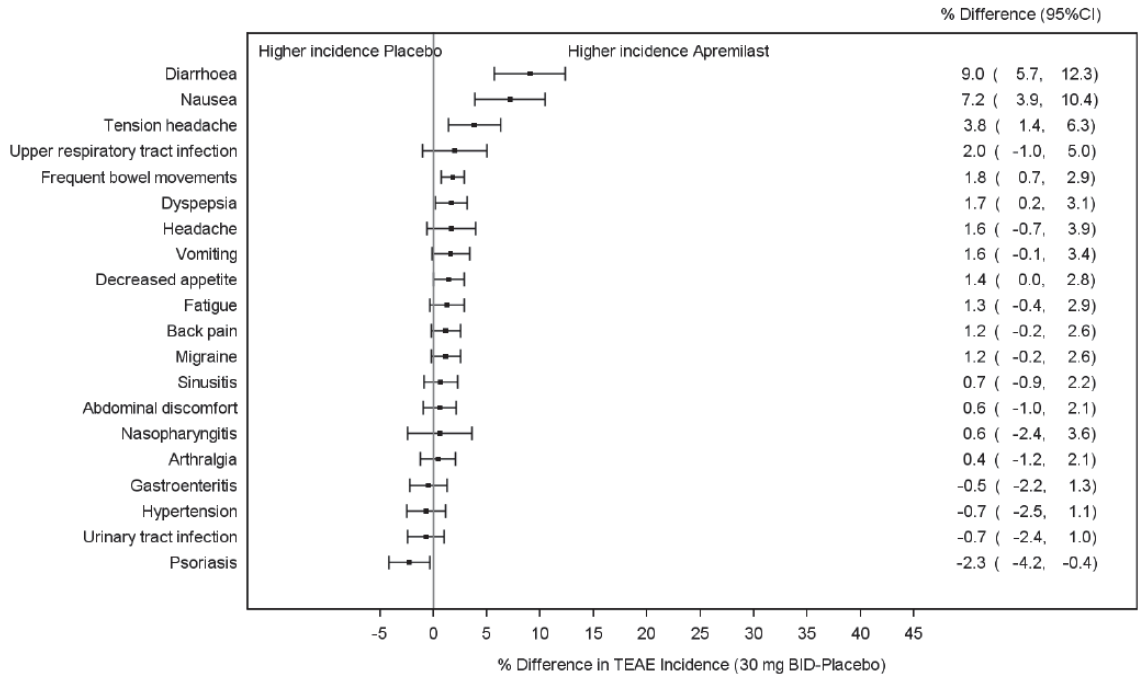

Figure 1. Percent difference (APR-placebo) in incidence of TEAE reported by 2% of subjects in any treatment group, Weeks 0-16 (subjects as treated). Source: summary of clinical safety, figure 1

Deaths:

A total of 8 subjects died during the apremilast clinical program, including: one death in the psoriatic arthritis studies (APR 20 mg BID group in study PSA-002), 6 deaths in the PSOR studies (3 deaths in PSOR-008, and one death each in studies PSOR-004, PSOR-005-E-LTE, PSOR-009), and one death in an investigator-initiated study in rheumatoid arthritis. Five deaths occurred in apremilast-treated subjects, 2 deaths occurred in placebo subjects, and one death occurred in a subject initially randomized to apremilast and re-randomized to placebo in the randomized withdrawal phase.

1. PSA-002: subject PSA-002-9051004, 52 year-old White female randomized to APR 20 mg BID, also receiving concomitant methotrexate, diagnosed with Vitamin B12 deficiency anemia prior to apremilast. Also noted prior to APR were elevated LDH (878 U/L) and CRP. On study Day 2 (Sept 30, 2011), the subject complained of mild weakness and nausea, which were untreated. On Day 28 (Oct 26, 2011), her LDH remained elevated at 742 U/L; on Nov 16, 2011, hematology results were reportedly normal and no chemistry was performed. [redacted] (b) (6), it was reported that the subject had died at another hospital. An autopsy was performed but was not released at the family's request. According to the sponsor, the death certificate indicated that the "direct cause of death was multi-organ failure, specifying that severe B12 deficiency anemia led up to the event of multi-organ failure." The sequence of events leading to the fatal outcome was not provided; the last dose of study medication was [redacted] (b) (6).

2. PSOR-004: subject PSOR-004-0020009, 398-pound, 48 year-old White male, randomized to APR 20 mg BID, history of cardiac arrhythmia treated with cardiac ablation procedure, experienced an unwitnessed death (b) (6) after the start of apremilast treatment and (b) (6) days after the dose was increased from 20 to 30 mg BID. The cause of death was reported (based on an unconfirmed verbal report from "significant other") as myocardial infarction, heart arrhythmia, and hypertensive changes. An autopsy was performed; the sponsor states that numerous attempts to obtain an autopsy report or death certificate were unsuccessful.

3. PSOR-005: subject PSOR-005-E-LTE-0421019, 63 year-old male, randomized to placebo, found unresponsive by wife with "unusual pink complexion" on Study Day (b) (6) in his closed garage with motorcycle running; autopsy showed no suspicious findings" and labeled the event as "accidental death."

4. PSOR-008: subject PSOR-008-4031002, 30 year-old White female with history of depression (concomitant medication included escitalopram oxalate) , obesity (screening BMI 35 kg/m2) and alcohol use, found dead by partner (b) (6) after taking the last dose of apremilast, Study Day (b) (6). Autopsy report revealed diffuse lung congestion and bilateral edema, consistent with acute heart failure; at the time of death, the subject's BMI was 40.6 kg/m2. Per the sponsor, previous CXR (Jul 21, 2011), ECGs (Jul 21, 2011 and Aug 3, 2011) and laboratory tests (Jul 2011, Aug 2011, Sep 2011, Oct 14 and 26 2011) did not reveal abnormalities; toxicology report was negative for those drugs included in the analysis.

   Reviewer: Cause of death unclear, but acute heart failure would be unusual in a 30 year-old with no cardiac history. The event occurred (b) (6) days after stopping study drug, making it less likely to be an acute drug reaction. Additional possibilities include concomitant medication (Escitalopram labeling contains warnings for clinical worsening/suicide risk as well as postmarketing reports of cardiac failure) or alcohol (if not included in toxicology testing).

5. Study PSOR-008: subject PSOR-008-1051011, 69 year-old White male who received placebo during the placebo-controlled phase, followed by APR 30 mg BID for a total of 666 days; on Study Day (b) (6), the subject experienced symptoms of stroke, became unresponsive and died (b) (6) (b) (6). No treatment was reported and no autopsy was performed. The type of stroke was reported as unknown.

6. PSOR-008: subject PSOR-008-0251014, 28 year-old White female, committed suicide via gunshot wound. The subject was randomized to placebo and received the last dose on Day (b) (6).

7. Study PSOR-009: subject PSOR-009-1191012, 51 year-old White female, died on Study Day (b) (6) due to intracranial hemorrhage, (b) (6) days after the last dose of apremilast while in the randomized withdrawal phase. The subject had received apremilast for 224 days followed by placebo in the randomized withdrawal phase; the event occurred on Study Day (b) (6).

8. Study AP-RA-PI-024, an investigator-initiated study in RA, subject 0011002, an 82 year-old female who previously received APR 30 mg BID died due to acute myeloid leukemia (diagnosed approximately 6 months after receiving apremilast). The subject had a history of breast cancer and uncontrolled rheumatoid arthritis for 4 years prior to study entry; prior treatment included adalimumab, methotrexate, and other TNF-alpha inhibitors. The subject died (b) (6) years after reciving her last dose of apremilast. *Reviewer comment: Noncardiovascular event by history.*

Adjudicated evaluation of MACE and potential MACE:

MACE (major adverse cardiac events) were defined as TEAEs of sudden unwitnessed death, cardiovascular death (sudden cardiac death, death due to: myocardial infarction, heart failure, stroke, or other cardiovascular causes), myocardial infarction and nonfatal stroke.

Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularization procedure, transient ischemic attack (TIA), re-hospitalization for recurrent ischemia, embolic events and deep vein thrombosis.

Events from 5 (1.2%) subjects in the placebo group and 19 (1.6%) subjects in the APR 30 mg BID group were identified for adjudication; events from 1 placebo and 2 APR (30 mg BID) subjects were not evaluable.

	MACE events	Incidence rates (subject-years)	Potential MACE events	Incidence rates (subject-years)
Placebo	1	0.2% (0.9/100 subject-years)	1	0.2% (0.9/100 subject-years)
APR 30 mg BID	6	0.5% (0.5/100 subject-years)	9	0.8% (0.8/100 subject-years)

Reviewer comment: When adjusted for subject-years (exposure), there does not appear to be an increase in MACE or potential MACE events with APR.

Exposure-adjusted adjudication results for MACE and potential MACE (subjects as treated)

		Apremilast	
	Placebo (N=1411, SY=429.5)	**APR 30 BID (N=2357, SY=2241.5)**	**APR Total (N=4089, SY=3541.0)**
	EAIR	**EAIR**	**EAIR**
MACE	0.2	0.3	0.3
Potential MACE	0.5	0.6	0.6

APR = apremilast; BID = twice daily; EAIR = exposure-adjusted incidence rate; MACE = major adverse cardiac event; SY = subject-years.
Note: The placebo group includes all data during the placebo-controlled period of each study. For the apremilast groups, all data for subjects exposed to apremilast are included regardless of when the apremilast exposure started.
Each subject is counted once for each applicable event type. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).
Source: Table 3.20.2.

From the original application (psoriatic arthritis indication), I am including Dr. Nikolay's review of MACE events:

"Cardiovascular disorders were identified as events of interest for monitoring and analyses. Adverse events related to MACE included sudden unwitnessed death, cardiovascular death(i.e., sudden cardiac death, death due to MI, death due to heart failure, death due to stroke,death due to other cardiovascular causes), MI, and non-fatal stroke. Potential MACE was defined as unstable angina

requiring hospitalization, coronary revascularization procedures, transient ischemic attack (TIA), re-hospitalization for recurrent ischemia, embolic events, and deep vein thrombosis.

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

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

COMMENTS:

1. Given the applicant's phase 3 study design, there is a higher exposure to apremilast than placebo. The incidence of adverse events should be adjusted to account for this imbalance in exposure.
2. When adjusted for the difference in exposure, there does not appear to be a significant or meaningful increase in MACE events between apremilast and placebo.
3. Based on results of the TQT study, there does not appear to be a signal of regulatory concern for QT prolongation; however, the interdisciplinary QT review team should be formally consulted to review this study.
4. One should note the low numbers of MACE events in placebo-treated subjects, possibly due to the imbalance in exposure, the relatively short duration of placebo-controlled data, or that the enrolled study population was not at high risk of MACE events (e.g., median age < 50 years and 3% of subjects with prior cardiac history). The low numbers of MACE events limit conclusions concerning cardiac safety and limit extrapolation to a higher-risk population.
5. We have no labeling recommendations at this time.

Thank you. If you have any further questions please feel free to contact us.

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/s/

SHARI L TARGUM
06/02/2014

NORMAN L STOCKBRIDGE
06/02/2014

CLINICAL REVIEW

Application Type	NDA 505(b)(1)
Application Number(s)	20-6088
Priority or Standard	Standard
Submit Date(s)	September 23, 2013
Received Date(s)	September 23,2013
PDUFA Goal Date	September 23, 2014
Division / Office	DDDP/ODEIII
Reviewer Name(s)	Snezana Trajkovic
Review Completion Date	May 23, 2014
Established Name	Apremilast
(Proposed) Trade Name	OTEZLA
Therapeutic Class	Phosphodiesterase 4 (PDE4) inhibitor
Applicant	Celgene Corporation
Formulation(s)	10mg; 20mg; 30mg tablet
Dosing Regimen	30mg twice daily
Indication(s)	Moderate to severe plaque psoriasis
Intended Population(s)	18 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that apremilast 30mg BID tablet be approved for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

1.2 Risk Benefit Assessment

In this NDA, the applicant requests approval for their product, apremilast 30mg tablet, for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. In support of this indication, the applicant conducted two well controlled Phase 3 trials.

The primary evidence of efficacy was based on two well-controlled Phase 3 trials of similar design, PSOR-008 and PSOR-009. These two Phase 3 trials were randomized, multicenter, double-blind, placebo-controlled, 52-week trials evaluated the safety and efficacy of 30mg apremilast tablet administered twice daily for the treatment of adult subjects with moderate to severe psoriasis who were candidates for phototherapy or systemic therapy. Two trials enrolled 1257 subjects, 18 years of age and older, who had a psoriasis body surface area involvement (BSA) of ≥10%, Psoriasis Global Assessment (sPGA) score of ≥3 (moderate to severe), Psoriasis Area Severity Index (PASI) score ≥12, and were candidates for phototherapy or systemic therapy. Subjects took 30mg apremilast tablet twice daily or placebo twice daily, for 52 consecutive weeks.

The primary endpoint was the proportion of subjects who achieved at least a 75% reduction from baseline in the PASI score at Week 16. After 16 weeks of treatment, in PSOR-008, 33.1% of apremilast treated subjects achieved PASI-75 score, compared to 5.3% of placebo treated subjects, a treatment effect of 27.8% ($p<0.0001$). In PSOR-009, 28.8% of apremilast treated subjects achieved PASI-75 score, compared to 4.4% of placebo treated subjects, a treatment effect of 24.4% ($p<0.0001$).

A major secondary endpoint was the proportion of subjects who achieved sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline, at Week 16. In PSOR-008, 21.7% of apremilast treated subjects and 3.9% of placebo treated subjects achieved sPGA response, a treatment effect of 17.8%,($p<0.0001$). In PSOR-009, 20.4% of apremilast subjects and 4.4% placebo treated subjects achieved sPGA response, a treatment effect of 16% ($p<0.0001$).

The data from these two Phase 3 trials provided evidence of efficacy for 30mg apremilast tablet in the target population. Efficacy was consistent across sub-groups (by age, gender, race, baseline disease severity) and across study centers.

The assessment of safety for the apremilast 30mg BID was primarily based on analysis of data from two Phase 3 trials (PSOR-008 and PSOR-009) and one Phase 2 trial (PSOR-005). The safety population included 1308 subjects exposed to repeated dosing of apremilast at the proposed dose of 30mg BID.

During apremilast development program for the psoriasis indication, although deaths were reported, detailed analysis these events did not suggest a causal relationship. Review of serious adverse events (SAEs) did not reveal safety signals.

Analysis of psychiatric adverse events identified an increased incidence of depression in apremilast-treated subjects compared to placebo-treated subjects. No increased risk for suicide or suicidal behavior was identified. Current labeling includes information about the risk of depression in section 5 WARNINGS AND PRECAUTIONS. This reviewer recommends an addition of information on depression obtained from psoriasis trials.

The most frequently reported adverse reactions (ARs) were diarrhea, upper respiratory tract infection and nausea. The highest incidence of diarrhea started during the first 30 days of apremilast treatment, and in 20% of subjects lasted over 30 days. Significant weight loss (more than 5% of body weight) was also observed in subjects treated with apremilast compared to placebo treated subjects. A greater proportion of subjects who experienced weight loss of >5% of body weight also reported diarrhea compared to subjects who had weight loss of <5% of body weight. The mean weight loss in apremilast treated subjects was greatest during the first 16 weeks of treatment and continued up to Week 52. Based on these results, this reviewer concludes that there is temporal and clinical association of weight loss and diarrhea and such association should be included in labeling. Weight loss is included in the current labeling in the section 5 WARNINGS AND PRECAUTIONS, and this reviewer recommends inclusion of diarrhea in the same section.

In this reviewer's opinion, the applicant provided adequate evidence of safety of apremilast 30mg BID. Review of the safety database did not identify a safety signal that would preclude an approval of apremilast.

This reviewer concludes that 30mg apremilast tablet, administered twice daily, has acceptable risk/benefit profile for the treatment of subjects with moderate to severe plaque psoriasis. An approval action for this NDA is recommended, pending final labeling negotiations with the applicant.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

For pediatric patients, ages 6 to 17 years, information is needed on pharmacokinetic and safety of apremilast for the treatment of moderate to severe psoriasis. Deferred pediatric studies in pediatric patients ages 6 to 17 years will be conducted as required by PREA.

Under PREA, the following studies are recommended as a PMR:

- Conduct of dose finding, pharmacokinetic and safety trial in pediatric patients with moderate to severe plaque psoriasis age 6 to (b) (4).

- Conduct a trial in pediatric patients with moderate to severe plaque psoriasis age 6 to (b) (4) to evaluate efficacy and safety of apremilast tablet.

2 Introduction and Regulatory Background

2.1 Product Information

Apremilast is an approved drug product indicated for the treatment of active psoriatic arthritis (NDA 205437; March 21, 2014). Apremilast is an inhibitor of phosphodiesterase type 4 (PDE4) that modulates intracellular inflammatory mediators. PDE4 is cyclic adenosine monophosphate (cAMP)-specific PDE, a dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels which in turn down-regulates the inflammatory response by modulating the expression on TNF-α, IL-23, IL-17 and other inflammatory cytokines.

The applicant's proposed indication is for treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. The proposed dose and dosing regimen is as follows: after upward titration over 6 days, 30mg twice daily (BID) thereafter.

Apremilast tablets are diamond shaped; film coated, and supplied in the following dosage strengths: 10mg; 20mg and 30mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant proposes their product for "treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy." In the trials relied on to support the marketing application, disease of this severity was defined on a Physician Global Assessment of ≥3 (moderate or greater), Psoriasis Area and Severity Index (PASI) score of ≥12 and Body Surface Area (BSA) involvement of ≥10%.

Phototherapy entails exposure to UVA in combination with photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA , or UVB (including narrowband). The risk of squamous cell carcinoma is increased with cumulative high-dose exposure to PUVA. Products currently available for the applicant's target population are presented in Table 1.

Table 1: Currently Available Treatment for Proposed Indication

Product	**Class**	**Warnings/Precautions**
Acitretin	Retinoid	Teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	Folate antagonist	Liver fibrosis, hematologic toxicity; teratogen
Cyclosporine	Inhibits IL-2	Hypertension, nephrotoxicity; serious infections; malignancies
Alefacept	Inhibits LFA-3/CD2 interaction	Lymphoma, serious infections; malignancies
Adalimumab	TNF blocker	Serious infections (including TB); CNS demyelinating disorders; hematologic events (pancytopenia); malignancies
Etanercept	TNF blocker	Serious infections (including TB); CNS demyelinating disorders; hematologic events (pancytopenia); malignancies
Infliximab	TNF blocker	Serious infections (including TB); CNS demyelinating disorders; hematologic events (pancytopenia); malignancies
Ustekinumab	Inhibits IL-12 and IL-23	Serious infections, malignancies; CNS reversible posterior leukoencephalopathy syndrome
Methoxalen	Psoralen	Skin carcinomas including malignant melanoma,

2.3 Availability of Proposed Active Ingredient in the United States

The product is currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Apremilast is a PDE4 inhibitor that modulates inflammatory cytokines (TNF-α; IL-23; IL-17; IL-10) and therefore a potential immunosuppressant. In general, risks associated with immunosuppressive therapy include serious infections, opportunistic infections and malignancy.

An approved drug product, roflumilast (NDA 22522; February 28, 2011) indicated as a treatment to reduce the risk of COPD exacerbation, is also PDE4 inhibitors and is associated with an increase of psychiatric adverse reactions (including depression, anxiety, suicidal ideation and suicide) and decrease weight (WARNINGS AND PRECAUSIONS, Section 5.1 and 5.2).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for the psoriasis indication was conducted under IND 70270 submitted on July 28, 2004. Key pre-submission regulatory activities included the following:

- End-of-Phase 2 meeting (March 12, 2010)
- Advice letter regarding two Phase 3 protocols submitted by the applicant (6/3/11)
- Pre NDA meeting (5/15/13)

End-of-Phase 2 meeting was held on March 12, 2010.
The following advice was conveyed to the sponsor:

- The proposed dose of 30mg BID to be used in the Phase 3 trials is reasonable.
- The Agency did not agree with sponsor's proposed primary efficacy endpoint of PASI 75 at Week 16. For evaluation of efficacy, the Agency recommended a composite endpoint based on Physician Global Assessment (PGA) and on Psoriasis Area and Severity Index 75 (PASI 75).
- The Agency recommended use of 5-point PGA scale where success was defined as achieving "clear" or "almost clear" combined with 2 point reduction on the scale. PGA scale should be based on description on the overall disease severity.

Advice letter regarding proposed two Phase 3 protocols.
Two Phase 3 protocols were submitted on January 6, 2011 and January 10, 2011. The sponsor did not request Special Protocol Assessment. The Agency conveyed the following advice:

- If the sponsor elected to keep PASI 75 as a component of the primary endpoint and does not use composite endpoint (sPGA and PASI) then they should design the trial to establish efficacy on the basis of co-primary endpoint rather than assigning sPGA as a key secondary endpoint.

Reviewer's comments: As discussed above, for the evaluation of efficacy the Agency recommended a co-primary endpoint of PASI 75 and PGA. However, in their two Phase

3 trials, the applicant used PASI 75 as a primary endpoint and PGA as a secondary endpoint.

Pre-NDA meeting was held on May 15, 2013
The content and format of the proposed NDA submission was discussed.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Office of Scientific Investigations (OSI) inspections were requested for 4 Phase 3 study sites, selected because they had some of the largest enrollments and greatest treatment effects.

Study PSOR-008
- Investigator: Tiffani Hamilton, Study site #08; enrolled 13 subjects

Study PSOR-009
- Investigator: Norman Wasel; Study site #122; enrolled 20 subjects
- Investigator: Yves Poulin; Study site #120; enrolled 18 subjects

At the time of closure of this review the reports of inspections were pending.

3.2 Compliance with Good Clinical Practices

The applicant stated that studies were designed, monitored, and conducted in accordance with Good Clinical Practice (GCP) requirements and the ethical principles. Trial protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The applicant obtained an approval from IRB prior to trial initiation.

3.3 Financial Disclosures

The sponsor certified (Form 3454) that they had not entered into any financial arrangements with any of the clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Control (CMC) reviewer recommends approval of apremilast. The applicant provided sufficient information to assure identity, strength, purity and quality of the drug product.

Apremilast is a diamond shaped, film coated tablet in the following dosage strengths: 10mg pink tablet, 20mg brown tablet and 30mg beige tablet.

The reader is referred to the CMC review of apremilast by Caroline Strasinger, 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 Preclinical Pharmacology/Toxicology

Results from standard series of genetic toxicity studies (Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay) were negative for apremilast.

There were no definitive apremilast related malignancies in the two-year oral carcinogenicity studies in mice and rats.

Reproductive and developmental toxicology studies were conducted using mouse and monkey models. Apremilast treatment in mice produced no effects on male fertility. Fertility studies in female mice showed prolonged estrous cycle due to an increase in the diestrus period that resulted in a longer time until mating. Mice that became pregnant had increased incidences of early post-implantation losses.

In embryo-fetal development studies in mice, no teratogenic findings due to apremilast were observed. Reductions in the number of litters and litter size, attributed to post-implantation losses, were observed. There was an increased incidence of skeletal variations that were mostly related to incomplete ossification sites of tarsals, skull, sternebra, and vertebrae.
In embryo-fetal development studies in cynomolgus monkeys, a dose-related increase of spontaneous abortions was observed. There was no evidence for teratogenic effects; however, aborted fetuses were not evaluated.

In studies evaluating pre- and post-natal development in mice, in the apremilast high dose group, dystocia, reduced viability, and reduced birth weights was observed. There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring

In the approved OTEZLA label under the NDA 205437, the pregnancy category for apremilast is designated as C. A pregnancy exposure registry is established to monitor and control the risk of OTEZLA.

Pharmacology/Toxicology reviewer, Dr. Jianyong Wang, is recommending an approval of this NDA. No postmarketing requirement was recommended by Dr. Wang.

The reader is referred to the Pharmacology/Toxicology review by Jianyong Wang, PhD, for detailed analysis of the non-clinical pharmacology and toxicology aspects of this application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Apremilast is a small molecule, a selective phosphodiesterase type IV (PDE4) inhibitor. The applicant purports that apremilast modulates pro-inflammatory (TNF-α; IL-23; IL-17) and anti-inflammatory mediators (IL-10). PDE4 is a cyclic adenosine monophosphate c(AMP)-specific PDE, a dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn activates protein kinase A and other downstream effectors, resulting in inhibition of pro-inflammatory cytokines' transcription and other cellular responses such as neutrophil degranulation, chemotaxis, and adhesion to endothelial cells. These pro-inflammatory and anti-inflammatory mediators have been implicated in psoriasis.

4.4.2 Pharmacodynamics

The applicant conducted pharmacodynamic study (PSOR-001) assessing the effect of apremilast on epidermal thickness of psoriatic lesions; the effects on inflammatory biomarkers (quantitative K16, ICAM-1, HLA-DR, and filaggrin) in epidermal cells of psoriatic skin lesions, the effects on whole blood TNF-α production following bacterial endotoxin (LPS) challenge and immunohistochemical analysis of epidermal thickness. Treatment with apremilast was associated with mean reduction from baseline in the epidermal thickness of psoriatic lesions and reduction in epidermal and dermal Tcells. In subjects who at baseline had inflammatory biomarkers present in psoriatic skin lesions, an absence of these markers after 29 days of treatment with apremilast was observed.

In addition, there was a decrease of whole blood TNF- α production following bacterial endotoxin challenge.

The applicant also evaluated clinical efficacy of the apremilast treatment by assessing improvement from baseline in PASI score, sPGA score and total BSA.
Compared to baseline, 18% of subjects had 50% reduction of PASI score; 53% of subjects had at least one grade improvement of sPGA score and 60% of subjects had improvement of total BSA.

Reveler's comments: improvement of 50% of PASI score or one grade improvement of sPGA score is not considered clinically significant improvement.

The applicant considered that this study provided the correlation between histologic/immunohistologic findings from skin biopsies (epidermal thickness and dermal and epidermal T cells) and the clinical efficacy of apremilast. (b) (4)

Discussion: Temporal relationship between histologic/immunohistologic skin changes and clinical efficacy appear to be suggestive of the correlation between these events, (b) (4)

4.4.3 Pharmacokinetics

The applicant conducted PK trial PSOR-004 in which plasma pharmacokinetic parameters (C_{max}, T_{max}, and AUC_{0-12}) for apremilast 20mg BID dose and 30mg dose were evaluated in subjects with recalcitrant psoriasis. Apremilast was rapidly absorbed with median T_{max} of 2 hours post dose following either single or multiple dose administration. There was an approximately 62% and 68% increase in C_{max} and AUC_{0-12} at steady state relative to the single dose data, suggesting an accumulation ratio of approximately 1.7. The steady state exposure to apremilast following the 30mg BID regimen was roughly comparable to the 20mg BID regimen.
The mean terminal half-life at steady states ranged from 6 to 8 hours with either the 20mg or 30mg dose regimen. The mean through plasma concentration of apremilast with 30mg BID regimen was higher than that for the 20mg BID regimen.
Clinical Pharmacology reviewer, Chinmay Shukla, Ph.D., recommended an approval for this NDA. For the detailed Clinical Pharmacology review refer to the review by Dr. Shukla.

5 Sources of Clinical Data

The applicant conducted 6 clinical trials in the development program for psoriasis.

5.1 Tables of Studies/Clinical Trials

Table 2: Trials Supporting the Application

Trial number	Objective	Study design	Test product; dosage; regiment	Number of subjects	Study subjects	Duration of treatment
Phase 3 **PSOR-008** (9/14/10-12/21/12	PASI-75 at Week 16	Randomized, double blind, placebo controlled	Placebo-controlled ph.: Apremilast 30mg BID Placebo Maintenance ph.: Apremilast 30mg BID Randomized Treatment Withdrawal phase: Apremilast 30mg BID Placebo Apremilast 30mg ± topicals , UVB Long-term Extension Apremilast 30mg BID	844 Placebo 282 APR. 562	Moderate to severe plaque psoriasis	16 weeks + 16 weeks + 20 weeks + 208 weeks
Phase 3 **PSOR-009** (11/22/10-12/21/12	PASI-75 at Week 16	Randomized, double blind, placebo controlled	Placebo-controlled ph.: Apremilast 30mg BID Placebo Maintenance ph.: Apremilast 30mg BID Randomized Treatment Withdrawal phase: Apremilast 30mg BID Placebo Apremilast 30mg ± topicals , UVB Long-term Extension Apremilast 30mg BID	413 Placebo 138 APR 30mg BID 275	Moderate to severe plaque psoriasis	16 weeks + 16 weeks + 20 weeks + 208 weeks

Table 2: Trials Supporting the Application (continued)

Phase 2b PSOR-005 (9/24/08-7/21/11)	PASI-75 at Week 16	Randomized, double blind, placebo controlled	Placebo-controlled ph.: Apremilast 10mg BID Apremilast 20mg BID Apremilast 30mg BID Placebo Active-controlled and Extension phase: Apremilast 10mg BID Apremilast 20mg BID Apremilast 30mg BID Long-term Extension: Apremilast 30mg BID	352 Placebo 88 APR 10mg BID: 89 APR 20mg BID 87 APR 30mg BID 88	Moderate to severe plaque psoriasis	16 weeks + 8 weeks + 28 weeks + 4 years
Phase 2 PSOR-003 (4/23/06-2/7/07)	PASI-75 at Week 12	Randomized, double blind placebo controlled	Placebo Apremilast 20mg BID Apremilast 20mg QD	260	Moderate to severe plaque psoriasis	12 weeks
Phase 2 PSOR-004 (8/20/07-5/12/09)	≥20% of subjects with 1 point reduction in sPGA at Week 12	Open label	Treatment period: Apremilast 20mg BID In Extension period: Apremilast 20mg BID Apremilast 30mg BID	30	Recalcitrant psoriasis who failed prior psoriasis Tx	12 weeks + 12 weeks
Phase 2 PSOR-001 (1/11/05-10/17/05)	≥20% reduction of epidermal thickness from baseline to Day 29	Open label, single arm	Apremilast 20mg QD	19	Severe plaque psoriasis	29 days

Source: Modified form applicant's submission, Module 5.3.5.3 ISE, Table 2, page 17

5.2 Review Strategy

For safety, trials PSOR-008; PSOR-009 and PSOR-005 will be reviewed as pooled data and discussed in section 7 of this review. Three remaining trials (PSOR-001; PSOR-004 and PSOR-003) will be reviewed as part of Psoriasis Data Pool that incorporates all clinical trials supporting this NDA (PSOR-008; PSOR-009; PSOR-005; PSOR-001; PSOR-004 and PSOR-003).
For efficacy, two Phase 3 trials will be reviewed separately and pooled, and discussed in section 6 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Two Phase 3 trials (PSOR-008 and PSOR-009) and four Phase 2 trials (PSOR-001; PSOR-003; PSOR-004; and PSOR-005) support this NDA.

Phase 3 Trial: PSOR-008

Study Title: A Phase 3, multicenter, randomized double-bling, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.

Study Period: September 22, 2010 to November 2, 2011.

Study Objective: To evaluate the clinical efficacy and safety of apremilast 30mg BID, compared to placebo, in subjects with moderate to severe plaque psoriasis.

Study Design: This was randomized, double-blind, placebo-controlled, multi-center trial.

Number of Centers: 72 centers in Australia, Belgium, Canada, France, Germany, Italy, the United Kingdom and the United States.

Number of Subjects: 844 subjects were randomized

Study Population
Key Inclusion Criteria:
1. Males or females, ≥ 18 years of age.
2. Diagnosis of chronic plaque psoriasis for at least 12 months prior to screening
3. Had moderate to severe plaque psoriasis at screening and baseline as defined by:
    a. PASI score ≥ 12; and
    b. Body surface area (BSA) ≥ 10%; and
    c. sPGA ≥ 3 (moderate)
4. Candidate for phototherapy and/or systemic therapy
5. Met the following laboratory criteria:
    a. White blood cell count ≥3000/mm3 (≥3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    b. Platelet count≥ 100,000/μL (≥ 100 x 10^9/L)
    c. Serum creatinine ≤ 1.5 mg/dL (≤132.6 μmol/L)
    d. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2 x upper limit of normal (ULN)
    e. Total bilirubin ≤ 2 mg/dL (34μmol/L)
    g. Hemoglobin A1c (HbA1c) ≤9.0 %
6. Females of childbearing potential (FCBP) must have had a negative pregnancy test at screening and baseline. FCBP who engaged in activity in which conception was

possible had to use contraception while on investigational product (IP) and for at least 28 days after taking the last dose of IP, where contraception was one of the following:

a. One highly effective form (non-oral hormonal, intrauterine device [IUD], tubal ligation, vasectomized partner); or
b. An oral hormonal contraceptive PLUS one additional form of barrier contraception (male or female latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane], diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or
c. Two forms of barrier contraception (male or female latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) PLUS one of the following (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide).

7. Male subjects (including those who had a vasectomy) who engaged in activity in which conception was possible must have used barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on IP and for at least 28 days after the last dose of IP.

Psoriasis Area Severity Index (PASI)
The Psoriasis Area Severity Index was determined for all subjects throughout the study. The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI scores range from 0 to 72, with higher scores indicating greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score[1].

Table 3: PASI

PSORIASIS AREA AND SEVERITY INDEX (PASI)

Please write in the appropriate number for rows 1 - 3 using the scale below:
0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe

	Head	Trunk	Upper Limbs	Lower Limbs
1. Erythema				
2. Thickness				
3. Scaling				
4. Total Each Column				
AREA OF PSORIATIC INVOLVEMENT				
5. Degree of Involvement	0 = No involvement 1 = < 10% 2 = 10 < 30% 3 = 30 < 50% 4 = 50 < 70% 5 = 70 < 90% 6 = 90 - 100%			
6. Insert Degree of Involvement from Row 5				
7. Multiply Row 4 by Row 6				
8.	x .10	x .30	x .20	x .40
9. Multiply Row 7 by Row 8				

10. Total PASI SCORE (Add together each column in Row 9)	

Source: Applicant's submission.

Static Physician Global Assessment (sPGA)
The sPGA is an assessment by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the 3 signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall severity, the investigator was instructed to factor in areas that had already been cleared (ie, have scores of 0) and not just to evaluate remaining lesions for severity, ie, the severity of each sign was to be averaged across all areas of involvement, including cleared lesions. In the event of different severities across disease signs, the sign that is the predominant feature of the disease was to be used to help determine the sPGA score.

Table 4: Static Physician Global Assessment (sPGA)

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

Source: Applicant's submission.

Body Surface Area
Body surface area is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total BSA.

Exclusion Criteria:
1. Other than psoriasis, history of any clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, which would have placed the subject at unacceptable risk if he/she were to have participated in the study.
3. Any condition that confounded the ability to interpret data from the study.
4. Pregnant or breast feeding.
5. History of allergy to any component of the investigational product (IP).
6. Hepatitis B surface antigen positive at screening.
7. Anti-hepatitis C antibody positive at screening.
8. AST or ALT > 1.5 X ULN **and** total bilirubin > ULN and/or albumin < LLN.
9. Active tuberculosis (TB) or a history of incompletely treated TB.
10. Clinically significant abnormality on 12-lead ECG at screening.

11. Clinically significant abnormality based upon chest radiograph with at least posterior/anterior (PA) view (radiograph must have been taken within 12 weeks prior to screening or during the screening visit). An additional lateral view was strongly recommended but not required.
12. History of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
13. Active substance abuse or a history of substance abuse within 6 months prior to screening.
14. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of screening. Any treatment for such infections must have been completed at least 4 weeks prior to screening.
15. Malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia [CIN] or carcinoma in situ of the cervix with no evidence of recurrence).
16. Psoriasis flare or rebound within 4 weeks prior to screening.
17. Evidence of skin conditions that would interfere with clinical assessments.
18. Topical therapy within 2 weeks of randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Exceptions: low-potency corticosteroids (Class 6 or 7) were allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study. Subjects with scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. An un-medicated skin moisturizer (eg, Eucerin) was permitted for body lesions only. Subjects should not have used these topical treatments within 24 hours prior to the clinic visit.
19. Systemic therapy for psoriasis within 4 weeks prior to randomization (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters)
20. Use of phototherapy within 4 weeks prior to randomization (ie, ultraviolet light B [UVB], PUVA).
21. Adalimumab, etanercept, efalizumab, infliximab, or certolizumab pegol within 12 weeks prior to randomization.
22. Alefacept, briakinumab, or ustekinumab within 24 weeks prior to randomization.
23. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever was longer).
24. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources.
25. Prior treatment with apremilast.

Study Visits and Procedures

This trial consisted of 3 major Phases: Placebo-controlled Phase; Maintenance Phase and Randomized Treatment Withdrawal Phase.

Placebo-controlled Phase (Week 0-16)
Subjects were randomly assigned in 2:1 ratio to receive apremilast tablet 30mg by mouth (PO), twice daily (BID) or matching placebo PO BID for 16 consecutive weeks.

Maintenance Phase (Weeks 16-32).
After 16 weeks of treatment, subject who were randomized to placebo at the Baseline were switched to apremilast 30mg BID and subjects originally randomized to apremilast 30mg BID were to remain on apremilast 30mg BID. All subjects were to remain on apremilast 30mg BID through Week 32.

Randomized Treatment Withdrawal Phase (Weeks 32-52)
At Week 32, subjects were assessed for PASI responses and managed as follows:

- **Subjects originally randomized to apremilast at Week 0:**
  Responders (≥ PASI-75) were re-randomized in 1:1 ratio to maintain apremilast 30mg BID dosing or switch to Placebo (treatment withdrawal). Subjects randomized to placebo who experienced loss of response (ie, loss of PASI-75), were to restart apremilast 30mg BID treatment. This resumption of apremilast 30mg BID treatment was to occur no later than Week 52, regardless of whether or not the subject lost PASI-75.

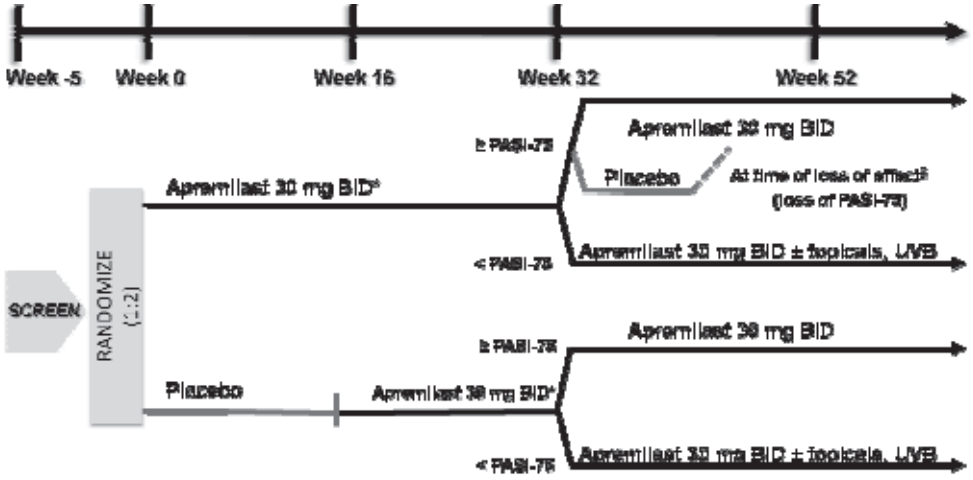
  Partial responders (PASI-50 to PASI-74) and nonresponders (< PASI-50) had the option of adding topical therapies and/or phototherapy to their apremilast 30mg BID treatment. The decision to add these treatments during this phase could only be made at the Week 32 visit, and was based on the discretion of the investigator.

- **Subjects originally randomized to Placebo at Week 0 and switched to apremilast 30mg BID at Week 16:**
  All subjects were to maintain apremilast 30mg BID dosing. Nonresponders (< PASI-50) and partial responders (PASI-50 to PASI-74) had the option of adding topical therapies and/or phototherapy to their treatment regimen. The decision to add these treatments during this phase could only be made at the Week 32 visit, and was based on the discretion of the investigator. Subjects originally randomized to placebo with a PASI-75 response were also included in this group, but were maintained on apremilast 30mg BID.

Long-term Extension Phase (Weeks 52- 260)
Subjects are being followed and evaluated for safety and efficacy for up to an additional 4 years (years 2 through 5).

A schematic of the trial design is presented in Figure 1 below.

Figure 1: Trial Design Schematic for PSOR-008



Source: Applicant's submission, Clinical Study Report PSUR-008, Section 9.1; Figure 1; page 26.

Observational Follow-up Phase

Subjects who complete the trial, or those subjects who discontinue investigational product (IP) prior to the completion of the trial, were asked to participate in the 4-week Observational Follow-up Phase.

The schedule of study procedures is presented in Table 5 below.

Table 5: Study Design and Schedule of Assessments (Week 1-52) for PSOR-008

	Screening	Baseline	Placebo-controlled Phase[a]					Maintenance Phase[b]				Randomized Treatment Withdrawal Phase[c]					
Visit[d]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17[e]
Week	Up to 35 Days	0	2	4	8	12	16	20	24	28	32	34	36	40	44	48	52
Informed Consent[f]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical and Disease History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concurrent Medications/ Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																	
CXR[g]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatitis B and C[h]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	X	-	-	-	-	-	X	-	-	-	X	-	-	-	-	-	X
Complete Physical Examination	X	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	X
Limited Physical Examination	-	X	-	-	X	-	X	-	-	X	X	-	-	X	-	-	-
Pregnancy Test for FCBP and Contraception Education[i]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
12-Lead ECG	X	X	-	-	-	-	X	-	-	-	X	-	-	-	-	-	X
Clinical Laboratory Evaluations	X[j]	X	-	X	X	X	X[j]	X	X	X	X[j]	-	X	X	X	X	X[j]

Table 5: Study Design and Schedule of Assessments (Week 1-52) for PSOR-008 continued

	Screening	Baseline	Placebo-controlled Phase[a]					Maintenance Phase[b]				Randomized Treatment Withdrawal Phase[c]					
Visit[d]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17[e]
Week	Up to 35 Days	0	2	4	8	12	16	20	24	28	32	34	36	40	44	48	52
Hemoglobin A1c	X	-	-	-	-	-	X	-	-	-	X	-	-	-	-	-	X
Psoriasis Flare or Rebound Assessment	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Efficacy Assessments																	
PASI, BSA, sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nail Assessments/ NAPSI[l]	-	X	-	-	-	-	X	-	X	-	X	-	-	X	-	-	X
ScPGA[k], PPPGA[k]	-	X	X	X	X	X	X	-	X	-	X	-	-	X	-	-	X
Pruritus VAS	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin Discomfort/ Pain VAS	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psoriatic Arthritis Disease Activity VAS[k]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Global Assessment of Psoriasis Disease Activity VAS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health-related Quality of Life Assessments																	
DLQI, SF-36v2, PHQ-8	-	X	-	X	X	-	X	-	X	-	X	-	-	X	-	-	X
EQ-5D, WLQ-25	-	X	-	-	-	-	X	-	-	-	X	-	-	-	-	-	X
Pharmacokinetic (PK) Assessments																	
PK Blood Draw[m]	-	-	-	-	-	-	-	-	X	-	X	-	X	X	X	X	-

	Screening	Baseline	Placebo-controlled Phase[a]					Maintenance Phase[b]				Randomized Treatment Withdrawal Phase[c]					
Visit[d]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17[e]
Week	Up to 35 Days	0	2	4	8	12	16	20	24	28	32	34	36	40	44	48	52
Photography																	
Photography[n]	-	X	-	-	-	-	X	-	-	-	X	-	-	-	-	-	X
IP Dosing																	
Dispense IP	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Return IP, Count for Compliance	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BSA = body surface area; CXR = chest radiograph; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EQ-5D = European Quality of Life – 5 Dimensions; IP = investigational product; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Activity and Severity Index; PHQ-8 = Patient Health Questionnaire; PK = pharmacokinetic; PPPGA = Palmoplantar Psoriasis Physician Global Assessment; SF-36v2 = Medical Outcomes Study 36-item Short Form Health Survey; sPGA = static Physician Global Assessment; ScPGA = Scalp Physician Global Assessment; VAS = visual analog scale; WLQ-25 = The Work Limitations Questionnaire-25.

[a] Visits in the Placebo-controlled Phase were to be performed ± 4 days.
[b] Visits in the Maintenance Phase were to be performed ± 1 week.
[c] Subjects were to be instructed to call the site between regularly scheduled visits during the Randomized Treatment Withdrawal Phase to determine the need for an office visit if their psoriasis had worsened. These visits were conducted as unscheduled visits. Visits in the Randomized Treatment Withdrawal Phase were to be performed ± 1 week.
[d] Subjects who discontinued IP during the first year of the study were asked to enter the 4-week Observational Follow-up Phase.
[e] Visit 17 also served as the early study termination visit for all subjects who discontinued IP dosing during the first year of the study.
[f] Written informed consent was to be obtained by the principal investigator or designee prior to any study procedures, including washouts from prior medications.
[g] CXRs taken within 12 weeks prior to screening were accepted. CXRs were to be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines were not available/applicable, routine CXRs were to be performed when clinically indicated.
[h] Hepatitis B surface antigen; anti-hepatitis C antibody.
[i] Females of child bearing potential (FCBPs) only. Serum pregnancy test was to be performed at screening and urine dipstick pregnancy test was to be performed at baseline. Serum pregnancy test at Visit 17, Week 52, was only required for subjects who discontinued IP during the first year of the study or for those subjects who discontinued at Visit 17, Week 52, as this visit also served as the discontinuation visit for the first year. The investigator was to educate

Source: Applicant's submission; Clinical Study Report; PSOR-008; Section 9.1; Table 3; page 35.

Investigational Product

Investigational product was to be taken orally twice daily, 12 hours apart, without restriction of food or drink. In order to minimize potential gastrointestinal side effects of mild-to-moderate nausea, dose titration over period of 6 days was implemented during the first week of treatment and again during the 17th week of treatment (Table 6). Apremilast was provided as 10mg, 20mg or 30mg tablets. Subjects assigned to placebo received identically appearing 10mg, 20mg and 30mg tablets.

Table 6: Dosage 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
10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

Source: Modified from applicant's submission; Amendment #4; Clinical study repost PSOR-008; Section 8.2 ; Table 3; page 46

Concomitant Medication

The following topical therapies were permitted:

- Low-potency or weak corticosteroids (eg, Class 6 or 7 in the US, such as hydrocortisone, desonide, alclometasone dipropionate) were allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study.
- Subjects with scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.
- An unmedicated skin moisturizer (eg, Eucerin) was permitted for body lesions only.
- At Week 32, all partial responders (PASI-50 to PASI-74) and nonresponders (< PASI-50) had the option of adding topical therapies and/or phototherapy to their treatment regimen.

The following medications were not permitted during the study:

- Topical therapy unless otherwise specified (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol)
- Systemic Therapy including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters.
- Phototherapy: UVB or PUVA unless otherwise specified
- Biologic agents: adalimumab, etanercept, efalizumab, infliximab, or certolizumab pegol, alefacept, briakinumab, or ustekinumab
- Prolonged sun exposure or use of tanning booths or other ultraviolet light sources

Discussion: Study subjects were permitted to use low potency topical corticosteroids, coal tar shampoo and/or salicylic acid scalp preparations. Low potency topical corticosteroids allowed in two Phase 3 trials are approved for the treatment of psoriasis and therefore may have impacted efficacy results. The effect of concomitant topical corticosteroid use on the efficacy results will be further explored (refer to section ***6.1.10 Additional Efficacy Issues/Analyses*** *of this review).*

Safety Evaluation

The following safety assessments were performed:

- Chest radiograph (CXR) (PA and lateral views) was to be obtained during screening.
- Hepatitis testing included hepatitis B surface antigen and anti-hepatitis C antibody and was performed during the Screening Period.
- Vital signs, including temperature, pulse, and seated blood pressure, were measured at all visits. Height was recorded at screening; weight was measured at screening Week 16; Week 32 and Week 52.
- Complete physical examinations at Screening, Week 24, and Week 52.
- Vasculitis assessment was performed throughout the study.
- Psychiatric evaluation included identification of major psychiatric illness requiring hospitalization, attempted suicide or suicidal ideation was performed through the study.
- Laboratory evaluations: cholesterol panel; clinical chemistry; complete blood count (CBC); urinalysis; and high-sensitivity C-reactive protein (hs-CRP) were performed at all visits.
- Hemoglobin A1c (HgbA1c) was performed at Screening, Week 16, Week 32 and Week 52.
- Serum pregnancy test for female subjects of childbearing potential was performed at Screening, Baseline and Week 52.
- A 12-lead ECG was recorded at Screening, Baseline, Week 16, Week 32 and Week 52.

Pharmacokinetic Assessment
Approximately 100 subjects (PASI-75 responders at Week 24 only) at selected sites in North America were to participate in the PK evaluation. A single blood sample was to be obtained from subjects either predose or after the morning dose.

Efficacy Evaluation
The **Primary Endpoint** was the proportion of subjects who achieved at least a PASI 75 at Week 16 in comparison to Baseline.

The major **Secondary Endpoint** was the proportion of subjects with a sPGA score of clear (0) or almost clear (1) with at least 2-point reduction from Baseline at Week 16.

*Discussion: For the evaluation of efficacy, the applicant is relying on the results from evaluation using PASI 75 and assigned assessment on sPGA as a major secondary endpoint. The Agency recommended a co-primary endpoint based on Physician Global Assessment (sPGA) and on Psoriasis Area and Severity Index 75 (PASI 75). For the approval of apremilast for the treatment of moderate to severe plaque psoriasis, the applicant will need to show that apremilast is statistically significantly more effective compared to placebo based on **both**, sPGA and PASI 75.*

Phase 3 trial: PSOR-009

Study Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (VV-10004) in subjects with moderate to severe plaque psoriasis.

Study Period: November 30, 2010 to November 24, 2011.

Study Objective: To evaluate the clinical efficacy and safety of apremilast 30mg BID, compared to placebo, in subjects with moderate to severe plaque psoriasis.

Study Design: This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial.

Number of Centers: 40 centers in the United States, Canada, Austria, Denmark, France, Germany, Italy, Spain, and Switzerland.

Number of Subjects: 413 subjects were randomized.

Study Population
Inclusion Criteria/Exclusion Criteria were the same as in trial PSOR-008 (see above).

Study Visits and Procedures

Overall design of trial PSOR-009 was the same as the trial PSOR-008 with the exception of Randomized Treatment Withdrawal Phase described below:

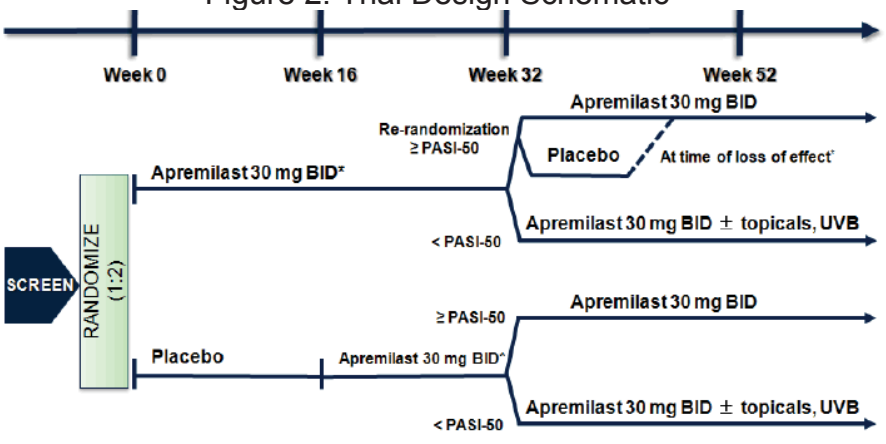
Randomized Treatment Withdrawal Phase – Weeks 32 to 52

To evaluate the durability of response, relapse, rebound, and time to relapse/loss of effect, at Week 32 subjects were assessed for PASI response and managed as follows:

- Subjects originally randomized to apremilast at baseline (Week 0):
  a. At Week 32, responders (≥ PASI-75) and partial responders (PASI-50 to PASI- 74) were re-randomized 1:1 to maintain apremilast 30mg BID dosing or switch to Placebo (treatment withdrawal). If subjects experienced loss of response (ie, loss of 50% of the improvement of PASI score compared to baseline), they were to resume apremilast 30mg BID treatment. Resumption of apremilast 30mg BID treatment was to occur no later than Week 52, regardless of whether or not the subject lost response.
  b. At Week 32, nonresponders (< PASI-50) had the option of adding topical therapies and/or phototherapy to their apremilast 30mg BID treatment regimen.

- Subjects originally randomized to placebo Week 0 and switched to apremilast 30mg BID at Week 16:
  a. At Week 32, all subjects were to maintain apremilast 30mg BID dosing. Nonresponders (< PASI-50) had the option of adding topical therapies and/or phototherapy to their treatment regimen.

Figure 2: Trial Design Schematic



Source: Applicant's submission, Clinical Stud Report PSOR-009; Section 9.1, Figure 1; page 28.

Safety Evaluation
Safety evaluation was the same as in study PSOR-008.

Efficacy and Endpoint Measures
Primary and secondary endpoints were the same as in trial PSOR-008.

Phase 2 Trial PSOR-005

Study Title: A Phase 2B, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate-to-Severe Plaque-Type Psoriasis (PSOR-005) and Two Extension Studies (PSOR-005E & PSOR-005LTE)

Study Period: September 24, 2008 to July 21, 2011.

Study Objective: To evaluated the clinical safety and efficacy of three oral doses of apremilast tablet (10mg BID; 20mg BID; and 30mg BID) compared to placebo in subjects with moderate-to-severe plaque psoriasis.

Study Design: This was multicenter, randomized, double-blind, placebo-controlled trial.

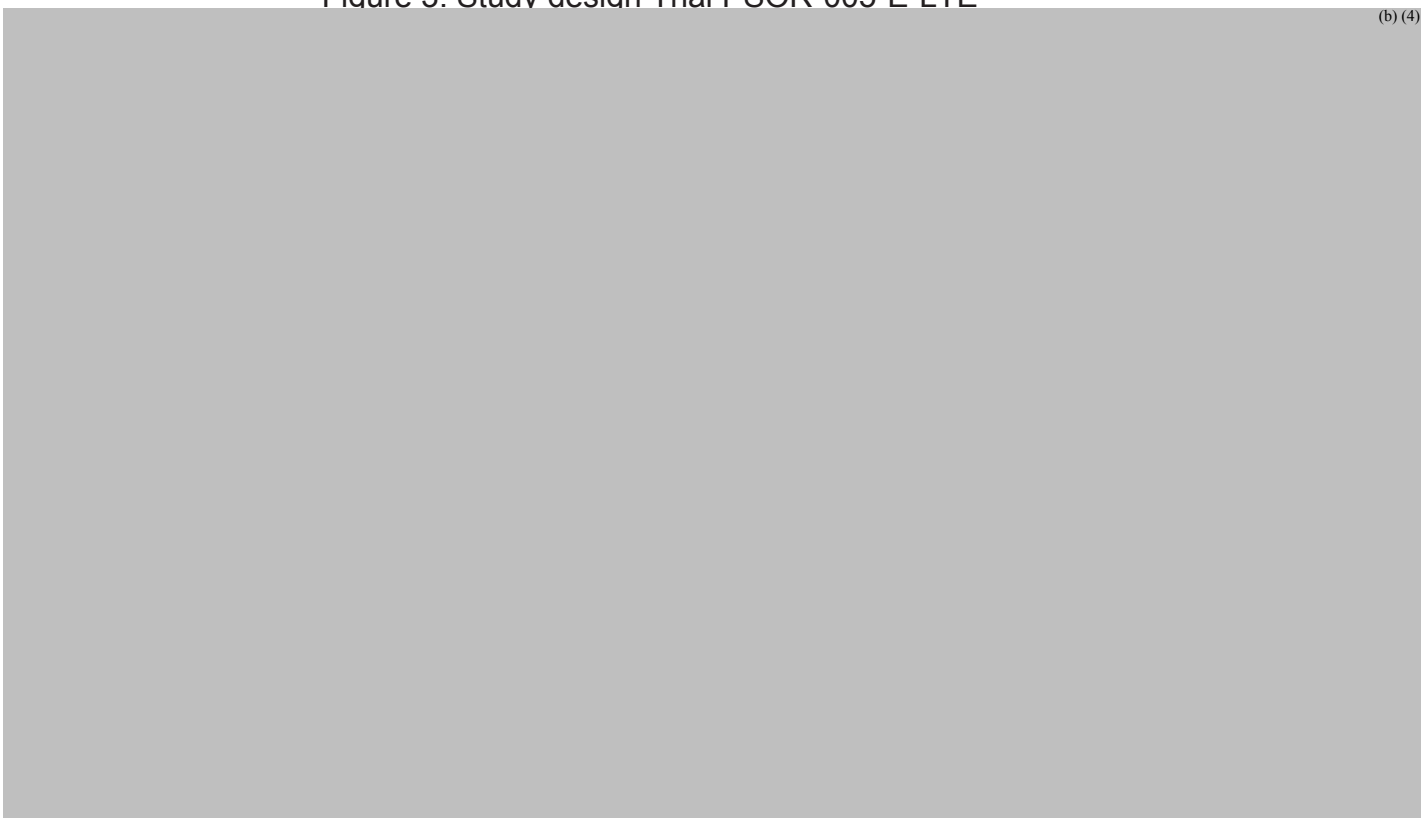
Number of Centers: 20 study sites in US and 15 sites in Canada.

Number of Subjects: 352

Study Population: : Adult subjects (18 years of age or older) with moderate-to-severe plaque psoriasis (PASI ≥12 and BSA of ≥10%) who were candidates for systemic/phototherapy.

Study Visits and Procedures
This trial consisted of 3 separate studies: Core Study (PSOR-005), an Extension Study (PSOR-005E) and Long-Term Study (PSOR-005LTE). During the Core study, subjects were treated with apremilast (10mg BID; 20mg BID; and 30mg BID) or placebo for 16 weeks. At Week 16, subjects who were on placebo were re-randomized to apremilast (20mg BID or 30mg BID), and subjects on apremilast continued their therapy. All subjects continued treatment for additional 8 weeks. Subjects who completed Core study were enrolled into Extension Study, without dosing interruption, for additional 28 weeks of dosing. At week 52, subjects who completed 52 weeks of dosing were enrolled into Long-Term Study and dosed with apremilast (either 20mg BID or 30mg BID) for additional 4 years. Study design schematic is presented in Figure 3 below.

Figure 3: Study design Trial PSOR-005-E-LTE



Source: Applicant's submission, Clinical Study Report PSOR-005; Section 9.5; Table 3; page 38.

Safety Evaluation
The following safety evaluations were performed: physical examination, PPD, Hepatitis B and C testing, vital signs, hematology panel, serum chemistry panel, liver function test, urinalysis, lipid panel, insulin, homocysteine, ANA, high sensitivity CRP (hs-CRP), serum atineutrophilic cytoplasmic antibody (ANCA), pregnancy test, 12-lead ECG, fibrinogen, erythrocyte sedimentation rate (ESR), lymphocyte subsets, HbA1c.

Efficacy and Endpoint Measures
The primary endpoint of the Core Study was the proportion of subjects treated with apremilast (10, 20, or 30 mg BID) who achieved a PASI-75 at Week 16 in reference to the Baseline visit compared with placebo.

Phase 2 Trial PSOR-001

Study Title: Open-label, Single-Arm Pilot Study to Evaluate the Pharmacodynamic, Pharmacokinetics, Safety and Preliminary Efficacy of CC-10004 (apremilast) in Subjects with Severe Plaque Type Psoriasis.
Study Period: January 11, 2005 to October 17, 2005

Study Objective: To evaluate the pharmacodynamic effect of orally administered apremilast capsule 2X10mg daily when taken for 29 days, in reducing epidermal thickness in subjects with severe plaque type psoriasis and to evaluate the steady state pharmacokinetics of apremilast on Day 29.
Study Design: Multicenter, open-label, single-arm study
Number of Centers: 3 study sites in the United States
Number of Subjects: 19
Study Population: Adult subjects (18-65 years of age) with severe psoriasis (BSA of 15% and at least 1 psoriatic plaque ≥2.5cm in diameter) and candidates for photo/systemic therapy.
Study Visits and Procedures
Subjects were treated with two 10mg capsules (20mg) of apremilast once daily for 29 days. Blood samples were collected on Day 29 for determination of apremilast concentration at steady state.
Safety Evaluation
The following evaluations were performed: physical examination, vital signs, hematology panel, serum chemistry panel, liver function tests (LFTs), total protein and albumen, lipase, urinalysis, Antinuclear Antibody (ANA), C-reactive protein (CRP), pregnancy test, ECG, PPD, Chest X-Ray, T-cell lymphocyte subtypes by flow cytometry.

Phase 2 Trial PSOR-003

Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Comparison Study of CC-10004 in Subjects with Moderate-to-Severe Plaque Type Psoriasis.
Study Period: April 23, 2006 to February 7, 2007.
Study Objective: To compare the clinical efficacy of 2 oral doses of apremilast (20mg once daily and 20mg twice daily) with placebo when taken for 12 weeks.
Study Design: This was multicenter, randomized, double-blind, placebo-controlled, parallel group trial.
Number of Centers: 34 study sites in Canada, Germany and Czech Republic.
Number of Subjects: 259
Study Population: Adult subjects (18 years of age or older) with moderate-to-severe plaque psoriasis (PASI ≥10 and BSA of ≥10%) who were candidates for systemic/phototherapy.
Study Visits and Procedures: Subjects were randomized to one of three treatments: apremilast capsule 20mg BID, apremilast capsule 20mg QD or identical matching placebo capsule. Treatment was administered for 12 consecutive weeks.
Safety Evaluation
The following safety evaluations were performed: physical examination, Chest X-Ray, vital signs, hematology panel, serum chemistry panel, LFTs, urinalysis, ANA, CRP, serum atineutrophilic cytoplasmic antibody (ANCA), pregnancy test, 12-lead ECG.
Efficacy and Endpoint Measures

The following efficacy measures were used: PASI score at Visit 1 through 9, sPGA score assessed at Visit 1 through 9 and BSA at Visit through 9.

Phase 2 Trial PSOR-004
Study Title: A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacodynamics, Pharmacokinetics and Efficacy of CC-10004 in Subjects with Recalcitrant Plaque-Type Psoriasis
Study Period: August 20, 2007 to May 12, 2009
Study Objective: To evaluate safety and tolerability of apremilast capsule (20mg BID) in subjects with recalcitrant plaque psoriasis.
Study Design: This was multicenter, open-label study.
Number of Centers: 4 study sites in US
Number of Subjects: 30
Study Population: Adult subjects (18 years of age or older) with a diagnosis of psoriasis who were either unresponsive to standard systemic therapy (oral or injectable) or were intolerant to or had medical contraindications to standard systemic therapy or biological intervention for psoriasis and severity of disease of at least score of 3 on sPGA and BSA ≥10%.
Study Visits and Procedures
Subjects were treated with apremilast capsule 20mg BID for 12 consecutive weeks. Subjects who achieved PASI-75 at the end of 12 weeks were allowed to continue treatment with apremilast for additional 12 weeks (Extension Period). Subjects who did not achieve PASI-75 were given an opportunity to continue into Extension Period and escalate the dose of apremilast to 30mg BID.
Safety Evaluation
The following safety evaluations were performed: physical examination, vital signs, chest X-Ray, PPD, pregnancy test, serum chemistry, LFTs, hematology, urinalysis, immunology (ANA, total immunoglobulins, CRP, ANCA), 12 lead ECG.

6 Review of Efficacy

Efficacy Summary

The primary evidence of efficacy was based on two well-controlled Phase 3 trials of similar design (PSOR-008 and PSOR-009). Two Phase 3 trials were randomized, multicenter, double-blind, placebo-controlled, 52-week trials evaluating the safety and efficacy of 30mg apremilast tablet administered twice daily for the treatment of adult subjects with moderate to severe psoriasis who were candidates for phototherapy or systemic therapy.
Two trials enrolled 1257 subjects, 18 years of age and older, who had a psoriasis body surface area involvement (BSA) of ≥10%, Psoriasis Global Assessment (sPGA) of ≥3 (moderate to severe), Psoriasis Area Severity Index (PASI) score ≥12, and were candidates for phototherapy or systemic therapy. Subjects took 30mg apremilast tablet twice daily or placebo twice daily, for 52 consecutive weeks.

The primary endpoint was the proportion of subjects achieving at least a 75% reduction from baseline in the PASI score at Week 16. After 16 weeks of treatment, in PSOR-008, 33.1% of apremilast treated subjects achieved PASI-75 score, compared to 5.3% of placebo treated subjects, a treatment effect of 27.8% ($p<0.0001$). In PSOR-009, 28.8% of apremilast treated subjects achieved PASI-75 score, compared to 4.4% of placebo treated subjects, a treatment effect of 24.4% ($p<0.0001$).

Major secondary endpoint was the proportion of subjects who achieved sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline, at Week 16. In PSOR-008, at Week 16, 21.7% of apremilast treated subjects and 3.9% of placebo treated subjects achieved sPGA response, a treatment effect of 17.8%,($p<0.0001$). In PSOR-009, at Week 16, 20.4% of apremilast subjects and 4.4% placebo treated subjects achieved sPGA response, a treatment effect of 16% ($p<0.0001$).
Efficacy was consistent across sub-groups (by age, gender, race, baseline disease severity) and across study centers.

In this NDA, in two Phase 3 trials, the applicant showed that apremilast was effective in the treatment of moderate to severe psoriasis.

6.1 Indication

The applicant's proposed indication is for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

6.1.1 Methods

The applicant is relying on two Phase 3 trials, PSOR-008 and PSOR-009, to provide evidence of efficacy to support approval.

The primary analysis population for both Phase 3 trials was Full Analysis Set (FAS). The FAS consisted of all subjects who were randomized. Subjects randomized in error and did not have study drug dispensed were excluded for the FAS. In PSOR-008, all randomized subjects were included in the FAS, while in PSOR-009, 2 subjects were randomized in error and did not have study drug dispensed, and therefore were excluded for the FAS. Efficacy results from two Phase 3 trials were analyzed separately and pooled.

6.1.2 Demographics

Baseline characteristics of the study population are presented in the Table 7 and Table 8. Overall, baseline demographics were similar across the study arms. More subjects were male (68%), White (90%), of approximately 46 years of age and overweight to

obese. A total of 108 (9%) subjects were 65 years of age and older, and 9 (1%) subjects were 75 years of age and older. These demographic characteristics are consistent with that of psoriasis population.

Table 7: Baseline Demographic Characteristics (PSOR-008 and PSOR-009; FAS)

	PSOR-008		PSOR-009	
Demographics	**Placebo (N=282)**	**APR 30mg BID (N=562)**	**Placebo (N=137)**	**APR 30mg BID (N=274)**
Age (y) n (%)				
Mean ± SD	46.5 (12.7)	45.8 (13.1)	45.6 (13.4)	45.3 (13.1)
<65	258 (91.5)	514 (91.5)	123 (89.8)	252 (92.0)
≥65	24 (8.5)	48 (8.5)	14 (10.2)	22 (8.0)
Gender				
Male	194 (68.8)	379 (67.4)	100 (73.0)	176 (65.2)
Female	88 (31.2)	183 (32.6)	37 (27.0)	98 (35.8)
BMI				
Mean ± SD	31.3 (7.4)	31.2 (6.7)	30.7 (7.1)	30.9 (6.7)
Race				
White	250 (88.7)	507 (90.2)	128 (93.4)	250 (91.2)
Asian	16 (5.7)	28 (5.0)	6 (4.4)	8 (2.9)
Black or African American	10 (3.5)	18 (3.2)	2 (1.5)	13 (4.7)
Other	6 (2.1)	9 (1.6)	1 (0.7)	3 (1.1)

Source: Statistical review by Dr. Guerra.

Pooled analysis of baseline demographic characteristics for trials PSOR-008 and PSOR-009 are presented in Table 8 below.

Table 8: Baseline Demographic Characteristics, PSOR-008 and PSOR-009 (Pooled Analysis)

	PSOR-008 and PSOR-009	
Demographics	**Placebo (N=419)**	**APR 30mg BID (N=836)**
Age (y) n (%)		
Mean ± SD	46.2 (12.9)	45.6 (13.0)
<65	381 (90.9)	766 (91.6)
≥65	38 (9.1)	70 (8.4)
Sex		
Male	294 (70.2)	555 (66.4)
Female	124 (29.7)	279 (33.5)
BMI		
Mean ± SD	31.09 (7.3)	31.12 (6.7)
Race		
White	378 (90.2)	757 (90.6)
Asian	22 (5.3)	36 (4.3)
Black or African American	12 (2.9)	31 (3.7)
American Indian or Alaska Native	6 (1.4)	3 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.2)	6 (0.7)
Other	0	3 (0.4)

Source: Modified from applicant's submission, Module 5.3.5.3, ISE, section 3.2.3.1.2, Table 11, page 58.

The baseline disease characteristics were generally balanced across the treatment arms (Table 9, pooled analysis).

Table 9: Baseline Disease Characteristics, PSOR-008 and PSOR-009 (Pooled Analysis)

Disease Characteristics	Placebo (N=419)	APR 30mg BID (N=836)
Duration of Plaque Psoriasis (years since diagnosis)		
n	415	833
Mean ± SD	18.7 (12.3)	19.2 (12.5)
History of:		
Guttate, Pustular, or Erythrodermic Psoriasis, or of a Sudden Intensification in Psoriasis	27 (6.4)	51 (6.1)
[redacted] (b) (4)		
Psoriatic arthritis	63 (15.0)	165 (19.7)
Total PASI Score at Baseline		
Mean ± SD	19.59 (7.59)	19.07 (7.29)
PASI Score Category, n (%)		
≤ 20	283 (67.5)	597 (71.4)
≥ 20	136 (32.5)	239(29.9)
BSA (%)		
Mean	26.07 (15.05)	24.75 (14.94)
sPGA, n (%)		
0 (clear)	0	0
1 (almost clear)	0	0
2 (mild)	1 (0.2)	1 (0.1)
3 (moderate)	280 (66.8)	599 (71.7)
4 (severe)	138 (32.9)	236 (28.2)

Source: Modified from applicant's submission, Module 5.3.5.3, ISE, section 3.2.3.1.2, Table 13, page 65.

6.1.3 Subject Disposition

Placebo Controlled Period (Week 0-16)

The Table 10 and Table 11 below present all subjects who received at least one dose of study drug during period Week 0-16. A total of 1257 subjects were randomized across two studies: 420 subjects randomized to placebo (of whom, 418 subjects receive at least one dose of placebo) and 836 subjects randomized to apremilast (of whom 832 received at least one dose of apremilast). The main reasons for discontinuation were adverse events. More subjects in the apremilast group discontinued due to adverse events, 35 (4.2%), than in the placebo group 13 (3.1%). More subjects discontinued due to lack of efficacy in placebo treatment group (2.1%) than in apremilast treatment group (0.6%).

Table 10: Disposition of Subjects during Treatment Period Weeks 0-16; PSOR -008 and PSOR-009 (Randomized Subjects)

	PSOR-008		PSOR-009	
	Placebo (N=282)	**APR 30mg (N=562)**	**Placebo (N=138)**	**APR 30mg (N=275)**
Randomized	282	562	138	275
FAS	282	562	137	274
Discontinued	33 (11.7)	59 (10.5)	25 (18.2)	35 (12.8)
Adverse event	5	23	8	12
Death	1	0	0	0
Lack of Efficacy	7	2	2	3
Lost to Follow-up	9	7	6	6
Non-compliance with study drug	0	7	0	1
Other	1	1	1	2
Protocol Violation	19	7	1	2
Withdrawal by Subject		12	7	9

Source: Statistical review by Dr. Guerra.

Table 11: Disposition of Subjects during the Treatment Period Weeks 0-16, PSOR-008 and PSOR-009 (Pooled Analysis)

Disposition	**Placebo (N=420) n (%)**	**Apremilast 30mg BID (N=837) n (%)**
Entered Placebo-controlled Phase	419 (99.8)	836 (99.9)
Took at least one dose of study drug	418 (99.5)	832 (99.4)
Completed	361 (86)	742 (88.6)
Completed and entered Maintenance Phase (Week 16-32)	353 (84)	728 (87)
Completed and did not enter Maintenance Phase (Week 16-32)	8 (1.9)	14 (1.7)
Discontinued	58 (13.8)	94 (11.2)
Primary Reason for Discontinuation		
Adverse event	13 (3.1)	35 (4.2)
Lack of efficacy	9 (2.1)	5 (0.6)
Noncompliance with study drug	0	8 (1.0)
Withdrawal by subject	16 (3.8)	21 (2.5)
Death	1 (0.2)	0
Lost to followup	15 (3.6)	13 (1.6)
Protocol violation	2 (0.5)	9 (1.1)
Other	2 (0.5)	3 (0.4)
Missing	0	0

Source: Applicant's submission, Module 5.3.5.3.ISE, Section 3.1.1.2, Table 8; page 50.

6.1.4 Analysis of Primary Endpoint(s)

The efficacy results of individual Phase 3 trials as well as pooled analysis results will be discussed in this section. As previously stated, the primary efficacy endpoint for both Phase 3 trials was the proportion of subjects achieving at least a 75% reduction from baseline in the PASI score at Week 16.
Apremilast was statistically superior to placebo (p<0.001) on the primary endpoint (PASI 75) at Week 16. Table 12 presents the results of the analysis of the primary endpoint.

Table 12: Proportion of Subjects Achieving PASI-75 at Week 16; PSOR-008 and PSOR-009 (FAS; LOCF)

Endpoint	PSOR-008		PSOR-009	
	Placebo (n=282)	APR 30mg BID (n=562)	Placebo (n=137)	APR 30mg BID (n=274)
Subjects achieving PASI-75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
Treatment comparison (apremilast – placebo)				
Difference in proportions (95% CI)	--	27.8 (23.1, 32.5)	--	23 (16.3, 29.6)
2-sided p-value	--	<0.0001	--	<0.0001

Source: Applicant's submission, Module 5.3.5.3.ISE, Section 3.2.1.1.1, Table 16, page 73. Full analysis set. LOCF: last observation carried forward

Discussion: The applicant demonstrated that apremilast was statistically superior to placebo measured as 75% improvement in PASI score compared to baseline, in both Phase 3 clinical trials.

6.1.5 Analysis of Secondary Endpoints(s)

The major secondary endpoint in both trials was the proportion of subjects achieving sPGA score of 0 (clear) or 1 (almost clear), with at least a 2-point reduction from baseline, at Week 16.

Apremilast was statistically superior to placebo (p<0.001) on the major secondary endpoint (sPGA) at Week 16. Results were similar across two trials.
The following table presents the results of the analysis of the major secondary endpoint.

Table 13: Proportion of Subjects Achieving Response on sPGA at Week 16; PSOR-008 and PSOR-009 (FAS, LOCF)

Endpoint	PSOR-008		PSOR-009	
	Placebo (n=282)	APR 30mg BID (n=562)	Placebo (n=137)	APR 30mg BID (n=274)
Subjects achieving sPGA of 0 or 1 with at least a 2-point reduction from baseline, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
Treatment comparison (apremilast – placebo)				
Difference in proportions (95% CI)	--	17.8 (13.7, 21.9)	--	16.1 (10.2, 21.9)
2-sided p-value	--	<0.0001	--	<0.0001

Source: Applicant's submission, Module 5.3.5.3.ISE, Section 3.2.1.1.2., Table 18, page 76. FAS: Full analysis set. LOCF: last observation carried forward.

Discussion: The applicant demonstrated that apremilast was statistically superior to placebo measured as "clear" or "almost clear" with at least 2-point reduction from baseline on sPGA compared to baseline, in both Phase 3 clinical trials.

Conclusion: Based on the combined results for the primary and major secondary endpoint, the applicant demonstrated that the apremilast was superior to placebo in the treatment of moderate to severe plaque psoriasis.

6.1.6 Other Endpoints

(b) (4)

6.1.7 Subpopulations

For the proportion of subjects achieving PASI-75 response and the proportion of subjects achieving sPGA score of 0 or 1 (clear or almost clear) at Week 16, the applicant evaluated the following subgroups: demographic characteristics (gender, race, age, weight, BMI, geographic region, baseline PASI, sPGA, and BSA; alcohol and smoking status), baseline disease characteristics (ie., phototherapy, conventional systemic therapy, and biologic therapy) and baseline disease severity (baseline PASI and sPGA scores).

Results for PASI-75 and sPGA outcomes at Week 16, for each presented subgroups (age, race, gender and baseline disease severity), were generally consistent with the overall results from the Phase 3 trials. For the results of this analysis refer to statistical review by Dr. Matthew Guerra.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Because the efficacy of a 30mg BID dose was evaluated during the conduct of two Phase 3 studies no additional analysis regarding other doses or dosing regimens could be performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy was evaluated during Maintenance Phase (Week 16 through 32) in both Phase 3 trials. PASI-75 and sPGA were evaluated at Week 24 and Week 32. Subjects originally randomized to apremilast at Week 0 maintained PASI-75 and sPGA responses at Week 32.

Table 14: PASI-75 Score and sPGA Response in the Maintenance Phase (Week 16 through 32; Pooled Analysis; FAS)

Endpoint Visit	APR 30mg BID/ APR 30mg BID (n=836)
PASI-75, n (%) [95% CI]	
Week 24	249 (29.8) [26.7, 33.0]
Week 32	227 (27.2) [24.1, 30.3]
sPGA n (%) [95% CI]	
Week 24	193 (23.1) [20.3, 26.1]
Week 32	184 (22.0) [19.2, 25.0]

Source: Modified from applicant's submission, Module 5.3.5.3. ISE, Section 3.2.3.2.1.1, Table 89 and Table 90, page 219 and 220.

Discussion: Due to open label design of this portion of the trial, the results regarding maintenance effect do not represent results of the well-controlled clinical investigations, and therefore will not be included into labeling.

During the Randomized Withdrawal Phase (Week 32 to 52), in order to evaluate time to loss of effect , subjects who were originally randomized to apremilast and achieved PASI-75 response (study PSOR-008) or at least PASI-50 (study PSOR-009) at Week 32, were rerandomized to either apremilast 30mg BID or placebo. Time to loss of PASI-75 or PASI-50 is presented in Table 15 below.

Table 15: Time to Fist Loss of PASI Response During the Randomized Withdrawal Phase (Week 32 to 52); trials PSOR-008 and PSOR-009

	PSOR-008		**PSOR-009**	
Endpoint	**APR 30mg BID/ APR 30mg BID/Placebo** (n=77)	**APR 30mg BID/ APR 30mg BID/ APR 30mg BID** (n=77)	**APR 30mg BID/ APR 30mg BID/Placebo (n=62)**	**APR 30mg BID/ APR 30mg BID/ APR 30mg BID (n=61)**
Number of subjects who lost PASI-75 or PASI-50, n (%)	63 (81.8)	40 (51.9)	35 (56.5)	7 (1.5)
Median time to loss in weeks (95% CI)	5.1 (4.1, 8.1)	17.7 (13.0, --)	12.4 (8.3, 20.1)	21.9 (--,--)
Hazard ration (95% CI)	--	2.649 (1.768, 3.969)		7.700 (3.408, 17.399)
2-sided p-value	--	<0.0001		<0.0001

Source: Modified from Applicant's submission, Module 5.3.5.3 ISE, page 129 and 131.

Discussion: The median time to loss of PASI-75 response was 5 weeks. This reviewer recommends that this information be included into labeling as it is useful to prescribers when switching therapies. PASI-50 response is not considered a clinically meaningful and further loss of this response does not provide meaningful clinical information.

6.1.10 Additional Efficacy Issues/Analyses

The applicant allowed use of low-potency or weak corticosteroids (Class 6 or 7, such as hydrocortisone, desonide, alclometasone dipropionate) as background therapy for treatment of the face, axillae, and groin. In addition, subjects with scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. As these products may have confounded efficacy results, Dr. Guerra performed a subgroup analysis to investigate the potential impact of concomitant medication, presented in Table 16 below.

Table 16: Efficacy Results at Week 16 by Concomitant Topical Medication Use

	Study 008		Study 009	
	OTEZLA (N=562)	Placebo (N=282)	OTEZLA (N=274)	Placebo (N=137)
Concomitant Medication				
Yes	48 (8.5%)	25 (8.9%)	15 (5.5%)	24 (17.5%)
No	514 (91.5%)	257 (91.1%)	259 (94.5%)	113 (82.5%)
PASI-75				
Concomitant -Yes	13/48 (27.1%)	0/25 (0%)	8/15 (53.3%)	1/24 (4.2%)
Concomitant -No	173/514 (33.7%)	15/257 (5.8%)	71/259 (27.4%)	7/113 (6.2%)
Success[(2)] on sPGA				
Concomitant -Yes	10/48 (20.8%)	0/25 (0%)	5/15 (33.3%)	1/24 (4.2%)
Concomitant -No	112/554 (21.8%)	11/257 (4.3%)	51/259 (19.7%)	5/113 (4.3%)

Source: Statistical review by Matthew Guerra, PhD.

Dr. Guerra's analysis revealed no impact on the either, PASI-75 or sPGA responses, in trial PSOR-008. In trial PSOR-009, subjects treated with apremilast and concomitant topical medications had higher PASI-75 and sPGA responses than subjects treated only with apremilast. However, the number of subjects treated with concomitant topical medications is small therefore, meaningful conclusion cannot be drawn. For the results of this analysis refer to the review by statistical reviewer, Matthew Guerra, PhD.

7 Review of Safety

Safety Summary

The assessment of safety for the apremilast 30mg BID was based on analysis of data from two Phase 3 trials (PSOR-008 and PSOR-009) and one Phase 2 trial (PSOR-005). Safety population included 1308 subjects exposed to repeated dosing of apremilast at the proposed dose of 30mg BID.

During the development of apremilast for the psoriasis indication, a total of 1739 adult (18-83 years of age) subjects were exposed to repeated dosing with apremilast, of whom 1308 subjects received the 30mg BID dose and 431 received lower doses. Of subjects who received the 30mg BID dose, 1053 subjects received apremilast for at least 24 weeks, 586 subjects received apremilast for 52 weeks and 211 subjects received apremilast for 78 weeks. The exposure to apremilast, with regard to the size of safety database and duration of exposure, was adequate for evaluation of safety for the indication of treatment of moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.

During apremilast development program for the psoriasis indication, six deaths were reported (3 deaths in PSOR-008; and one each in PSOR-004, PSOR-005 and PSOR-

009). One additional death each was reported in the psoriatic arthritis trial (PSA-002) and in investigator-initiated trial in rheumatoid arthritis. Of six deaths reported in psoriasis trials, two were reported in subjects treated with placebo and four in subjects treated with apremilast. Detailed analysis of the individual deaths, including temporal relationship to apremilast dosing, does not suggest causal relationship (refer to section 7.3.1).

In trials comprising safety database, during the placebo controlled period (Week 0 -16), a total of 12 (2.6%) subjects in the placebo-treatment group and 21 (2.0%) subjects in the apremilast-treatment group reported SAEs. During apremilast exposure period (Week 0-52), 59 apremilast-treated subjects reported SAE. Most SAEs were reported by one subject. The review of these SAE cases did not reveal safety signals.

Analysis of adjudicated events for major adverse cardiac events, malignancies, and serious infections did not reveal imbalance between apremilast-treated subjects and placebo-treated subjects. Analysis of tuberculosis, hepatobiliary and vasculitis adverse events identified no safety signals.

Analysis of psychiatric adverse events identified increased incidence of depression in apremilast-treated subjects compared to placebo-treated subjects. No increased risk for suicide or suicidal ideation and behavior was identified. Current labeling includes information about te risk of depression in section 5 WARNINGS AND PRECAUTIONS. This reviewer recommends addition of information on depression obtained from psoriasis trials, into current labeling.

Review of common adverse reactions (ARs) revealed that the most frequently reported ARs were diarrhea, upper respiratory tract infection and nausea. The highest incidence of diarrhea and nausea occurred during first 30 days of apremilast treatment, however the duration of these ARs extended over 30 days in 20% of subjects.

Significant weight loss (more than 5% of body weight) was observed in trials for psoriasis indication. A greater proportion of subjects treated with apremilast experienced weight loss of >5% of body weight compared to placebo treated subjects. The mean weight loss in apremilast treated subjects was greatest during the first 16 weeks of treatment and continued up to Week 52. Approximately 2% of apremilast-treated subjects experienced weight loss of ≥10% of body weight during the first 16 weeks of treatment and by the end of Week 52, approximately 5% of apremilast subjects had weight loss of ≥10% of body weight.
In addition, a greater proportion of subjects who experienced weight loss of >5% of body weight also reported diarrhea than subjects who had weight loss of <5% of body weight. Based on these results, this reviewer concludes that there is temporal and clinical relationship between weight loss and diarrhea and such relationship should be included in labeling. Weight loss is included in the current labeling in the section 5

WARNINGS AND PRECAUTIONS, and this reviewer recommends inclusion of diarrhea in the same section.

Vital signs (blood pressure, pulse, body weight) were monitored during conduct of Phase 2/3 trials. With the exception of weight loss discussed above, no other clinically significant differences from baseline to the end of Week 52 or trends of abnormalities were identified (refer to section 7.4.3.)

Laboratory evaluations (hematology; serum chemistry, ECG) that markedly abnormal laboratory results were infrequent, transient and did not lead to study drug discontinuation. No cases of hepatic failure or LFT elevations meeting Hy's Law criteria were observed (refer to section 7.4.2 and 7.4.4).

In this reviewer's opinion, the applicant provided adequate evidence of safety of apremilast 30mg BID and no safety signals that would preclude an approval were identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database primarily consists of two Phase 3 trials, PSOR-008 and PSOR-009, and one Phase 2 trial, PSOR0-005. These trials were chosen as the focus of the safety review due to their similarity of study design; enrolled subjects were the targeted patient-population for proposed indication; and the treatment was at doses that reflect anticipated use (30mg twice daily).
Safety data was also derived from the Phase 1/2 clinical trials that assessed safety of apremilast during the development program for the psoriasis indication.

7.1.2 Categorization of Adverse Events

Adverse events were classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system, Version 14.0.

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

The primary focus of this safety review will be data from Phase 3 trials (PSOR-008 and PSOR-009), and data from 30mg dosing group from Phase 2 trial PSOR-005. Data from these three trials will be pulled together to compare incidences of adverse events (AEs). These studies were chosen as the focus of the safety review because of the similarity of design and enrolled subjects, large number of subjects, 16-week placebo-controlled periods and the apremilast doses and dosing regimen that reflects anticipated use. Data

obtained during the placebo-controlled portion of these trials allowed the direct comparison of AE rates in apremilast treated subjects to rates of AEs in placebo treated subjects. Data from the non-controlled periods of these trials were used to assess potential safety signals that may occur at later time points following longer exposure to apremilast. However, data from non-controlled periods is difficult to interpret due to lack of a comparison arm. Exposure-adjusted incidence rates (EAIR) will be used to account for the difference in duration of exposure between treatment arms.

The applicant conducted pooled data analysis using the following strategy:

- **PSOR Phase 3 Data Pool**: PSOR-008 and PSOR-009.
- **PSOR Data Pool:** PSOR-001, PSOR-003, PSOR-004 PSOR-005, PSOR-008 and PSOR-009.
- **Apremilast Data Pool**: PSOR-001, PSOR-003, PSOR-004 PSOR-005, PSOR-008 and PSOR-009, PSA-001, PSA-002, PSA-003, PSA-004, RA-002.

For the PSOR Phase 3 Data Pool, the applicant provided safety analysis for 3 periods:

1. Treatment Duration Period Week 0-16.
2. Treatment Duration Period Weeks 0-52
3. Apremilast Exposure Period (data from the first dose of apremilast to the safety cutoff date)

For the PSOR Data Pool the applicant provided safety analysis for 2 periods:

1. Placebo Controlled Period
2. Apremilast Exposure Period

The shortcoming of PSOR Data Pool is in that it includes the same data used in Phase 3 Data Pool (PSOR-008 and PSOR-009). This data will be presented without detailed analysis. This reviewer will present safety data from trials PSOR-001, PSOR-003 and PSOR-004 as part of Psoriasis data pool (see below), because of different study design, shorter trial duration, lower doses of apremilast used, and different dosing regimen.
For the Apremilast Data Pool, the applicant used studies across different indications. This data pool will not be discussed given the differences in the subject population, different study designs and apremilast dosing.

This reviewer will present safety analysis as two data pools:

- Phase 2/3 Data Pool (PSOR-008; PSOR-009 and PSOR-005)
- Psoriasis Data Pool (PSOR-001, PSOR-003, PSOR-004 PSOR-005, PSOR-008 and PSOR-009)

For Phase 2/3 Data Pool, safety data will be presented for 2 periods:

1. Placebo Controlled Period (Week 0-16)
2. Apremilast Treatment Period (Week 0-52)

For Psoriasis Data Pool (PSOR-001, PSOR-003, PSOR-004 PSOR-005, PSOR-008 and PSOR-009) for 2 periods:

1. Placebo Controlled Period (Week 0-16)
2. Apremilast Exposure Period (data from the first dose of apremilast to the safety cutoff date)

7.2 Adequacy of Safety Assessments

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

Phase 2/3 Data Pool

During the development of apremilast for psoriasis indication, a total of 1739 subjects were exposed to apremilast, of whom 1308 subjects received the 30mg BID dose. Of subjects who received 30mg BID dose, 1053 subjects received apremilast for at least 24 weeks, 586 subjects received apremilast for 52 weeks and 211 subjects received apremilast for 78 weeks.

Overall Exposure to apremilast in terms of dose, frequency and duration of dosing, and the target population was adequate for evaluation of safety.

Table 17: Overall Exposure to Apremilast

	Apremilast Treated Subjects				
Exposure	**APR 30mg BID** (N=1308) n (%)	**APR 20mg BID** (N=236) n (%)	**APR 20mg QD** (N=106) n (%)	**APR 10mg QD** (N=89) n (%)	**Total** (N=1739) n (%)
≥ 1 day	1308 (100)	235 (100)	106 (100)	89 (100)	1739 (100)
≥ 4 weeks	1254 (95.9)	219 (92.8)	99 (93.4)	84 (94.4)	1656 (96.2)
≥ 8 weeks	1212 (92.7)	205 (86.9)	74 (69.8)	82 (92.1)	1573 (90.5)
≥ 12 weeks	1173 (89.7)	181 (76.7)	63 (59.4)	80 (89.9)	1497 (86.1)
≥ 24 weeks	1053 (80.5)	88 (37.3)	0	61 (68.5)	1202 (59.8)
≥ 32 weeks	927 (70.9)	70 (29.7)	0	43 (48.3)	1040 (59.8)
≥ 52 weeks	586 (44.8)	15 (6.4)	0	14 (15.7)	615 (35.4)
≥ 78 weeks	211 (16.1)	11 (4.7)	0	5 (5.6)	227 (13.1)
≥ 91 weeks	86 (6.6)	9 (3.8)	0	5 (5.6)	100 (5.8)
≥ 104 weeks	36 (2.8)	9 (3.8)	0	5 (5.6)	50 (2.9)

Source: Modified from applicant's submission, Module 5.3.5.3. ISS, link to Table 1.0 on page 43.

Demographic characteristics of subjects between placebo and apremilast treated subjects were similar. The majority of subjects were White (90%); Male (57%-70%); and less than 65 years of age (90%). The study population was consistent with population of patients with psoriasis in the US[4]. The baseline disease severity, measured by PASI, BSA and sPGA, and prior systemic therapy were similar between treatment arms.

Baseline study population characteristics in trials PSOR-008; PSOR-009 and PSOR-005 are presented in Table 18; Table 19 and Table 20 below.

Table 18: Baseline Demographic Characteristics in PSOR-008; PSOR-009 and PSOR-005

	PSOR-008 and PSOR-009		PSOR-005	
Demographics	**Placebo (N=418)**	**APR 30mg BID (N=832)**	**Placebo (N=88)**	**APR 30mg BID (N=88)**
Age (y) n (%)				
Mean ± SD	46.3 (12.9)	45.6 (13.0)	44.1 (13.7)	44.1 (14.7)
Median (Min; Max)	46.0 (20;82)	46.0 (18; 83)	44.0 (18; 74)	45.0 (18; 72)
<65	380 (90.9)	762 (91.6)	81 (92.0)	79 (89.9)
≥65	38 (9.1)	70 (8.8)	7 (8.0)	9 (10.2)
Sex				
Male	297 (70.3)	553 (66.7)	53 (60.2)	50 (56.8)
Female	124 (29.7)	279 (33.5)	35 (39.8)	38 (43.2)
Race				
White	377 (90.2)	753 (90.5)	83 (94.3)	80 (90.9)
Asian	22 (5.3)	36 (4.3)	4 (4.5)	4 (4.5)
Black or African American	12 (2.9)	31 (3.7)	1 (1.1)	2 (2.3)
American Indian or Alaska Native	6 (1.4)	3 (0.4)	0	1 (1.1)
Native Hawaiian or Other Pacific Islander	1 (0.2)	6 (0.7)	0	0
Other	0	3 (0.4)	0	1 (1.1)

Source: Modified from applicant's submission: Module 5.3.5.3. ISS, Table 10, page 47; and Module 5.3.5.1 Study report CC-10004-PSOR-005-E-LTE, Table 11, page 72.

Table 19: Baseline Disease Characteristics; PSOR-008 and PSOR-009

	PSOR-008		PSOR-009	
Disease Characteristics	**Placebo (N=282)**	**APR 30mg BID (N=562)**	**Placebo (N=137)**	**APR 30mg BID (N=274)**
Duration of Plaque Psoriasis				
n	280	562	135	271
Mean ± SD	18.7 (12.3)	19.7 (13.0)	18.7 (12.0)	17.9 (11.3)
History of:				
Guttate, Pustular, or Erythrodermic Psoriasis, or of a Sudden Intensification in Psoriasis	12 (4.3)	26 (4.6)	15 (10.9)	25 (9.1)
(b) (4)				
Psoriatic arthritis	50 (17.7)	123 (21.9)	13 (9.5)	42 (15.3)
Total PASI Score at Baseline				
Mean ± SD	19.37 (7.39)	18.74 (7.18)	20.04 (7.99)	18.93 (7.05)
PASI Score Category, n (%)				
≤ 20	195 (69.1)	404 (71.9)	88 (64.2)	193 (70.4)
≥ 20	87 (30.9)	158 (28.1)	49 (35.8)	81 (29.6)
BSA (%)				
Mean	25.34 (14.6)	24.4 (14.7)	27.58 (15.8)	26.46 (15.4)
sPGA, n (%)				
0 (clear)	0	0	0	0
1 (almost clear)	0	0	0	0
2 (mild)	1 (0.4)	0	0	1 (0.1)
3 (moderate)	192 (68.1)	401 (71.4)	88 (64 .2)	198 (72.3)
4 (severe)	89 (31.6)	161 (28.6)	49 (35.8)	75 (27.4)
Prior Phototherapy				
Yes	88 (31.2)	175 (31.3)	31 (22.6)	83 (30.3)
No	194 (68.8)	386 (68.7)	106 (77.4)	191 (69.7)
Prior Convectional Systemic Therapy				
Yes	102 (36.2)	212 (37.7)	53 (38.7)	106 (38.7)
No	180 (63.8)	350 (62.3)	84 (61.3)	168 (61.3)
Prior Biologic Therapy				
Yes	80 (28.4)	162 (28.8)	44 (32.1)	92 (33.6)
No	202 (71.6)	400 (71.2)	93 (67.9)	182 (66.4)
Prior TNF Blocker Therapy				
Yes	28 (17.0)	101 (17.0)	30 (21.9)	72 (26.3)
No	234 (83.0)	461 (82.0)	107 (78.1)	202 (73.7)

Source: Module 5.3.5.1, Study Report CC-10004-PSOR-008, Section 11.2.2, Table 13, page 78 and Study Report CC-10004-PSOR-009, Section 11.2.2, Table 14, page 79.

Table 20: Baseline Disease Characteristics PSOR-005

	PSOR-005	
Disease Characteristics	**Placebo (N=88)**	**APR 30mg BID (N=88)**
Duration of Plaque Psoriasis		
Mean ± SD	19.6 (11.6)	19.2 (12.0)
History of, n (%):		
Guttate, Pustular, or Erythrodermic Psoriasis	2 (2.3)	5 (5.7)
[redacted] (b) (4)		
History of Psoriatic Arthritis	17 (19.3)	21 (32.9)
Prior Systemic Therapy		
Yes	39 (44.3)	47 (53.4)
No	49 (55.7)	41 (46.6)
Total PASI Score		
Mean ± SD	18.1 (5.6)	19.1 (7.0)
BSA		
Mean ± SD	21 (11.1)	25 (15.3)
sPGA, n (%)		
0 (clear)	0	0
1 (minimal)	0	0
2 (mild)	1 (1.1)	16 (4.5)
3 (moderate)	61 (69.3)	206 (58.5)
4 (marked)	22 (25.0)	118 (33.5)
5 (severe)	4 (4.5)	12 (3.4)

Source; Modified from applicant's submission, Module 5.3.5.1, Study report CC-10004-PSOR-005-E-LTE, page 74

7.2.2 Explorations for Dose Response

The apremilast dose response evaluation was conducted in Phase 2 trials: PSOR-005, PSOR-004 and PSOR-003. In two Phase 3 trials, PSOR-008 and PSOR-009, only 30mg BID dose was evaluated.

The applicant selected the apremilast 30mg BID dose based on the results from trial PSOR-005 during which 3 different doses of apremilast were evaluated. A total of 352 subjects with psoriasis (baseline PASI score ≥12; BSA ≥10% and candidates for photo/systemic therapy) were randomized into 4 groups: 10mg BID; 20mg BID; 30mg BID or placebo. The primary endpoint was PASI-75 response at Week 16.

After 16 weeks of treatment, PASI 75 was achieved in: 5.7% of placebo treated subjects; 11.2% in apremilast 10mg BID treated subjects; 28.7% in apremilast 20mg BID treated subjects and 40.9% in apremilast 30mg BID treated subjects. The efficacy of apremilast 20mg BID and 30mg BID were both statistically significant while the efficacy of 10mg BID doses was not. These results demonstrated a dose response. Safety evaluation did not reveal safety signals for either 20mg BID or 30mg BID dose. Based on the efficacy and safety results, the applicant selected 30mg BID dose as the one with the best benefit-risk profile and conducted Phase 3 trials using this dose.

7.2.3 Special Animal and/or In Vitro Testing

In vitro effect of apremilast on ionic currents in voltage-clamped human embryonic kidney cells that express hERG gene were evaluated. Four concentrations of apremilast were evaluated: 16.8μM; 49.7μM; 87.5μM and 249.7μM. In addition, vehicle control (physiological saline solution with 0.3% of DMSO) and positive control (terfenadine at 60nM were tested. The results of evaluation are presented in Table 21 below.

Table 21: hERG Current Inhibition Results

APR Concentration	hERG Current Inhibition (%)
16.8μM;	6.3 ±0.9
49.7μM	19.3±1.4
87.5μM	28.5±0.6
249.7μM	59.0±1.7
Negative control	
Saline solution	1.6±0.3
Positive control	
Terfenadine	87.1

Source: Applicant's submission, Section 4.2.1.3, Study report #031206DFN Appendix B, page 16.

Because these results showed partial hERG currents inhibition by apremilast, the applicant evaluated cardiovascular and respiratory effects of intravenously administered apremilast to anaesthetized dogs.
In the anesthetized dog study, vehicle control and apremilast at dosses of 0.5mg/kg, 1mg/kg and 5mg/kg, were evaluated. The following parameters were monitored: respiration rate, heart rate, ECG (RR and QT intervals, QTc interval).
At a dose of 0.5mg/kg, apremilast did not have a major effect on cardiovascular system when compared to vehicle. At doses of 1mg/kg and 5mg/kg, the apremilast induced moderate increase in heart rate and dP/dt_{max}; decrease in RR and QT intervals and had no effect on QTc interval.
These results showed minimal effects of apremilast at doses on 0.5mg/kg and 1mg/kg in comparison to vehicle. A no effect dose could not be established because of the significant effect on dP/dt_{max} at the lowest dose.

7.2.4 Routine Clinical Testing

Routine safety monitoring included clinical evaluation and laboratory testing at specified time points. The following safety monitoring was performed:

- A chest radiograph
- Hepatitis B surface antigen and anti-hepatitis C antibody
- Vital signs, including temperature, pulse, and blood pressure
- A complete physical examination.

- Vasculitis assessment.
- Psychiatric evaluation.
- Laboratory evaluations: cholesterol panel; clinical chemistry; complete blood count; urinalysis; and high-sensitivity C-reactive protein, hemoglobin A1c, serum pregnancy test for female subjects of childbearing potential, and 12-lead ECG.

The following testing was done only in Phase 2 trials:

- ANA; ANCA; IgA; IgG; IgM; Lymphocyte Safety Subsets (CD3+; CD4+; CD8+), PPD.

Overall, safety monitoring performed during the conduct of trials supporting this NDA was appropriate and adequate for evaluation of safety of apremilast.

7.2.5 Metabolic, Clearance, and Interaction Workup

Discussion of the drug metabolism, clearance and drug-drug interaction is presented in section **4.4 Clinical Pharmacology** of this review and the review by Dr. Chinmay Shukla.

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

Apremilast belongs to class of PDE-4 inhibitors. Currently marketed product in this drug class is roflumilast (NDA 22522, approved on February 28, 2011) approved for the treatment to reduce the risk of COPD exacerbations. The **WARNING AND PECAUTIONS** section of drug labeling includes "**Psychiatric Events including Suicidality"** and **"Weight Decreases"**.
In roflumilast labeling, psychiatric adverse reactions included: suicidal ideation and behavior, including completed suicide, insomnia, anxiety and depression. Commonly reported adverse reactions included diarrhea, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite.

The applicant defined a set of adverse events of special interest based on the mechanism of action of apremilast and possible class effects. The applicant evaluated psychiatric adverse events that included depression, suicide, suicidal ideation and behavior.

7.3 Major Safety Results

7.3.1 Deaths

During apremilast development program for psoriasis indication, 6 deaths were reported (3 deaths in PSOR-008; and one each in PSOR-004; PSOR-005 and PSOR-009). One

additional death was reported in the psoriatic arthritis trial (PSA-002) and one in investigator-initiated trial in rheumatoid arthritis.

In psoriasis trials, 4 deaths occurred in apremilast treated subjects and two in placebo treated subjects. Narrative summaries and discussion of deaths in psoriasis trials are presented below.

Table 22: Death Listings

Trial	Center	Patient #	Age (years)	Dose (mg)	Time (Days)	Description
PSOR-008	025	0251014	28	Placebo	(b) (6)	Suicide
PSOR-008	403	4031002	30	APR 30mg BID		Cardiac failure
PSOR-008	105	1051011	69	APR 30mg BID		CVA
PSOR-009	119	1191012	51	APR 30mg BID		Hemorrhagic CVA
PSOR-005	042	421019	63	Placebo		Not determined
PSOR-004	002	0020009	48	APR 20mg BID increased to 30mg BID		Not determined

Source: Applicant's submission, Module 5.3.5.3 ISE, Section 5.3.1, page 124.

Trial PSOR-008

Subject #0251014 was a 28 years old white female who was on placebo during the Placebo-controlled Phase of the study, completed suicide via gunshot wound on study (b) (6), twenty six days after the last dose of placebo. The subject had a medical history of bipolar disorder, depression, attempted suicide, insomnia, and alcohol abuse. Concomitant medication included trazodone, medroxyprogesterone acetate, lansoprazole, duloxetine hydrochloride, lamotrigine, salbutamol and cetirizine hydrochloride/pseudoephedrine hydrochloride. The investigator considered this death not suspected to be related to IP.

Subject #4031002 was a 30 years old white female who died on Study Day (b) (6) while in the Placebo-controlled treatment phase of the study. The autopsy revealed lung congestion and bilateral edema consistent with cardiac failure. The subject received apremilast 30 mg BID for a total of 104 days. The subject had a medical history of

depression, obesity (BMI at screening] was 35.1 kg/m^2), and alcohol use (1-14 drinks per week). An electrocardiogram (ECG) at Screening was normal and at Baseline was abnormal with left axis deviation, poor R wave progression with late R wave transition, and normal sinus rhythm. Blood pressure and pulse at Baseline were 120/80 mmHg and 78 bpm, respectively. Blood pressure and pulse at her last attended study visit (Study Day (b) (6)) were 110/75 mmHg and 68 bpm, respectively. Concomitant medication included escitalopram oxalate. On Study Day (b) (6) days after her last dose of active treatment, the subject was found dead in her bed by her housemate. Review of her blister card indicated that the subject had not taken study medication for the (b) (6) preceding her death. No obvious cause of death was identified. Previous chest x-ray, ECGs and laboratory tests had not revealed any underlying abnormality. At the time of death, the subject's BMI was 40.6 kg/m^2. An autopsy did not indicate any anomaly other than a diffuse lung congestion and bilateral edema, consistent with acute cardiac failure, which was reported as the cause of death. The cardiovascular system was normal. The summary of autopsy findings included the following: 1. Morbid obesity, 2. Internal organs showed early decompositional changes, 3. Lungs were congested and edematous, 4. Fibroid uterus. The toxicology report results were negative, confirming that she did not die due to an overdose of drugs included in the toxicology analysis (substance abuse associated with drugs that were not included in the toxicology analysis, could not be ruled out). The investigator considered this event of lung congestion and bilateral edema consistent with cardiac failure as suspected of being related to apremilast.

Subject #1051011 was a 69 years old white male who experienced a fatal cerebrovascular accident on study Day (b) (6) while in the long-term Extension phase of the trial. The subject received placebo in the Placebo-controlled treatment phase, followed by apremilast 30mg BID for a total of 666 days. The subject was an ex-smoker and his medical history included hypertension, hyperlipidemia, type 2 diabetes mellitus, obesity (BMI of 42.6 kg/m^2, alcohol use (1-14 drinks per week), chronic obstructive pulmonary disease (COPD), chronic bronchitis, anemia, and benign prostatic hyperplasia. At Screening and Baseline, his blood pressure was 154/57 mmHg and 166/69 mmHg, respectively. The ECG at baseline was assessed as abnormal but not clinically significant, with findings of sinus arrhythmia and sinus bradycardia (mean heart rate was 56 bpm). Laboratory results at Screening showed lipid levels within normal ranges. Concomitant medication included valsartan, bisoprolol, atorvastatin calcium, fluticasone propionate, metformin, allopurinol, alfuzosin, and oxycodone / acetaminophen. On study Day 744; at the study visit preceding the serious event, the subject's ECG showed worsening compared to baseline, with old or age indeterminate anteroseptal myocardial infarction and sinus bradycardia (mean heart rate was 53 bpm). The subject was asymptomatic, and the investigator did not consider the results to be significant; the ECG results were forwarded to the subject's family doctor. On study Day (b) (6), while at home, the subject began experiencing symptoms of stroke. In the emergency room, the subject was found to be non-responsive. The subject died in the emergency room due to acute CVA. No treatment was given. The type of stroke was

reported as unknown. An autopsy was not performed. A death certificate was not available. The investigator considered the event of CVA as not suspected of being related to apremilast.

PSOR-009

Subject #1191012 was 51 years old white female who died on study Day (b) (6) due to intracranial hemorrhage, 127 days after the last dose of apremilast while in the Randomized Treatment Withdrawal Phase. The subject received apremilast 30 mg BID for a total of 224 days, followed by placebo in the randomized withdrawal phase. The subject's medical history included depression, bipolar disorder type 1, and menopause. The subject had no other significant co-morbidities or history of aneurysm. An ECG at Baseline showed sinus bradycardia, blood pressure and pulse were 128/68 mmHg and 62 bpm, respectively. Concomitant medication included lithium and venlafaxine.
On Study Day 352, one hundred twenty seven days after the last dose of apremilast, the subject complained of a headache before going to bed. She was last seen well at approximately 1:00 am on Study Day (b) (6) and at approximately 5:00 am she was found unresponsive on the floor. She was brought to the hospital, where a computed tomography (CT) scan of the head without contrast revealed the following: a large intracranial hematoma in the left hemisphere centered in the basal ganglia region with intraventricular extension and small bilateral subarachnoid component; midline shift by 1.7 cm as well as evidence of left uncal and tonsilar herniation; hematoma filled the third and fourth ventricles. A neurosurgeon reviewed the imaging and recommended palliative therapy. On neurological examination the subject was unresponsive to noxious stimuli to any of her extremities with a Glasgow coma scale of 3. Pupils were approximately 3 mm, equal, and reactive to light. Laboratory values and investigations (normal ranges and some units not provided) revealed WBC count 20.5 x 109/L, hemoglobin 13.4 x 109/L, platelet count 260, INR 1.1, creatinine 58; chemistry panel was within normal limits. ECG showed sinus rhythm with QTc of 494 msec. revealed no lung abnormalities. The subject was pronounced brain dead the next day. An autopsy was not performed. The investigator considered the event of intracranial hemorrhage as not suspected of being related to study medication. An alternative etiology was not provided.

PSOR-005 E-LTE

Subject #0421019 was a 63-year old male who died on study day (b) (6). He received placebo in the placebo controlled phase for a total of 84 days. The subject's medical history included 35 pack/year smoking, COPD, left bulla excision, pneumonia, migraine headaches antecedent bifascicular disease, significant bradycardia, and alcohol use (1-14 drinks per week). Concomitant medications included sumatriptan and hydroxyzine. Baseline electrocardiogram (ECG) findings were consistent with left anterior hemiblock and first degree AV block which were unchanged throughout the study; the subject was asymptomatic. On study Day (b) (6), the subject was found at home by his wife, unresponsive on the floor of the garage with his motorcycle running. The subject's wife reported that he was "still warm and had an unusual pink complexion." The main garage

door was shut, but the side door was open. EMS was called and resuscitation attempts were unsuccessful. The subject was reported by his wife as 'a happy-go-lucky type', he had no apparent illness, no significant stressors at home, and no apparent suicidal ideation. Police investigations reportedly noted no suspicious findings. An autopsy was performed and a preliminary verbal report from the coroner to the wife which noted "no suspicious findings and had labeled the event as an accidental death." A written report was not available at that time. Toxicology studies were still pending. The subject has been cremated since the time of this report. The investigator felt that the subject's death was likely due to a cardiovascular system (CVS) event. The coroner report was not available. The investigator considered this event as not suspected of being related to Apremilast.

PSOR-004
Subject #0020009 was a 48-year old white male who received the apremilast 20mg for 12 weeks after which the dose was increased to 30mg twice daily (total treatment duration of 140 days). The subject had relevant medical history of cardiac arrhythmia (2000), status post cardiac ablation procedure, gout, childhood asthma, and obesity (height 72 inches, weight 400 pounds). No concomitant medication was reported. (b) (6) days after the start of study medication and (b) (6) days after the dose increased to apremilast 30mg twice daily the was found dead next to his home. The investigator was informed of the subject's death by the subject's significant other in an unconfirmed verbal report. The verbal report of cause of death was based on the subject's significant others but not the investigator, as this event was suspected to be related to a heart arrhythmia and hypertensive changes in addition to heart attack. No evidence of the cause of death was made available. The cause of death was not medically confirmed and was not made by the investigator. The investigator also attributed the subject's history of cardiac ablation and obesity as preexisting risk factor for the cause of death. The investigator reported that the subject was considered compliant with study visits and had not abused alcohol to her knowledge. In the initial report however, the investigator attributed alcohol abuse as alternative cause of death. An autopsy was performed. The sponsor repeatedly contacted the investigative site to request that an autopsy report or death certificate be obtained. Despite numerous written and verbal attempts by the sponsor over a six month period, including a site visit by a Clinical Research Physician from the team, the site was unable to provide documentation of this event beyond the verbal reports from the subject's significant other, which cannot be confirmed or verified. The Investigator considered the events as not being related to the study medication.

Deaths in other trials:

- Subject #PSA-002-9051004 from psoriatic arthritis trial PSA-002 was a 52 year-old female who had comorbid condition of vitamin B_{12} deficiency and treatment with methotrexate. The subject was treated with apremilast 20mg BID. On Day (b) (6) of the trial the subject died due to multi-organ failure.

- Subject #0011002, from investigator-initiated rheumatoid arthritis trial AP-RA-PI-024, was an 82 year-old female with past history of breast cancer and uncontrolled RA. Prior treatment included adalimumab, methotrexate and other TNF α inhibitors. The subject received 30mg BID of apremilast for (b) (6) days. The subject was diagnosed with acute myeloid leukemia 1 year after receiving apremilast. Subject died (b) (6) years after receiving last dose of apremilast. The investigator assessed the events as being unrelated to the study drug administration.

Discussion: Detailed analysis of the individual deaths, including temporal relationship to apremilast dosing, does not suggest a causal relationship, for the following reasons:

- *Two subjects (#0251014 and #0421019) were treated with placebo and therefore not related to apremilast.*

- *Subject (#1191012), a 51 years old white female, who died 127 days after the last dose of apremilast. Apremilast has terminal elimination half-life of approximately 6-9 hours therefore at the time of adverse event no drug was present in the subject's circulation. In addition, taking into consideration the mechanism of action of apremilast, its effect would not be expected to be present at the time of the event.*

- *Subject #4031002, a 30 year-old female, who died due to acute cardiac failure also had comorbid condition of depression, sleep apnea and severe obesity /morbid obesity. Morbid obesity is associated with increased risk of sudden and unexpected cardiac death due to eccentric/concentric cardiac hypertrophy[2] and increased irritability of the myocardium leading to ventricular arrhythmias (in the absence of left ventricular dysfunction or clinical heart failure[3]). In addition, sleep apnea is associated with increased risk of cardiac arrhythmias[5]. This event of death occurred (b) (6) days after the subject received last dose of apremilast therefore, the drug was not expected to be present in subject's circulation at the time of the event.*

- *Subject #1051011, a 69 year-old male, who died of cerebrovascular accident, had also comorbid conditions of: hypertension; hyperlipidemia; type 2 diabetes mellitus; morbid obesity (BMI 42,6kg/m^2) and COPD. Subject's age and all of comorbid conditions listed above are associated with increased risk of cardiovascular and cerebrovascular events.*

- *Subject #0020009, a 48 year-old male who died of undetermined cause had a comorbid condition of cardiac arrhythmia, status post cardiac ablation, and morbid obesity (weigh of 400lb). Subject's comorbid conditions are associated with an increased risk of sudden cardiac death.*

7.3.2 Nonfatal Serious Adverse Events

Phase 2/3 Data Pool

I. Placebo Controlled Period (Week 0-16)

During treatment period Week 0-16, a total of 13 (2.6%) subjects on placebo and 21 (2.0%) subjects on apremilast reported SAEs. Only SAEs that were reported by two or more subjects in apremilast treatment group were abdominal pain and myocardial infarction. All other SAEs in apremilast treated subjects were reported by 1 subject. Subjects with treatment emergent SAEs are presented in Table 23 below. The applicant included two pregnancies (trial PSOR-005) in their report of SAEs. These events were not included in tables below and were discussed separately in section **7.6.2 Human Reproduction and Pregnancy Data,** of this review.

Table 23: Serious Adverse Events for PSOR-008; PSOR-009 and PSOR-005 (Week 0-16)

Preferred Term	**Placebo (N=506) n (%)**	**Apremilast 30mg BID (N=920) n (%)**
Any Serious TEAE	**13 (2.6)**	**19 (2.0)**
Pneumonia	1 (0.2)	1 (0.1)
Clostridium difficile colitis	1 (0.2)	0 (0.0)
Anal cancer	1 (0.2)	0 (0.0)
Microcytic anemia	0 (0.0)	1 (0.1)
Gout	0 (0.0)	1 (0.1)
Personality disorder	0 (0.0)	1 (0.1)
Suicide attempt	0 (0.0)	1 (0.1)
Completed suicide	1 (0.2)	0 (0.0)
Transient ischemic attack	0 (0.0)	1 (0.1)
Syncope	2 (0.5)	0 (0.0)
Cardiac failure	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.2)	2 (0.2)
Palpitations	1 (0.2)	0 (0.0)
Supraventricular tachycardia	1 (0.2)	0 (0.0)
Orthostatic hypotension	0 (0.0)	1 (0.1)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)
Chronic obstructive pulmonary disease	0 (0.0)	1 (0.2)
Abdominal pain	0 (0.0)	2 (0.2)
Inguinal hernia	1 (0.2)	1 (0.1)
Dysphagia	0 (0.0)	1 (0.1)
Cholecystitis	1 (0.2)	0 (0.0)
Psoriasis	0 (0.0)	1 (0.1)
Urticaria	0 (0.0)	1 (0.1)
Psoriatic arthropathy	0 (0.0)	1 (0.1)
Pyrexia	0 (0.0)	1 (0.1)

Table 23: Serious Adverse Events for PSOR-008; PSOR-009 and PSOR-005 (Week 0-16) continues

Non-cardiac chest pain	1 (0.2)	0 (0.0)
Heart rate increased	0 (0.0)	1 (0.1)
Blood bilirubin increased	1 (0.2)	0 (0.0)
Concussion	0 (0.0)	1 (0.1)
Multiple injuries	0 (0.0)	1 (0.1)
Road traffic accident	0 (0.0)	1 (0.1)
Prostate cancer	0 (0.0)	1 (0.1)
Asthma	0 (0.0)	1 (0.1)
Drug eruption	1 (0.2)	0 (0.0)

Source: Modified from applicant's submission, Module 5.3.5.3; ISS; Section 5.3.2.1.1.; Table 1.23.1, link page 126.

II. Apremilast Treatment Period Week 0-52

During apremilast exposure period (Week 0-52), 59 subjects reported 95 SAEs. Most SAEs were reported by one subject. SAEs reported by two or more subjects who received at least one dose of apremilast are presented in Table 24 below.

Table 24: Serious Adverse Events Reported in Two or More Apremilast Treated Subjects for PSOR-008; PSOR-009 and PSOR-005 (Week 0-52)

Preferred Term	**Apremilast 30mg BID (N=1308) n (%)**
Any SEA	61 (4.7)
Myocardial infarction	4 (0.3)
Coronary artery disease	3 (0.2)
Nephrolithiasis	3 (0.2)
Urinary tract infection	2 (0.1)
Brest cancer	2 (0.1)
Transient ischemic attack	2 (0.1)
Chronic obstructive pulmonary disease	2 (0.1)
Abdominal pain	2 (0.1)
Intervertebral disc protrusion	2 (0.1)
Psoriasis	2 (0.1)
Prostate cancer	2 (0.1)

Source: Modified from applicant's submission. Module 5.3.5.3, ISS, Table 53, page 128.

Discussion: Review of SAE during the Placebo-controlled or Apremilast treatment period did not reveal a safety signal.

Out of 95 SAEs (period Week 0-52), 10 subjects reported 10 SAEs suspected by the investigator of being related to the study drug administration. All of these 10 subjects

were on apremilast. The list of SAE related to the study drug administration is presented in the Table 25 below.

Table 25: Listing of Subjects with Serious Adverse Events Related to Apremilast PSOR-008 and PSOR-009 (Weeks 0 through Week 52)

Subject No.	Age/Sex/Race	SAE Preferred Term	Start/End Day	Severity
PSOR-008-0151007	35/M/White	Urinary tract infection	195/210	Moderate
PSOR-008-0261006	67/F/White	Transient ischemic attack	81/88	Mild
PSOR-008-0481003	80/M/White	Microcytic anemia	48/50	Moderate
PSOR-008-1081020	41/M/White	Pneumonia	30/83	Moderate
PSOR-008-4031002	30/F/ White	Cardiac failure	(b) (4)	Severe
PSOR-008-8021002	61/M/White	Pyrexia	393/404	Severe
PSOR-009-0451028	69/F/White	Duodenal ulcer hemorrhage	136/148	Severe
PSOR-009-1191014	38/M/White	Pneumonia staphylococcal	625/647	Severe
PSOR-009-3201012	36/M/White	Psoriasis worsening	201/210	Severe
PSOR-009-9221002	26/M/White	Infectious mononucleosis	464/532	Moderate

Source: Modified from the applicant's submission, Module 5.3.5.3, ISS, Section 5.3.2, Table 214, link on page 126.

Discussion: Detailed review of SAEs that were deemed being related to the study drug administration (by the investigator), did not reveal definite causal relationship or safety signal for apremilast.

Psoriasis Data Pool

I. Placebo Controlled Period (Week 0-16)
In Psoriasis Data Pool a total of 3% of subjects in the placebo group and 2.3% of subjects in apremilast 30mg BID treatment group, reported SAEs. Most SAEs were reported by one subject. SAEs of abdominal pain, psoriasis and pregnancy were the only ones reported by 2 or more subjects.

II. Apremilast Exposure Period
Approximately 5.7% of subjects treated with apremilast 30mg BID reported SAE. Most SAEs were reported by one subject. SAEs reported by 3 or more subjects were: coronary artery disease, myocardial infarction, psoriasis, nephrolithiasis and osteoarthritis.

Discussion: No safety signals were identified for Psoriasis Data Pool.

7.3.3 Dropouts and/or Discontinuations

Phase 2/3 Data Pool
I. Placebo Control Period (Week 0-16)
During the treatment period Week 0-16, 21 (4.1%) subjects treated with placebo and 57 (6.1%) subjects treated with apremilast, discontinued due to adverse events. There was

one death (see discussed in section 7.3.1 of this review). The most frequently reported AEs leading to drug discontinuation were: nausea, diarrhea and headache.
AEs leading to study drug discontinuation, reported in 2 or more subjects, are presented in Table 26 below.

Table 26: AEs that Led to Drug Withdrawal, Reported in 2 or More Subjects For Trials PSOR-008; PSOR-009 and PSOR-005 (Week 0-16)

	Week 0 through Week 16	
Preferred Term	**Placebo (N=506) n (%)**	**Apremilast 30mg BID (N=920) n (%)**
Any TEAE Leading to Withdrawal	21 (4.1)	57 (6.1)
Nausea	1 (0.2)	15 (1.6)
Diarrhea	1	8 (1.0)
Headache	0	7 (0.8)
Psoriasis	4 (1.0)	4 (0.5)
Vomiting	1 (0.2)	2 (0.2)
Dyspepsia	0	3 (0.4)
Abdominal discomfort	1 (0.2)	2 (0.2)
Tension headache	0	2 (0.2)
Fatigue	0	2 (0.2)
Migraine	0	2 (0.2)
Frequent bowel movements	0	2 (0.2)
Asthenia	0	2 (0.2)
Hematochezia	0	2 (0.2)
Abdominal pain upper	0	2 (0.2)
Pregnancy	0	2 (0.2)

Source: Modified from applicant's submission, Module 5.3.5.3 ISS; Table 58, page 137.

II. Apremilast Treatment Period Week 0-52

During the treatment period Week 0 through Week 52, the most frequently reported AEs leading to drug discontinuation were: nausea, diarrhea and worsening of psoriasis. AEs leading to study drug discontinuation, reported in 2 or more subjects during the apremilast treatment period (Week 0 through 52), is presented in Table 27 below.

Table 27: AEs Leading to Drug Withdrawal Reported in Two or More Apremilast Treated Subjects for Trials PSOR-008; PSOR-009 and PSOR-005 (Week 0-52)

Preferred Term	**Apremilast 30mg BID (N=1308) n (%)**
Any AE that Led to Drug Withdrawal	106 (8.1)
Nausea	19 (1.5)
Diarrhea	11 (0.8)
Psoriasis	10 (0.8)
Vomiting	5 (0.4)
Headache	7 (0.5)
Tension headache	3 (0.2)
Dyspepsia	3 (0.2)
Abdominal discomfort	3 (0.2)
Haematochezia	3 (0.2)
Dizziness	2 (0.2)
Migraine	2 (0.2)
Angina pectoris	2 (0.2)
Abdominal pain upper	2 (0.2)
Psoriatic arthropathy	2 (0.2)
Asthenia	2 (0.2)
Fatigue	2 (0.2)
Squamous cell carcinoma of skin	2 (0.2)
Prostate cancer	2 (0.2)
Pregnancy	2 (0.2)

Source: Modified from applicant's submission, Module 5.3.5.3. ISS, Section 5.3.3.1.2., Table 1.19.2, link on page 138. Data for all subjects exposed to apremilast are included regardless of when the apremilast exposure started.

Discussion: The most frequently reported AEs were nausea and diarrhea. Similar common adverse event profile was reported for roflumilast. It appears that these gastrointestinal AEs may represent a class effect. More detailed discussion regarding gastrointestinal AEs is presented ***Section 7.3.5 Submission Specific Primary Safety Concerns*** *of this review.*

Psoriasis Data Pool

For the **Placebo Controlled Period** and **Apremilast Exposure Period,** discontinuation rates and reason for discontinuation were similar between placebo and apremilast treatment arms. Most frequently reported reasons for discontinuation were: adverse events, lack of efficacy and withdrawal by subject.

7.3.4 Significant Adverse Events

No additional significant adverse events were reported during the conduct of studies that support this application.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest (AESI) were selected based on the mechanism of action of apremilast (PDE4 inhibition), animal toxicity data, possible class effects, known comorbidities of psoriasis, and safety issues identified with currently marketed drugs in the proposed indication. These events include the following: cardiovascular events [Major Adverse Cardiac Events (MACE) and potential MACE]; malignancies; serious infections; opportunistic infections; GI events (diarrhea, nausea); psychiatric disorders (depression, suicide, suicidal ideation and behavior); vasculitis; headache (including tension headache); and weight change. A subset of AESI (MACE and potential MACE, malignancies, serious infections, and TB) was adjudicated by independent, blinded, subspecialty adjudicators.
The applicant performed broader safety assessment for the following adverse events: upper respiratory tract infections, cardiac disorders (cardiac failure and tachyarrhythmia), GI pain/abdominal pain, acute renal failure, liver-related investigations, gallstones and gallbladder system, and hypersensitivity. These events were analyzed using either MedDRA preferred terms (PTs), standardized MedDRA queries (SMQs), or sponsor created queries (SCQs). SMQs included two types of searches: *Narrow* to identify cases that are highly likely to represent the condition of interest, and *Broad* to identify all possible cases, including some that may prove to be of little or no interest on closer scrutiny. SCQs used applicable MedDRA preferred terms (PTs).

The applicant also conducted an analysis of published epidemiologic literature to estimate the incidence of cardiovascular events, malignancies, tuberculosis, serious infections, and depression in the general psoriasis population and to compare these data with the event rates in apremilast treated subjects.

MACE and Potential MACE
Phase 2/3 Data Pool
MACE were defined as TEAEs of sudden unwitnessed death, cardiovascular death (sudden cardiac death; death due to: myocardial infarction, heart failure, stroke or other cardiovascular causes), myocardial infarction and nonfatal stroke. Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularization procedure, transient ischemic attack (TIA), re-hospitalization for recurrent ischemia, embolic events, and deep vein thrombosis.

I. Placebo Controlled Period
Table 28 below presents all cases adjudicated as MACE or potential MACE during the placebo controlled period (Week 0 through 16) in trials PSOR008, PSOR-009 and PSOR-005. There was no increase in rates of MACE and potential MACE in the apremilast treated subjects compared to placebo subjects, during this period.

Table 28: Adjudication Results for MACE and Potential MACE, Week 0-16 (PSOR-008; PSOR-009 and PSOR-005)

	Placebo (N=506) n (%)	EAIR	Apremilast 30mg BID (N=920) n (%)	EAIR
Subjects sent for adjudication	6 (1.2)		6 (0.7)	
Subjects adjudicated as not evaluable	1 (0.2)		2 (0.2)	
Subjects adjudicated as an event	2 (0.5)		4 (0.4)	
MACE	1 (0.2)	0.7	2 (0.2)	0.8
Potential MACE	1 (0.2)	0.7	2 (0.2)	0.8

Source: Applicant's submission. Module 5.3.5.3 ISS, Table 4.4.2, Response to information request.

II. Apremilast Treatment Period Week 0-52

Table 29 below presents adjudicated cases of MACE or potential MACE for trials only PSOR-008; PSOR-009 and PSOR-005. Data for all subjects exposed to apremilast regardless when the apremilast exposure started, are presented. A total of 24 (1.8%) adverse events were identified for adjudication. Two events were not evaluable. Seventeen events (1.3%) were adjudicated as MACE or potential MACE.

Table 29: Adjudication Results for MACE and Potential MACE, Week 0-52, PSOR-008; PSOR-009 and PSOR-005

	Week 0-16 Placebo (N=506) n (%)	EAIR	Week 0-52 Apremilast 30mg BID (N=1308) n (%)	EAIR
Subjects sent for adjudication	6 (1.2)		24 (1.8)	
Subjects adjudicated as not evaluable	1 (0.2)		3 (0.2)	
Subjects adjudicated as an event	2 (0.5)		17 (1.3)	
MACE	1 (0.2)	0.7	8 (0.6)	0.5
Potential MACE	1 (0.2)	0.7	10 (0.8)	0.7

Source: Applicant's submission. Module 5.3.5.3 ISS, Table 1.27.2 link on page 149.
EAIR: exposure adjusted incidence rate. [1] All subjects exposed to apremilast are included regardless of when the apremilast exposure started.

When adjusted for the duration of exposure, no increase in rate of MACE or potential MACE was identified in apremilast treated subjects compared placebo treated subjects.

Comparison with Epidemiologic Data

The applicant compared Exposure Adjusted Incidence Rates (EAIR) of adjudicated MACE events of apremilast 30mg BID exposed subjects during two Phase 3 trials [0.5 in Phase 3 trials data pool; 0.3 in Apremilast Data Pool) to incidence rates reported in individual studies (0 to 4.6 per 100 person-years) in the mata-analysis of psoriasis patients receiving biologic agents conducted by Ryan et al. (2011). The EAIR per 100 subject-years was lower in apremilast Phase 3 trials than the weighted average (1.3 per 100 person-years) from IL 12/23 studies (Ryan, 2011).

In addition, the applicant cited the published study in which the General Practice Research Database (GPRD) was used to estimate incidence rate of MACE (defined as acute myocardial infarction, ischemic stroke, death due to myocardial infarction, and arrhythmia) in the psoriasis population (Mehta, 2011). In this study, the estimated incidence rate of MACE was 1.64 per 100 person-years as compared to 0.5 in applicant's Phase 3 trials. GPRD contains information on patients from United Kingdom and therefore the applicability of data to the population of the United States is not clear.

Malignancies

Phase 2/3 Data Pool

I. Placebo Controlled Period, Week 0-16

Table 30 below presents adjudicated cases of malignancies in trials PSOR-008, PSOR-009 and PSOR-005 for the treatment period Week 0 to 16. During the conduct of trial PSOR-005, no subjects in apremilast 30mg BID group reported skin malignancy.

Table 30: Adjudication Results for Malignancies Events, Week 0-16, Trials PSOR-008; PSOR-009 and PSOR-005

	Placebo (N=506) n (%)	EAIR	APR 30mg BID (N=920) n (%)	EAIR
Subjects sent for adjudication	2 (0.5)		6 (0.7)	
Subjects adjudicated as not evaluable	0 (0.0)		0 (0.0)	
Subjects adjudicated as an event	2 (0.5)		6 (0.7)	
Skin (excluding melanoma)	1 (0.2)	0.7	5 (0.5)	1.9
Solid (including melanoma)	1 (0.2)	0.7	1 (0.1)	0.4

Source: Applicant's submission. Module 5.3.5.3 ISS, Table 1.27.1 link on page 152.
The placebo group includes data for Week 0-16.

More skin malignancies were reported during this period in apremilast treatment group in comparison to the placebo treatment group. Taking into the consideration the latency period for development of malignancies, it is unlikely that reported skin malignancies were caused by the apremilast.

II. Apremilast Treatment Period (Week 0 through Week 52)

Skin Malignancies (excluding melanoma)

During the conduct of trial PSOR-005 no subjects in apremilast 30mg BID group reported skin malignancy. Twelve (1.0%) subjects treated with apremilast reported 13 skin malignancies (one subject reported one case of basal cell carcinoma and one case of squamous cell carcinoma) and one subject in the placebo group reported skin malignancy.

Table 31: Adjudication Results for Skin Malignancies Events for PSOR-008; PSOR-009 (Week 0-52)

	Placebo (N=418) n (%)	EAIR	APR 30mg BID (N=1184) n (%)	EAIR
Skin (excluding melanoma)	1 (0.2)	0.9	12 (1.0)	1.1

Source: Applicant's submission. Module 5.3.5.3 ISS, Table 1.27.1 link on page 152.
The placebo group includes data for Week 0-16 and apremilast group includes all subjects exposed to apremilast regardless af when the apremilast exposure started.

Of reported skin malignancies 10 were basal cell carcinomas (all in the apremilast group) and 4 were squamous cell carcinomas (one in the placebo and 3 in the apremilast treatment group). Ten subjects with skin malignancies reported these AEs during first 16 weeks of exposure to apremilast. The majority of subjects with reported skin malignancies had prior history of treatment with PUVA or immunosuppressive therapy (TNFs, methotrexate, cyclosporine) or both.

Discussion: Given the timepoints at which malignancies were reported (not reflective of the generally long latency periods for development of malignancies) it is in this reviewer's opinion that the study drug was unlikely a causative agent.

Solid Malignancies (including melanoma)
In trials PSOR-008; PSOR-009 and PSOR-005, a total of 7 (0.5%) subjects treated with apremilast 30mg BID and one subject (0.1%), reported solid malignancies. Of subjects in the apremilast group who were diagnosed solid malignancies, two subjects were diagnosed with breast cancer, two with prostate cancer, one subject each was diagnosed with rectal cancer, renal cell carcinoma and uterine cancer.

Discussion: Given the timepoints at which malignancies were reported (not reflective of the generally long latency periods for development of malignancies) it is in this reviewer's opinion that the study drug was unlikely a causative agent.

Hematologic Malignancies
No hematologic malignancies were reported during the development program for psoriasis indication.

Serious Infections
Phase 2/3 Data Pool
No serious infections or opportunistic infections were reported during the conduct of trial PSOR-005. Data for all subjects exposed to apremilast 30mg BID are included regardless of when the apremilast exposure started.

In two Phase 3 trials, no cases of systemic or non-systemic opportunistic infections were reported. There was no increase of serious infections in apremilast treated subjects in comparison to placebo treated subjects.

Table 32: Adjudication Results for Serious Infections Events; Trials PSOR-008 and PSOR-009

	Placebo (n=418)		APR 30mg BID (n= 1184)	
	n (%)	EAIR(SY)	n (%)	EAIR (SY)
Subjects sent for adjudication	2 (0.4)		1 (0.7)	
Subjects adjudicated as a serious infection	2 (0.4)	2 (0.4)	1 (0.7)	
Subjects adjudicated as a non-opportunistic serious infection	2 (0.4)	1.7	11 (0.9)	1.0
Subjects adjudicated as an opportunistic serious infection	0	0	0	0

Source: Applicant's submission. Module 5.3.5.3 ISS, Table 4.4.3, response to information request.

Tuberculosis

There were no cases of TB reactivation in any of trials conducted in the psoriasis indication. Two subjects reported positive QuatiFERON-TB Gold test. Both cases were sent for adjudication and only of was adjudicated as latent TB, however it could not be determined if the subject had latent TB prior to study enrollment (no screening TB test was required). None of these subjects had abnormal chest radiograph. Both cases were treated prophylactically with TB therapy.

Psychiatric Disorders

Psychiatric adverse reactions included: suicidal ideation and behavior, including completed suicide, insomnia, anxiety and depression were evaluated by the applicant.

Suicide and self-injury

During the conduct of two Phase 3 trials, one completed suicide (subject #0251014) and one suicide attempt (subject #3241011) were reported. Subject who completed suicide was on the placebo and subject who reported attempted suicide was on apremilast 30mg BID. In the trial PSOR-005, there were no reported cases of suicide or attempted suicide.

Subject # 3241011: This subject was a 66-year old, white, male who attempted suicide on Study Day (b) (6) while in the placebo-controlled phase of the study. The subject received apremilast 30 mg BID for a total of 117 days. The subject's pertinent medical history included sleep apnea, hypertension, hypercholesterolemia, and deafness. The subject had no prior history of depression or suicidal ideation. He did not consume alcohol. Concomitant medication included candesartan / hydrochlorothiazide.

On Study Day (b) (6) the subject made suicide attempt by taking 10 tablets of zopiclone 7.5 mg because of a conflict with his wife and neighbor. The subject was hospitalized for the treatment of depression and attempted suicide. Study medication was permanently discontinued due to this adverse event. The subject was discharged from the hospital with a referral for additional psychiatric counseling.
The investigator considered this event of attempted suicide as not suspected of being related to apremilast.

*Discussion: Based on these results, the association between apremilast therapy and suicide/attempted suicide cannot be made at this time. In the **WARNING AND PRECAUTION** section of current labeling, subsection **5.1 Depression,** discuses reports of suicidal ideation and behavior in psoriatic arthritis trials. This reviewer recommends addition of information regarding suicide/attempted suicide from psoriasis trials in this section of labeling.*

Depression
Phase 2/3 Data Pool
There were no reports of depression in apremilast 30mg BID group during the conduct of trial PSOR-005. There were 3 cases of depression in lower dose groups: two in apremilast 20mg BID and one in 10mg BID groups.
No cases of depression were reported in 30mg BID group in trial PSOR-005.

I. Placebo controlled period

During the placebo controlled period (Week 0-16), the incidence of depression three times higher in subjects treated with apremilast than in placebo treated subjects. The incidence of depression during placebo controlled period is presented in Table 33 below.

Table 33: Reports of Depression during Week 0-16; Trials PSOR-008; PSOR-009 and PSOR-005

Proffered Term	Placebo (N=506) n (%)	Placebo (N=506) EAIR	APR 30mg BID (N=920) n (%)	APR 30mg BID (N=920) EAIR
Depression	2 (0.4)	1.4	12 (1.3)	4.6

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 72, page 164.

No subject was withdrawn from the treatment due to depression. None of the reported cases of depression were considered severe.

II. Apremilast Treatment Period (Week 0-52)

During the treatment period Week-52, a total of 23 apremilast treated subjects reported depression. When rates of depression of these subjects were adjusted for the duration of exposure, incidence rates of depression were again higher in the apremilast treated subjects compared to the placebo treated subjects (2.6 vs. 1.7 per 100 subject years).

Table 34: Reports of Depression for Trials PSOR-008; PSOR-009

Proffered Term	Placebo (N=418)[#] n (%)	EAIR	APR 30mg BID (N=1184)[*] n (%)	EAIR
Depression	2 (0.4)	1.7	23 (1.9)	2.6

Source: Source: Modified from applicant's submission. Module 5.3.5.3 ISS, Table 1.23.1 link on page 164.[#] Data for subjects treated with placebo during period Week 0-16 are included. [*] Data from subjects exposed to apremilast regardless of when the apremilast exposure started are included.

During the treatment period Week 0-52, study drug was discontinued in one apremilast treated subject due to depression. One apremilast treated subject reported depression as SAE and one subjects reported severe depression.

Comparison with Epidemiologic Data
The applicant compared the incidence of depression from conducted studies to a retrospective analysis of the general practice research database that reported incidence of depression in patients with mild or severe psoriasis. Patients with mild psoriasis had an incidence of 2.57 per 100 person-years, while patients with severe disease had and incidence of 3.18 per 100 person-years.

Additionally, the applicant cited, two published literature reviews (Rieder, 2012 and Russo, 2004) who reported prevalence of depression in psoriasis patients ranging from 10% to 62%.

Discussion: *Data presented above showed that higher proportion of subjects exposed to the apremilast reported depression compared to subjects exposed to the placebo. Most subjects reported depression during the first several weeks of exposure to apremilast. The number of subjects that reported depression continued to increase with increased duration of exposure. It is in this reviewer's opinion that depression represents a safety signal for apremilast. Because current labeling contains depression in section* ***5 WARNINGS AND PRECAUSIONS,*** *this reviewer recommends addition information regarding depression from psoriasis trials.*

The Division of Dermatology and Dental Products obtained consultation from the Division of Psychiatry Products and the following conclusion was made by Gregory M. Dubitsky, M.D.:
"Overall, these data do not support an inference that apremilast causes depression or suicidal thoughts or behavior in patients with psoriasis. Nevertheless, a causal link cannot be definitively ruled out. As noted above, these trials excluded subjects with a history of significant psychiatric illness. So, it is possible that when apremilast is used by patients with a history of or predisposition to depression that the risk of depression or suicidal thoughts or behavior will be greater. Also, systematic, prospective assessments for treatment-emergent suicidal thoughts and behavior were not performed in these trials." Dr. Dubitsky recommended the following labeling language:

"Treatment with apremilast is associated with an increase in adverse reactions of depression. During the 0 to 16 weeks placebo-controlled period of 3 controlled clinical trials in psoriasis in which patients were treated with apremilast 30mg twice daily, 1.4% (13/920) of patients treated with apremilast reported depression or depressed mood compared to 0.4% (2/506) treated with placebo. During this treatment, no patients treated with apremilast or placebo discontinued treatment due to depression or depressed mood. Depression was reported as serious in 0.1% (1/920) of patients exposed to apremilast, compared to none in placebo treated patients (0/506). Instances of suicidal behavior were observed in 0.1% (1/920) of patients while receiving apremilast, compared to 0.2% (1/506) placebo treated patients. One patient who received placebo committed suicide compared to none among apremilast-treated patients"

For detailed information regarding psychiatric adverse events reader is referred to the review by Gregory M. Dubitsky, M.D.

Vasculitis

Preclinical evaluation of apremilast in mice revealed arteritis (acute inflammatory cell infiltrate in all layers of the vessel wall) of aorta, thymus, and lung. Vasculitis was also noted in 4-week oral toxicity study in cynomolgus monkeys. Because of these findings, the applicant conducted evaluation for vasculitis during their clinical trials.

No cases of vasculitis were reported during the development program for psoriasis indication. There were two cases of vasculitis reported in Phase 2 trials for rheumatoid arthritis indication (RA-002). A small vessel cutaneous vasculitis was reported in one subject treated with apremilast 30mg BID and one in a subject treated with placebo. Small vessel cutaneous vasculitis is one of the manifestations of rheumatoid arthritis and therefore causal relationship between the apremilast and the event could not be established.

Nausea

Phase 2/3 Data Pool.

I. **Placebo Controlled Period (Week 0-16) and**
II. **Apremilast Treatment Period (Week 0-52)**

Only data from two Phase 3 trials will be presented below.
In two Phase 3 trials, during placebo-controlled period more subjects in the apremilast treatment group (16.6%) reported nausea compared to 6.7% in the placebo group.

Table 35: AEs of Nausea Reported for Trials PSOR-008 and PSOR-009

Nausea	Week 0-16		Week 0-52
	Placebo N=418 n (%)	APR 30mg BID N=832 n (%)	APR 30mg BID N=1184 n (%)
Any TEAE	28 (6.7)	138 (16.6)	185 (15.6)
Any severe TEAE	1 (0.2)	2 (0.2)	3 (0.3)
Any TEAE leading to drug withdrawal	1 (0.2)	13 (1.6)	17 (1.4)
Any serious TEAE	0	0	0

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 75, page 169.

Time of Onset of Nausea

During the placebo-controlled period, of apremilast subjects who reported nausea, 85% reported nausea during the first 30 days of treatment.

Table 36: TEAE of Nausea by Time of Onset in Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Nausea	**Placebo n (%)**	**APR 30mg BID n (%)**	**APR 30mg BID* n (%)**
Total Number of Events	31	154	225
Day: 1-30	27 (87.1%)	131 (85.1)	156 (69.3)
Day: 1-3	11 (35.5)	64 (41.6)	80 (35.6)
Day:4-7	4 (12.9)	31 (20.1)	32 (14.2)
Day:8-15	6 (19.4)	27 (10.4)	20 (8.9)
Day:16-23	3 (9.7)	9 (5.8)	9 (4.0)
Day: 24-30	3 (9.7)	11 (7.1)	15 (6.7)
Day: 31-60	2 (6.5)	14 (9.1)	16 (7.1)
Day: 61-90	1 (3.2)	7 (4.5)	7 (3.1)
Day:91-120	1 (3.2)	2 (1.3)	5 (2.2)
Day:121-150			9 (4.0)
Day:151-180			9 (4.0)
Day:181-210			4 (1.8)
Day:211-240			6 (2.7)
Day:241-270			4 (1.8)
Day:271-300			3 (1.3)
Day:301-330			4 (1.8)
Day:331-360			2 (0.9)

Source: Modified from applicant's submission, Section 5.3.5.3, ISS; Table 1.28.1 and Table 1.28.2 link on page 169.
* For subjects treated with apremilast, all subjects exposed to at least one dose of apremilast are included.

Duration on Nausea

The duration of AEs of nausea are presented in Table 37 below. Approximately 14% of apremilast subjects who reported AE of nausea had duration of the event between 16 and 30 days. Approximately 20% of apremilast subjects with nausea had duration of the event between 30 and 120 days.

Table 37: Nausea Reported by Duration in Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Nausea	**Placebo n (%)**	**APR 30mg BID n (%)**	**APR 30mg BID n (%)**
Total Number of Events	31	154	225
1-30 Days	26 (83.9)	102 (66.2)	146 (64.9)
1-3 Days	12 (38.7)	22 (14.3)	37 (16.4)
4-7 Days	5 (16.1)	30 (19.5)	36 (16.0)
8-15 Days	8 (25.8)	28 (18.2)	37 (16.4)
16-23 Days	1 (3.2)	13 (8.4)	19 (8.4)
24-30 Days	0	9 (5.8)	17 (7.6)
31-60 Days	1 (3.2)	15 (9.7)	31 (13.8)
61-90 Days	1(3.2)	10 (6.5)	13 (5.8)
91-120 Days	0	6 (3.9)	8 (3.6)
121-150 Days			4 (1.8)
151-180 Days			6 (2.7)
181-210 Days			3 (1.3)
211-240 Days			1 (0.4)
241-270 Days			2 (0.9)
271-300 Days			2 (0.9)
301-330 Days			0
331-360 Days			0

Source: Modified from applicant's submission, Section 5.3.5.3, ISS; Table 1.29.1, link on page 171.

Discussion: *The majority of apremilast subjects (66%) who reported AE of nausea, reported the event during the first 30 days of exposure. However, the duration of the event lasted between 30 and 120 days in 20% of subjects.*

Diarrhea

I. Placebo Controlled Period (Week 0-16) and

II. Apremilast Treatment Period (Week 0-52)

During the placebo-controlled period, there were more AEs of diarrhea reported in the apremilast treatment arm (18%) than in the placebo arm (7%) (Table 38).

Table 38: AEs of Diarrhea Reported for Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Diarrhea	**Placebo N=418 n (%)**	**APR 30mg BID N=832 n (%)**	**APR 30mg BID N=1184 n (%)**
Any TEAE	28 (6.7)	148 (17.8)	205 (17.3)
Any severe TEAE	1 (0.2)	2 (0.2)	3 (0.3)
Any TEAE leading to drug withdrawal	1 (0.2)	8 (1.0)	11 (0.9)
Any serious TEAE	0	0	0

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 74, page 166.

During the placebo-controlled period, more subjects in apremilast treatment group 29 (3.4%) reported moderate or severe diarrhea compared to 6 (1.4%) subjects in placebo treatment group.

Time of Onset of Diarrhea

In the apremilast treatment group, 83% of adverse events of diarrhea were reported during the first 30 days of dosing (Table 39 below).

Table 39: TEAE of Diarrhea by Time of Onset in Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Diarrhea	**Placebo n (%)**	**APR 30mg BID n (%)**	**APR 30mg BID n (%)**
Total Number of Events	32	177	275
Day: 1-30	22 (68.8%)	147 (83.1)	172 (52.5)
Day: 1-3	8 (25.0)	68 (38.4)	81 (29.5)
Day:4-7	3 (9.4)	31 (17.5)	33 (12.0)
Day:8-15	6 (18.8)	27 (15.3)	33 (12.0)
Day:16-23	2 (6.3)	16 (9.0)	18 (6.5)
Day: 24-30	3 (9.40	5 (2.8)	7 (2.5)
Day: 31-60	6 (18.8)	14 (7.9)	25 (9.1)
Day: 61-90	2 (6.3)	11 (6.2)	16 (5.8)
Day:91-120	2 (6.3)	5 (2.8)	15 (5.5)
Day: 121-150			12 (4.4)
Day: 151-180			12 (4.4)
Day: 181-210			3 (1.1)
Day: 211-240			10 (3.6)
Day: 241-270			6 (2.2)
Day: 271-300			2 (0.7)
Day: 301-330			2 (0.7)
Day: 331-360			0 (0.0)

Source: Modified from applicant's submission, Section 5.3.5.3, ISS, Table 1.28.1 and Table 1.28.2 link on page 166.

Duration of Diarrhea

The duration of AEs of diarrhea are presented in Table 40 below. Approximately 9% of apremilast subjects who reported AE of diarrhea had duration of the event between 16 and 30 days. Approximately 20% of apremilast subjects with diarrhea had duration of the event between 30 and 90 days.

Table 40: Diarrhea Reported by Duration in Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Diarrhea	**Placebo n (%)**	**APR 30mg BID n (%)**	**APR 30mg BID n (%)**
Total Number of Events	32	177	275
1-30 Days	22 (68.8%)	105 (59.3)	161 (58.5)
1-3 Days	12 (37.5)	32 (18.1)	49 (17.8)
4-7 Days	5 (15.6)	30 (16.9)	43 (15.6)
8-15 Days	3 (9.4)	28 (15.8)	41 (14.9)
16-23 Days	1 (3.1)	11 (6.2)	16 (5.8)
24-30 Days	1 (3.1)	4 (2.3)	12 (4.4)
31-60 Days	2 (6.3)	22 (12.4)	37 (13.5)
61-90 Days	1(3.1)	15 (8.5)	18 (6.5)
91-120 Days	2 (6.3)	8 (4.5)	13 (4.7)
121-150 Days	0	0	0
151-180 Days			9 (3.3)
181-210 Days			1 (0.4)
211-240 Days			5 (1.8)
241-270 Days			3 (1.1)
271-300 Days			2 (0.7)
301-330 Days			0
331-360 Days			0

Source: Modified from applicant's submission, Section 5.3.5.3, ISS, Table 1.29.1, link on page 168.

Discussion: *The majority of apremilast subjects (60%) who reported AE of diarrhea reported the event during the first 30 days of exposure. However, in 20% of subject the diarrhea lasted between 30 and 90 days. Diarrhea duration of more than 4 weeks is considered a chronic diarrhea. Twice as many subjects in apremilast treatment group (3.4%) reported moderate or severe diarrhea compared to subjects in the placebo treatment group (1.4%).*

Weight Change

Phase 2/3 Data Pool

I. Placebo-controlled period

Trials PSOR-008 and PSOR-009

During the placebo-controlled period (Week 0 -16), the placebo treatment group had mean weight change of -0.02kg compared to a mean weight change in the apremilast treatment group of -1.45kg (Table 41 below). Subjects, who were treated with apremilast at Week 0 and continued to Week 52, had mean weight change from baseline of -1.67kg (data not shown).

Table 41: Change in Weight from Baseline to the End of Week 16; Trials PSOR-008 and PSOR-009

Treatment Group Weight, kg	n	Baseline Mean ± SD	End of Period Mean ± SD	Change form Baseline (kg)	
				Mean ± SD	(Min, Max)
Placebo	382	92.12 ± 21.936	92.09 ± 22.133	-0.02 ± 3.017	(-10.6; 13.2)
APR 30mg BID	784	92.79 ± 22.057	91.35 ± 21.673	-1.45 ±3.891	(-34.9; 28.0)

Source: Modified from applicant's submission, Section 5.3.5.3; ISS, Table 79, page 179.

Approximately 14% of subjects in the apremilast-treated subjects reported weight loss of more than 5% of body weight compared to 5.5 % of placebo-treated subjects, and approximately 2% of apremilast treated subjects had weight loss of more than 10% of body weight.

Table 42: Weight Percent Change Category from Baseline to the End of Week 16; Trials PSOR-008 and PSOR-009

Weight % Change	Placebo (N=418)	APR* 30mg BID (N=832)
	m=382	m=784
<-20%	0	1 (0.1)
>=-20% to <-10%	3 (0.8)	13 (1.7)
>=-10% to <-5%	18 (4.7)	97 (12.4)
>5% to <0%	155 (40.6)	380 (44.5)
0%	33 (8.6)	73 (9.3)
>0% to <=5%	150 (39.3)	198 (25.3)
>5% to <=10%	19 (5.0)	15 (1.9)
>10% to <= 20%	4 (1.0)	6 (0.8)
>20%	0	1 (0.1)

Source: Modified from applicant's submission, Section 5.3.5.3; ISS, Table 1.32.1, link on page 183.
m: number of subjects with a baseline value and at least one post-baseline value, percentages are based on m.

II. Apremilast Treatment Period (Week 0-52)

Trials PSOR-008 and PSOR-009

In two Phase 3 trials, mean weight change by timepoint (Week 0-52) in subjects treated with apremilast is presented in Table 43 below.

Table 43: Change in Weight from Baseline by Timepoint in Apremilast* Treated Subject (Week 0-52) Trials PSOR-008; PSOR-009

Time Point	Baseline Mean	Time Point Mean	Change from Baseline (kg)
Week 4	84.09	83.70	-0.39
Week 8	94.50	94.14	-0.36
Week 16	92.76	91.25	-1.51
Week 24	89.79	87.50	-2.29
Week 32	93.40	91.62	-1.78
Week 40	92.35	90.27	-2.08
Week 52	92.97	90.98	-1.99

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 1.33.2.2, link on page 180. *Apremilast subjects with baseline and at least one post baseline value.

Of subjects who were treated with apremilast regardless of when the exposure started (Week 0-52), approximately 19% lost ≥5% of body weight, and approximately 5% lost ≥10% of body weight.

Table 44: Weight Percent Change Category from Baseline to the End of Week 52 for Trials PSOR-008; PSOR-009

	APR 30mg BID m*=1133 (%)
Weight % Change	
<20%	6 (0.5)
>=20% to <-10%	52 (4.6)
>=-10% to <-5%	159 (14.0)
>-5% to <0%	481 (42.5)
0%	87 (7.7)
>0% to <=5%	286 (25.2)
>5% to <=10%	49 (4.3)
>10% to <= 20%	13 (1.1)
>20%	0

Source: Modified from applicant's submission, Module 5.3.5.3, ISS; Table 81, page 182. m: number of subjects with a baseline value and a least 1 post-baseline value, percentages are based on m.

Two subjects discontinued the trial due to AE of decreased weight. Subject PSOR-009-1181016 had weight loss of -8% of body weight, and subject PSOR-009-8221003 had weight loss of-11.5% of body weight, at the time of discontinuation.

In two Phase 3 trials, at any time during apremilast treatment period (Week 0-52), 3 subjects in the placebo group and 98 subjects in the apremilast 30mg BID group experienced weight loss of at least 10% body weight compared to baseline (data not shown, module 5.3.5.3 ISS, page 183). In these subjects, weight loss continued throughout the treatment period.

Nine subjects in apremilast treatment group had weight loss of more than 20%. Of these subjects, weight loss was probably related to apremilast treatment in 5 subjects and in other 4 subjects weight loss was due to other causes (2 subjects had gastric bypass surgery 2-3 months prior to screening, one developed gastropathy, and one subject abused cocaine). None of subjects in placebo group had weight loss of more than 20%.

In order to determine the relationship between weight loss and gastrointestinal adverse events (diarrhea, nausea, vomiting and abdominal pain), the applicant conducted an analysis presented in Table 45 below. More subjects who had diarrhea also had weight loss of more than 5% of body weight. However, these data do not reveal clear association between weight loss and nausea, vomiting or abdominal pain.

Table 45: TEAEs by Subject's Weight Loss in Apremilast Treated Subjects during the Apremilast Exposure Period (Week 0 to Cut-off Date), PSOR-008 and PSOR-009

APR 30mg BID				
TEAE Preferred Term	**Lost >5% Body Weight N=232 n (%)**	**EAIR**	**Lost ≤5% Body Weight N=901 n (%)**	**EAIR**
Diarrhea	60 (25.9)	22.7	149 (16.5)	16.3
Nausea	40 (17.2)	14.2	144 (16.0)	15.7
Vomiting	18 (7.8)	5.6	41 (4.6)	3.9
Abdominal pain	10 (6.9)	3.0	25 (2.8)	2.4
Abdominal pain upper	5 (4.3)	1.5	23 (2.6)	2.2
Abdominal pain lower	2 (0.9)	0.6	4 (0.4)	0.4

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Response to information request, Table 7. Cut off date: August 30, 2013.

Discussion Regarding Weight Loss

Review of data revealed that the subjects treated with apremilast had more pronounced weight loss during the first 16 weeks of treatment (-1.45kg) than during the remainder or treatment period Week 16-52 (-0.22kg) [subjects treated with apremilast at Week 0 to Week 52]. Approximately 5% of subjects had weight loss between 10% and 20% of body weight. Current labeling includes weight loss in the ***Warning and Precisions*** *section.*

During the placebo-controlled period, more subjects (18%) in the apremilast treatment group reported diarrhea compared to subjects (7%) in the placebo group. The majority of subjects who reported AE of diarrhea, reported the event during the first 4 weeks of exposure to apremilast. Approximately 29% of subjects who reported diarrhea during the first 16 weeks of exposure, had symptoms that lasted between 24 and 120 days. During the placebo-controlled period, twice as many subjects in apremilast treatment group (3.4%) reported moderate or severe diarrhea compared to subjects in the placebo treatment group (1.4%). In addition, during the apremilast exposure period (Week 0-Cut off period), more subjects (26%) who had weight loss of >5% of body weight reported AE of diarrhea, compared to 16% of subjects who had weight loss of ≤5% of Body Weight and reported AE of diarrhea.

Therefore, it is reasonable to conclude that the weight loss that occurred in subjects treated with apremilast during the placebo-controlled period was associated with diarrhea. Although the diarrhea events were reported during the first 30 days of exposure to apremilast, these events had prolonged duration and therefore have temporal and clinical association with the weight loss. In addition, 5% of subjects had weight loss of 10% to 20% of body weight, which is considered a clinically severe weight loss.

*On the basis of these data, this reviewer recommends that information regarding diarrhea that may lead to severe weight loss be included into **Warning and Preclusions** section of labeling.*

Headache

I. Placebo Controlled Period (Week 0-16) and

II. Apremilast Treatment Period (Week 0-52)

The applicant conducted query for AE of headache. During the placebo-controlled period (Week 0-16), more subjects in the apremilast treatment group experienced headache/ tension headache compared to subjects in the placebo group (Table 44). For the period Week 0-52, the exposure adjusted incidence rate of headache/tension headache was similar between apremilast treated subjects and placebo treated subjects (Table 46).

Table 46: Analysis of Headache/Tension Headache in Trials PSOR-008 and PSOR-009

	Week 0-16				Week 0-52	
Headache/ Tension Headache	**Placebo N=418 n (%)**	**EAIR**	**APR 30mg BID N=832 n (%)**	**EAIR**	**APR 30mg BID N=1184 n (%)**	**EAIR**
Tension headache	14 (3.3)	12.4	61 (7.3)	27.5	109 (9.2)	10.7
Headache	14 (3.3)	12.4	48 (5.8)	21.2	76 (6.4)	7.1

Source: Modified from applicant's submission, Section 5.3.5.3, ISS, Table 76 and Table 78, pages172 and 177.

The majority of headache/tension headache occurred during the first 2 weeks of treatment (Table 47).

Table 47: Analysis of Headache/Tension Headache by Time of Onset in Trials PSOR-008 and PSOR-009

	Week 0-16		Week 0-52
Headache/Tension Headache	**Placebo n (%)**	**APR 30mg BID n (%)**	**APR 30mg BID n (%)**
Total Number of Events	33	143	273
1-30 Days	26 (68.8%)	104 (59.3)	133 (48.7)
1-3 Days	9 (25.o)	34 (23.8)	43 (15.8)
4-7 Days	5 (9.4)	24 (16.8)	29 (10.6)
8-15 Days	6 (18.8)	22 (15.4)	30 (11.0)
16-23 Days	4 (6.3)	14 (9.8)	16 (5.9)
24-30 Days	2 (6.1)	10 (7.0)	15 (5.5)
31-60 Days	2 (6.1)	22 (15.4)	32 (11.7)
61-90 Days	2 (6.1)	10 (7.0)	11 (4.0)
91-120 Days	2 (6.1)	7 (4.9)	15 (5.5)
121-150 Days	0	0	12 (4.4)
151-180 Days			14 (5.1)
181-210 Days			19 (7.0)
211-240 Days			7 (2.6)
241-270 Days			7 (2.6)
271-300 Days			4 (1.5)
301-330 Days			4 (1.5)
331-360 Days			0

Source: Modified from applicant's submission, Section 5.3.5.3, ISS, Table 1.28.1; link on page 173

*Discussion: Headache/ Tension headache are included in the proposed labeling in section **6 ADVERSE REACTIONS**.*

Hypersensitivity Adverse Events

During the placebo-controlled period (Week 0-16), higher number of apremilast treated subjects reported AE of hypersensitivity compared to placebo treated subjects.
For the period Week 0-52, the exposure adjusted incidence rate of hypersensitivity was similar between apremilast and placebo treated subjects, per 100 subject years (Table 48).

Table 48: Analysis of Hypersensitivity Adverse Events in Trials PSOR-008 and PSOR-009

	Week 0-16				Week 0-52	
	Placebo N=418 n (%)	EAIR	APR 30mg BID N=832 n (%)	EAIR	APR 30mg BID N=1184 n (%)	EAIR
Hypersensitivity	1 (0.2)	0.9	3 (0.4)	1.3	8 (0.7)	0.7
Drug hypersensitivity					1(0.1)	0.1

Source: Modified from applicant's submission, Section 5.3.5.3, ISS, Table 95 and Table 96, pages 205.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

I. Placebo-controlled period (Week 0-16)

Trials PSOR-008, PSOR-009 and PSOR-005
During the placebo-controlled period, most frequently reported treatment emergent AEs in more than 1% in the apremilast 30mg BID treatment group and higher than in the placebo treatment group were: diarrhea; nausea; upper respiratory tract infection and tension headache (Table 49).

Table 49: Incidence of TEAE with Subject Incidence of ≥1% in Apremilast 30mg BID and Higher than the Placebo Group (Week 0 through Week 16) Trials PSOR-008, PSOR-009 and PSOR-005

Preferred Term	Placebo (N=506) n (%)	APR 30mg BID (N=920) n (%)
Diarrhea	32 (6.3)	160 (17.4)
Nausea	35 (6.9)	155 (16.8)
Upper respiratory tract infection	31 (6.1)	84 (9.1)
Tension headache	21 (4.2)	75 (8.2)
Nasopharyngitis	36 (7.1)	66 (7.2)
Headache	19 (3.8)	55 (6.0)
Abdominal pain*	11 (2.2)	39 (4.2)
Vomiting	8 (1.6)	35 (3.8)
Fatigue	9 (1.8)	29 (3.2)
Dyspepsia	6 (1.2)	29 (3.2)
Decrease appetite	5 (1.0)	26 (2.8)
Sinusitis	8 (1.6)	21 (2.3)
Insomnia	4 (0.8)	21 (2.3)
Back pain	4 (0.8)	20 (2.2)
Migraine	5 (1.0)	19 (2.1)
Abdominal discomfort	6 (1.2)	19 (2.1)
Frequent bowel movements	1 (0.2)	17 (1.8)
Dizziness	7 (1.4)	16 (1.7)
Gastroesophageal reflux disease	5 (1.0)	15 (1.6)
Depression	2 (0.4)	12 (1.3)
Bronchitis	2 (0.4)	12 (1.3)
Rhinitis	3 (0.6)	12 (1.3)
Tooth abscess	0 (0.0)	10 (1.1)
Folliculitis	0 (0.0)	9 (1.0)
Sinus headache	0 (0.0)	9 (1.0)
Psoriatic arthropathy	4 (0.8)	9 (1.0)
Osteoarthritis	3 (0.6)	9 (1.0)

Source: Modified from applicant's submission, Section 5.3.5.3, FDA Request; Table 4.2.
* Also includes preferred terms: abdominal pain upper; abdominal pain lower.

Adverse Reactions were defined as TEAEs that were reported in ≥2% of subjects and ≥1% higher in the apremilast 30mg BID treatment group than in the placebo group, as well as other TEAEs that might be associated with the mode of action of the drug or considered by the applicant to be medically relevant events. This reviewer presented adverse reactions reported in ≥1% of subjects and ≥1% higher in the apremilast 30mg BID treatment group than in the placebo group that might be associated with the mode of action of the drug or medically relevant (Table 50).

Table 50: Incidence of Adverse Reactions with Subject Incidence of ≥1% in Apremilast 30mg BID Treatment Group and Higher by 1% than the Placebo Treatment Group (Week 0-16) Trials PSOR-008, PSOR-009 and PSOR-005

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

Source: Modified from applicant's submission, Section 5.3.5.3, FDA Request; Table 4.2.
* Also includes preferred terms: abdominal pain upper; abdominal pain lower.

II. Apremilast Treatment Period (Week 0-52)

Trials PSOR-008; PSOR-009

Incidence of AEs reported in apremilast 30mg BID treated subjects during Week 0-52, are similar to AEs reported during the placebo controlled period (Week 0-16). No new safety signals were reported with increase of duration of exposure to apremilast.

Table 51: Incidence of TEAE with Subject Incidence of ≥2% in Apremilast 30mg BID (Treatment Period Week 0-52) Trials PSOR-008 and PSOR-009

Preferred Term	APR 30mg BID (N=1184) n (%)
Diarrhea	205 (17.3)
Nausea	185 (15.6)
Upper respiratory tract infection	183 (15.5)
Nasopharyngitis	166(14.0)
Tension headache	106 (9.0)
Headache	74 (6.3)
Abdominal pain*	62 (5.2)
Vomiting	57 (4.8)
Back pain	56 (4.7)
Arthralgia	54 (4.6)
Sinusitis	45 (3.8)
Hypertension	43 (3.6)
Dyspepsia	42 (3.5)
Gastroenteritis	42 (3.5)
Migraine	40 (3.4)
Bronchitis	39 (3.3)
Fatigue	38 (3.2)
Urinary tract infection	37 (3.1)
Cough	35 (3.0)
Insomnia	31 (2.6)
Decreased appetite	31 (2.6)
Psoriasis	27 (2.3)
Gastroesophageal reflux disease	26 (2.2)
Abdominal discomfort	25 (2.1)
Frequent bowel movements	25 (2.1)
Gastroenteritis viral	25 (2.1)
Psoriatic arthropathy	24 (2.0)
Dizziness	24 (2.0)
Muscle strain	24 (2.0)
Depression	23 (1.9)

Source: Applicant's submission, Module 5.3.5.3 ISS, Section 5.2.1.2, page 87, Table 32. For apremilast, data for the first 52 weeks of exposure are included regardless of when exposure started (Week 0 of Week 16).

The most frequently reported adverse reactions during apremilast treatment period were diarrhea, nausea and headache (Table 52).

Table 52: Incidence of Adverse Reactions with Subject Incidence of ≥1% in Apremilast 30mg BID Treatment Group Treatment Group (Week 0-52) Trials PSOR-008 and PSOR-009

Preferred Term	APR 30mg BID (N=1184) n (%)
Diarrhea	173 (14.6)
Nausea	159 (13.4)
Tension headache	57 (4.8)
Headache	44 (3.7)
Abdominal pain*	35 (3.0)
Vomiting	33 (2.8)
Upper respiratory tract infection	32 (2.7)
Nasopharyngitis	30 (2.5)
Dyspepsia	26 (2.2)
Frequent bowel movements	25 (2.1)
Decrease appetite	23 (1.9)
Abdominal discomfort	23 (1.9)
Fatigue	16 (1.4)
Migraine	15 (1.3)
Gastroesophageal reflux disease	14 (1.2)

Source: Applicant's submission, Module 5.3.5.3 ISS, SUR Table 1.4.12.

7.4.2 Laboratory Findings

Hematology Values over Time (Trials PSOR-008 and PSOR-009)
Summary statistics of observed values and changes form baseline over time were assessed for hematology parameters. At the end of placebo controlled period, the change from baseline in platelet count was higher in the apremilast 30mg BID group (7.9 $x10^9$/L) compared to the placebo group (0.5 x 10^9/L). At the end of apremilast exposure period (Week 52), change from baseline in platelet counts in the subjects initially treated with apremilast at Week 0, were similar to those noted at the end of placebo controlled period. This increase in platelet counts did not worsen over time and was not considered clinically significant.
Additional analysis was performed assessing shifts from baseline to the end of the placebo-controlled period or apremilast treatment period. Review of data did not reveal any clinically meaningful differences between treatment arms of shifts from baseline. The most frequently reported abnormal values during the placebo-controlled period were for lymphocytes (<0.8 $x10^9$/L) in 3% of placebo subjects and 1.1% of apremilast 30mg BID subjects.

Table 53: Change From Baseline in Hematology Parameters

Hematology Parameter	Week 0-16		Week 0-52
	Placebo (n=401)	APR 30mg BID (n=815)	APR 30mg BID (n=1165)
Hematocrit			
Mean baseline value	0.45 ± 0.038	0.45±0.04	0.45± 0.04
Mean change from baseline	0 ± 0.029	-0.002±0.028	-0.007± 0.03
Hemoglobin (g/dL)			
Mean baseline value	14.72±1.32	14.70±1.39	14.68± 1.35
Mean change from baseline	-0.16±0.67	-0.19±0.71	-0.38± 0.81
Leukocytes (10^9/L)			
Mean baseline value	7.48 ± 1.98	7.49 ± 1.95	7.46± 1.93
Mean change from baseline	-0.04	0.16± 1.62	0.20± 1.68
Lymphocytes (10^9/L)			
Mean baseline value	1.86 ± 0.62	1.94± 0.59	1.92± 0.59
Mean change from baseline	-0.004± 0.38	0.02 ± 0.43	0.03± 0.44
Neutrophils (10^9/L)			
Mean baseline value	4.89 ±1.61	4.83± 1.60	4.82± 1.58
Mean change from baseline	-0.04± 1.37	0.13± 1.44	0.16± 1.46
Platelets			
Mean baseline value	270.3± 68.65	275.0± 67.55	272± 67.13
Mean change from baseline	0.5 ± 41.41	7.9± 43.01	6.0± 44.74

Source: Modified from applicant's submission. Module 5.3.5.3 ISS, Table 97 and Table 98, page 208 and 210.

Review of laboratory data revealed that mean changes from baseline in hematology parameters in both treatment arms were small and not clinically significant.

Marked abnormalities in laboratory values occurred at similar rates in placebo and apremilast treated subjects. Marked elevation in platelet count ≥600x10^9/L was reported in 5 subjects treated with apremilast. This increase was transient, and returned to normal or baseline values.

Table 54: Subject Incidence of Marked Abnormalities in Hematology Laboratory Parameters

Hematology Parameter	Week 0-16		Week 0-52
	Placebo (n=418) %	APR 30mg BID (n=832)	APR 30mg BID (n=1184)
Hemoglobin			
Male < 10.5 g/dL, or female <8.5 g/dL	0.7	0.2	0.7
Male > 18.5 g/dL, or female >17 g/dL	0	0.9	0.9
Lymphocytes			
<0.8 x 10^9/L	3.0	1.1	2.9
Neutrophils			
<1 x 10^9/L	0	0	0.3
Platelets			
>600 x10^9/L	0.2	0	0.4

Source: Modified from applicant's submission. Module 5.3.5.3 ISS, Table 102, page 217

Clinical Chemistry Values over Time (Trials PSOR-008 and PSOR-009)
Summary statistics of observed values and changes form baseline over time were assessed for clinical chemistry parameters. During the placebo controlled period, the mean change from baseline in clinical chemistry parameters, in both treatment arms, were similar and not clinically significant.

Table 55: Clinical Chemistry Changes over Time

Clinical Chemistry Parameter	Week 0-16		Week 0-52
	Placebo (n=401)	APR 30mg BID (n=815)	APR 30mg BID (n=1165)
Alanine Aminotransferase (U/L)			
Mean baseline value	29.6 ± 14.98	29.5±16.61	29.3± 16.18
Mean change from baseline	-0.7 ± 11.71	-2.1± 12.51	-1.7± 13.84
Aspartate Aminotransferase (U/L)			
Mean baseline value	25.2±10.46	24.9±10.83	24.9± 10.92
Mean change from baseline	0.1±9.76	-1.8.19±8.64	-1.2± 11.04
Bilirubin (µmol/L)			
Mean baseline value	7.8 ± 4.45	7.5 ± 4.14	7.6± 4.24
Mean change from baseline	-0.2± 3.22	0.3± 3.47	-0.2± 3.41
Blood Urea Nitrogen (mmol/L)			
Mean baseline value	5.13 ± 1.45	5.18± 1.64	5.2± 1.59
Mean change from baseline	-0.11± 1.25	0.14 ± 1.26	0.03± 1.28
Calcium (mmol/L)			
Mean baseline value	2.35 ±0.10	2.36± 0.09	2.36± 0.09
Mean change from baseline	-0.008± 0.10	0.01± 0.10	0.04± 0.10
Creatinine (µmol/L)			
Mean baseline value	74.5± 14.07	75.7± 15.57	75.4± 15.33
Mean change from baseline	0.3 ± 8.66	0.2± 9.17	0.4± 9.27
Potassium (mmol/L)			
Mean baseline value	4.21± 0.34	4.25 ± 0.37	4.24±0.37
Mean change from baseline	0±0.36	-0.03± 0.38	-0.01± 0.39
Sodium (mmol/L)			
Mean baseline value	140.1± 2.17	140.2± 2.13	140.2±2.12
Mean change from baseline	0±2.37	-0.2± 2.27	0± 2.29

Source: Modified from applicant's submission. Module 5.3.5.3 ISS, Table 109, page 228.

Markedly abnormal liver function tests (LFTs) reported at any time during the trial was noted in 27 subjects [ie. ALT ≥3 x Upper Limit of Normal (ULN); AST≥ 3 x ULN; of bilirubin >1.8 x ULN]. Of these subjects, 4 subjects had elevated LFTs before drug exposure and 3 subjects had elevated LFTs during the exposure to placebo. Of the remaining 20 subjects with markedly elevated LFTs, 18 subjects had marked elevated transaminase (≥3x ULN) without concomitant marked elevation of bilirubin (≥1.8 x ULN) and two subjects experienced marked elevation of bilirubin of ≥1.8 x ULN without marked elevation of transaminases.
Of 18 subjects with marked elevation of transaminases, 16 subjects had underlying conditions (obesity, diabetes, hepatic steatosis, hyperlipidemia, alcohol use) or used concomitant drugs known to cause transaminitis or hepatic damage (methotrexate, statins, NSAID, amoxicillin/clavulanic acid, acetaminophen). Two subjects did not have underlying cause of transaminase elevation.

Two of 18 subjects were discontinued due reasons other than abnormal LFTs (one due to lack of efficacy and the other due to infectious mononucleosis). For the remaining 16 subjects, the treatment remained unchanged, and the transaminases returned to normal or near baseline values without recurrence.

Of two subjects with markedly abnormal bilirubin values, one had history of alcohol use and concomitant use of NSAIDs and the other had a significant past history of methotrexate induced elevation of LFTs. Bothe subjects had episodic elevation of transaminases that did not coincide with the elevation of bilirubin. Bilirubin and transaminases returned to baseline values with continuation of treatment with apremilast.

No cases of LFT elevation meeting Hy's Law criteria were reported during the conduct of two Phase 3 trials.

Increased incidence of marked abnormalities in clinical chemistry parameters over time was noted for glucose and triglycerides (presented in Table 54 below).
For glucose, 2.1% of subjects in the apremilast treatment group had glucose level >13.9mm/L at Week 16 compared to 1.7% in the placebo group. At Week 52, 2.7% of subjects had elevated glucose levels of >13.9mm/L. However, there was no increase in incidence of subjects with marked increase of hemoglobin A1c during treatment period Week 0-16 (0.5%) or Week 0-52 (0.5%) indicating that non-fasting glucose levels may have been the cause of these abnormalities. During the placebo controlled period, there was no clinically meaningful change in mean glucose levels in placebo or apremilast treatment groups (data not shown). Similar results were obtained in apremilast subjects treated during Week 0- 52 (data not shown).
For triglycerides, at Week 16, 10.6% of placebo subjects and 10.8 of apremilast subjects had markedly elevated values. At Week 52 however, 19.5% of apremilast subjects had elevation of triglycerides. This increased further during 120-day SUR period to 21.1%. During the placebo controlled period, there was no clinically meaningful change in mean triglyceride levels in both placebo and apremilast treatment groups (data not shown). Similar results were obtained in apremilast subjects treated during Week 0-52 (data not shown).

Table 56: Incidence of Marked Elevation in Clinical Chemistry Parameters

Clinical Chemistry Parameter	**Week 0-16**		**Week 0-52**
	Placebo (n=418)	**APR 30mg BID (n=832)**	**APR 30mg BID (n=1184)**
	n/m (%)	**n/m (%)**	**n/m (%)**
Glucose			
>13.9 mmol/L	7 /404 (1.7)	17/818 (2.1)	31/1168 (2.7)
Triglycerides			
>3.4 mm/L	40/377 (10.6)	84/776 (10.8)	220/1131 (19.5)
Hemoglobin A1C			
>9%	2/378 (0.5)	4/777 (0.5)	

Source: Modified from applicant's submission, Module 5.3.5.3 ISS, Table 117, page 245.

Discussion: Laboratory evaluations (hematology; serum chemistry) revealed that markedly abnormal laboratory results were infrequent, transient and did not lead to study drug discontinuation. No cases of hepatic failure or LFT elevations meeting Hy's Law criteria were observed. No safety signals were revealed.

7.4.3 Vital Signs

I. Placebo controlled period (Week 0-16)
During the placebo controlled period, the mean change from baseline to the end of the period in systolic blood pressure was -1.2 mmHg in subjects treated with placebo and -0.1mmHg in subjects treated with apremilast. For diastolic blood pressure, mean change from baseline to the end of placebo controlled period was -0.6mmHg in the placebo treated subjects and -0.9mmHg in the apremilast treated subjects.

Mean change in the pulse rate from baseline to the end of placebo controlled period was 0.6 beats per minute (bpm) in the placebo subjects and 1.0 bpm in the apremilast treated subjects.

II. Apremilast Exposure Period (Week 0-52)
During the apremilast exposure period, the mean change from baseline to the end of the treatment period in systolic blood pressure was -0.6 mmHg and 1.1mmHg in diastolic blood pressure.
Mean change in the pulse rate from baseline to the end of apremilast treatment period was 0.6 beats per minute (bpm).

Discussion: Results presented above showed no clinically significant changes in vital sings during the treatment with apremilast.

7.4.4 Electrocardiograms (ECGs)

During the conduct of two Phase 3 trials, 3 subjects (all from study PSOR-009) on apremilast 30mg BID had AEs of ECG abnormalities: ECG T wave abnormal (subject #0521011); ECG QT prolonged (subject #0571007) and ECG abnormal (subject #1191022). At baseline, all 3 subjects had normal ECGs with normal variants or with poor R wave progression.

- Subject #0521011 was 74 year old female with pertinent medical history of HTN, angina pectoris, coronary artery disease. On study Day 112, subject developed ECG T wave abnormality and concomitant right bundle branch block. Additional ECG evaluation at Week 32 and 52 revealed poor R wave progression. Study subject continued treatment with the study drug and no additional treatment was required.

- Subject #1191022 was 32 year old male with no pertinent medical history had baseline ECG with early repolarization and sinus arrhythmia, considered normal variant. At Week 16, ECG showed prolonged QTcF and at Week 32, ECG was normal. ECG at early term visit (Day 274) was abnormal with prolonged QTcB, sinus arrhythmia and sinus bradicardia. Study drug was discontinued and subject required additional treatment.

- Subject #0571007 was 63 year old male with pertinent medical history of HTN, palpitations, arrhythmia, and supraventricular tachycardia. Subject had normal ECG with early repolarization (normal variant). Subject reported two AEs of palpitations (Day 86 and 452) each lasting one day. Subject continued treatment with the study drug. No additional treatment was required.

During the conduct of two Phase 3 trials, 6 subjects who were on apremilast 30mg BID had change from baseline in QTcB ≥60msec and 5 subjects had change from baseline in QTcF≥60msec. All of these subjects had an abnormal ECG at screening or at baseline. In addition, three subjects had concomitant pertinent cardiovascular medical history. In the placebo treatment group, two subjects had QTcB ≥60msec change from baseline.

Discussion: Based on the data presented, it is reasonable to conclude that ECG monitoring is not required with apremilast treatment.

7.4.5 Special Safety Studies/Clinical Trials

A thorough study (CC-10004-PK-008) to investigate the potential of apremilast to prolong the QT/QTc interval was conducted by the applicant and is discussed in this section. This was a randomized, blinded, four arm crossover study in 60 male subjects who received apremilast (30mg and 50mg administered BID for 9 doses), placebo and a single oral dose of moxifloxacin 400mg.

For moxifloxacin, the lower limit of the two-sided 98% confidence interval for each-placebo corrected, change from baseline least-square mean individual corrected QT (QTcI) value was greater than 5msec from 2 hours and 4 hours post dose, indicating that the assay sensitivity was established.

All placebo-corrected change-from-baseline least-square mean QTcI values for the 30mg and 50mg dose, were below 1msec. The upper limit of the two-sided 90% confidence interval for both doses at all time points, were below 10 msec (the threshold for regulatory concern as per guidance for industry ICH E14).

In conclusion, this analysis demonstrated that apremilast did not have significant QT prolongation effects when administered at 30mg BID or 50mg BID doses.

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

During two Phase 3 trials the only dose evaluated was 30mg BID. In Phase 2 trial, PSOR-005, doses of 10mg BID; 20mg BID; 30mg BID and placebo were evaluated. During Placebo-controlled Period (Week 0 through Week 16), there was incremental increase of adverse events (SEAs; AEs leading to drug withdrawal, any severe TEAEs; any drug related AEs, any TEAE) with the increase of apremilast dose, the highest being in 30mg BID group. For the period Week 0 through Week 52, when adjusted for the duration of exposure, again, there was dose-dependent increase of AEs for all categories of adverse events.

7.5.2 Time Dependency for Adverse Events

The overall exposure adjusted incidence rate (EAIR) for AEs in the apremilast treatment arm for the period Week 0-16 and Week 0-52 were 536.4 and 317.2, respectively. This indicates that more AEs were reported during the beginning of dosing with apremilast. This was especially true for the most frequently reported AEs of diarrhea, nausea and upper respiratory tract infection.

7.5.3 Drug-Demographic Interactions

Age
Of the 1250 subjects who enrolled in to two Phase 3 trials, 1142 (91%) subjects were <65 years of age and 108 (9%) were ≥65 years of age.
During the Placebo-controlled Period, no clear effect of age was observed on the overall incidence of AEs. However, the incidence of SAE and AEs that led to drug withdrawal was higher in subjects who were ≥65 years of age in both treatment groups with more pronounced difference in the apremilast treatment group. Higher incidence of diarrhea, nausea, and fatigue were reported in apremilast treated subjects ≥65 years of age. Higher incidence of nasopharyngitis, upper respiratory tract infections, tension headache and headache were reported in subjects <65 years of age.

Sex
During the placebo controlled period, higher overall incidence of AEs; SAE and AEs that led to drug withdrawal was observed in female subjects compared to male subjects in both treatment groups with more pronounced difference in the apremilast treatment group. In the apremilast treatment group, there was higher incidence of female subjects

who reported AEs of diarrhea, nausea, vomiting, tension headache, nasopharyngitis, upper respiratory tract infection, and urinary tract infection.
Similar trends were observed for Weeks 0-52.

Race
In the two Phase 3 trials, 90% of subjects were White, 4.6% were Asian, 3.4% were Black or African American and the remainder were of other races (less than 1% each). Due to the small number of subjects of non-White race, no meaningful conclusions could be drawn with regard to race.

Ethnicity
In the two Phase 3 trials, 8% of subjects were Hispanic or Latino and 92% were neither Hispanic nor Latino. Due to the small number of Hispanic or Latino subjects, no meaningful conclusions could be drawn with regard to ethnicity.

Region
Incidence of AEs was evaluated by the following regions: North America, Europe and Rest of the World.
During the placebo controlled period, the type and pattern of AEs were similar across all three regions, with diarrhea, nausea, nasopharyngitis and tension headache being the most frequent.
Similar type and pattern of AEs were observed for the apremilast treatment period Week 0-52.

7.5.4 Drug-Disease Interactions

The potential for drug-disease interaction were evaluated in Clinical Pharmacology and Phase 3 clinical trials. For the Phase 2/3 trials, drug-disease interaction was assessed in subject with: anxiety disorders and symptoms, appetite and general nutritional disorders, cardiac arrhythmias, coronary artery disease, depressed mood disorders, gallbladder disorders, diabetes, lipid metabolism disorders, vascular hypertensive disorders, renal related and hepatic related diseases.

1. Anxiety disorders and symptoms: there was higher incidence of AEs in apremilast treated subjects with the history of anxiety disorders and symptoms compared to apremilast subjects without the history of anxiety disorders and symptoms.
2. Appetite and general nutritional disorders: the incidence of AEs for placebo and apremilast treatment groups was higher in subjects with the history of appetite and generally nutrition disorders compared to subjects who did not have history of appetite and general nutrition disorders.
3. Cardiac arrhythmias: the incidence of AEs for the apremilast treatment group was higher in subjects with the history of cardiac arrhythmias compared to subjects who did not have a history of cardiac arrhythmia.

4. Coronary artery disease: in the apremilast treatment group, there was similar incidence of reported AEs in subjects with and without history of coronary artery disease.
5. Depressed mood disorders: the incidence of AEs reported was higher in subjects with a history of depressed mood disorders compared to subjects without history of depressed mood disorders.
6. Gallbladder disorders: in the apremilast treatment group, there was similar incidence of reported AEs in subjects with and without gallbladder disorders.
7. Glucose metabolism disorder: incidence of AEs reported was higher in subjects without history of glucose metabolism disorder regardless of treatment group.
8. Lipid metabolism disorders: incidence of AEs was similar in subjects with and without history of lipid metabolism disorder for both placebo and apremilast treatment groups.
9. Vascular hypertensive disorders: the incidence of AEs was higher in subjects with a history of vascular hypertensive disorders compared to those without a history of vascular hypertensive disorders, regardless of treatment group.
10. Renal disorders: In the apremilast treatment group, the incidence of AEs was higher in subjects with a history of renal disorders compared to subjects without renal disorders.
11. Hepatic and hepatobiliary disorders: in the apremilast treatment group, the incidence of AEs was higher in subjects with a history of hepatic and hepatobiliary disorders compared to subjects without hepatobiliary disorders. Due to the small number of subjects with history of hepatobiliary disorders, meaningful comparison could not be made.

Evaluation in Special Populations

1. Renal impairment: evaluation in subjects with renal impairment was conducted in Clinical Pharmacology trial CC-10004-CP-19 and during Phase 3 trials.
   In the Clinical Pharmacology study, in the subjects with severe renal impairment, a single oral administration of 30mg apremilast resulted in an increase in overall mean exposure ($AUC_{0-\infty}$) by 88.5% relative to matched healthy subjects. Simulations suggest a 30mg QD dose produces apremilast exposure in subjects with severe renal impairment comparable to that of 30mg BID dose in subjects without renal impairment. Therefore, the dose should be reduced to 30mg QD in subjects with severe renal impairment (eGFR<30mg/min/1.73m^2 or creatinine clearance <30mL/min). No dosage adjustment is required in patients with mild renal impairment.
   In Phase 3 trials, analysis of AEs for subjects with normal to moderate renal impairment demonstrated higher incidence of AEs in apremilast treated subjects with moderate renal impairment when compared to incidence of AE in subjects with comparable renal function in the placebo treatment group. The incidence of AEs in subjects with mild renal impairment was similar to incidence of AEs in subjects with normal renal function for both treatment groups. Therefore, no dosage adjustment is required in patients with mild renal impairment.

2. Hepatic impairment: evaluation in subjects with hepatic impairment was conducted in Clinical Pharmacology trial CC-10004-CP-11. Clinical Pharmacology trial assessed the effect of moderate and severe hepatic impairment on the PK of apremilast. A single apremilast dose of 30mg was administered to subjects with moderate hepatic impairment and a single apremilast 20mg dose was administered to subjects with severe hepatic impairment. The results indicate comparable exposure between the moderate hepatic impaired subjects and matched healthy subjects. In addition, the exposure was comparable between the severe hepatic impaired subjects and the matched healthy subjects. Therefore, no dosage adjustment is necessary for patients with any degree of hepatic impairment.

7.5.5 Drug-Drug Interactions

The potential for drug-drug interactions were evaluated in both the Clinical Pharmacology and Phase 3 clinical trials. Potential drug-drug indications during Phase 3 trials were evaluated by prior exposure to biologics, TNF, phototherapy, and conventional systemic therapy. Additionally, drug-drug interactions were evaluated by concomitant use of the following drugs: lipid lowering drugs, analgesics, psychoanaleptics, psycholeptics, diabetics, acid lowering drugs, antidiarrheals, intestinal antiinflammatory and antirheumatic drugs, anti-infectives, agents acting on renin-angiotensin system, beta blockers, calcium channel blockers, diuretics, and vaccines. In Clinical Pharmacology trials, drug-drug interactions were evaluated with methotrexate, ketoconazole, rifampin and oral contraceptives.

Placebo Controlled Period (Week 0-16) and Apremilast Treatment Period (Week 0-56)

1. Prior biologic and TNF exposure: small increase in common AEs in apremilast and placebo treated subjects who did not have prior exposure to biologics and TNF agents.
2. Prior phototherapy: small increase in common AEs in apremilast and placebo treated subjects who had history of prior phototherapy.
3. Prior conventional systemic therapy: similar incidence of AEs was reported among subjects in the placebo and apremilast treatment groups regardless of prior conventional systemic therapy.
4. Concomitant use of anti-inflammatory and anti-rheumatic drugs: there was similar trend of increase in common AEs in apremilast and placebo treated subjects who concomitantly used anti-inflammatory or anti-rheumatic drugs compared to subjects who did not use concomitant anti-inflammatory or anti-rheumatic drugs.
5. Concomitant use of lipid lowering agents: similar incidence of AEs was reported among subjects in the placebo and apremilast treatment groups regardless of concomitant use of lipid lowering agents.

6. Concomitant use of analgesics: there was higher incidence of AEs reported in subjects treated with placebo and apremilast with concomitant use of analgesics compared to subjects without use of analgesics.
7. Concomitant use of psychoanaleptic drugs: there was higher incidence of AEs in subjects treated with placebo and apremilast with concomitant use of psychoanaleptic drugs compared to subjects without concomitant use of psychoanaleptics.
8. Concomitant use of psycholeptic drugs: there was a similar pattern of AEs in subjects treated with placebo and apremilast with and without concomitant use of psycholeptic drugs.
9. Concomitant use of diabetic drugs: similar incidence of AEs was reported among subjects in the placebo and apremilast treatment groups regardless of concomitant use of diabetic drugs.
10. Concomitant use of anti-hypertensive drugs: due to a small number of subjects who concomitantly used anti-hypertensive drugs, meaningful conclusions could not be drawn.
11. Concomitant use of gastric acid-related disorder drugs: incidence of AEs was higher in placebo and apremilast treated subjects who concomitantly used gastric-related disorder drugs.
12. Concomitant use of anti-diarrheal/ intestinal anti-inflammatory/anti-infective drugs: due to a small number of subjects who concomitantly used anti-diarrheal/ intestinal anti-inflammatory/anti-infective drugs, meaningful conclusions could not be drawn.
13. Concomitant use of agents that are acting on renin-angiotensin system: similar incidence of AEs was reported among subjects in the placebo and apremilast treatment groups regardless of concomitant use of agents that are acting on renin-angiotensin system.
14. Concomitant use of beta blockers: the incidence of AEs was higher in subjects with concomitant use of beta blockers for both the placebo and the apremilast treatment groups.
15. Concomitant use of calcium channel blockers: the incidence of AEs was similar in subjects with and without concomitant use of calcium channel blockers for both the placebo and apremilast treatment groups.
16. Concomitant use of diuretic drugs: there was a similar pattern of AEs in subjects treated with placebo and apremilast with and without concomitant use of diuretics.
17. Concomitant use of vaccines: because of the small number of subjects who reported concomitant use of vaccines, no meaningful conclusions could be drawn.

Clinical Pharmacology Studies Exploring Drug Interactions

1. Drug Interaction Study with Methotrexate: there were no changes in PK parameters between apremilast (30mg BID) and methotrexate in subjects with psoriatic arthritis or rheumatoid arthritis.

2. Drug Interaction Study with Ketoconazole: apremilast can be administered concomitantly with ketoconazole and other drugs known to be CYP3A4 inhibitors without concerns of clinically significant effect on apremilast exposure that would require adjustment in either dose or schedule of apremilast administration.
3. Drug Interaction Study with Rifampin: apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (eg. Rifampin) and may result in reduced clinical response.
4. Drug Interaction Study with Oral Contraceptives: coadministration of apremilast has no effect on the PK of an oral contraceptive (Ortho Tri-Cyclen) and therefore this contraceptive may be administered without change in dose or schedule.

7.6 Additional Safety Evaluations

No additional safety evaluations were conducted.

7.6.1 Human Carcinogenicity

Malignancies (skin and solid tumors) were reported during in the development program of apremilast. Given the timepoints at which malignancies were reported (not reflective of the generally long latency periods for development of malignancies), it is in this reviewer's opinion that it is unlikely that the study drug was a causative agent. It is unclear to what extent the immunosuppression induced by apremilast may contribute to aggressive behavior of tumors (e.g. metastasis). No pattern to the type of malignancies was observed.

7.6.2 Human Reproduction and Pregnancy Data

During the development of apremilast in psoriasis, women of childbearing potential were required to use effective means of contraception during the participation in the trial and for additional 28 days thereafter. Male subjects who engage in sexual activity were required to use condoms during the participation in the trial and 28 days thereafter.

During the apremilast clinical trials (includes trials for several indications), a total of 22 pregnancies were reported, 7 pregnancies were reported in female subjects and 15 pregnancies in female partners of male subjects.

In psoriasis trials, a total of 13 pregnancies were reported, 5 in female subjects and 8 in female partners of male subjects. Of 13 pregnancies, 4 female subject and 6 female partners of male subject were treated with apremilast.

Table 57: Outcome of Pregnancies Reported in Apremilast Clinical Trials

	Pregnant Female Subjects			Female Partners of Male Subjects			
	Placebo or Pre-Tx	Blinded	Apremilast	Placebo or Pre-Tx	Blinded	Apremilast	Total
Spontaneous abortion	2	0	0	0	0	2	4
Elective termination	0	0	2	0	0	1	3
Ongoing pregnancy	0	0	1	0	1	1	5
Live birth	0	0	2	2	0	5	8
Unknown (lost to follow-up)	0	0	0	1	0	2	2
Total	2	0	5	3	1	11	22

Source: Applicant's submission, Module 5.3.5.3 ISS, Table 212, page 448.

Pregnancy outcomes in female subjects
There were no congenital anomalies reported in any babies born to female subjects exposed to apremilast or to blinded therapy. There were no spontaneous abortions in subjects exposed to apremilast. At the time of study reports one subject was still pregnant and two healthy babies were born to subjects exposed to apremilast.

Pregnancy outcomes in female partners of male subjects
There were no congenital anomalies reported in any babies born to female partners of males subjects exposed to apremilast or to blinded therapy. There were two spontaneous abortions. Babies born to female partners of male subjects exposed to apremilast were full term and healthy.

7.6.3 Pediatrics and Assessment of Effects on Growth

All trials supporting this application were conducted in adult subjects (18 years of age and older), for the population for whom the applicant seeks approval.

The applicant submitted a request for a partial waiver for pediatric patients 0 to less than 6 years of age. The reason stated for waiving pediatric studies in this age group is that trials are "impossible or highly impracticable (because, for example, the number of patients in that age group is so small or the patients in that age group are geographically dispersed)".
For children and adolescents 6 to 17 years of age, the applicant submitted a request for deferral. The reason is that "the drug or biologic product is ready for approval for use in adults".

The applicant proposes to conduct the following trials in pediatric subjects 6 to 17 years of age:

- Phase 2 Pharmacokinetic and safety trial of apremilast tablets in (b) (4) pediatric subjects 6-17 years of age.
- Phase 3 study efficacy and safety trials in (b) (4) pediatric subjects 6-17 years of age.

The applicant proposes to submit final protocol for Phase 2 trial in January 2016, to complete the trial by May, 2017 and submit final report in January 2018.

For the Phase 3 trial, the applicant proposes to submit the final protocol in January 2018, to complete the trial by January 2020, and to submit the final report in July 2020.

At the time of closure of this review the presentation of applicants Pediatric Study Plan to the Pediatric Review Committee (PeRC) was pending.

This reviewer agrees with the applicant's proposed Pediatric Study Plan. Deferred pediatric studies in pediatric patients ages 6 to 17 years should be conducted as required by PREA as a part of PMR.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the two Phase 3 trials, there were total of 8 AEs of "overdose". All of these AEs were reported as an accidental overdose. No adverse events associated with cases of overdose were reported.
In dose-escalation studies (CC-10004-PK-001 and CC-10004-PK-008) several healthy subjects were exposed to a maximal dose of 50mg BID for up to 4.5 days without dose-limiting toxicities.

Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency of apremilast.

Psoriasis rebound was evaluated during the two Phase 3 trials. Rebound was defined as a severe and sudden worsening of disease that occurred after treatment has been discontinued or a new generalized pustular, erythrodermic, or more inflammatory psoriasis after stopping therapy or demonstrated a PASI≥125% of baseline score.

In PSOR-008 no subject reported rebound and one subject (1.1%) reported as a psoriasis flair after the active treatment was withdrawn (ie, subject was re-randomized to placebo and then resumed APR 30mg BID) in Treatment Withdrawal Phase of the trial.

In PSOR-009, 3 (4.8%) subjects reported rebound (re-randomized to placebo) and 2 (6.3%) subjects reported flair (re-randomized to placebo and then resumed APR 30mg BID) entering Treatment Withdrawal Phase of the trial.

The results suggest that rebound may occur after discontinuation or interruption of apremilast treatment, however the number of subjects who experienced rebound were low. This reviewer recommends that this information be included into labeling in Section 6 ADVERSE REACTIONS.

7.7 Additional Submissions / Safety Issues

120-Day Safety Update
As of the data cutoff date for 120-day Safety Update Report (SUR), 383 (32.3%) subjects were still ongoing. A total of 796 subjects (67.2%) discontinued during the Phase 3 trials. The most frequent reasons for discontinuation in the 120-day SUR are similar to those of original NDA and were: lack of efficacy (30.7%): withdrawal by subject (14.9%): and AEs (9.8%).

The adverse event data for this time period demonstrated a similar safety profile for apremilast with that presented in the original NDA. The overall number, type and pattern of adverse events did not change. Discussion regarding reported AEs for this time period is presented below.

AEs for 120-Day Safety Update
Deaths: No new deaths were reported for this 120-day SUR.

Serious Adverse Events: A total of 20 new subjects reported SAEs in this 120-day SUR. Most SAEs were reported by 1 or 2 subjects. When adjusted for the exposure, EAIR was 6.4 per 100-subject years for 120 day SUR compared to 6.2 for the original NDA. At individual preferred term level there was no increase in EAIR and therefore this small increase of EAIR was not driven by any particular event but with longer exposure.

AEs leading to Drug Withdrawal: A total of 16 additional subjects discontinued Phase 3 trials during 120-day SUR period. The most frequently reported reasons for discontinuation were: nausea, psoriasis, and diarrhea.

Adverse Events of Special Interest (AESI)

1. MACE and Potential MACE: During the 120 day SUR period, events that were adjudicated as MACE were reported in 2 additional subjects (EAIR 0.6 per 100 subject years) compared to EAIR 0.5 per 100 subject years for the original NDA.

   Table 58: Adjudicated MACE and Potential MACE Events for Apremilast Subjects

	Original NDA APR 30mg BID	120 Day SUR APR 30mg BID
Adjudicator Classification	EAIR	EAIR
MACE	0.5	0.6
Potential MACE	0.8	0.7

Source: Modified from applicant's submission 4-minth safety update report; Table 19, page 59.

During the 120 day SUR period events that were adjudicated as potential MACE were reported in additional one subject (EAIR 0.7 per 100 subject years) compared to EAIR 0.8 per 100 subject years for the original NDA.

Overall frequency of MACE and potential MACE were not increased in apremilast treated subjects.

2. Malignancies
   During the 120 day SUR period, events that were adjudicated as skin malignancies were reported in 2 additional subjects (EAIR 0.9 per 100 subject years) compared to EAIR 1.1 per 100 subject years for the original NDA.

   During the 120 day SUR period, events that were adjudicated as solid malignancies were reported in 2 additional subjects (EAIR 0.5 per 100 subject years) compared to EAIR 0.4 per 100 subject years for the original NDA.

   One subject reported hematologic malignancy during 120 day SUR period. No hematologic malignancies were reported in Phase 3 trial during apremilast treatment period Week 0-52.

Table 59: Adjudicated Malignancy Events for Apremilast Subjects

	Original NDA APR 30mg BID	**120 Day SUR APR 30mg BID**
Adjudicator Classification	EAIR	EAIR
Hematologic	0.0	0.1
Skin (excluding melanoma)	1.1	1.0
Solid (including melanoma)	0.4	0.5

Source: Modified from applicant's submission 4-minth safety update report; Table 21, page 62.

3. Serious Infections
   No non-systemic or systemic opportunistic infections were reported during 120-day SUR.
   During the 120 day SUR period, events that were adjudicated as serious non-opportunistic infections were reported in 2 additional subjects (EAIR 0.9 per 100 subject years) compared to EAIR 1.0 per 100 subject years for the original NDA.

Table 60: Adjudicated Serious Infections for Apremilast Subjects

Adjudicator Classification	**Original NDA APR 30mg BID**	**120 Day SUR APR 30mg BID**
	EAIR	EAIR
Non-opportunistic serious infections	1.0	0.9

Source: Modified from applicant's submission, 4-minth safety update report; Table 23, page 66.

4. Suicide and Suicidal Ideation and Behavior
   No additional cases of suicide or suicidal ideation and behavior were reported during 120 day SUR.

5. Depression
   During the 120-day SUR period, one additional SAE of depression was reported (EAIR 2.2 per 100 subject years) compared to EAIR 2.1 per 100 subject years for the original NDA.

6. Weight Change
   Mean weight change from baseline was stable during 120-day SUR period. Report of mean weight change from baseline is presented in Table below.

Table 61: Mean Weight Change over Time

APR 30mg BID	Mean Change from Baseline (kg)
Week 16	
Original NDA	-1.51
120-day SUR	1.51
Week 32	
Original NDA	-1.78
120-day SUR	-1.78
Week 52	
Original NDA	-1.99
120-day SUR	-1.97
Week 65	
Original NDA	2.33
120-day SUR	-2.10
Week 78	
Original NDA	-2.72
120-day SUR	-2.05
Week 91	
Original NDA	-2.29
120-day SUR	-1.88

Source: Modified from applicant's submission, 4-minth safety update report; Table 26, page 74.

7. Vasculitis
   During the 120-day SUR period no cases of vasculitis were reported.

8. Additional AESI
   The applicant summarized incidence of AESI by SMQ or SCQ for the 120-day safety update.

Table 62: AESI during 120-day SUR

SMQ or SCQ AESI	Original NDA APR 30mg BID	120 Day SUR APR 30mg BID
	EAIR	EAIR
SCQ URTI	53.5	45.7
SCQ Diarrhea	25.0	20.4
SCQ Headache	18.4	15.0
SCQ GI Pain and Abdominal Pain	6.2	1.9
SMQ Liver-related investigations Signs and Symptoms	1.9	1.6
SCQ Hypersensitivity	0.7	0.7
SCQ Gallstone and Gallbladder Symptoms	0.4	0.4
SMQ Cardiac Failure	0.2	0.2

Source: 4-minth safety update report; Table 29, page 80.

9. Laboratory Values
   During the 120-day SUR period there were no marked hematology abnormalities that revealed new safety signals.

   For clinical chemistry, greater proportion of subjects had markedly increased of glucose, glycosylated hemoglobin, and triglyceride levels during the 120-day SUR period compared with that of original NDA. For results during Week 0-52 for placebo and apremilast treatment group refer to section **7.4.2 Laboratory Findings** of this review.

Overall, the data in the 120-day safety update increased the duration of total exposure to apremilast and the safety information was consistent with the data provided in this NDA. No new safety signals were identified during the 120-day SUR period.

8 Postmarket Experience

Apremilast was approved for the treatment of active psoriatic arthritis (NDA 205437) on March 21, 2014. At the time of this review, no postmarketing experience data was available for review.

9 Appendices

9.1 Literature Review/References

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7. Hyuck Hoon Kwaon, Sun Jae Na, Seoung Jin Jo, Jai Il Youn. Epidemiology and clinical features of pediatric psoriasis in tertiary referral psoriasis clinic.

9.2 Labeling Recommendations

The applicant submitted proposed labeling in the format that complies with Physician's Labeling Rule. Professional and patient labeling, as well as carton and container labels, were reviewed (by DNP, DMEPA and DDMAC).
For this reviewer's labeling recommendations refer to section **7.3.5 Submission Specific Primary Safety Concerns** and section **7.6.4 Overdose, Drug Abuse, Withdrawal and Rebound** of this review.

Labeling negotiations are ongoing at the time of this review.

9.3 Advisory Committee Meeting

NDA 206088 was not presented to the Dermatology Drug Advisory Committee because no safety or efficacy issues were identified that would warrant advisory committee input.

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/s/

SNEZANA TRAJKOVIC
05/23/2014

JILL A LINDSTROM
05/30/2014
I concur.

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11-433

Consultant Reviewer:	Gregory M. Dubitsky, M.D. Medical Officer Division of Psychiatry Products
Consultation Requestor:	Dawn Williams Regulatory Project Manager Division of Dermatology and Dental Products
Subject of Request:	NDA 206-088 (Apremilast)
Date of Request:	March 5, 2014
Date Received:	March 5, 2014
Desired Completion Date:	May 5, 2014

I. Background

Apremilast is an inhibitor of phosphodiesterase type 4 (PDE4), the predominant form of PDE in inflammatory cells. This inhibition increases intracellular cyclic adenosine monophosphate (cAMP) in immune cells and cells within the CNS. This in turn down-regulates the inflammatory response by modulating expression of TNF-α, IL-23, IL-17, and other inflammatory cytokines. In addition, increases in cAMP also modulate anti-inflammatory cytokines, such as IL-10.

These pro- and anti-inflammatory mediators have been implicated in a number of immune-related inflammatory conditions such as psoriasis, psoriatic arthritis, and rheumatoid arthritis. Thus, these conditions are targets for the development of apremilast.

NDA 206-088, sponsored by Celgene, is intended to support the approval of apremilast for the treatment of moderate to severe psoriasis. During the review of this application by the Division of Dermatology and Dental Products (DDDP), it was noted that the incidence of depression was more higher in apremilast-treated patients. Thus, DDDP has requested that the Division of Psychiatry Products (DPP) assess the reported psychiatric adverse events, recommend relevant labeling language, and, if needed, suggest additional data or analyses to evaluate the psychiatric safety of this small molecule.

II. Review Of Clinical Data

A. Selection of Relevant Clinical Trials

Six Phase 2/3 trials with apremilast (APR) were conducted in psoriasis, as described in Table 1 below.

Table 1: Apremilast Trials in Psoriasis	
Trial	**Trial Design**
PSOR-001	Open-label, uncontrolled trial with APR 20 mg/day x29 days.
PSOR-003	Randomized, double-blind, placebo-controlled trial with APR 20 mg/day versus 20mg bid x12 weeks.
PSOR-004	Open-label, uncontrolled trial with APR 20mg bid x12 weeks followed by 30mg bid x12 weeks.
PSOR-005-E-LTE	(b) (4)
PSOR-008	Randomized (2:1 ratio), double-blind, placebo-controlled trial with APR 30mg bid x16 weeks (total N=844), maintenance treatment of all subjects x16 weeks, and re-randomization of active drug responders to withdrawal of active treatment or APR (and APR 30mg bid for non-responders and original placebo patients) x20 weeks, with an ongoing 4 year extension of active drug treatment.
PSOR-009	Essentially identical to PSOR-008 (total N=413 randomized in placebo-controlled phase).

This review will discuss mainly the placebo-controlled phases of PSOR-005, PSOR-008, and PSOR-009 because these data are likely to be most informative, by design, regarding the occurrence of psychiatric adverse events at the dose proposed for marketing (APR 30mg bid).

B. Psychiatric Inclusion/Exclusion Criteria

The exclusion criteria for all three trials include any history of clinically significant psychiatric disease. Although this criterion is not further specified, I assume that patients with a history of a major depressive episode at some point in the past would have been excluded from these trials.

C. Psychiatric Safety Monitoring

Psychiatric adverse events were recorded at each visit in all three trials. For trial PSOR-005, post-baseline visits took place at weeks 1, 2, 4, 6, 8, 10, 12, 14, and

16. For trials PSOR-008 and PSOR-009, post-baseline visits were at weeks 2, 4, 8, 12, and 16.

All three studies also assessed the Short-Form 36-item Health Survey (SF-36) at baseline and on study drug. Two domains of the SF-36 are relevant to mental health: general mental health and limitations in usual activities because of emotional problems. The sponsor provided analyses of data derived from the mental health domain (termed the Mental Component Summary or MCS score) in the Summary of Clinical Efficacy. However, because of an apparent flaw in the rating of items subsumed by this domain, this measure has questionable validity and will not be further considered in this review.[1] Nonetheless, both domains relevant to mental health have limited usefulness from a regulatory perspective because neither is capable of reflecting a specific psychiatric symptom to which impairment or distress can be attributed.

Additionally, the Patient Health Questionnaire-8 item (PHQ-8) has been used to diagnose depression in clinical trials and was assessed in PSOR-008 and PSOR-009. This version of the PHQ omits the suicide item. The PHQ-8 was assessed at baseline and then at weeks 4, 8, and 16 in trials PSOR-008 and PSOR-009.

The Columbia-Suicide Severity Rating Scale (C-SSRS) apparently was not monitored in any of these three trials.

During trials PSOR-008 and PSOR-009, any subject who was identified as having attempted suicide or having a major psychiatric illness requiring hospitalization was to be immediately withdrawn from the trial and referred for care. In addition, any subject who had thoughts of suicide was to be evaluated to determine if true suicidal ideation was experienced. If so, the subject was to be referred to a psychiatrist for evaluation and treatment, as appropriate. The evaluation was to be completed within 3 weeks of referral and the subject could remain on study drug in the interval. If a risk of suicide was confirmed, the subject was to be discontinued from the trial. Otherwise, the subject could remain in the trial. A copy of the psychiatric report was to be placed in the subject's source document.

D. Coding of Psychiatric Adverse Events

Investigator (verbatim) adverse event terms were coded to MedDRA preferred terms for all three trials under consideration. For each of these trials, I examined the ae.xpt tabulation file to evaluate the acceptability of this coding for psychiatric adverse events. In each trial, I found the coding to be generally satisfactory.

[1] The five items in the mental health domain are each rated from 1 (all the time) to 5 (none of the time). For three of the items (9b, 9c, and 9f), a lower score indicates increased pathology. However, for two of the items (9d and 9h), a lower score signifies greater health. Because of this paradox, the Mental Health domain as a whole lacks face validity.

However, there were three instances where coding appeared to be clearly suboptimal:

• a subject in trial PSOR-005 experienced an event described as “dysthymia” which was coded to the preferred term “dysthymic disorder.” Because dysthymia is a chronic type of depressive disorder, treatment emergent “dysthymia” is more appropriately coded to the preferred term “depression.”
• a subject in trial PSOR-008 experienced “nightmares each night” which was coded to the preferred term “nightmares.” Although this is not objectionable on face, other subjects had events coded to the preferred term “abnormal dreams,” some of which may have been nightmares. Thus, in order to avoid minimizing the incidence of these events by splitting, this event should be coded to “abnormal dreams” as well.
• a subject on trial PSOR-009 experienced an “inability to cope with an exacerbation of psoriasis” which was coded to the preferred term “personality disorder.” This event resolved after the psoriasis improved. Based on the information provided, this event does not represent a personality disorder, which is long-standing maladaptive thinking and behavior. Although the precise psychiatric symptoms experienced by this subject is unknown, the preferred term “stress,” while somewhat arbitrary, is likely to be more accurate.

The numerators for these events were corrected accordingly in the adverse event data displays in the following sections.

E. Review of Psychiatric Adverse Event Data

I evaluated psychiatric adverse event reporting rates in the psoriasis clinical trials using two overlapping sources of placebo-controlled data:

• fixed dose trial PSOR-005 for the purpose of assessing dose-relatedness.
• the pool of data from PSOR-005 (apremilast 30mg bid and placebo only) and PSOR-008 and PSOR-009 to determine the reporting rates in a larger database.

I will also describe important psychiatric adverse events (serious events or events that led to dropout) that were reported in any phase of these 3 trials.

<u>Psychiatric Adverse Events in Trial PSOR-005</u>
Psychiatric adverse events reported during the 16-week, placebo-controlled portion of this Phase 2b dose-ranging trial are shown in Table 2 below. This table was derived from data contained in the ae.xpt and dm.xpt tabulation files for trial PSOR-005-E-LTE for psychiatric events with a start day ≤116 (the upper limit of the timeframe for assessments during the placebo-controlled phase).

Table 2: Proportions of Patients Reporting Psychiatric Adverse Events Trial PSOR-005 Placebo-Controlled Phase				
AE Preferred Term	**Treatment Group**			
	APR 10mg bid N=89	**APR 20mg bid N=87**	**APR 30mg bid N=88**	**Placebo N=88**
Insomnia	4.5%	1.1%	1.1%	0%
Apathy	1.1%	0%	0%	0%
Depression	1.1%	0%	0%	0%
Abnormal Dreams	0%	0%	1.1%	0%
Anxiety	0%	1.1%	0%	0%
Nervousness	0%	0%	1.1%	0%
Panic Attack	0%	1.1%	1.1%	0%
Stress	0%	0%	1.1%	0%

Although the rates of these events were higher among certain apremilast-treated dose groups compared to placebo-treated patients (who reported none of these events), the small numbers of events and patterns of occurrence by dose group do not suggest that they were related to apremilast treatment.

Psychiatric Adverse Events in Trials PSOR-005, PSOR-008, and PSOR-009

Because the placebo-controlled portions of trials PSOR-005, PSOR-008, and PSOR-009 were identical in duration (16 weeks) and involved administration of the proposed dosing regimen (30mg bid), they were pooled for purposes of evaluating the rates of psychiatric adverse events in a larger database.

The reporting rates of psychiatric adverse events during the 16-week, placebo-controlled portions of these trials are shown in Table 3 below. This table was derived using the same general approach as that used to generate Table 2.

Table 3: Reporting Rates of Psychiatric Adverse Events Placebo-Controlled Treatment with Apremilast 30mg bid Pool of Trials PSOR-005, PSOR-008, and PSOR-009				
	APR 30mg bid N=920 Exposure=260.8 subj-yrs		**Placebo N=506 Exposure=140.3 subj-yrs**	
	Crude Rate	**Adj Rate/100 yrs**	**Crude Rate**	**Adj Rate/100 yrs**
Insomnia	2.4%	8.4	1.0%	3.6
Depression	1.4%	5.0	0.4%	1.4
Anxiety	0.4%	1.5	0.6%	2.1
Abnormal Dreams	0.2%	0.8	0.2%	0.7
Nervousness	0.2%	0.8	0.2%	0.7
Stress	0.3%	1.2	0.0%	0.0
Suicide Attempt	0.1%	0.4	0.0%	0.0
Completed Suicide	0.0%	0.0	0.2%	0.7
Libido Decreased	0.0%	0.0	0.2%	0.7
Libido Increased	0.1%	0.4	0.0%	0.0
Mood Altered	0.1%	0.4	0.0%	0.0
Panic Attack	0.1%	0..4	0.0%	0.0
Sleep Disorder	0.0%	0.0	0.2%	0.7

The above rates for insomnia and depression differ slightly from those reported in Table 4.1 of the sponsor's February 18, 2014, submission. This is most likely because of the above recoding of a few adverse events and the inclusion of events that occurred on or before study day 116 (as opposed to study day 112) in Table 3 above.

Only for insomnia and depression were the crude reporting rates appreciably higher in apremilast-treated subjects compared to placebo. The difference was not statistically significant for depression (p=0.10) but approached significance for insomnia (p=0.07).[2]

The rate of suicidal behavior, including completed suicide, was slightly higher in the placebo group than in the apremilast group (apremilast 0.1% (1/920) versus placebo 0.2% (1/506)). Both cases are described in the following section. Although no adverse events were coded specifically to suicidal ideation, the incidence of suicidal ideation cannot be determined from these data because of the lack of prospective, systematic assessment of suicidal thoughts in these trials.

Serious Psychiatric Adverse Events

Four psychiatric adverse experiences that occurred during the placebo-controlled phases of these trials were classified as serious:

• Subject PSOR-005-042-1019 was a 63 year old male in the placebo treatment arm who was found unresponsive on his garage floor with his motorcycle running and the main garage door closed on study day (b) (6). There was no reported history of suicidal ideation or depression in this subject. The subject had a history of COPD and bradycardia. Although this death was classified as caused by a cardiovascular event, an autopsy did not reveal a cause of death and it is suspicious for a completed suicide. To be conservative, this event is considered to be a completed suicide.

• Subject PSOR-008-025-1014 was a 28 year old female in the placebo group who committed suicide by gunshot wound 26 days after her last dose of placebo; she did not receive apremilast. Her history was remarkable for a previous suicide attempt, bipolar disorder, depression, alcohol abuse, and insomnia. Although serious, this event occurred so long after study drug treatment that it seems unlikely to be related to that treatment and, thus, it is not counted as a completed suicide during placebo-controlled treatment in Table 2 above.

• Subject PSOR-009-324-1011 was a 66 year old male in the apremilast treatment group who attempted suicide by ingesting an overdose of zopiclone (75mg) related to a conflict with his wife and neighbor on study day (b) (6). There was no prior history of depression or suicidal ideation and he did not use alcohol. He was treated on a psychiatric ward for depression and recovered. He was discontinued from the trial.

[2] Crude rates were compared using a 2-tailed Fisher's exact test with an alpha level of 0.05.

• Subject PSOR-009-350-1003 was a 47 year old male who contacted his dermatologist and requested hospital admission because he could not cope with an exacerbation of his psoriasis since discontinuation of methotrexate about one month before. His inability to cope was coded to the preferred term "Personality Disorder." He received treatment with apremilast for a total of one day. His inability to cope resolved following recovery from his exacerbation of psoriasis. There was no previous history of a psychiatric disorder or use of alcohol.

Three psychiatric adverse events classified as serious were reported in other phases of these trials:

• Subject PSOR-005-003-1037 was a 53 year old male who presented to the emergency room with anxiety on day (b) (6) of active drug treatment. He was medically evaluated and released, with instructions to stop smoking and reduce stress. The anxiety resolved 3 days later. Apremilast 20mg bid was not discontinued.
• Subject PSOR-008-202-1015 was a 55 year old female who was hospitalized for depression (b) (6) days after stopping apremilast 30mg bid; she had been treated for 142 days prior to that. She also experienced insomnia at the time of hospitalization. She was treated with medication for both events and recovered from the depression one month later and from the insomnia six weeks later. Her past history was remarkable for depression over the prior 16 years (which required several different antidepressant treatments at various times) and alcohol use (1-14 drinks per week).
• Subject PSOR-009-324-1012 was a 70 year old female with a five year history of schizophrenia who experienced a schizophrenic decompensation and was hospitalized. She had been treated with apremilast 30mg bid for a total of 191 days. She was started on antipsychotic therapy and she recovered about three weeks later. Apremilast treatment was continued during this time.

Dropouts Due to Psychiatric Adverse Events
There were three subjects who dropped out because of a psychiatric adverse event during the placebo-controlled phases of these trials. Two of these subjects, PSOR-009-350-1003 and PSOR-009-324-1011, were discontinued for "personality disorder" and suicide attempt, respectively, and are described above. The third subject (PSOR-008-112-1007) was a 48 year old female in the apremilast treatment group who experienced moderate anxiety on study day 30, which led to study drug discontinuation on day 38. The anxiety resolved the next day. This subject experienced depression for four years prior to this event and was receiving treatment with venlafaxine.

Psychiatric adverse events that led to dropout in other phases of these trials were (in one subject each): depression, anxiety, insomnia, alcoholism, and alcohol withdrawal.

F. Sponsor's Standard MedDRA Query (SMQ) Analyses

The sponsor conducted analyses of 1) suicide and suicidal ideation and behavior and 2) depression based on SMQ searches of the PSOR Phase 3 Data Pool (studies PSOR-008 and PSOR-009) as well as the apremilast data pool (psoriasis studies PSOR-008 and PSOR-009, the psoriatic arthritis studies PsA-001, PsA-002, PsA-003, and PsA-004), and a rheumatoid arthritis study (RA-002). The MedDRA preferred terms subsumed under each SMQ are listed in Appendix 1.

Suicide and Suicidal Ideation and Behavior

For the placebo-controlled phase (weeks 0 to 16) of the studies in the PSOR Phase 3 Data Pool, the raw rates of suicide/self-injury SMQ events were 0.1% (1/832) in the apremilast group and 0.2% (1/418) for the placebo group. The exposure-adjusted incidence rates were 0.4 per 100 subject-years for apremilast and 0.9 per 100 subject years for placebo. The events consisted of only 1 suicide attempt in the apremilast group and 1 completed suicide in the placebo group. There were no other events during apremilast exposure in this study pool.

In the larger apremilast data pool, the exposure-adjusted incidence of these SMQ events during the placebo-controlled portion of the trials was slightly higher among apremilast 30mg bid-treated subjects (0.4 per 100 subject-years) compared to placebo (0.3 per 100 subject-years).[3]

Depression (excluding suicide and self-injury)

For the placebo-controlled portion of the trials in the PSOR Phase 3 Data Pool, the unadjusted rates of depression SMQ events were 1.4% (12/832) in the apremilast group and 0.5% (2/418) for the placebo group. The exposure-adjusted incidence rates were 5.1 per 100 subject-years for apremilast and 1.7 per 100 subject years for placebo. These events were all coded under the preferred term "depression." This apremilast SMQ adjusted reporting rate of depression was higher than the rate of depression seen in a GPRD-based cohort study among patients with mild psoriasis (2.57 per 100 subject-years (95% CI 2.53, 2.61)) and severe psoriasis (3.18 per 100 subject-years (95% CI 2.95, 3.43)).[4]

In the larger apremilast data pool, the exposure-adjusted incidence of these SMQ events during the placebo-controlled portion of the trials was higher among apremilast 30mg bid-treated subjects (3.4 per 100 subject-years) compared to placebo (1.9 per 100 subject-years).

[3] In this pool, the apremilast group received a range of dosing regimens: APR 10mg bid, 20mg daily, 20mg bid, 40mg daily, and 30mg bid.

[4] Kurd SK, et al. The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. Arch Dermatol 2010;146(8):891-895.

G. PHQ-8 Data

The PHQ-8 is based on DSM-IV criteria for major depression and includes the following 8 items:

- little pleasure or interest.
- feeling depressed.
- sleep disturbance.
- decreased energy level.
- increased or decreased appetite.
- feeling bad about oneself.
- impaired concentration.
- psychomotor changes (e.g., reduced activity level).

The patient indicates the number of days in the prior 2 weeks that each symptom was experienced, which is rated from 0 (not at all) to 3 (nearly every day). The total score is interpreted as follows:

0-4	No significant depressive symptoms.
5-9	Mild depressive symptoms.
10-14	Moderate depressive symptoms.
15-19	Moderately severe depressive symptoms.
20-24	Severe depressive symptoms.

In addition, subjects were queried about the degree of difficulty their checked symptoms made their functioning at work, home, and in social settings. The difficulty was rated as follows:

- Not difficult at all.
- Somewhat difficult.
- Very difficult.
- Extremely difficult.

In trials PSOR-008 and PSOR-009, subjects in all treatment groups experienced very mild depressive symptoms at baseline, on average. During the placebo-controlled portions of these trials, the mean and median changes in the PHQ-8 total scores were small and unlikely to be clinically significant in both the apremilast and placebo treatment groups (see Table 4).

Table 4: Changes in the PHQ-8 Total Scores Placebo-Controlled Phases of PSOR-008 and PSOR-009				
	PSOR-008		PSOR-009	
	APR	Placebo	APR	Placebo
Baseline N	554	272	267	130
Baseline Mean	5.4	5.2	5.3	5.4
Week 16 Mean Change	-0.6	+0.3	-0.8	+0.2
Week 16 Median Change	0.0	0.0	0.0	0.0

I conducted additional analyses to compare the incidence of outliers on the PHQ-8 total score and difficulty ratings between the apremilast and placebo groups for the pool of the placebo-controlled phases of trials PSOR-008 and PSOR-009. Outliers were defined in the following fashion:

• subjects with a baseline (Visit 2) PHQ-8 total score of 0 to 9, inclusive, who experienced a post-baseline (Visits 3 to 7) total score of 15 to 24, inclusive (i.e., the number of patients with no significant or only mild depressive symptoms at baseline who later experienced moderately severe or severe depressive symptoms).
• patients who reported no difficulty from depressive symptoms at baseline who later indicated that depressive symptoms made their functioning very difficult or extremely difficult.

The risk of meeting one of these two outlier criteria is shown in Table 5 below.

Table 5: Incidence of PHQ-8 Outliers Placebo-Controlled Phases of PSOR-008 Plus PSOR-009[5]				
	PHQ-8 Total Score		PHQ-8 Difficulty Score	
	Apremilast	Placebo	Apremilast	Placebo
% (N/n)[6]	4.1% (26/633)	3.8% (12/319)	2.5% (12/488)	2.0% (5/249)
p-value[7]	0.9		0.8	

Although the risk of experiencing an outlier value after baseline was numerically greater for apremilast-treated patients on both measures, the differences from placebo were not statistically significant.

[5] This table was derived from the qsph.xpt and dm.xpt tabulation files for these two trials.
[6] The denominators were the number of subjects meeting the baseline criterion and at risk for experiencing an outlier value after baseline.
[7] Based on a 2-tailed Fisher's exact test with a nominal alpha level of 0.05.

H. Suicidality Assessment Report

The sponsor conducted two assessments of suicidal ideation and behavior associated with apremilast, with a cutoff of July 6, 2012: one assessment using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) methodology and a second assessment using SMQ methodology. All blinded data remained blinded at the time of these assessments. The clinical trial encompassed 4,568 subjects representing 2,725 subject-years of apremilast exposure.

C-CASA Assessment

The apremilast clinical trial database for all Phase 2 and Phase 3 completed and ongoing studies (including indications for asthma, Behcet's disease, rheumatoid arthritis, psoriasis, and psoriatic arthritis) was searched for all data available up to July 06, 2012. Databases were searched by Celgene physicians using the methods described by Posner.[8] A total of 290 suspect verbatim adverse event terms were identified for further evaluation. Subject profiles were then constructed and examined by Celgene physicians and classified as either suicidal behavior or ideation as defined in the FDA guidance for assessing suicidality in clinical trials. This assessment revealed one completed suicide and 2 suicide attempts.[9] However, the treatment assignment for these cases was not specified, which renders this analysis of limited usefulness.

SMQ Assessment

The narrow SMQ for suicide/self-injury as well as the SMQ for depression (excluding suicide/self-injury) were used to search the Phase 2/3 safety databases as above. This evaluation revealed the same completed suicide and 2 attempted suicides discovered using the C-CASA methodology during placebo-controlled treatment: one in the 30mg bid group and 2 in the 20mg bid group. No placebo patients were identified. Examination of all apremilast treatment phases revealed no new cases of interest.

The SMQ search for depression uncovered 1.0% (18/1728) of APR and 0.6% (5/817) of placebo subjects who experienced treatment emergent depression. Exposure-adjusted incidence rates were 2.9/100 subject-years for apremilast and 2.0/100 subject-years for placebo.

Based on the event rates determined from these assessments in comparison to rates in similar populations reported in the literature and AERS and WHO databases, the sponsor concluded that there was no signal detected for suicide, suicidal ideation, suicidal behavior or attempts, or depression associated with apremilast treatment. However, in my opinion, this conclusion should be viewed

[8] Posner K, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035-43.
[9] The completed suicide (Subject PSOR-008-025-1014) is discussed above.

with skepticism because of the questionable validity of comparing adverse event rates across diverse databases.

III. Apremilast for Psoriatic Arthritis (Otezla)

Apremilast was approved for the treatment of psoriatic arthritis on March 21, 2014, and will be marketed under the tradename Otezla.

A consultative review was completed by Phillip Kronstein, M.D., Medical Officer in DPP, on January 17, 2014, as part of the apremilast NDA for the psoriatic arthritis indication (NDA 205-437). As part of his review, Dr. Kronstein examined the C-CASA evaluation conducted by the sponsor, which appears to be the same as that described in the Suicidality Assessment Report contained in this application. He stated that this examination appeared to be deficient because 1) it failed to detect one completed suicide as well as one suicide attempt that he discovered, 2) it was conducted by Celgene in-house physicians as opposed to independent experts in suicide and suicide assessment, and 3) the methodology for blinding the raters was not clear. Dr. Kronstein conducted his own review of all available serious adverse event narratives from the apremilast unblinded data and identified only two cases each of suicidal ideation and possible suicide attempts in apremilast-treated subjects. He concluded that there was no substantial signal for suicidal ideation or behavior. He did recommend adding a prospective assessment of suicidal ideation and behavior, such as the Columbia-Suicide Severity Rating Scale (C-SSRS), in future clinical trials.

The primary review division for that NDA (the Division of Pulmonary, Allergy, and Rheumatology Products) also determined that the data did not represent a clear signal for a psychiatric safety concern but, because some of the events were clinically significant, it was that felt that information about possible treatment-emergent depression and suicidal thinking and behavior should be included in labeling.[10] Thus, the approved labeling for Otezla includes a section under Warnings and Precautions regarding depression, including suicidal thoughts and behavior (see Appendix 2). There is also information regarding these events under Patient Counseling Information.

IV. Conclusions and Recommendations

In the pool of the 16-week, placebo-controlled phases of three Phase 2/3 trials among patients who received apremilast 30mg bid or placebo, the reporting rates for insomnia and depression were substantially, but not statistically significantly, higher in the apremilast group compared to placebo:

[10] See the Cross-Disciplinary Team Leader Memo for NDA 205,437 by Nikolay P. Nikolov, M.D., dated February 6, 2014.

Insomnia	Apremilast 2.4% (22/920)	Placebo 1.0% (5/506)
Depression	Apremilast 1.4% (13/920)	Placebo 0.4% (2/506)

The rates of suicidal behavior, including completed suicide, were low and slightly higher in the placebo group:

Suicidal Behavior	Apremilast 0.1% (1/920)	Placebo 0.2% (1/506)

Of these 2 cases, there was one presumed completed suicide in the placebo group.

PHQ-8 data in terms of changes from baseline scores, the frequency of outlier scores, and changes in functioning due to depressive symptoms revealed no significant differences between the apremilast and placebo groups in the two Phase 3 trials.

Overall, these data do not support an inference that apremilast causes depression or suicidal thoughts or behavior in patients with psoriasis. Nevertheless, a causal link cannot be definitively ruled out. As noted above, these trials excluded subjects with a history of significant psychiatric illness. So, it is possible that when apremilast is used by patients with a history of or predisposition to depression that the risk of depression or suicidal thoughts or behavior will be greater. Also, systematic, prospective assessments for treatment-emergent suicidal thoughts and behavior were not performed in these trials.

Given the very small number of suicide-related adverse events detected in my review of these data and the likelihood of poor ascertainment of suicidal ideation inherent in any retrospective search of clinical trial data, more rigorous analysis of suicidality using the methods described by Posner is not recommended.[11]

To reiterate the advice provided by DPP regarding the Otezla NDA, suicidal thoughts and behavior in clinical trials are best assessed prospectively using a validated instrument such as the Columbia-Suicide Severity Rating Scale (C-SSRS). The incorporation of this scale (or an equivalent scale) into future apremilast trials is highly recommended to systematically detect suicidal events.

In keeping with the labeling format for Otezla, the following text can be used in labeling to characterize the observed depression and suicidal behavior:

> Treatment with apremilast is associated with an increase in adverse reactions of depression. During the 0 to 16 weeks placebo-controlled period of 3 controlled clinical trials in psoriasis in which patients were treated with apremilast 30mg twice daily, 1.4% (13/920) of patients treated

[11] Op cit.

with apremilast reported depression or depressed mood compared to 0.4% (2/506) treated with placebo. During this treatment, no patients treated with apremilast or placebo discontinued treatment due to depression or depressed mood. Depression was reported as serious in 0.1% (1/920) of patients exposed to apremilast, compared to none in placebo treated patients (0/506). Instances of suicidal behavior were observed in 0.1% (1/920) of patients while receiving apremilast, compared to 0.2% (1/506) placebo treated patients. One patient who received placebo committed suicide compared to none among apremilast-treated patients.

Please let us know if we may be of further assistance.

Gregory M. Dubitsky, M.D.
Medical Officer
Division of Psychiatry Products

APPENDIX 1
ADVERSE EVENT TERMS SUBSUMED BY PSYCHIATRIC SMQs

Suicide and Self-Injury

COMPLETED SUICIDE
DEPRESSION SUICIDAL
INTENTIONAL OVERDOSE
INTENTIONAL SELF-INJURY
MULTIPLE DRUG OVERDOSE INTENTIONAL
POISONING DELIBERATE
SELF INJURIOUS BEHAVIOUR
SELF-INJURIOUS IDEATION
SUICIDAL BEHAVIOUR
SUICIDAL IDEATION
SUICIDE ATTEMPT

Depression (excluding suicide and self-injury)

ACTIVATION SYNDROME
ADJUSTMENT DISORDER WITH DEPRESSED MOOD
ADJUSTMENT DISORDER WITH MIXED ANXIETY AND DEPRESSED MOOD
AGITATED DEPRESSION
ANHEDONIA
ANTIDEPRESSANT THERAPY
CHILDHOOD DEPRESSION
DECREASED INTEREST
DEPRESSED MOOD
DEPRESSION
DEPRESSION POSTOPERATIVE
DEPRESSIVE SYMPTOM
DYSPHORIA
DYSTHYMIC DISORDER
ELECTROCONVULSIVE THERAPY
FEELING GUILTY
FEELING OF DESPAIR
FEELINGS OF WORTHLESSNESS
MAJOR DEPRESSION
MENOPAUSAL DEPRESSION
POST STROKE DEPRESSION
POSTPARTUM DEPRESSION

APPENDIX 2
OTEZLA (APREMILAST) LABELING OF PSYCHIATRIC AEs

5 WARNINGS AND PRECAUTIONS

5.1 Depression
Treatment with OTEZLA is associated with an increase in adverse reactions of depression. During the 0 to 16 weeks placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of patients treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of patients treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to OTEZLA, compared to none in placebo treated patients (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of patients while receiving OTEZLA, compared to none in placebo treated patients (0/495). In the clinical trials, two patients who received placebo committed suicide compared to none in OTEZLA treated patients.

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

17 PATIENT COUNSELING INFORMATION

Depression
Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. [see *Warnings and Precautions (5.1)*]

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/s/

GREGORY M DUBITSKY
04/28/2014

JING ZHANG
04/28/2014

MITCHELL V Mathis
04/28/2014