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APPLICATION NUMBER:

206088Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	206088
Submission Date:	September 23, 2013
Brand Name:	OTEZLA
Generic Name:	Apremilast
Dosage Form:	Tablets
Dosage Strength:	10, 20 and 30 mg
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	CAPT. Edward D. Bashaw, Pharm. D.
Pharmacometrics Reviewer:	Jeffry Florian, Ph.D.
OCP Division:	Division of Clinical Pharmacology -3
OND Division:	Division of Dermatology and Dental Products
Applicant:	Celgene Corporation
Relevant IND(s):	070,270
Submission Type:	New NDA
Indication:	Treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

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1. Executive Summary

Apremilast (APR) (OTEZLA®) was approved on March 21, 2014 for the treatment of psoriatic arthritis in adults (NDA 205437). With this NDA, the same applicant has proposed an indication for the treatment of moderate to severe plaque psoriasis in adult subjects who are candidates for phototherapy or systemic therapy. The applicant has adopted a 505(b)(1) regulatory pathway for this NDA.

The clinical program consists of two Phase 3 safety and efficacy trials in subjects with plaque psoriasis (Trial CC-10004-PSOR-008 and Trial CC-10004-PSOR-009). The clinical pharmacology trials are identical to those submitted under NDA 205437.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the applicant.

1.2 Post-Marketing Requirements/ Commitments

Post-Marketing Requirements:

1. A dose finding, pharmacokinetics and safety trial in subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years
2. Safety and efficacy trial in pediatric subjects with moderate to severe plaque psoriasis between ages of 6 to 17 years

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Since the Clinical Pharmacology and Biopharmaceutics information submitted under this NDA is identical to that submitted under NDA 205437, the review findings will not be re-summarized here. For the Clinical Pharmacology and Biopharmaceutics review findings, refer to Dr. Sheetal Agarwal's Clinical Pharmacology review dated November 20, 2013 and Dr. Minerva Hughes's Biopharmaceutics review dated November 21, 2013, respectively, in DARRTS, under NDA 205437. This review addresses only the additional materials which are not covered under NDA 205437.

Exposure in subjects with psoriasis: Based on cross trial comparison, the bioavailability (BA) of APR increased by approximately 2 fold in subjects with disease compared to healthy subjects, however, due to limited number of subjects with disease (n = 3) interpretation and implication of the comparative BA data should be made with caution. Population pharmacokinetic (PK) analysis in subjects with psoriasis demonstrated that the apparent clearance of APR was 20% lower in subjects with psoriasis compared to healthy volunteers.

Exposure response: Dose-response analysis supports the selection of APR 30 mg BID as an efficacious dose for the treatment of moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. Exposure-response analyses also support that APR 30 mg BID offers improvement in PASI-75 over placebo and lower doses of APR (10 and 20 mg BID) and suggests that higher doses of APR may not provide substantial additional improvement in PASI-75.

Drug interaction potential of metabolite M12: M12 is a major glucuronide metabolite of APR. In-vitro studies suggest that M12, at therapeutic concentration of APR, is not likely to induce cytochrome P450 (CYP) enzymes. In-vivo drug interaction with APR and the oral contraceptive Ortho Tri-Cyclen® suggest that M12 does not inhibit CYP3A. The inhibition potential of M12 on other CYP enzymes was not studied.

Pediatrics: NDA 205437 for psoriatic arthritis was approved with full pediatric waiver (see Approval Letter in DARRTS dated March 21, 2014). For this NDA, the applicant has proposed to conduct pediatric assessment down to 6 years of age. Below 6 years, the applicant has proposed to obtain a partial waiver due to limited number of subjects with moderate to severe psoriasis in this age group. This reviewer concurs with the applicant's proposal as outlined in Section 1.2 above. This NDA will be discussed with the Pediatric Review Committee (PeRC) on June 4, 2014.

1.4 Clinical Pharmacology briefing

An official briefing was not conducted for this NDA application.

2. Question Based Review

2.1 What is the regulatory history of NDA 206088?

On March 21, 2013, the applicant had submitted another NDA (NDA 205437) to Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the treatment of psoriatic arthritis. This application was considered as a New Molecular Entity (NME) and was approved on March 21, 2014.

When NDA 206088 was submitted to the Division of Dermatology and Dental Products (DDDP) in September 2013, this application was also classified as a NME due to pending action on NDA 205437 which was submitted ~ 6 months earlier. Since NDA 205437 is already approved, this NDA (NDA 206088) will no longer be considered as a NME.

With this NDA, the applicant indicated in the list of clinical trials, (b) (4) (b) (4). This trial was not included in NDA 205437. During filing of this NDA, it was noticed that the applicant had not submitted the study report of (b) (4). The applicant responded that this trial was planned but never initiated and necessary revisions have been made to their NDA submission to remove this trial from the list of clinical trials.

2.2 General Clinical Pharmacology

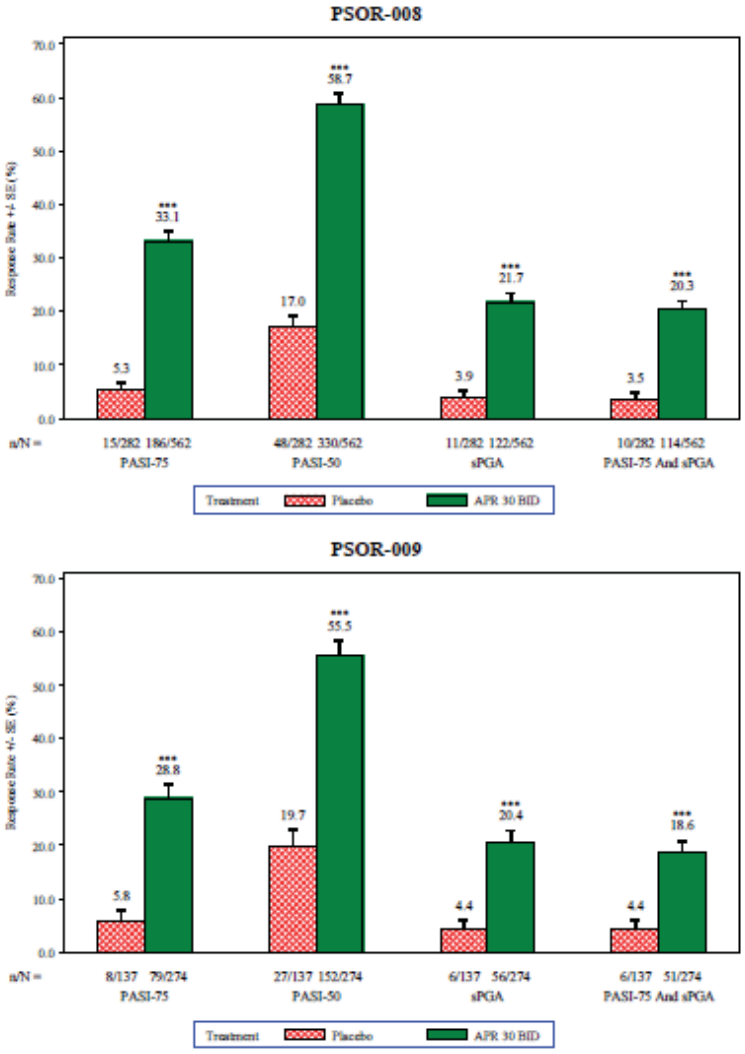
For the Clinical Pharmacology and Biopharmaceutics review findings, refer to Dr. Sheetal Agarwal's Clinical Pharmacology review dated November 20, 2013 and Dr. Minerva Hughes's Biopharmaceutics review dated November 21, 2013, respectively, in DARRTS, under NDA 205437. The focus of this review will be on materials that were not covered NDA 205437.

2.2.1 What is the exposure response in subjects with psoriasis?

Efficacy

The dose-response information from PSOR-005 and the response rates of APR compared to placebo in PSOR-008 and PSOR-009 support the selection of APR 30 mg BID as an efficacious dose for the treatment of moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. In study PSOR-005, APR 10 BID vs. APR 20 BID vs. APR 30 BID all achieved increases in PASI-75 response compared with placebo at week 16, though the increase was only significant for APR 20 and 30 BID (28.7%, and 40.9% versus 5.7% (for placebo), respectively; $p < 0.0001$ for both comparison). The APR 10 BID treatment group was not statistically significantly different than placebo (11.2% versus 5.7%, respectively; $p = 0.1846$). Similarly, the results from the two psoriasis Phase III trials (PSOR-008 and PSOR-009) support that APR 30 mg BID offers improvement over placebo for PASI-75, sPGA, and a composite of PASI-75/sPGA (Figure 1).

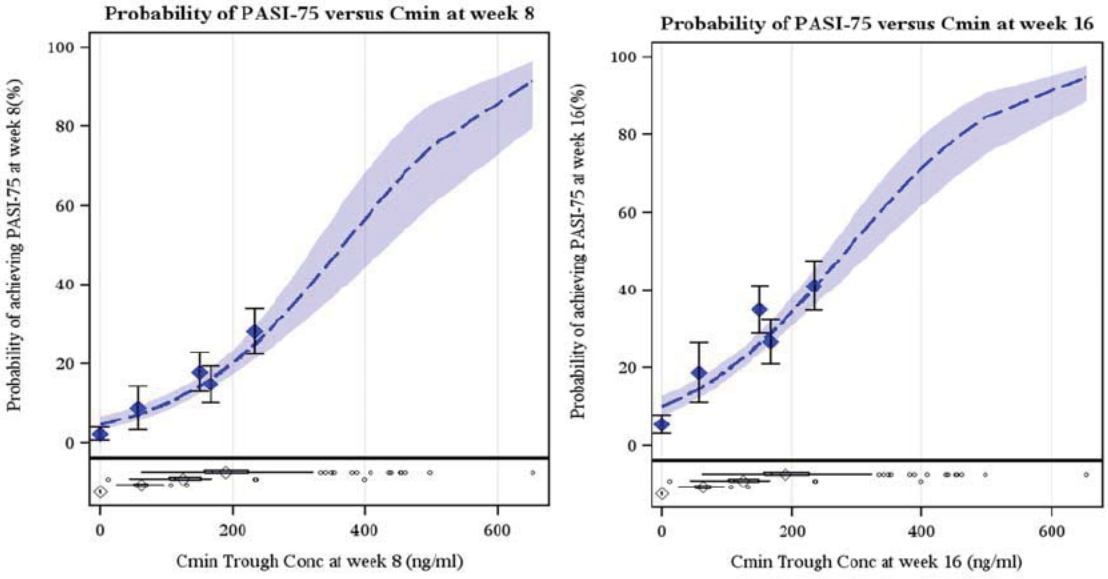
Figure 1: Proportion of Subjects Achieving PASI-75, PASI-50, sPGA Response, or PASI-75/sPGA Composite Response at Week 16 in Studies PSOR-008 and PSOR-009



Source: summary-clin-efficacy-psoriasis.pdf, Pg81, Figure 5

Exposure-response analyses also supports that APR 30 mg BID offers improvement in PASI-75 over placebo and lower doses of APR (10 and 20 mg BID) and suggests that higher doses of APR may not provide substantial additional improvement in PASI-75. A univariate exposure-response analysis was conducted based on data from PSOR-005 and PSOR-008. In all, treatment and pharmacokinetic data was available from 359, 83, 72 and 641 subjects at week 8 and 354, 79, 66 and 630 subjects at week 16 administered placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID, respectively. Across these range of doses, an exposure-response relationship was identified between PASI-75 response at week 8 and week 16 and APR C_{min} (Figure 2). For a typical subject administered placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID the predicted median APR C_{min} was 0, 57, 113, and 169 ng/mL, respectively. The predicted PASI-75 response for these treatment arms at week 8 was 5%, 7%, 10% and 17%, respectively. Likewise, the predicted PASI-75 response at week 16 for placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID was 10%, 16%, 20% and 30%, respectively. These observations support that APR 30 mg BID is an appropriate APR dose for achieving both increased PASI-75 response at week 8 and 16 compared to APR doses of 10 and 20 mg BID.

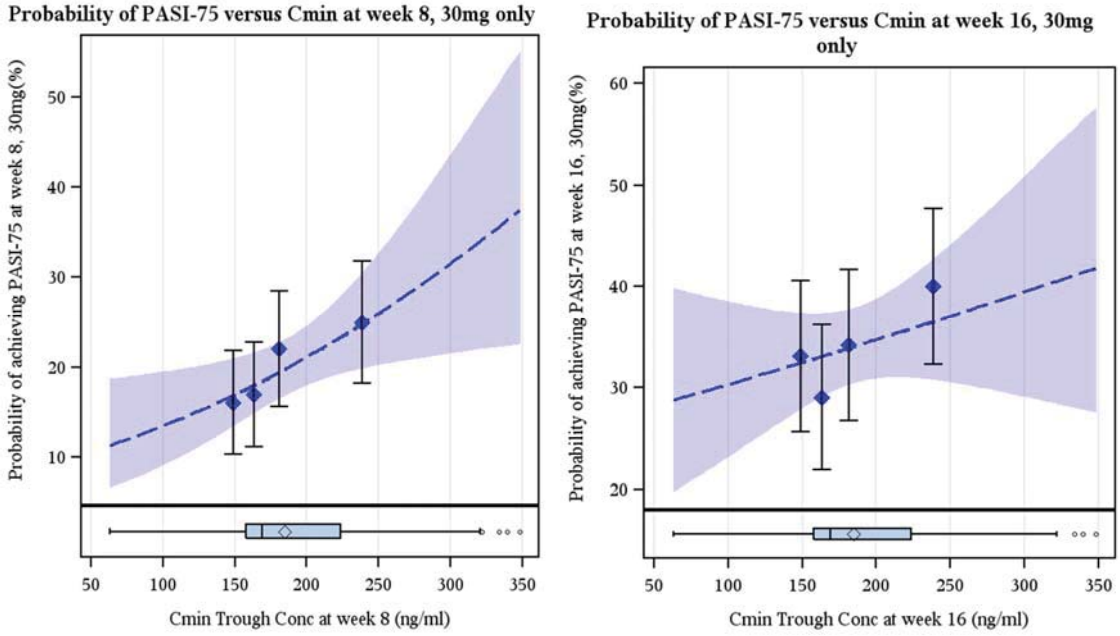
Figure 2: Exposure-response efficacy relationship based on PASI-75 vs. C_{min} concentration at week 8 (left) and week 16 (right) for subjects in PSOR-005 and PSOR-008.



In order to further explore the potential exposure-response relationship observed above, a subset analysis based only on those subjects from PSOR-008 administered APR 30 mg BID was conducted. The results of this analysis, which are shown in Figure 3, demonstrate that based on this subset of patients that exposure-response relationships are still evident at week 8 and 16, but that the relationship at week 16 is not as steep as that observed for week 8. Observed median APR concentrations in the 1st and 4th quartile

were 149 ng/ml and 240 ng/ml (a 1.6-fold difference) [median concentration of 169 ng/mL]. PASI-75 responses corresponding to 17% and 26% were observed for these two quartiles at week 8. The observed difference in PASI-75 between the two quartiles was 34% and 39% (predicted: 31% and 35%, respectively) was less at the week 16 assessment and supports that the APR exposure observed for 30 mg BID does not appreciably impact PASI-75. This observation suggests a higher dose than 30mg BID might not result in significant increase in the percentage of subjects achieving PASI-75.

Figure 3: Exposure-response efficacy relationship based on PASI-75 vs. C_{min} concentration at week 8 and 16 for subjects receiving APR 30 BID.



Safety

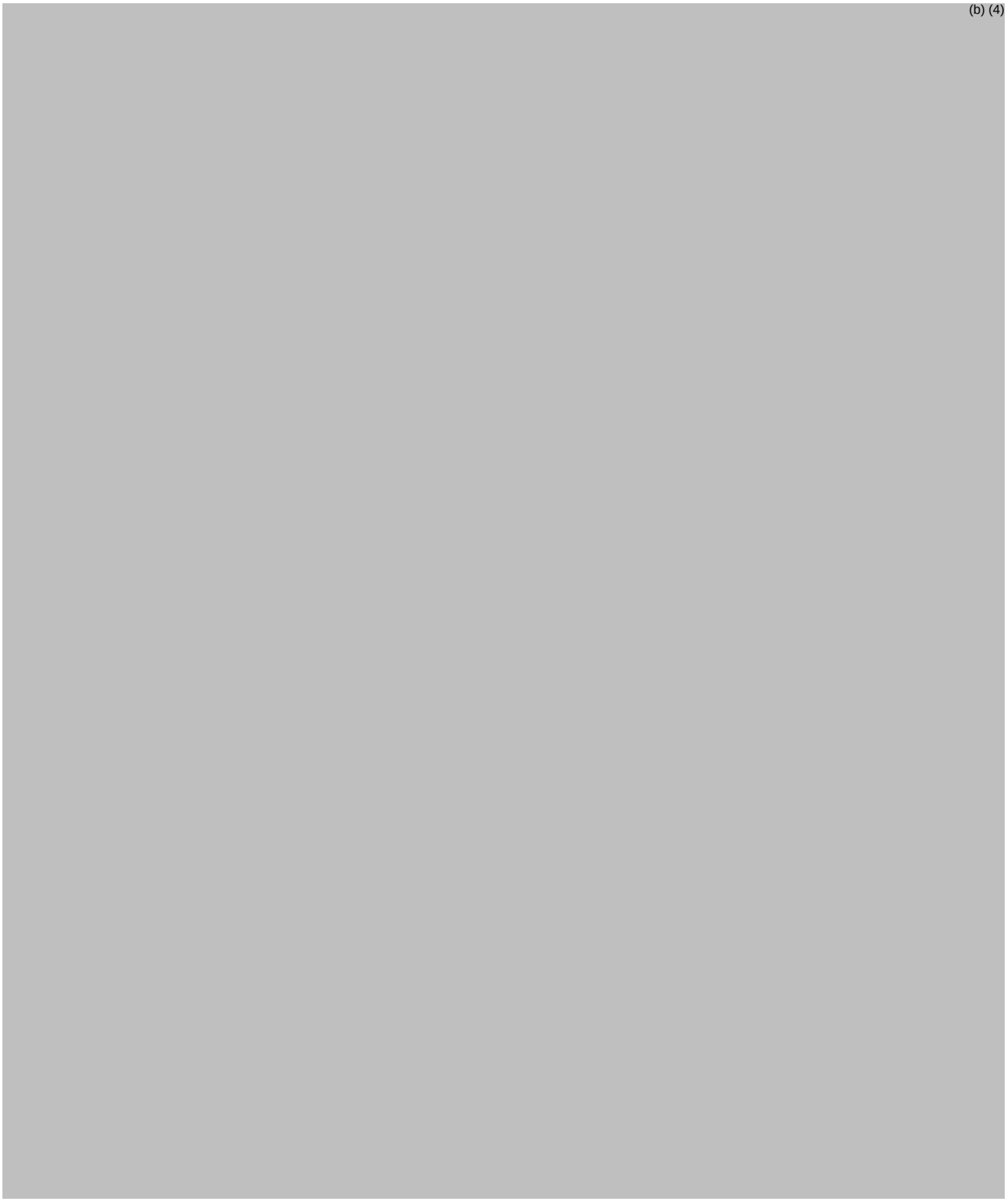
The previous review of APRfor psoriatic arthritis identified a dose-response relationship between placebo, APR 20 mg BID and APR 30 mg BID for events of diarrhea, nausea, and headaches. A similar analysis could not be conducted for the Phase III studies in psoriasis as only a single APR dose was evaluated (APR 30 mg BID); however, the adverse events more common in the APR treatment arm (nausea: 13.9%; diarrhea: 15.7%; headaches: 5.0%) than placebo (diarrhea: 6.7%; nausea: 6.7%; headaches: 3.3%) were similar to those identified from the psoriatic arthritis trials. In addition, a dose-response relationship with respect to the safety events noted above was identified in the Phase II trials for psoriasis (PSOR-001, -003, -004, and -005). These observations support that the differences noted between the APR treatment arm and placebo are due to drug exposure.

2.3 Effect of intrinsic factors on the PK of apremilast

2.3.1 Pediatric subjects

The applicant has requested for a waiver for conducting trials in pediatric subjects less than 6 years of age and the reason for the waiver request is that studies in children less than 6 years of age are impractical due to limited number of subjects with moderate to severe psoriasis in this age group. The applicant has also requested for a deferral of pediatric assessment in subjects 6 to 17 years because they believe that this product is ready for approval in adults before pediatric trials are complete.

(b) (4)



(b) (4)

2.3.2 What is the effect of disease on the pharmacokinetics of apremilast?

PK in subjects with psoriasis vs. healthy: The BA (Cmax and AUC) of APR increased by 2 fold in subjects with disease compared to healthy subjects. This information is obtained based on cross trial comparison between Trial CC-10004-PSOR-005-PK which assessed PK in subjects with psoriasis (n = 3) [using Formula 3 (tablet formulation)] and Trial CC-10004-PK-008 (n = 53), which was conducted in healthy subjects. However, since there were only 3 subjects with psoriasis that received the 30 mg BID dosing in Trial CC-10004-PSOR-005-PK, emphasis on the comparative PK results will not be made due to very few subjects with psoriasis. In addition to this, the applicant has submitted a population PK analysis in subjects with psoriasis which demonstrated that the apparent clearance of APR was 20% lower in subjects with psoriasis compared to healthy volunteers. The population predicted clearance in subjects with psoriasis (7.4 L/h) was similar in magnitude to that identified for patients with psoriatic arthritis (7.3 L/h) during the review of NDA 205437s (see Clinical Pharmacology review by Dr. Sheetal Agarwal's dated November 20, 2013).

2.4 Effect of extrinsic factors on the PK of apremilast

2.4.1 What is the drug interaction potential of metabolite M12?

M-12 is the major inactive metabolite. Based on the PK results from Trial CC-10004-CP-019, the AUC of M12 is 163% of the parent drug in healthy subjects. The potential of drug interaction with M12 was not addressed by the applicant and hence an IR was sent with the Day 74 letter (see communication in DARRTS dated December 05, 2013). Since M12 is a secondary glucuronide metabolite, the applicant was also asked to provide information on in-vitro evaluation of the (b) (4) responsible for the formation of metabolite M-12, in the Day 74 letter.

In response, the applicant indicated that M12 is a secondary metabolite and is an O-glucuronide conjugate of the inactive primary metabolite M3 (O-desmethyl apremilast) and not a direct metabolite of the parent. The (b) (4) involved in the metabolism of M3 to M12 have not been evaluated and as per the applicant performing such a study does not seem warranted at this time as it is unlikely that altering (b) (4) activity would affect the safety or efficacy of APR.

The applicant claims that both M12 and M3 metabolites have minimal pharmacologic activity with respect to PDE4 and TNF-α inhibition and hence altering the exposure to either metabolite will not alter the pharmacodynamic effects of APR in humans. Further, the safety profile and exposure of both metabolites M3 and M12 have been assessed as part of the 6-month mouse and the 12-month monkey APR toxicology studies (Table 2). Exposure to both M3 and M12 were substantially higher in the monkey at the NOAEL

than in the clinic, suggesting the potential toxicity of these metabolites was adequately evaluated even if exposures are elevated in the clinic due to alterations in (b) (4) activity.

Table 2: Comparison of Apremilast Metabolites M3 and M12 in Mouse, Monkey and Human

	Metabolite M3 (Male/Female)		Metabolite M12 (Male/Female)	
	AUC	**Ratio to human**	**AUC**	**Ratio to human**
Human[a]	Trace	NA	3930[d]	NA
6-month Mouse[b]	5.29/15.2	NC	1459/1856	0.37/0.47
12-month Monkey[c]	2768/1065	NC	90035/63662	23/16

AUC = area under the plasma concentration-time curve; NA = not applicable; NC = not calculated.
[a] Data for human exposures for M3 are from a single 20-mg dose in the human AME study (CC-10004-PK-002), and for M12 are from a 30 mg twice daily dose on Day 5 in clinical study CC-10004-PK-008.
[b] Data for mouse are from the 6-month mouse study (Report CC-10004-TOX-004) and are presented as male/female exposures.
[c] Data for monkey are from the 12-month monkey study (Report CC-10004-TOX-005) and are presented as male/female exposures.
[d] All data are presented as AUC_{24h} (ng·h/mL).

The applicant has provided with a literature reference which shows that previous drug interactions with (b) (4) enzymes have generally resulted in < 2-fold changes in exposures (Williams et al., 2004) and this usually is not considered a major change.

References: (b) (4)

As per *Guidance for Industry: Safety Testing of Drug Metabolites (February 2008)*, the Phase II conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation. However, if the conjugate forms a toxic compound such as acyl glycuronide, additional safety assessment may be needed. According to the applicant, metabolite M12 is an O-glucuronide and not an acyl glucuronide.

Based on this the applicant has concluded that the alterations in (b) (4) activity are unlikely to result in a clinically meaningful changes in safety or efficacy of APR, identification of the (b) (4) involved in the metabolism of M3 to M12 are not planned at this time.

Reviewer comments: *The solubility of M-12 is not known, but theoretically glucuronide conjugation reactions usually render the compound more water soluble. Keeping this assumption, this reviewer is of the opinion that identification of* (b) (4) *involved in the metabolism of M3 to M12 does not appear to be needed.*

Concerning the potential for metabolite M12 to affect CYP enzymes, the applicant has not conducted any specific evaluations and has provided results from in-vitro and in-vivo studies to suggest metabolite M12 does not induce CYP enzymes nor inhibit CYP3A.

As per the applicant, the Cmax of metabolite M12 were approximately 1 μM in healthy volunteers following 5 days of dosing (30 mg BID) (CC-10004-PK-008). Regarding the potential for metabolite M12 to induce CYP enzymes, an in-vitro study was performed with apremilast (up to 100 μM) in human hepatocytes and the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 were evaluated (CC-10004-DMPK-012).

Based on data from an in-vitro metabolism study using human hepatocytes (CC-10004-DMPK- 023), the formation of metabolite M12 in human hepatocytes was confirmed, with approximately 9% of APR being converted to metabolite M12 following 4 hour incubation.

Therefore, hepatocytes were exposed to significant concentrations of metabolite M12 (estimated as much as 9 μM of M12 at highest concentration of APR) during the APR CYP induction study. The results of the CYP induction study showed little or no increase in CYP1A2, CYP2B6, CYP2C9 or CYP2C19 activity at any APR concentration. There was also no effect on CYP3A4 activity at 1 and 10 μM APR. A 3.7-fold induction of CYP3A4 activity (roughly half the extent induced by rifampin) was observed at 100 μM. However, this effect is unlikely to be clinically relevant because 100 μM is approximately 70-fold higher than observed Cmax of APR in humans at 50 mg BID (CC-10004-PK-008). Based on these data, APR and its metabolites do not appear to induce the enzyme activities of CYPs 1A2, 2B6, 2C9, 2C19 and 3A4/5.

Reviewer comments: *Applicant's justification regarding not conducting an assessment of M-12 as an inducer of any of the CYP enzymes appears reasonable.*

As per the applicant, a clinical trial was performed to evaluate the potential for APR to affect the metabolism of oral contraceptives, metabolized primarily by CYP3A (CC-10004-CP-020). Since this trial was performed in-vivo, subjects were exposed to APR and all of the APR metabolites. In this trial, subjects were administered Ortho Tri-Cyclen® (containing norgestimate [NGM] and ethinyl estradiol [EE]) alone or in combination with APR (30 mg BID for 10 days) and plasma levels of NGM, EE and 17-deacetyl norgestimate (17-DNE; an active metabolite of NGM) were measured. APR co-administration did not alter the PK of NGM, 17-DNE, or EE, indicating APR and its metabolites did not induce or inhibit CYP3A activity in-vivo.

Based on this data, the applicant concluded that metabolite M12 is unlikely to inhibit CYP3A activity in-vivo.

Reviewer comments: *Metabolite M-12 is likely to have no inhibition potential for CYP3A. The inhibition potential of M12 on other CYP enzymes was not studied.*

3. Labeling recommendations: The applicant has submitted labeling which is very similar to what was submitted under NDA 205437. Labeling recommendations already addressed by Dr. Sheetal Agarwal's Clinical Pharmacology review will not be revisited in this review (see Dr. Agrawal's review in DARRTS dated November 20, 2013 under NDA 205437). Any additional labeling changes will be addressed in this review.

In this submission, the applicant added Section 12.2. This section was not included during labeling of NDA 205437. The following changes are recommended in the applicant's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

(b) (4)

Reviewer comments: *This reviewer contacted Medical Officer Dr. Snezana Trajkovic and Pharmacometrics reviewer Dr. Jeffry Florian. According to Dr. Trajkovic, a*

(b) (4)

4. Appendix - Pharmacometrics review:

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions.

Were any dose-response relationships identified between the primary efficacy (PASI-75 and/or sPGA) and safety variables?

The dose-response information from PSOR-003 and PSOR-005 and the response rates compared to placebo in PSOR-008 and PSOR-009 support the selection of APR 30 mg BID as an efficacious dose for the treatment of moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. In addition, the previous pharmacometrics review for APR conducted by Dr. Zhang identified a dose-response relationship between placebo, APR 20 mg BID and APR 30 mg BID for events of diarrhea, nausea, and headaches. Also, the safety events from the psoriasis Phase III trials were similar in nature to those observed in the trials supporting the psoriatic arthritis indication. As such, the reviewer similarly concludes that APR 30 mg BID is a safe and efficacious dose for the treatment of patients with moderate to severe psoriasis who are candidates for phototherapy or systemic therapy.

Dose-response efficacy relationship:

In PSOR-003, there was a statistically significant difference in the proportion of people reaching PASI-75 on APR BID compared to placebo: 24.4% (APR 20 BID) vs. 10.3% (in both the APR 20 QD and placebo treatment arms). In study PSOR-005, APR 10 BID vs. APR 20 BID vs. APR 30 BID all achieved increases in PASI-75 response compared with placebo at week 16, though the increase was only significant for APR 20 and 30 BID (28.7%, and 40.9% versus 5.7% (for placebo), respectively; $p < 0.0001$ for both comparison). The APR 10 BID treatment group was not statistically significantly different than placebo (11.2% versus 5.7%, respectively; $p = 0.1846$). Results from PSOR-005, a Phase 2b dose-ranging study, supported the selection of the APR 30 BID dose for evaluation in Phase 3 studies in subjects with moderate to severe plaque psoriasis.

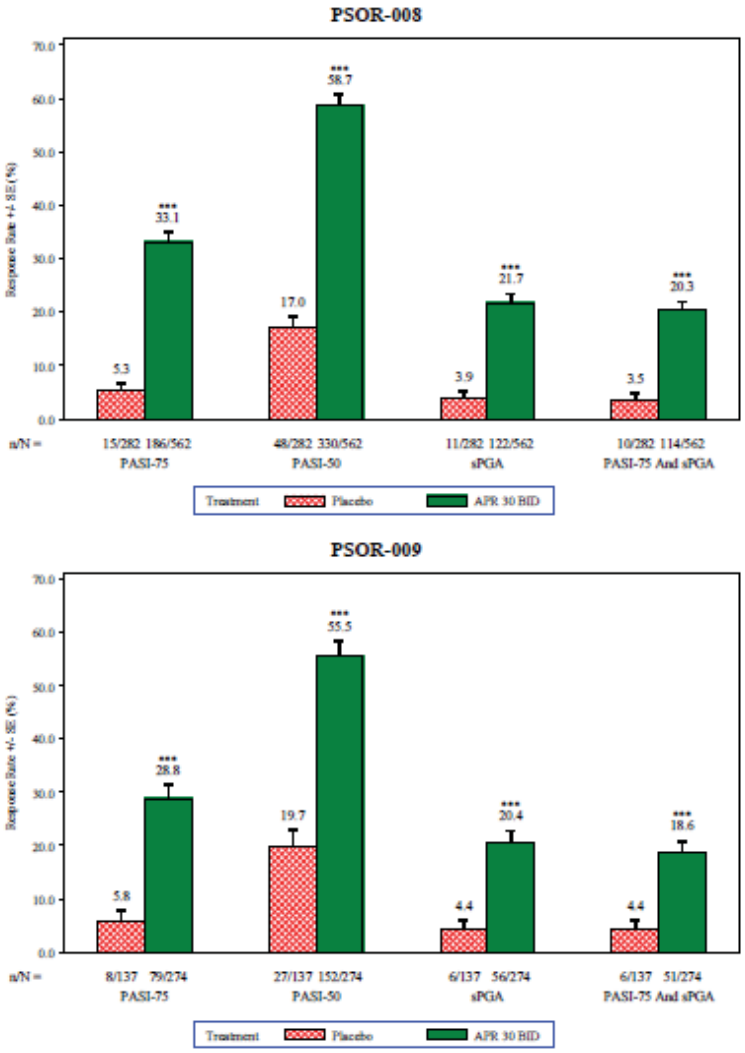
Table 1: Percentage of subjects achieving PASI-75 for different treatment arms (placebo and three APR doses) across three trials

Study	PLB	APR 10 BID	APR 20 BID	APR 30 BID
PSOR-005	5.7%	11.2%	28.7%	40.9%
PSOR-008	5.3%	-	-	33.1%
PSOR-009	5.8%	-	-	28.8%

The results of the two Phase III trials (PSOR-008 and PSOR-009) also support an improvement of in PASI-75 and sPGA for APR 30 BID compared to placebo, though dose-response analysis for these trials could not be conducted as only a single APR dose was studied. Overall response rates from the two Phase III trials for PASI-75, PASI-50,

sPGA, and a composite endpoint of PASI-75/sPGA are shown below in Figure 1. These results demonstrate improvement over placebo for APR 30 mg BID for all four endpoints at week 16.

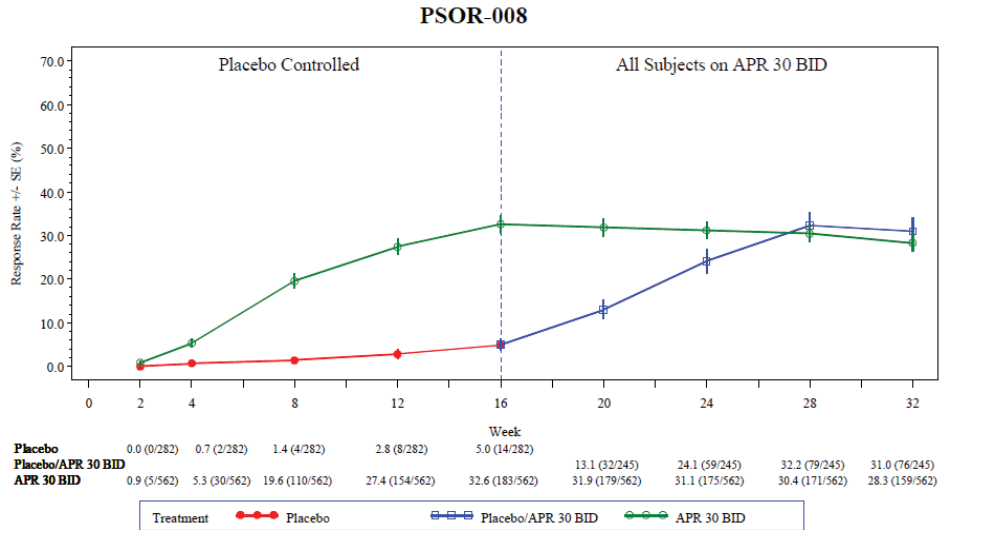
Figure 1: Proportion of Subjects Achieving PASI-75, PASI-50, sPGA Response, or PASI-75/sPGA Composite Response at Week 16 in Studies PSOR-008 and PSOR-009

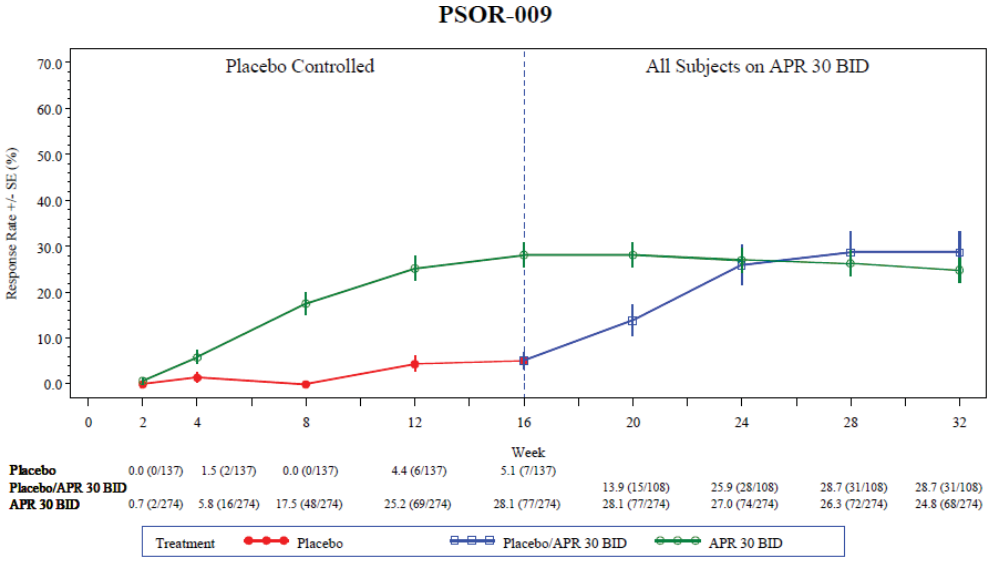


Source: summary-clin-efficacy-psoriasis.pdf, Pg81, Figure 5

Time course plots from the Phase III trials also support an improvement in PASI-75 for APR 30 mg BID compared to placebo. The proportion of subjects reaching the primary endpoint of PASI-75 (in PSOR-008) and PASI-50 (in PSOR-009) by week 16 are shown in Figure 2 and demonstrate a clear separation from placebo with a plateau of the PASI-75 response at approximately 16 weeks.

Figure 2: Proportion of subjects achieving PASI-75 during weeks 0-32 in studies PSOR-008 and PSOR-009





Source: sponsor, summary-clin-efficacy-psoriasis.pdf. pg 100.

Dose-response safety relationship:

APR was generally well tolerated by the subjects in the four phase II studies, PSOR-001, PSOR-003, PSOR-004 and PSOR-005. The most common AE were nausea and gastrointestinal (such as diarrhea), which demonstrated a dose-dependent increase in event rate. It should be noted that that the events listed below are for all grades and that the majority of events in the trials were Grade 1 or 2. A detailed discussion of the dose-response relationships associated with APR treatment can be found in the Pharmacometrics review by Dr. Zhang.

Table 2: Summary of rates of SAE and main AEs in the four phase II studies

	001	003		004		005		
	20QD	20QD	20BID	20BID	30BID	10BID	20BID	30BID
Severe AE/TEAE	5.3%(1/19)	5.7% (5/87)	4.7% (4/85)	25% (1/4)	14.3% (1/7)	3.4% (3/89)	7.4% (9/121)	10.5% (13/124)
Gastrointestinal	31.6% (6/19)	1.1% (1/87)	3.5% (3/85)	0	14.3% (1/7)	11.2% (10/89)	14.9% (13/87)	19.3% (17/88)
Nausea	42.1% (8/19)	3.4% (3/87)	1.2% (1/85)	0	28.6$% (2/7)	6.7% (6/89)	6.9% (6/87)	13.6% (12/88)

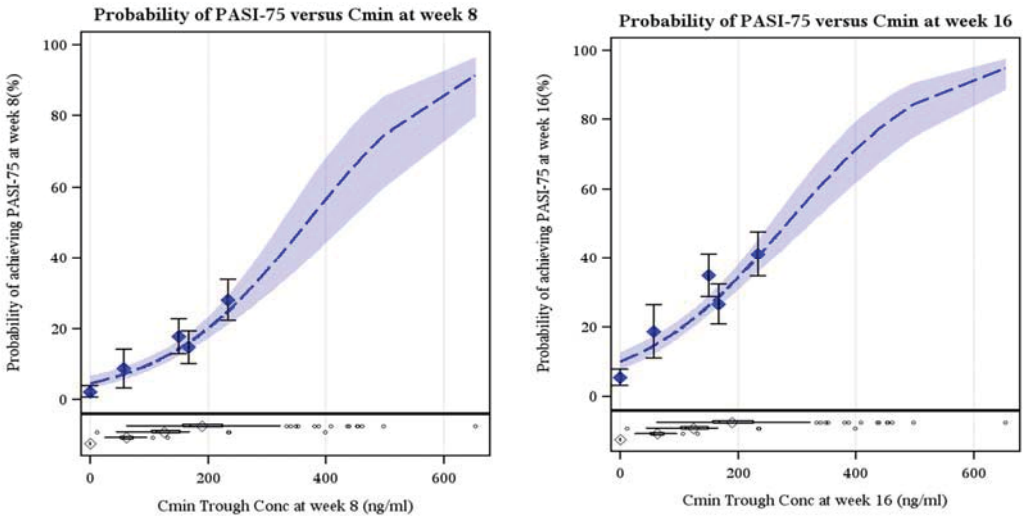
Do the exposure-response efficacy relationships based on PASI-75 at week 8 and 16 support the selection of APR 30 mg BID for the proposed psoriasis indication?

Yes, when data including placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID are combined in a univariate exposure-response analysis, a numerically significant (p<0.0001) increase in achieving PASI-75 at week 8 and week 16 was observed based on model-predicted APR C_{min} and AUC_{ss}. As model-predicted results for C_{min} and AUC_{ss} were correlated (0.98) and the analysis results were similar between the metrics, only the results for C_{min} are explored further. When the data was subset to just those patients administered APR 30 mg BID, a significant exposure-response relationships was still observed for PASI-75 at week 8 (p=0.004), but the relationship was no longer significant at week 16 (p=0.13). This observation is in agreement with the APR dose-response relationship discussed in Question 1.1.1 and supports that APR 30 mg BID offers improvement in PASI-75 over placebo and lower doses of APR (10 and 20 mg BID). In addition, the exposure-response relationship observed for APR 30 mg BID at week 8 suggests that patients with higher exposures may achieve a PASI-75 response faster. However, this did not translate to an increase in PASI-75 at week 16 for APR 30 mg BID as the exposure-response relationship predicts only a 4% increase in PASI-75 between the 1st and 4th exposure quartiles. The reviewer also evaluated other factors which may influence PASI-75 response at week 16, and identified baseline PASI score (>20), male gender, and body weight as associated with a decreased likelihood of achieving PASI-75 at week 16 (only male gender and body weight were significant for PASI-75 at week 8). It should be noted that body weight and male gender were covariates in the applicant's population PK analysis. A multivariate analysis based on the subjects administered APR 30 mg BID identified only baseline PASI score and body weight as significant covariates for predicting week 16 response. Altogether, the analyses support the selection of APR 30 mg BID and do not support that appreciable additional increases in PASI-75 would be achieved with higher APR doses in this population.

A univariate exposure-response analysis was conducted based on data from PSOR-005 and PSOR-008. In all, treatment and pharmacokinetic data was available from 359, 83, 72 and 641 subjects at week 8 and 354, 79, 66 and 630 subjects at week 16 administered

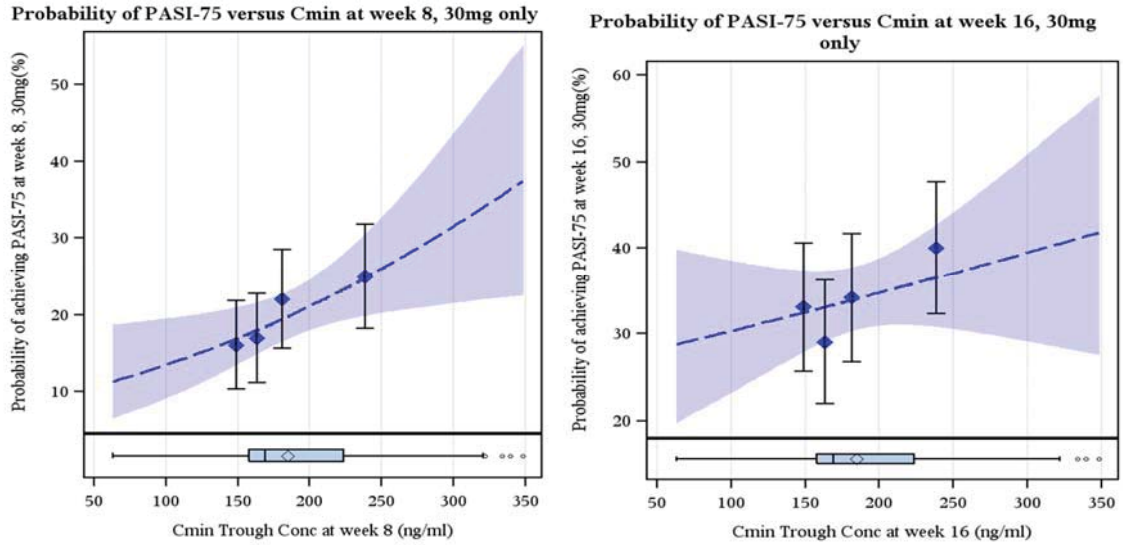
placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID, respectively. Across these range of doses, an exposure-response relationship was identified between PASI-75 response at week 8 and week 16 and APR C_{min} (Figure 3). For a typical subject administered placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID the predicted median APR C_{min} was 0, 57, 113, and 169 ng/mL, respectively. The predicted PASI-75 response for these treatment arms at week 8 was 5%, 7%, 10% and 17%, respectively. Likewise, the predicted PASI-75 response at week 16 for placebo, APR 10 mg BID, APR 20 mg BID, and APR 30 mg BID was 10%, 16%, 20% and 30%, respectively. These observations support that APR 30 mg BID is an appropriate APR dose for achieving both increased PASI-75 response at week 8 and 16 compared to APR doses of 10 and 20 mg BID.

Figure 3: Exposure-response efficacy relationship based on PASI-75 vs. C_{min} concentration at week 8 (left) and week 16 (right)



In order to further explore the potential exposure-response relationship observed above, a subset analysis based only on those subjects from PSOR-008 administered APR 30 mg BID was conducted. As before, this was a univariate analysis between PASI-75 and APR C_{min}. The results of this analysis, which are shown in Figure 4, demonstrate that based on this subset of patients that exposure-response relationships are still evident at week 8 and 16, but that the relationship at week 16 is not as steep as that observed for week 8. Observed median APR concentrations in the 1st and 4th quartile were 149 ng/ml and 240 ng/ml (a 1.6-fold difference) [median concentration of 169 ng/mL]. PASI-75 responses corresponding to 17% and 26% were observed for these two quartiles at week 8. The observed difference in PASI-75 between the two quartiles was 34% and 39% (predicted: 31% and 35%, respectively) was less at the week 16 assessment and supports that the APR exposure observed for 30 mg BID does not appreciably impact PASI-75. This observation suggests a higher dose than 30mg BID might not result in significant increase in the percentage of subjects achieving PASI-75. Furthermore, as discussed above in Question 1.1.1 and in the review by Dr. Zhang, a dose response relationship with respect to GI AEs was observed suggesting that further increase in APR dose may result in additional toxicity.

Figure 4: Exposure-response efficacy relationship based on PASI-75 vs. Cmin concentration at week 8 and 16 for subjects receiving 30 BID.



Is the dose titration scheme appropriate?

Yes, the dose titration scheme seems appropriate as a means of reducing gastrointestinal (GI) adverse events associated with the administration of APR, which is a PDE4 inhibitor. Dose titration was not evaluated as part of the psoriasis clinical program, but it was evaluated in CC-10004-PK-007 as part of the psoriatic arthritis clinical program. The dose titration scheme in CC-10004-PK-007 was 10 mg QD on day 1-3, 20 mg QD on days 4-6, and 40 mg QD on day 7-14. A comparison of adverse events in the treatment arm that included dose titration compared to the arm without titration indicated a decrease in GI associated events with dose titration (Table 3).

For additional details on this analysis, please refer to Dr. Li Zhang's pharmacometrics review of APR for PSA, section 1.1.2.

Table 3: Summary of most frequently reported TEAE by treatment-number of subjects reporting the event (percent of subjects dosed)

Type of AE	40 mg QD * 14 days (N=9) Not titrated	40 mg QD Titrated (N=9) (10 mg days 1-3, 20 mg days 4-6, 40 mg on days 7 – 14)	Placebo (N=10)
Total # of AEs reported	72	34	21
Nausea	7 (78%)	4 (44%)	1(10%)
Diarrhea	2 (22%)	1 (11%)	0 (0%)
# of subjects reporting AEs	7 (78%)	8 (89%)	5 (50%)

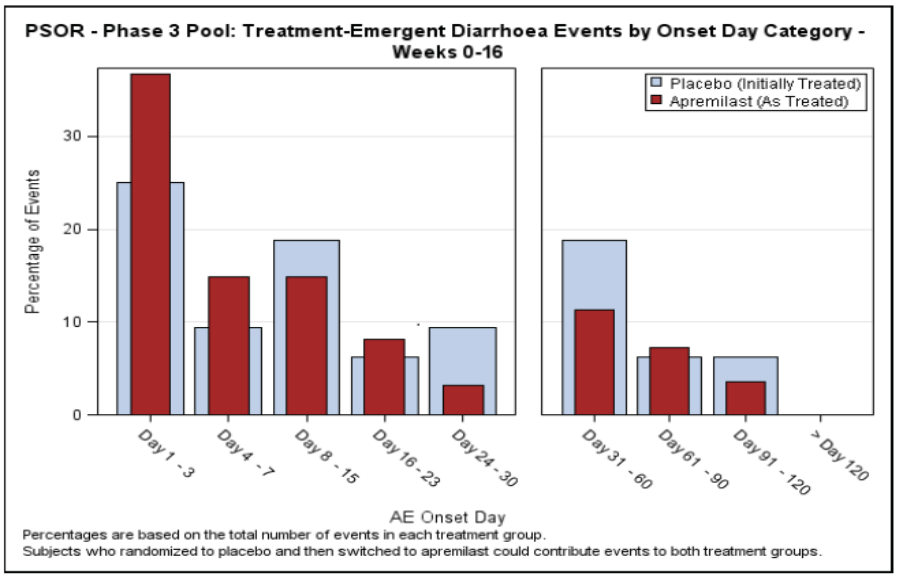
Source: Sponsor's Clinical Study Report CC-10004-PK-007, Pg 67, Table 15 & Table 16

The dose titration scheme utilized for APR in the psoriasis Phase III trials is shown below in Table 4 and is similar to that employed for the Phase III trial in psoriatic arthritis. In addition, a review of the Phase III safety data, which only include APR 30 mg BID and placebo, indicates that the majority of treatment-emergent diarrhea and nausea events occurred during the first 15 days of exposure, similar to that observed in the psoriatic arthritis Phase III trials. There is an elevation in diarrhea (Figure 5) and nausea (Figure 6) events in the APR arm compared to placebo over the first 7 days, which coincides with the initial APR titration schedule. However, from day 8 onwards to day 120, very little difference in the onset time of these side effects.

Table 4: Recommended dose titration scheme for psoriasis subjects with normal, mild, or moderate renal function

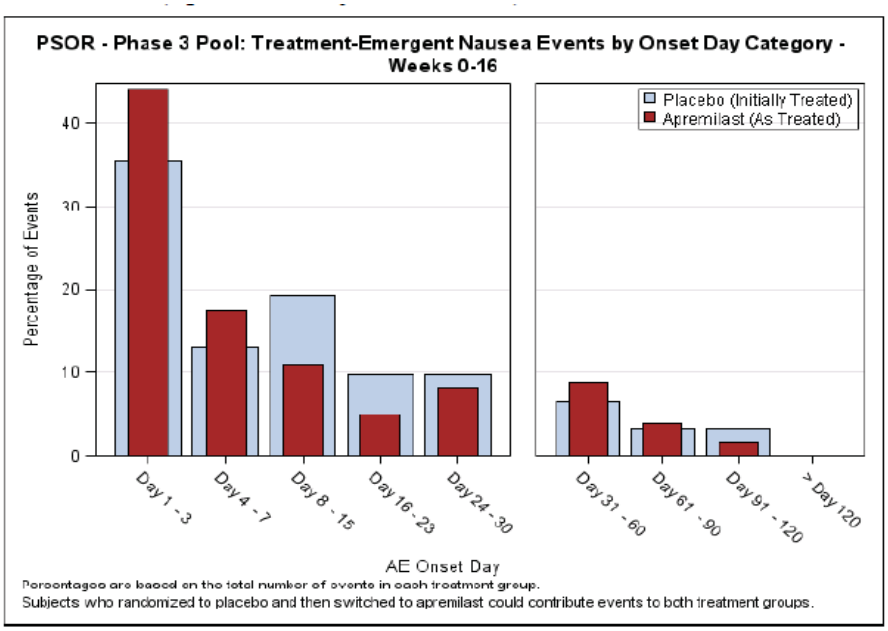
	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and after	
Dose	AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
30 mg BID	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Figure 5: PSOR Phase 3 Data Pool: Treatment-Emergent Diarrhea Events by Onset Day Category during the Treatment Duration Period Weeks 0-16 (Apremilast Subjects as Treated)



Source: summary-clin-safety.pdf, P58, Figure 2

Figure 6: PSOR Phase 3 Data Pool: Treatment-Emergent Nausea Events by Onset Day Category during the Treatment Duration Periods Weeks 0-16 (Apremilast Subjects as Treated)



Source: summary-clin-safety.pdf, P61, Figure 4

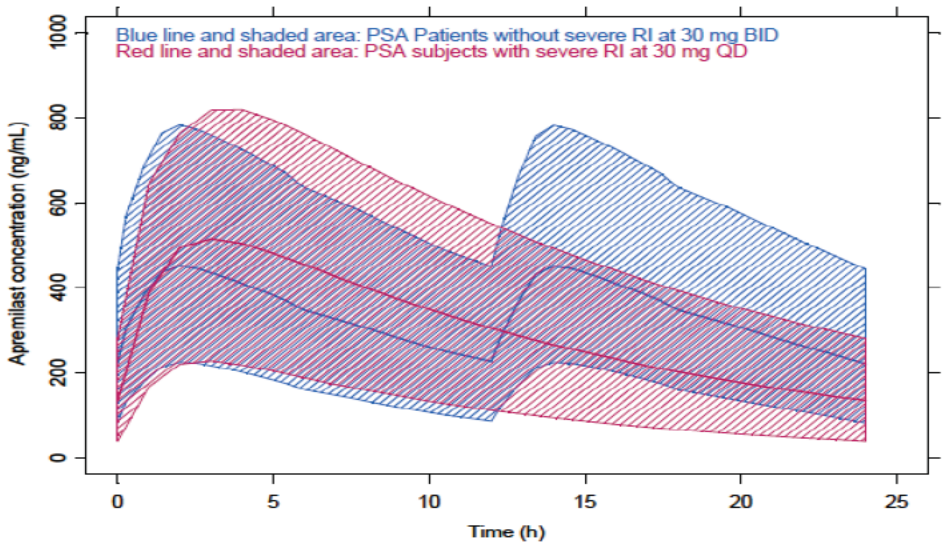
Is the dose regimen for the renal impairment population appropriate?

Yes, although the effect of mild and moderate renal impairment on APR PK was not directly assessed, the APR exposure in RA or PsA subjects with mild or moderate renal impairment was similar to RA or PsA subjects with normal renal function based on pop PK analysis. For patients with severe renal impairment, a combination of observations from a dedicated PK study and modeling and simulation support that a dose reduction to 30 mg QD will result in exposure similar to 30 mg BID. The proposed titration scheme, which is similar to that proposed for patients with psoriatic arthritis, is 10 mg QD on day 1-3, 20 mg QD on day 4-5, and 30 mg on day 6 and after. Full details of the modeling and simulation evaluation can be found in the Pharmacometrics Review by Dr. Zhang (Question 1.1.3). Summary tables for exposures in subjects with sever renal impairment compare to healthy volunteers are shown below in Table 5 and simulations based on the developed population PK model for the dosing two populations and the proposed dosing regimens is shown in Figure 7. Both results support that proposed dose adjustment in patients with severe renal impairment as an approach to achieve APR exposures in this population similar to that in subjects with normal renal function administered APR 30 mg BID.

Table 5: Geometric mean parameters in severally renal impaired patient vs. matched healthy subjects

Group	Geometric Mean (Geometric %CV)						
	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Severe renally impaired (n=8)	5333.7 (52.1)	5425.0 (53.0)	366.0 (34.5)	3 (1 – 6)	11.836 (17.6)	5.530 (52.9)	94.59 (49.3)
Matched healthy (n=7)	2848.7 (17.9)	2878.7 (17.8)	255.2 (39.7)	3 (2 – 4)	9.351 (18.1)	10.423 (17.9)	140.45 (21.8)

Figure 7: Simulated apremilast plasma concentration in severe renally impaired patients dosed APR 30QD vs. matched healthy subjects does APR 30BID.



Souorce: sponsor, summary-clin-pharm.pdf, pg 120

Is the PASI-75 and sPGA response observed at Week 16 predictive of the response at Week 32?

Yes, achieving a week 16 PASI-75 or sPGA of 0 or 1 (classified as a responder) was associated with an increased likelihood of also being a responder at the week 32 assessment.

Subjects in studies PSOR-008 and -009 were categorized into <=0, 0 to = <24, 25 to = <50, 51 to =<74 and >=75 for PASI (Table 6) and absolute change in sPGA score from baseline (Table 7) based on the week 16 and week 32 response. The number of subjects in each score stratum was counted and dropouts between week 16 and 32 were imputed as failures for the purposes of calculating responder rates at week 32.

Based on PASI score at week 16, it would appear that only subjects with at least a PASI score of 51 (categories of PASI 51 to <=74 and >=75) at week 16 had a significant likelihood of being a PASI-75 responders at week 32. For subjects having a PASI score between 51 to 74, there was a 20.5% (n=40/195) chance such subjects would achieve PASI-75 by week 32. Likewise, for subjects with a PASI score over 75 at week 16, there

is over 65.2% (n=174/267) that they will remain as PASI-75 responders. Consequently, of the subjects who did not achieve at least a PASI-50 by week 16, only 7.6% (n=20/262) were responders at week 32. Altogether, it would appear that PASI score at week 16 is a reasonable predictor of response at week 32. Specifically, achieving a PASI-75 was predictive of a maintained response at week 32 while not achieving at least a PASI-50 response by week 16 was associated with a low likelihood of achieving PASI-75 by week 32.

Similar trends were observed using the secondary endpoint of sPGA. In this analysis, patients were groups based on their sPGA change from baseline. For subjects with absolute change in sPGA score from baseline of 1 to -1 at week 16, 87% (443/511) remained as non-responders by week 32. Hence, for subjects who did not achieve a change in sPGA score of more than one point by week 16, the chance of them becoming responders at week 32 is low. For subjects who achieved a change in their sPGA score of more than -2, 69% (155/225) continued to be responders at week 32, with those achieving larger changes in baseline more likely to maintain a response at week 32. In subjects that achieved a -2 change in their sPGA score at week 16, 63% maintained response at week 32. In comparison, 89% of subjects that achieved a 3 point or larger change in their sPGA score at week 16 maintained response at week 32 Hence, it would also appear that the subject's sPGA score change at week 16 is a strong predictor of response rate at week 32 if the subject's sPGA changed by more than -2 points from the baseline value. Similarly, changes of less than 2 points in sPGA at week 16 were associated with a low likelihood of being classified as a responder (sPGA of 0 or 1) at week 32.

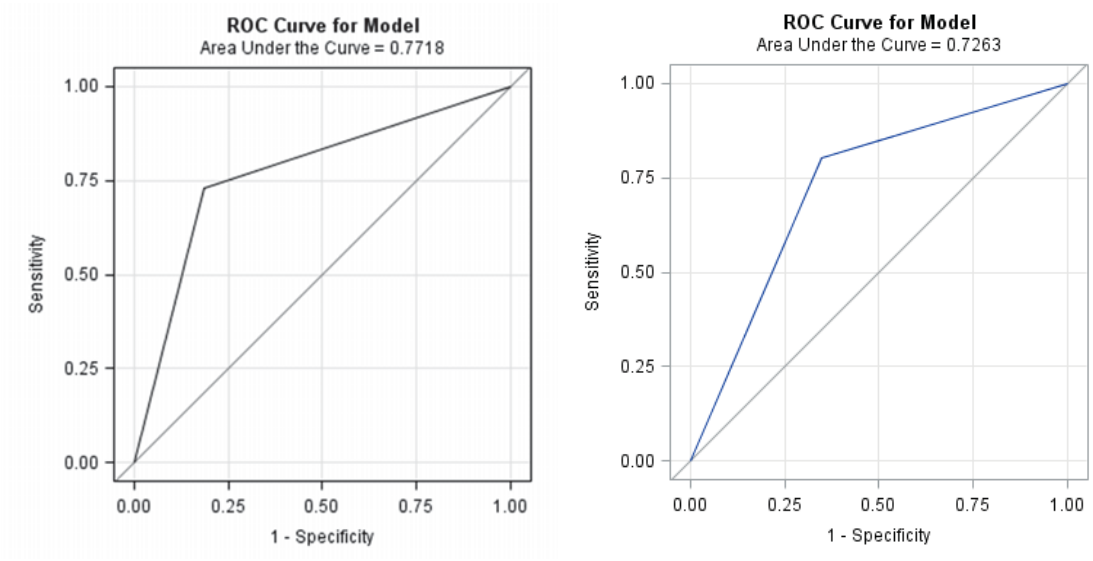
Table 6: PASI score of subjects from studies PSOR 008 and 009 at week 16 and at week 32.

PASI range	Week 16			Week 32	
	N	Dropout	Remain	Responder	Non-Responder
=<0	44	18	26	9.1%	90.9%
0 to =< 24	89	32	57	3.4%	96.6%
25 to =< 50	143	26	117	9.1%	90.9%
51to =< 74	195	24	171	20.5%	79.5%
>=75	267	17	250	65.2%	34.8%

Table 7: Change in sPGA score of subjects from studies PSOR 008 and 009 at week 16 and at week 32.

sPGA change	Week 16			Week 32	
	N	Dropout	Remain	Responder	Non-Responder
1	16	5	11	6.3%	93.7%
0	237	69	168	4.6%	95.4%
-1	258	38	220	21.7%	78.3%
-2	175	10	165	62.9%	37.1%
-3	44	2	42	88.6%	11.4%
-4	6	0	6	100%	0

Figure 8: ROC curves for the predictive capability of PASI-75 response at Week 16 (left) and PASI-50 response at Week 16 (right) for predicting the probability of reaching PASI-75 at Week 32 (Study PSOR-008).



The above conclusions are supported by a receiver operating characteristic (ROC) curve analysis conducted by the reviewer for PASI-75. The ROC curve for the predictive capability of PASI-75 response at week 16 was analyzed for its probability of predicting subjects' PASI-75 response at week 32 (Figure 8). The AUC under the ROC curve was 0.77 which is within the range of PASI-75 response rate at week 16 being a fair predictor of subject response at week 32. This means that based on the PASI-75 response of the subject at week 16, their PASI-75 response at week 32 could be predicted correctly around 77% of the time. When a more lenient criteria was used for the analysis (PASI-50 at week 16) the ROC curve for week 32 is similar to those seen in Figure 8, right. However, the AUC is a bit smaller in Figure 8, left. This analysis suggests that achieving a PASI-50 score by week 16 was also a reasonable predictor or achieving PASI-75 by week 32 based on the Phase III trial results.

Finally, as both PASI and sPGA have been considered by the reviewer in the above analyses, a concordance analysis between the two measures at week 16 (Table 8) and 32 (Table 9) was conducted. The far right column of both tables corresponds to patients who would be classified as responders based on PASI-75 while the top two rows are those patients who would be classified as responders based on sPGA. The red cells denote patients who would be considered as responders by both measures. It can be seen that a majority of the subjects considered as responders based on sPGA at week 16 and 32 would also have been considered responders based on PASI-75 (95% and 88% respectively). In contrast, achieving a PASI-75 response at week 16 and 32 was less likely to be associated with being classified as a responder by sPGA (68% and 62%, respectively). However, it should be noted that the discrepancies between the endpoints were typically within a single category of each other. In other words, those subjects classified as PASI-75 responders who did not meet the sPGA criteria for response had achieved at least a sPGA of 2. Likewise, those subjects who achieved sPGA responses but not PASI-75 had achieved at least a PASI-50 response.

Table 8: Concordance analysis between PASI and sPGA endpoints response at week 16

	Absolute sPGA at week 16	PASI <=0 At week 16	PASI 1 to 25 At week 16	PASI 26 to 50 At week 16	PASI 51 to 74 At week 16	PASI >=75 At week 16
sPGA responders	0					21
	1				9	142
sPGA non-responder	2		2		114	91
	3	25	61	100	67	11
	4	27	26	16	5	

Table 9: Concordance analysis between PASI and sPGA endpoints response at week 32.

	Absolute sPGA at week 32	PASI <=0 At week 32	PASI 1 to 25 At week 32	PASI 26 to 50 At week 32	PASI 51 to 74 At week 32	PASI >=75 At week 32
sPGA responders	0		1			33
	1				21	131
sPGA non-responder	2		3	22	95	67
	3	18	23	93	71	9
	4	7	12	11	1	

Recommendations

The proposed labeling guidelines for patients with severe renal impairment should be considered. In addition, the futility analysis conducted by the reviewer suggests that patients who do not achieve at least a PASI-50 response by week 16 or sPGA of 2 or lower by week 16 are unlikely to achieve PASI-75 or sPGA of 0 or 1 by week 32 of treatment. If the desired outcome in such patients is to achieve at least a PASI-75 or sPGA of 0 or 1, alternative treatments could be considered in such subjects based on week 16 response.

PERTINENT REGULATORY BACKGROUND

"APR (CC-10004) is a novel, orally available small molecule that specifically inhibits phosphodiesterase type 4 (PDE4), which increases intracellular cyclic adenosine

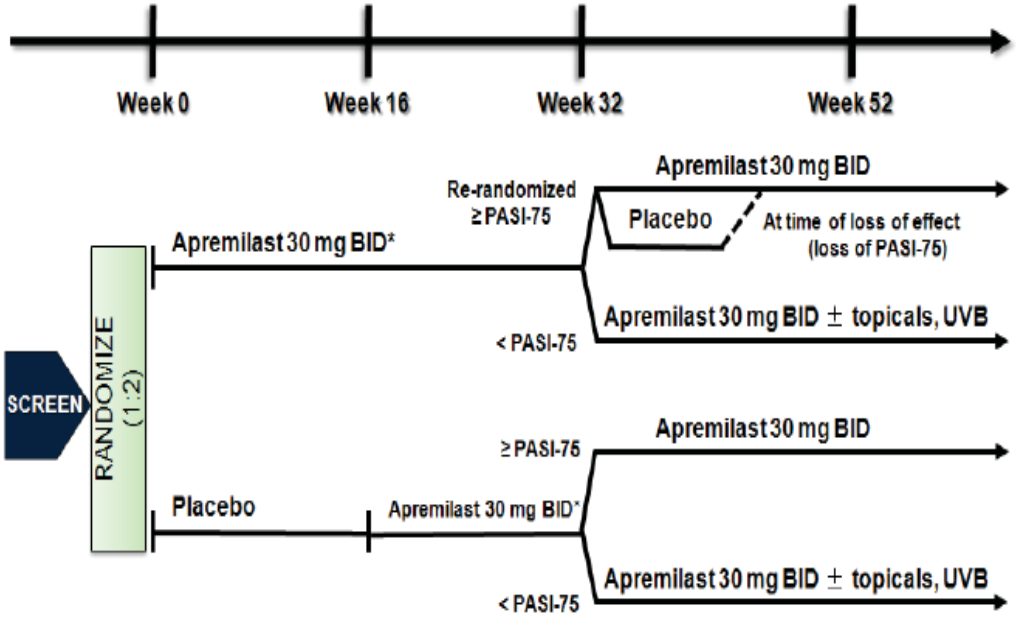
monophosphate (cAMP). This increase in cellular cAMP modulates multiple pro-inflammatory and anti-inflammatory mediators. APRis currently being developed for use in the treatment of immune-mediated inflammatory conditions psoriasis." *Source: clinical-overview.pdf, P6*

A summary of the dose-selection supporting studies is provided in Table 10 below.

Table 10: Summary of Primary and Key Secondary Efficacy Results From Clinical Studies of Apremilast in Plaque Psoriasis

Clinical Trial	Trial	Details	Endpoint	Result
Phase II, pilot, OL	PSOR-001	19 subjects. Severe plaque psoriasis APR20 QD, 29 days.	≥20% decrease in epidermal thickness at D29.	8/15 (95% CI)
Phase II, R, DB, PC, PG, DC.	PSOR-002	259 subjects. Moderate/severe psoriasis. APR 20 BID, APR 20 QD, placebo, 12 weeks.	PASI 75.	APR20 BID vs. Placebo (24.4% vs. 10.3%) APR20 QD vs. placebo (10.3% in each)
Phase II, OL	PSOR-004	30 subjects. Recalcitrant plaque. APR20 BID, 12 weeks. 12 weeks extension for responders or APR30 BID for nonresponders.	≥20% of subjects achieving 1 pt sPGA reduction. PASI-75	4 of APR20 BID had a ≥1 pt reduction in sPGA at week 12 and 24 (durability of APR). 9 had PASI-75, 4 had PASI-90 at week 12.
Phase IIb, R, DB, PC, DR	PSOR-005	352 subjects. Moderate/severe psoriasis. 1:1:1:1 placebo, APR10 BID, APR20 BID, APR30 BID. At 16 weeks placebo rerandomized to APR20 or 30 BID. Other maintained on apremilast until week 24. 28 weeks extension. At month 6 all subjects switched to APR30 BID for upto 4 years.	PASI-75 at week 16.	APR10 BID (11.2%), APR20 BID (28.7%), APR30 BID (40.8%) placebo (5.7%). Response increased in a dose-related manner.
Phase III,	PSOR-008	844 subjects. 16 weeks: R, DB, PC, 2:1 APR30 BID vs. placebo 16 weeks: DB maintenance, placebo to APR30 BID 20 weeks: R, DB, treatment withdrawal. APR30 BID with PASI-75 randomized to APR 30 BID or placebo 208 weeks: extension all on APR30 BID.	Primary: PASI-75 at week 16. Secondary: sPGA of 0 or 1 with ≥ 2 pt reduction from baseline at week 16.	APR30 BID PASI-75 at week 16: 33.1% vs. placebo 5.3% APR30 BID sPGA 21.7% vs. placebo 3.9%. Maintenance is better with continuous treatment. Median time to lose PASI-75 was 17.7 weeks for APR30 BID vs. 5.1 weeks for placebo. At week 52, 60% of APR30 BID has PASI-75 vs. 11.7% placebo.
Phase III,	PSOR-009 ongoing	413 subjects. 16 weeks: R, DB, PC, 2:1 APR30 BID vs. placebo 16 weeks: DB maintenance, placebo to APR30 BID 20 weeks: R, DB, treatment withdrawal. APR30 BID with PASI-50 randomized to APR 30 BID or placebo 208 weeks: extension all on APR30 BID.	Primary: PASI-75 at week 16. Secondary: sPGA of 0 or 1 with ≥ 2 pt reduction from baseline at week 16.	APR30 BID PASI-75at week 16: 28.8% vs. placebo 5.8% APR30 BID sPGA 20.4% vs. placebo 4.4%. Median time to lose PASI-50 was 21.9 weeks for APR30 BID vs. 12.4 weeks for placebo. At week 52, 80.3% of APR30 BID has PASI-75 vs. 24.2% placebo.

Figure 9: PSOR-008 study design. PSOR-009 is identical to PSOR-008 except a responder is defined as a subject achieving PASI-50 in PSOR-009.



BID = twice daily; PASI = Psoriasis Area and Severity Index; UVB = ultraviolet B light.
Note: * Doses of apremilast were titrated during the first 6 days of administration. During the Randomized Treatment Withdrawal Phase, subjects were switched to apremilast at the time of loss of PASI-75 (< PASI-75), but no later than Week 52. A responder was defined as a subject achieving ≥ PASI-75, a partial responder was defined as a subject achieving PASI-50 to PASI-74, and a nonresponder was defined as a subject achieving < PASI-50. Placebo-controlled Phase = Weeks 0 to 16, Maintenance Phase = Weeks 16 to 32, Randomized Treatment Withdrawal Phase = Weeks 32 to 52.

Source: clinical-overview.pdf, P26, Figure 1

3 RESULTS OF APPLICANT'S ANALYSIS

Population PK Analysis

Plasma concentration-time profiles of APR were previously described with a 1-compartment model with K_a and lag time based on data from a Phase 2 study (CC-10004-PSOR-005-E-LTE). The above model was reevaluated and fit to plasma concentrations from the Phase 3 study (CC-10004-PSOR-008), a Phase 2 study (CC-10004-PSOR-005-E-LTE) , and pooled data from six Phase 1 studies ((CC-10004-BA-001 (b) (4) formulation only], CC-10004-BA-002, CC-10004-PK-008, CC-10004-PK-010 [APR only], CC-10004-CP-022, and CC-10004-CP-024). Pharmacokinetic samples from a total of 413 subjects across 8 studies who were given a dose of APR and for which blood samples were collected after APR administration were available for the population PK analysis. Table 11 shows the number of plasma samples for included in pop PK analysis.

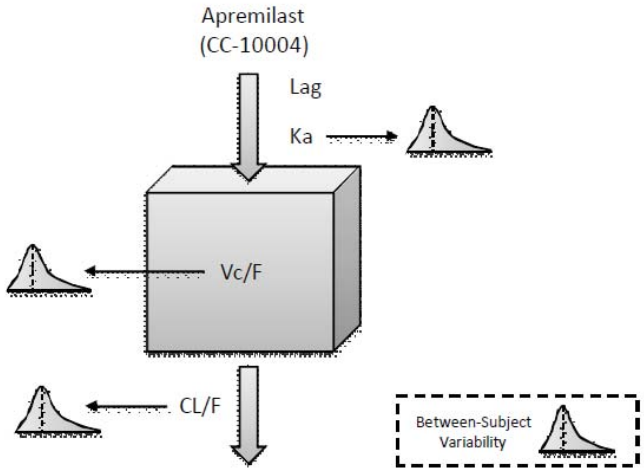
Table 11: Number of plasma samples for pop PK analysis for apremilast

Study	Number of Plasma Samples (%)		
	Excluded	**Included**	**Total**
BA-001	0 (0.000)	298 (100)	298
BA-002	0 (0.000)	763 (100)	763
CP-022	0 (0.000)	1061 (100)	1061
CP-024	0 (0.000)	430 (100)	430
PK-008	0 (0.000)	1080 (100)	1080
PK-010	0 (0.000)	289 (100)	289
PSOR-005-E-LTE	1 (0.161)	619 (99.8)	620
PSOR-008	46 (8.23)*	513 (91.8)	559
Total	47 (0.922)	5053 (99.1)	5100

Source: Sponsor's cc10004psor008pk pk-body.pdf Pg 31, Table 3

Figure 10 shows the schematic of the structural model for APR, a one-compartment model with lag time of absorption. A 2-compartment model was tested but did not perform well.

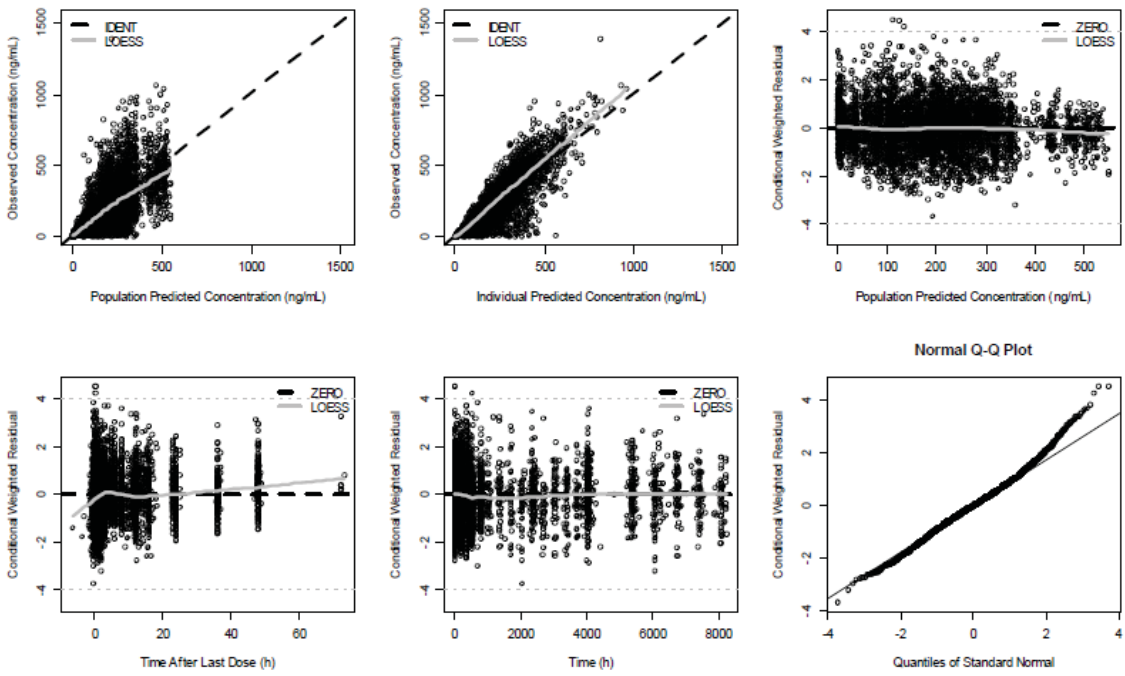
Figure 10: Schematic representation of structural PK model for apremilast.



CL/F = apparent clearance; Ka = first-order rate of absorption; Lag = lag time of absorption; Vc/F = apparent central volume of distribution.

Source: Sponsor's cc10004psor008pk pk-body.pdf Pg 35

Figure 11: Diagnostic plots for the final pop PK model for apremilast



Source: Sponsor's cc10004psor008pk pk-body.pdf Pg 39

From the diagnostic plots (Figure 11) it can be seen that the individual predicted concentrations of APR were very well fitted with the structural PK model and proportional error model. This was demonstrated by the concordance between observed

and individual predicted concentrations, which were tightly grouped along the identity curve (i.e., upper-middle panel).

The covariate effects of body weight on Vc/F and disease status and gender (male) on CL/F improved the population predicted concentrations for the higher APR concentrations. Overall CL/F in subjects with moderate to severe plaque psoriasis disease was ~20% slower than in healthy subjects. CL/F was ~31% slower in female subjects than male subjects. Women or subjects with moderate to severe plaque psoriasis appeared to have higher steady-state APR exposure (AUC_{ss}, $C_{min,ss}$, and $C_{max,ss}$) than men or subjects without moderate to severe plaque psoriasis. However, the exposure difference attributed to sex and disease status was generally ~ 31% and ~20%, respectively, which were within the BSV for CL/F.

Table 12: Pop PK parameters of apremilast derived from the final PK model

Population PK Parameters	**Geometric Mean (%RSE)**	**Bootstrap Results**		**Bias (%)**
		Median Value	**95% CIs**	
CL/F (L/h)	9.26 (3.6)	9.242	8.61 – 9.86	-0.2
Disease status				
If psoriasis =	0.800 (3.8)	0.801	0.746 – 0.863	0.14
If other/missing =	1.09 (10.1)	1.084	0.888 – 1.32	-0.51
Sex				
If Male =	1.31 (3.0)	1.314	1.23 – 1.39	0.32
Vc/F (L)	118 (2.3)	117.3	112 – 123	-0.58
Weight on Vc/F	0.57 (14.7)	0.567	0.407 – 0.74	-0.45
Lag (h)	0.282 (13.4)	0.284	0.22 – 0.35	0.75
Ka (1/h)	1.84 (12.7)	1.852	1.51 – 2.45	0.67

Source: Sponsor's cc10004psor008pk pk-body.pdf Pg 40

Reviewer's comment: *A population PK report for APR was previously reviewed in NDA 205437 by Dr. Zhang. The applicant conducted an updated analysis based on subjects with psoriasis who had PK data available. Overall, the conclusions of the two analyses are similar. Both identified a 1-compartment model with oral absorption and lag time as the structure that best described APR PK data. The identified apparent clearance and apparent volume of distribution were similar between the previous (11.5 L/h and 129 L) and the current (9.3 L/h and 118 L) analysis as were lag time (0.27 h vs. 0.28 h.) and k_a (1.61 and 1.81 h^{-1}). Similar covariates were also identified between the analyses with disease status and gender on clearance and body weight on volume of distribution. The only notable differences were the inclusion of body weight on apparent clearance and disease status on apparent volume of distribution in the previous analysis. The reviewer reevaluated the applicant's model and reached similar conclusions regarding the selected structure and covariates.*

Exposure-Response Analysis:
The population exposure-response analysis of APR was based on the primary endpoint and key secondary endpoint data collected in the CC-10004-PSOR-008 and CC-10004-PSOR-005-E-LTE studies. Placebo subjects were included in the exposure-efficacy population. Data collected from Studies CC-10004-PSOR-008 (i.e., up to Week 16) and CC-10004-PSOR-005-E-LTE (i.e., up to Week 24) were used in the exposure-response analysis. Table 13 shows the PASI-75 observations for different treatment through week 16 or 24.

Table 13: PASI-75 observations for pop PK/PD analysis through week 16 or 24.

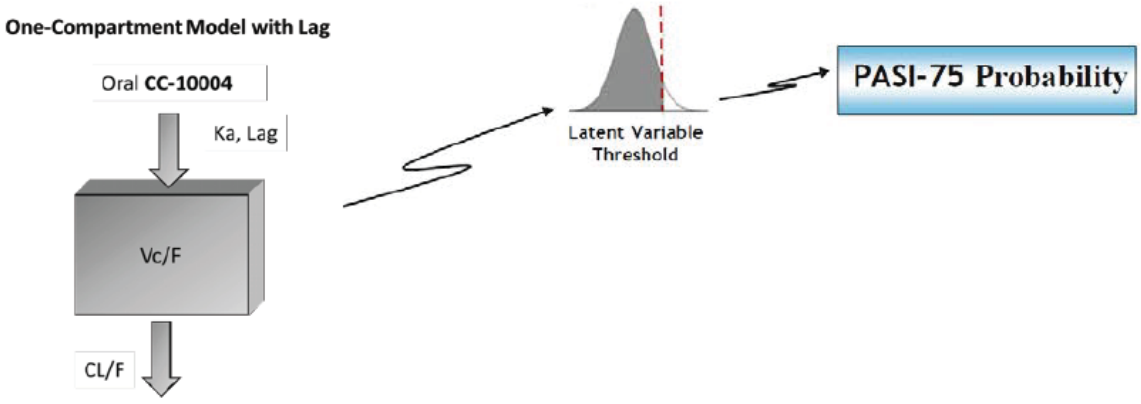
Treatment	Number of PASI-75 Observations		
	Non-responder	Responder	Overall
10 mg BID	572	67	639
20 mg BID	452	108	560
30 mg BID	2756	659	3415
Placebo	1835	45	1880
Placebo/20 mg BID	44	23	67
Placebo/30 mg BID	45	24	69
Total	5704	926	6630

Source: sponsor, cc10004psor008pk. Pk-body.pdf. pg. 47.

The exposure-response model included a logit function to characterize the probability of PASI-75, PASI-50 and sPGA responses driven by the extent exposure and/or time of exposure of APR. An indirect response maximum pharmacological effect (Emax) model driven by exposure of APR was used to characterize PASI-75, PASI-50 and sPGA values. Similar attempts were made to link a logit function to characterize the probability of AE events driven by the extent exposure and/or time of exposure of APR. The model was further customized using predicted AUC_{ss}, $C_{max,ss}$ and Cmin,ss of APR as well as sigmoid factors.

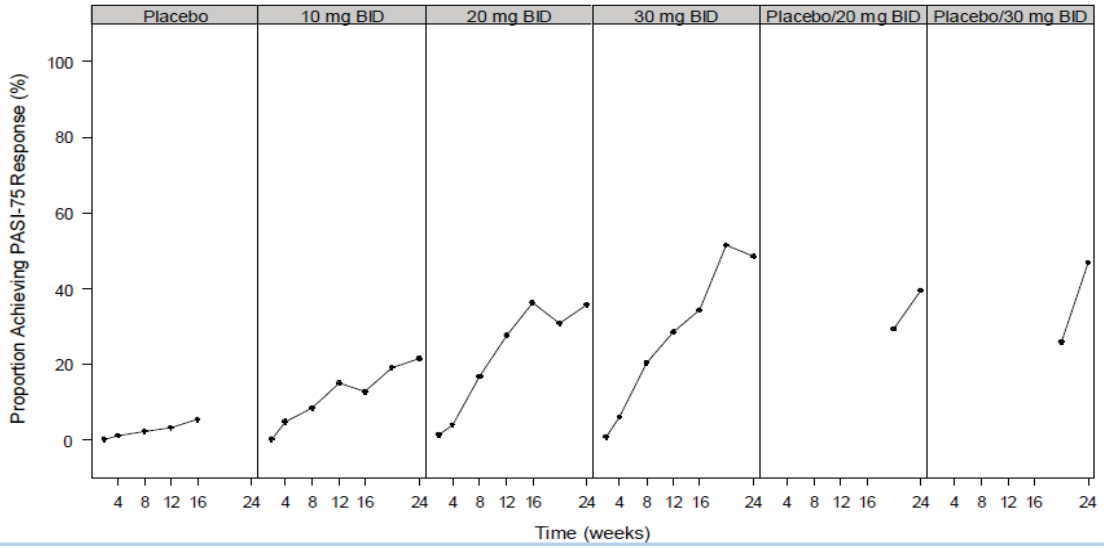
Differentiation and selection of exposure-response model were performed, using visual and statistical estimators. The performance of the models was evaluated with VPC. A schematic representation of the PK/PD model for APR is shown in Figure 12.

Figure 12: Schematic representation of the indirect response PK/PD model for apremilast.



The proportion of subjects achieving the primary endpoint of PASI-75 vs. time for studies CC-10004-PSOR-005 E-LTE and PSOR-008 are shown in Figure 13.

Figure 13: PASI-75 response achievers through to week 24 on different apremilast dosages.



Source: sponsor, cc10004psor008pk. Pk-body.pdf. pg. 51.

Mechanistic population dose-response and exposure-response models of APR/PASI-75 were developed using a sequential approach in NONMEM. The models considered included both linear and saturating Emax-type models, and time-fixed as well as time-varying effects. The model that best characterized the relationship between APR total daily amount (dose-response model) and PASI-75 response, and APR AUC at steady state and PASI-75 response (exposure-response model) included a placebo model with an exponential delay component, and an Emax-type effect model. This model can be seen in Figure 14. The PD parameters derived are provided in Table 14.

Figure 14: Emax-type effect model describing the PK/PD relationship for apremilast-PASI-75.

$$f_{placebo}(t_{ij},\theta) = \text{Intercept} + \text{PlaceboEffect}(1 - \exp(-k_{\text{placebo}} \cdot t_{ij}))$$

$$f_{DrugEffect}(x_i, t_{ij}, \theta) = \left(\frac{E_{\max,i} x_i}{E_{50,i} + x_i} \right)$$

Source: sponsor, cc10004psor008pk. Pk-body.pdf. pg. 51.

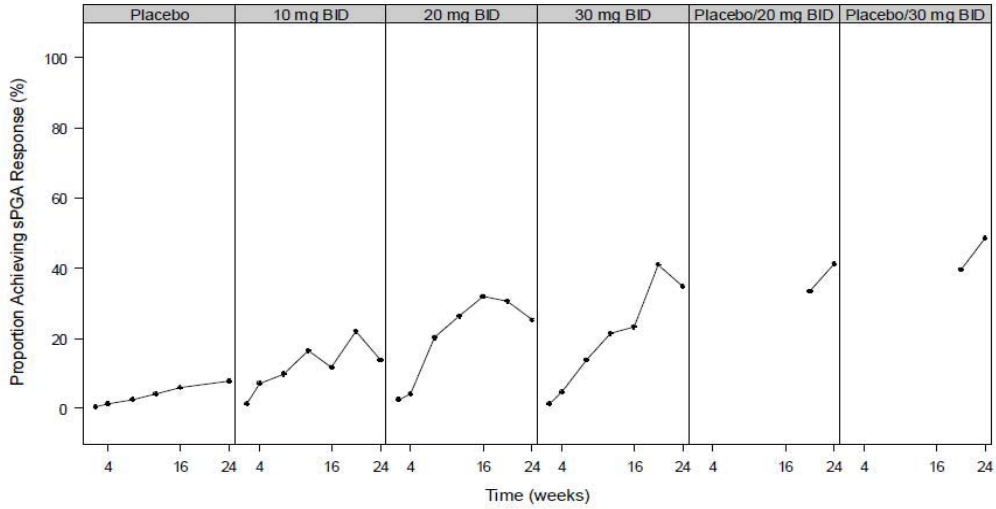
Table 14: Pop PD parameters of apremilast derived from the PK/PD model for PASI-75.

Population PD Parameter	Typical Value (RSE%)	Between Subject Variability (logit) (RSE%)
Intercept	-9.09 (9.0)	0 Fix (NA)
Placebo Effect (logit)	6.26 (11.3)	0 Fix (NA)
$K_{placebo}$ ($week^{-1}$)	0.248 (14.1)	0 Fix (NA)
E_{max}	3.60 (15.5)	0 Fix (NA)
E_{50} (ng.h/mL)	1750 (47.0)	0 Fix (NA)

Source: sponsor, cc10004psor008pk. Pk-body.pdf. pg. 52.

The change from baseline for the secondary endpoint, sPGA, is shown in Figure 15.

Figure 15: Change from baseline in sPGA vs. time for studies PSOR-005 and PSOR-008.



Source: Sponsor's report, cc10004psor008pk. Pk-body.pdf. pg. 55.

The model that best characterized the relationship between APR total daily amount (dose-response model) and the sPGA response is shown in Figure 16. The PD parameters derived are provided in Table 15.

Figure 16: Emax-type effect model describing the PK/PD relationship for apremilast, sPGA.

$$f_{placebo}(t_{ij},\theta) = \text{Intercept} + \text{PlaceboEffect}(1 - \exp(-k_{\text{placebo}} \cdot t_{ij}))$$

$$f_{DrugEffect}(x_i, t_{ij}, \theta) = \left(\frac{E_{\max,i} x_i}{E_{50,i} + x_i} \right)$$

Source: Sponsor's report, cc10004psor008pk. Pk-body.pdf. pg. 56.

Table 15: Population PD parameters of apremilast derived from the PK/PD model for sPGA.

Population PD Parameter	Typical Value (RSE%)	Between Subject Variability (logit) (RSE%)
Intercept	-7.19 (10.1)	0 Fix (NA)
Placebo Effect (logit)	4.65 (12.2)	0 Fix (NA)
$K_{placebo}$ ($week^{-1}$)	0.211 (19.2)	0 Fix (NA)
E_{max}	2.41 (17.5)	0 Fix (NA)
E_{50} (ng.h/mL)	1290 (56.8)	0 Fix (NA)

Source: Sponsor's report, cc10004psor008pk. Pk-body.pdf. pg. 56.

Conclusions:

- The proportion of subjects who achieved PASI-75, PASI-50 and sPGA responses increased with time over the 16-week treatment phase and was also dose-dependent.

- A minor improvement of PASI-75, PASI-50 and sPGA was observed for the placebo treatment. These placebo effects were included in the PK/PD models.

- The PASI-75, PASI-50, and sPGA responses to APR exposure were described by an Emax model for the drug effect on top of a time dependent placebo effect.

- Exposure-response analyses suggest that the 30 mg BID treatment is likely to provide greater probability of achieving PASI-75, PASI-50 and sPGA responses compared to the 20 mg BID or 10 mg BID treatments.

Reviewer's comments: *The ER analysis performed by the applicant suggests a dose-dependent relationship between 10mg BID to 30mg BID, which is in agreement with the ER analysis performed by the reviewer. The reviewer's ER analysis does not support higher dose than the recommended dose of 30mg BID, because the flatting of the ER efficacy curve between week 16 to week 32 (Figure 4) at 30mg BID. No significant efficacy may be gained at higher dose than 30mg BID, this together with the confirmed higher rate of AE at 40mg BID, further supports the recommended dose of 30mg BID.*

4 REVIEWER'S ANALYSIS FILES

Data Sets

Data sets used are summarized in Table 16.

Table16: Analysis Data Sets

Study Number	Name	Link to EDR
PSOR 008, PSOR 009	Adqssp, Adqsps	Apremilast_NDA206088_SCM\Sponsor Data and Reports\ise

Software

SAS 9.2

Models

N/A

Results

See section 1, Dose-response efficacy relationship.

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER, Futility, Futility_by_PASI_range, XPT_to_SAS	Collection of SAS codes for futility analysis, population subsetting, ER relationship analysis.	Apremilast\SAS\SAS code

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/s/

CHINMAY SHUKLA
05/05/2014

JEFFRY FLORIAN
05/05/2014

DOANH C TRAN
05/05/2014

EDWARD D BASHAW
05/05/2014
Concur with proposed PMRs, section 1.2

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206088	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	23 September 2013		
Division:	Division of Dermatology and Dental Products	**Team Leader:** Tapash Ghosh, Ph.D.	
		Acting Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	Celgene Corp	**Secondary Reviewer:** Team Leader	
Trade Name:	To be determined	**Date Assigned:**	6 November 2013
		GRMP Date: **PDUFA Date:**	6 May 2014 9 September 2014
Generic Name:	Apremilast	**Date of Review:**	2 May 2014
Indication:	Psoriasis	**Type of Submission:** - 505(b) NDA	
Formulation/ strengths	IR Tablet/ 10 mg, 20 mg, and 30 mg		
Route of Administration	Oral		
Biopharmaceutics Review Focus: Dissolution method and acceptance criterion; Relative bioavailability studies supporting formulation changes			

SUBMISSION:

Apremilast is a selective phopshodiesterase (PDE4) inhibitor, which is believed to modulate the levels of anti-inflammatory cytokines implicated in psoriatic disease. NDA 206088 was submitted in accordance with section 505(b)(1) of the FDC act for the use of apremilast in the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

The proposed drug product is a film-coated immediate release (IR) tablet supplied in 10, 20, and 30 mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and (b) (4) Film Coating (b) (4) Pink/Brown/Beige. The recommended dose is 30 mg twice daily with an initial dose titration up to 30 mg.

BIOPHARMACEUTIC INFORMATION:

Reference is made to NDA 205437 Otezla (apremilast) Tablets, approved on 21 March 2014 for the treatment of psoriatic arthritis, for all chemistry, manufacturing, and controls (CMC) information (i.e., dissolution method development). The apremilast tablets approved under NDA 205437 are the same tablets intended for marketing under NDA 206088. In addition, the biopharmaceutics studies supporting formulation changes that are submitted to NDA 206088 are the same as those previously reviewed under NDA 205437. Reference is made to the Quality Biopharmaceutics Review for NDA 205437 dated 11 November 2013 by this Reviewer for additional details.

The following Biopharmaceutics review conclusions from NDA 205437 are applicable to this NDA.

- All tablet formulation changes during development were satisfactorily bridged.
- The following dissolution method and acceptance criterion are acceptable with a commitment for continued development.
  - USP Apparatus II, 0.3% SLS in 25 mM Sodium Phosphate Buffer, pH 6.8, 900 mL, 75 rpm
  - Q = (b) (4) % at 30 minutes

Any future changes to the dissolution method, or CMC information, submitted to NDA 205437 will be incorporated into NDA 206088 by reference.

RECOMMENDATION: From the perspective of Biopharmaceutics, NDA 206088 for apremilast tablets is recommended for **APPROVAL**.

Minerva Hughes, Ph.D.	**Tapash Ghosh, Ph.D.**
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

MINERVA HUGHES
05/02/2014

TAPASH K GHOSH
05/02/2014