CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205437	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	21 March 2013 (submitted) 28 June 2013 (IR response)		
Division:	Division of Pulmonary and Allergy and Rheumatology Products	**Team Leader:** Angelica Dorantes, Ph.D.	
		Acting Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	Celgene	**Secondary Reviewer:** Team Leader	
Trade Name:	Otezla (proposed)	**Date Assigned:**	10 April 2013
		GRMP Date: **PDUFA Date:**	21 Nov 2013 21 March 2014
Generic Name:	Apremilast	**Date of Review:**	21 Nov 2013
Indication:	Psoriatic Arthritis	**Type of Submission:** - 505(b) NDA - New Molecular Entity - QbD elements	
Formulation/strengths	Tablet/ 10 mg, 20 mg, and 30 mg		
Route of Administration	Oral		

Biopharmaceutics Review Focus:
- Dissolution method and acceptance criterion
- Qualification of the to-be-marketed formulation

SUBMISSION: NDA 205437 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 active psoriatic arthritis (PsA). The proposed drug product is a film-coated 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 without regard to food; however, an initial dose titration up to 30 mg is required.

Data from three pivotal Phase 3, double-blind, placebo-controlled, parallel-group studies in approximately 1500 subjects with active PsA were submitted in support of the proposed indication. Also, the pharmacokinetic (PK) disposition of apremilast was characterized in 16 clinical pharmacology studies.

BIOPHARMACEUTIC INFORMATION: This Biopharmaceutics review evaluated the adequacy of the proposed dissolution method and acceptance criterion for its intended use. The Applicant's proposed dissolution method and acceptance criterion were found suboptimal for product quality assurance and the following post approval commitment to optimize the dissolution method and finalize the acceptance criterion was agreed to in the 4 November 2011 amendment.

Post Approval Commitment: Complete additional dissolution method optimization studies and submit a final dissolution method development and validation report within 6 months of the action letter date. The report should include the details of the methodology, method validation results, bridging study results using current and revised methods for commercial and stability batches, and a

new acceptance criterion. The new acceptance criterion should include batch analysis data from a minimum of 50 commercial batches, 12 months long term and 6 months accelerated stability data from (b) (4) validation batches, and 6 months long term and accelerated stability data from Celgene International validation batches.

RECOMMENDATION: From the perspective of Biopharmaceutics, the NDA 205437 for apremilast tablets is recommended for approval with a Post Marketing Commitment

The following dissolution method and acceptance criterion are acceptable on an interim basis for release and stability testing.

- 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

It is recommended that the above interim dissolution method/acceptance criterion and the Post Marketing Commitment be included in the NDA's action Letter

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
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Office of New Drug Quality Assessment

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/s/

MINERVA HUGHES
11/21/2013

ANGELICA DORANTES
11/21/2013

CLINICAL PHARMACOLOGY REVIEW
NDA 205437 APREMILAST

NDA No.	205437
Submission Date	3/21/2013
PDUFA Goal Date	4/21/2014
Proposed Brand Name	Otezla
Generic Name	Apremilast Tablets 10, 20, 30 mg
Clinical Pharmacology Reviewer	Sheetal Agarwal, Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm. D., Ph.D.
Pharmacometrics Reviewer	Li Zhang, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Celgene
Submission Type; Code	505(b)(1); standard review
Formulation and Strength(s)	10, 20 and 30 mg oral tablets
Proposed Indication	For the treatment of adult patients with active psoriatic arthritis
Dosage Regimen	30 mg BID with an initial titration phase of 7 days to develop GI tolerability (b) (4)

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1. Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 205-437 requesting approval of apremilast, a phosphodiesterase-4 (PDE4) inhibitor, is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Background

Celgene Corp has submitted NDA 205437 seeking marketing approval for apremilast, 10, 20 and 30 mg oral tablets, for the treatment of psoriatic arthritis (PsA) in adult patients. Apremilast is a phosphodiesterase-4 (PDE4) inhibitor. Celgene is currently planning to develop apremilast for other immune-mediated inflammatory conditions as well, such as psoriasis (PSOR), rheumatoid arthritis (RA), Behçet's disease (BD), and ankylosing spondylitis.

Celgene Corp met with the Agency to discuss their NDA submission in March 2010 (EOP2 meeting) as well as in June and December 2012 (written correspondence and pre-NDA meeting respectively). This submission includes three Phase 3 studies to evaluate the efficacy and safety of apremilast in PsA subjects, 2 dose-finding Phase 2 studies (one in PsA and one in PSOR) to support dose selection of apremilast, and sixteen Phase 1 studies that include 2 studies to bridge formulations which will be reviewed by the Biopharmaceutics reviewer and 1 TQT study that has been reviewed prior to NDA submission.

Dose selection

- ***Rationale for Dose and Dosing Frequency Selection***

The proposed dosing regimen of apremilast is 30 mg BID with an initial titration phase of 7 days. Two dosing regimens of apremilast, 20 and 30 mg BID, both employing the proposed titration scheme, were tested in Phase 3 studies in PsA patients. The dosing regimen, including the selection of Phase 3 doses and dosing frequency, was established in the dose-ranging studies for both PsA and PSOR populations. In addition, dose titration as proposed in the final product labeling was employed in all the Phase 2 and Phase 3 studies. Justification for dose titration is provided through measurement of frequency of adverse events when apremilast is titrated vs. not titrated in a dedicated PK study.

- ***Dose Titration***

Study CC-10004-PK-007 evaluated the frequency of adverse events when apremilast 40 mg QD is titrated (10 mg first 3 days, 20 mg next 3 days and finally 40 mg on the 7th day) vs.

when not titrated. The study noted that the total number of adverse events reported for the titrated group was 34 as compared to 72 in the non-titrated group. Based on this observation, all future studies for apremilast were conducted employing an initial 7-day dose titration scheme.

- ***Dose Selection including Dose Frequency***

Phase 3 evaluated 20 and 30 mg BID dosing regimens for apremilast. These dosing regimens were selected on the basis of results from 2 Phase 2 dose-ranging studies. Study CC-10004-PSA-001 tested 20 mg BID and 40 mg QD dosing regimens of apremilast in PsA patients whereas study PSOR-005 tested 10, 20 and 30 mg BID dosing regimens of apremilast in PSOR patients.

Study CC-10004-PSA-001 indicated that as compared to placebo group, apremilast 20 mg BID treatment group achieved statistically better ACR 20 and ACR 50 responses at Week 12 (43.5% versus 11.8%, $p < 0.001$ and 17.4% versus 2.9%, $p = 0.012$, respectively) whereas apremilast 40 mg QD treatment group achieved statistical significance only for ACR 20 (35.8% versus 11.8%, $p = 0.002$) as compared to placebo. Furthermore, from a PK perspective, it was noted that 20 mg BID dosing regimen produced exposure similar to 40 mg QD dosing regimen with a lower Cmax (by ~28%) and higher Cmin (by ~112%).

Further, the study also indicated that AEs such as fatigue, dizziness, and pruritus were more common in subjects on 40 mg QD than on either 20 mg BID or placebo. These events are associated with the PDE4 inhibitor class of drugs. In addition, the 20 mg BID dosing regimen of apremilast was better tolerated than the 40 mg QD regimen in terms of GI disorders such as diarrhea (26.9%; 18/67 on 40 mg QD; 20.3%; 14/69 on 20 mg BID), and nausea (22.4%; 15/67 on 40 mg QD; 17.4%; 12/69 on 20 mg BID).

Study PSOR-005 indicated that there is a noticeable dose-response relationship in PSOR patients between the 3 doses tested, i.e., 10, 20 and 30 mg BID doses and the primary endpoint in that study which was the proportion of subjects achieving Psoriasis Area and Severity Index (PASI-75) response at Week 16. The primary endpoint of the study, the proportion of subjects achieving PASI-75 response at Week 16, was achieved in the apremilast 20 mg BID and 30 mg BID treatment groups (28.7% and 40.9% PASI-75 responses, respectively, versus 5.7% with placebo; $p < 0.001$ for both comparisons), but not in the in the apremilast 10 mg BID treatment group (11.2%). The safety and tolerability profile of apremilast was acceptable and comparable in both the 20 mg BID and 30 mg BID treatment groups, with no clinically significant safety signals observed at either of these doses. Given the genetic and immunologic association between PSOR and PsA, it was considered reasonable to extrapolate that a similar safety and efficacy profile would also apply to the PsA population.

Based on the above 2 Phase 2 dose ranging studies, the 20 and 30 mg BID dosing regimens were further evaluated in Phase 3.

- ***Dose Selection Based on Phase 3 Trials***

The efficacy and safety data collected from ~1500 PsA patients in three Phase 3 clinical trials (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) demonstrated that apremilast 20 mg BID and 30 mg BID treatment groups, both met their primary endpoint ACR 20 response, versus placebo, in all 3 individual studies. The safety and tolerability profiles of apremilast 20 mg BID and 30 mg BID dosing regimens were found to be comparable. The 30 mg dosing regimen was selected for marketing over the 20 mg BID dosing regimen as in 2 of the 3 studies, a dose dependent treatment effect, favoring apremilast 30 mg BID over apremilast 20 mg BID, was observed for the primary endpoint. For further assessment of the Phase 3 safety and efficacy results, refer to the clinical (Dr. Keith Hull) and statistical reviews (Dr. Robert Abugov).

Pharmacokinetics

ADME

- Cmax 2.5 h, t1/2 ~ 5-7 h, average oral bioavailability = 70%
- Linear PK up to 50 mg BID or 80 mg QD, with no accumulation up to 40 mg QD dosing.
- Dividing a daily dose to BID or using dose titration appeared to improve the GI tolerability of apremilast.
- No food effect on absorption.
- Plasma protein binding is 68%
- Vd = 87 L
- About 50% metabolism of apremilast in humans is observed, which seems to be predominantly mediated via CYP enzymes, amongst which CYP3A4 seems to be involved to a large extent, in addition to CYP1A2 and CYP2A6. CYP metabolites are further glucuronidated.
- Primarily eliminated as metabolites formed via both CYP-mediated oxidative metabolism (and subsequent glucuronidation) and non-CYP mediated hydrolysis.
- The mean total urinary and fecal recovery of radioactive [14C]-apremilast and its metabolites was 97.1%, with mean contributions of 57.9% and 39.2% from urine and feces, respectively. Less than 3% of the dose was excreted renally as unchanged apremilast. A glucuronide conjugate of O-demethylated apremilast (M12) was the major circulating metabolite and its urinary excretion represented approximately 34% of the total administered dose. The M12 metabolite inhibited PDE4 enzymatic function with an IC50 value of 5.5 μM, and inhibited production of TNF-α from lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (hPBMC) with an IC40 value of 10 μM in an *in vitro* pharmacology study. These enzymatic and cellular activities for M12 were approximately 69-fold and 909-fold less potent than the parent compound, respectively, in these same experiments, hence it is not expected to be pharmacologically active in humans. No other metabolites of apremilast were present to a significant extent in the human circulation.

DDI Potential

- No DDI with concomitantly administered CYP3A4 substrates was observed (oral contraceptive Ortho Tri-Cyclen® containing EE and NGM)

- At systemic concentrations, apremilast is not expected to inhibit/induce CYPs.
- DDI study with rifampin (CYP inducer) led to decrease in apremilast exposure by 3 fold: Labeling language should include a statement reflecting avoidance of co-administration with CYP inducers
- Apremilast has shown to be a substrate for P-gp *in vitro*, but *in vivo* bioavailability is more than 70% and DDI study with ketoconazole (CYP3A and P-gp inhibitor) did not reveal the potential of a significant interaction (~5% increase in Cmax and ~36% increase in AUC). Therefore, apremilast is not expected to inhibit P-gp at systemic concentrations.
- Apremilast is not a substrate for breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, or OATP1B3, and does not inhibit or is a weak inhibitor of BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, multidrug resistance protein (MRP)1, MRP2, MRP3 and MRP4 (IC50 > 10 μM)
- No DDI with a frequently co-administered drug, methotrexate (MTX) no significant effect of apremilast on MTX or vice versa

PK in PsA Subjects vs. Healthy

- PK is different in PsA subjects:
    - Cmax increased by 57% and AUC by 38%
    - 36% lower clearance observed in PsA patients compared to healthy subjects.

Special Populations

- ***Renal Impairment***

The effect of renal function on the PK of apremilast was evaluated in Study CC-10004-CP-019. The study enrolled severe renal impairment subjects and healthy volunteers. An increase in AUC of ~88% and decrease in clearance of ~47% was observed in severe renal impairment subjects. Based on this data and PK simulations attempting to match plasma apremilast exposures to non renal impaired subjects, the sponsor proposed an alternative dosing regimen for severe renal impairment subjects, i.e., 30 mg QD. In addition to a modified dosing regimen, a modified dose titration scheme as shown below is recommended for this group based on PK simulations conducted by the PM reviewer, Dr. Li Zhang (Appendix 3).

Titration scheme for PsA subjects:

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Titration scheme for severe renal impairment subjects:

For initial dosage titration in this group, it is recommended that TRADE NAME be titrated using only the AM schedule and the PM dose be skipped.

- ***Hepatic Impairment***

The effect of mild, moderate and severe hepatic function on the PK of apremilast was evaluated in Study CC-10004-CP-011. No dose adjustment is needed in these subjects.

- ***Other Demographic Factors***

Plasma concentration-time profiles of apremilast were modeled with a one-compartment model with first-order absorption (Ka) and lag time. The covariates tested were age, weight, height, body mass index (BMI), ideal body weight, lean body mass weight, creatinine clearance, sex, race, smoking status, and PsA disease status. No other covariates were identified as significant factors of plasma apremilast exposure differences. Thus, no dose adjustments are warranted for any other demographic factors. See PM review by Dr. Li Zhang (Appendix 3).

- ***Pharmacogenomics***

No pharmacogenomic studies were included in this application. Apremilast does not appear to be metabolized to a major extent by genetically polymorphic enzymes. At this time, no established, clinically actionable genetic variants in PDE4 or other genes in the drug's mechanistic pathway for psoriatic arthritis are likely to contribute significantly to response variability.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology studies and the clinical studies with PK and/or PD information submitted in the NDA.

In vitro studies conducted with apremilast are listed **Error! Reference source not found.**1, the clinical pharmacology studies are summarized in Table 2 and the clinical efficacy/safety studies in PsA subjects are summarized in Table 3.

Table 1: In Vitro Studies Conducted with Apremilast Included in NDA Submission

Nonclinical Study	Objective	Biomaterial	Apremilast Concentration
Protein Binding			
CC-10004-DMPK-026	In vitro protein binding determination of apremilast in mouse, rat, rabbit, monkey and human plasma	Human plasma, and plasma from mouse, rat, rabbit and monkey	0.25, 0.75 and 2.5 µg/mL
Identification of Metabolic Pathways			
CC-10004-DMPK-023	In vitro metabolism of [^{14}C]-apremilast in hepatocytes from mouse, rat, rabbit, dog, monkey and human	Human hepatocytes and hepatocytes from mouse, rat, rabbit, dog and monkey	5 and 25 µM
1398/261	In vitro metabolism of [^{14}C]-apremilast in liver microsomes from mouse, rat, rabbit, dog, monkey and human	Human liver microsomes and liver microsomes from mouse, rat, rabbit, dog and monkey	1, 10 and 50 µM
CC-10004-DMPK-038	In vitro metabolism of apremilast in adult and juvenile liver microsomes from mouse and human and hepatocytes from human	Human adult and juvenile hepatocytes and liver microsomes, and liver microsomes from adult and juvenile mouse	1 and 10 µM
1398/393	Identification of CYP enzymes responsible for human in vitro metabolism in human liver microsomes	Human liver microsomes and cDNA-expressed human CYP isozymes	200 µM
Cytochrome P450 Induction/Inhibition and Drug Transporters			
1398/227	Evaluation of apremilast as an inhibitor of CYP activities in human liver microsomes	Human liver microsomes	1, 10 and 100 µM
CC-10004-DMPK-039	Evaluation of apremilast as an inhibitor of CYP activities (2A6, 2B6, 2C8) in human liver microsomes	Human liver microsomes	0.1, 0.3, 1, 3, 10, 30 and 100 µM
CC-10004-DMPK-012	In vitro evaluation of apremilast as an inducer of CYP expression in cultured human hepatocytes	Human hepatocytes	1, 10 and 100 µM
CC-10004-DMPK-017	In vitro assessment of apremilast as a substrate or inhibitor of P-gp	LLC-PK1 cells expressing human P-gp	0.01, 0.03, 0.08, 0.2, 0.51, 1, 1.3, 3, 3.2, 8, 10, 20, 35 and 50 µM

CC-10004-DMPK-027	In vitro assessment of apremilast as a inhibitor of OAT1 and OAT3	Human OAT1- and OAT3-injected *Xenopus laevis* oocytes	2 and 10 μM	
CC-10004-DMPK-036	In vitro assessment of apremilast as a inhibitor of BCRP, MRP1, MRP2, MRP3, MRP4 and MRP8	Membrane vesicles containing human BCRP, MRP1, MRP2, MRP3, MRP4 and MRP8	2 and 20 μM	
CC-10004-DMPK-040	In vitro assessment of apremilast as a inhibitor of OCT2, OATP1B1 and OATP1B3	Human OCT2-, OATP1B1- and OATP1B3-expressing HEK293 cells	2 and 20 μM	
CC-10004-DMPK-1347	In vitro assessment of apremilast as a substrate of BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3	Human BCRP-expressing LLC-PK1 cells; human OCT2-, OAT1- and OAT3-expressing S_2 cells; human OATP1B1- and OATP1B3-expressing HEK293 cells	1 and 10 μM	

Table 2: Clinical Pharmacology Studies Conducted with Apremilast Included in NDA Submission (Note that formulation bridging studies CC-10004-BA-001 and CC-10004-BA-002 were reviewed by the Biopharmaceutics reviewer and are not included here).

Report Number No. of Study Sites (Country)	Study Design Population	Duration of Treatment Study Status	Treatment Groups (Total Daily Dose)	No. of Subjects Treated[a]	No. of Subjects Discontinued / Completed Treatment
CC-10004-PK-001 1 site (UK)	Single-center, double-blind, placebo-controlled, ascending single- and multiple-dose Healthy male and surgically sterile/postmenopausal female subjects	6 days Completed	Placebo 1 × 10 mg apremilast QD (10 mg) 2 × 10 mg apremilast QD (20 mg) 4 × 10 mg apremilast QD (40 mg) 4 × 10 mg apremilast BID (80 mg) 1 × 50 mg apremilast BID (100 mg)	10 6 6 6 6 6	0/40
CC-10004-PK-007 1 site (UK)	Single-center, double-blind, randomized, placebo-controlled, ascending multiple dose Healthy male subjects	14 days Completed	Placebo 40 mg apremilast QD (40 mg) 60 mg apremilast QD (60 mg) 80 mg apremilast QD (80 mg) 40 mg apremilast BID (80 mg) 40 mg apremilast QD (40 mg) with dose titration (10 mg QD [Days 1-3], 20 mg QD [Days 4-6], and 40 mg QD [Days 7-14]	10 9 9 9 9 9	2/53
CC-10004-PK-002 1 site (US)	Single-center, open-label, single-dose ADME Healthy male subjects	Single dose Completed	20 mg [^{14}C]- apremilast as a suspension (100 μCi/20 mg)	6	0/6

CC-10004-CP-012 1 site (UK)	Single-center, open-label, 5-period , crossover absolute and regional bioavailability study Healthy male subjects	Single dose Completed	20 mg apremilast tablet administered orally followed by an IV infusion of 100 µg apremilast containing ~210 nCi of [^{14}C]-apremilast, starting at 1 hr 45 min after the oral dose 20 mg apremilast filled (b) (4) capsule to the colon as particulate 20 mg apremilast filled (b) (4) capsule to the colon as solution 20 mg apremilast filled (b) (4) capsule to the distal small bowel as particulate 20 mg apremilast filled (b) (4) capsule to the proximal small bowel as particulate	12	3/9
CC-10004-CP-022 1 site (US)	Single-center, open-label, randomized, 2-period study, effect of food on PK Healthy male and female subjects	2 x single dose Completed	30 mg single dose: fasted 30 mg single dose: fed	46	2/44
CC-10004-PK-005 1 site (UK)	Single-center, open-label, ketoconazole effects on apremilast metabolism Healthy male subjects	2 x single dose Completed	2 × 10 mg apremilast (20 mg)	18	0/18
CC-10004-CP-025 1 site (US)	Single-center, open-label, 3-period study, effect of rifampin on PK Healthy male and female subjects	3 x single doses	30 mg single dose 30 mg single dose followed by 30-min IV infusion of rifampin QD rifampin doses x 15 days (Days 7 to 21), with single 30 mg dose apremilast coadministered with rifampin on Day 20	21	1/20
CC-10004-CP-020 2 sites (US)	Multicenter, open-label, 2-sequence, 2-way crossover study, effect of an oral contraceptive on PK Healthy female subjects	10 days for apremilast 56 days for oral contraceptive Completed	Oral contraceptive QD x 28 days Oral contraceptive QD x 28 days PLUS apremilast 30 mg BID x 10 days	40	5/35
CC-10004-PK-010 2 sites (US)	Multicenter, open-label, 1-sequence, 3-period PK interaction with methotrexate Subjects with RA or PsA on stable doses of MTX	7 days Completed	30 mg apremilast BID x 7 days 2 single doses of MTX (stable dose between 7.5 mg and 20 mg)	15	0/15
CC-10004-CP-011 2 sites (US)	Multicenter, open-label, single-dose, effect of hepatic impairment on PK Subjects with moderate and severe hepatic impairment, matching healthy subjects	Single dose Completed	30 mg single dose for subjects with moderate hepatic impairment and matching healthy subjects 20 mg single dose for subjects with severe hepatic impairment and matching healthy subjects	32	0/32

CC-10004-CP-019 2 sites (US)	Multicenter, open-label, single-dose, effect of renal impairment on PK Subjects with severe renal impairment, matching healthy volunteers	Single dose Completed	30 mg single dose	16	0/16
CC-10004-CP-018 2 sites (US)	Multicenter, 3-period, single dose, double-blind, placebo-controlled, race/ethnicity effect on PK Healthy male subjects	3 x single doses Completed	Placebo Single dose of 20 mg apremilast Single dose of 40 mg apremilast	36	1/35
CC-10004-CP-024 2 sites (US)	Multicenter, open-label, parallel-group study, effect of age and sex on PK Healthy male and female subjects	Single dose Completed	30 mg single dose	36	0/36
CC-10004-PK-008 1 site (US)	Double-blind, randomized, crossover, 4-period, 4-treatment, 4-sequence thorough QTc study Healthy male subjects	5 days per treatment Completed	Placebo BID x 5 days 30 mg BID apremilast x 5 days 50 mg BID apremilast x 5 days Placebo BID x 4 days followed by 400 mg single dose of moxifloxacin	60	8/52

Table 3: Clinical Efficacy/Safety Studies Conducted with Apremilast for Psoriatic Arthritis Included in NDA Submission

PSA-002	83	02 Jun 2010 – 28 Mar 2012	504 randomized 444 completed Week 24 visit 60 withdrew prior to Week 24	Placebo-Controlled Phase: randomized, double-blind, placebo-controlled, parallel-group study Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: randomized, double-blind, parallel-group study Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2 , 30 mg on Day 3, 40 mg on Day 4 and thereafter, in divided doses APR 30 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses thereafter	249 male, 255 female 50.4 years (range, 19 – 83 years) 455 white, 24 Asian, 3 Native Hawaiian/ Pacific Islander, 3 American Indian/ Alaska Native, 2 black, 17 other	ACR 20[d] at Week 16

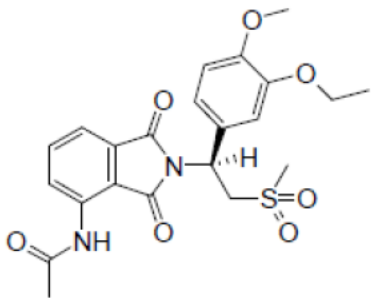
PSA-003	84	27 Sep 2010 – 4 Jul 2012	488 randomized (4 not treated)[c] 428 completed Week 24 visit 56 withdrew prior to Week 24	Placebo-Controlled Phase: randomized, double-blind, placebo-controlled, parallel-group study Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: randomized, double-blind, parallel-group study Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2 , 30 mg on Day 3, 40 mg on Day 4 and thereafter, in divided doses APR 30 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses thereafter	209 male, 275 female 50.9 years (range, 19 – 80 years) 460 white 13 Asian 4 black 6 other 1 missing	ACR 20[d] at Week 16
PSA-004	89	30 Sep 2010– 9 Jul 2012	505 randomized 438 completed Week 24 visit 67 withdrew prior to Week 24	Placebo-Controlled Phase: randomized, double-blind, placebo-controlled, parallel-group study Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: randomized, double-blind, parallel-group study Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2 , 30 mg on Day 3, 40 mg on Day 4 and thereafter, in divided doses APR 30 BID: Titration by 10 mg per day: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses thereafter	236 male, 269 female 49.7 years (range, 18 – 77 years) 482 white 15 Asian 2 black 1 Native Hawaiian/ Pacific Islander 5 other	ACR 20[d] at Week 16

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

Apremilast is the S-enantiomer of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl] acetamide. In vivo, interconversion of apremilast to its R-enantiomer, was not observed. Apremilast is practically insoluble in water. Apremilast is proposed to be marketed in 10, 20, and 30 mg tablet strengths, which include strengths that will be used in the initial dose titration period. The structure, molecular formula, and molecular weight of apremilast are shown in Figure 1. The qualitative and quantitative composition of apremilast tablets is provided in Table 4.

Figure 1: Structure, Molecular Formula, and Molecular Weight of Apremilast



Molecular Formula: $C_{22}H_{24}N_2O_7S$

Molecular Weight: 460.5 g/mol

Chirality: Apremilast contains one chiral center.

Table 4: Qualitative and Quantitative Composition of Apremilast Tablets

			Tablets Strength (mg/tablet)		
Component	**Function**	**Quality Standard**	**10 mg**	**20 mg**	**30 mg**
Apremilast	Active ingredient	In-house	10.0	20.0	30.0
Microcrystalline Cellulose	(b) (4)	NF / Ph. Eur	(b) (4)		
Lactose Monohydrate		NF / Ph. Eur			
Croscarmellose Sodium		NF / Ph. Eur			
Magnesium stearate		NF / Ph. Eur			
(b) (4)		In-house			
		In-house			
		In-house			
		USP/ Ph. Eur.			
		Total	104.00	208.00	312.00
(b) (4)					

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Apremilast (CC-10004) is a novel, oral small molecule inhibitor of phosphodiesterase 4 (PDE4) that works intracellularly to modulate a network of pro- and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and considered the dominant PDE in inflammatory cells. PDE4 inhibition is postulated to elevate intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of tumor necrosis factor (TNF)-α, interleukin (IL)-23, IL-17 and other inflammatory cytokines. Elevation of cAMP is also believed to increase anti-inflammatory cytokines. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis (PsA).

Apremilast is currently being developed for use in the treatment of immune-mediated inflammatory conditions such as PsA, PSOR, rheumatoid arthritis (RA), Behçet's disease (BD), and ankylosing spondylitis. The current NDA is submitted for a potential indication of treatment of active PsA in adult patients.

2.2.3 What are the proposed dosages and routes of administration?

The proposed dose is 30 mg BID via oral administration. A dose titration phase [redacted] (b) (4) is recommended to help develop tolerability to GI side effects related to apremilast such as nausea, vomiting, and diarrhea.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

PsA is a chronic disorder with progressive and additive joint inflammation and destruction over time in a subset of patients. Current pharmacologic treatment for PsA often consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and use of intra-articular corticosteroids. In the U.S. there are no oral DMARDs approved for PsA. The DMARDs commonly used for PsA are methotrexate (MTX) and sulfasalazine (SSZ). Cyclosporine, azathioprine, leflunomide (LEF), and antimalarial drugs are also used. In addition, the biologic tumor necrosis factor (TNF) blockers etanercept, adalimumab, infliximab, and golimumab have demonstrated clinically robust responses in PsA along with improved quality of life.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology studies and the clinical studies used to support dosing or claims?

The clinical pharmacology studies supporting this NDA and their design features are listed under section 2.1. Studies

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Sponsor has used a well-established primary endpoint for inflammatory diseases such as PsA, i.e., ACR 20 (day 85) in Phase 2 dose-ranging studies conducted in PsA patients. ACR 20 at week 16 was employed as the primary endpoint in the 3 pivotal Phase 3 studies (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004).

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Apremilast is the only active moiety found in plasma, the other metabolites including the major metabolite M12 (a glucuronide conjugate) are not considered pharmacologically active. In an *in vitro* pharmacological study, M12 metabolite inhibited PDE4 enzymatic function with an IC50 value of 5.5 μM, and inhibited production of TNF-α from lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (hPBMC) with an IC40 value of 10 μM. These enzymatic and cellular activities for M12 were approximately 69-fold and 909-fold less potent than the parent compound CC-10004 (apremilast), respectively, in these same experiments.

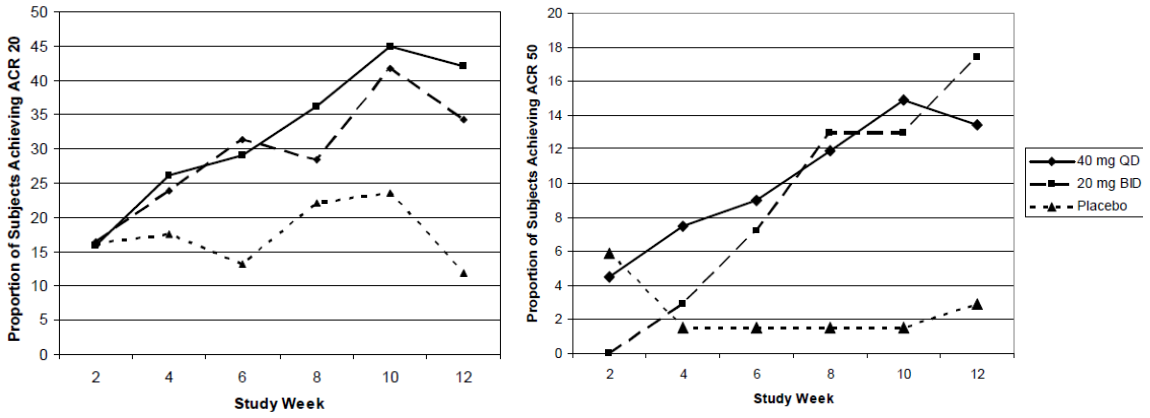
2.4 Exposure-Response

2.4.1 Are the dose regimens selected for the Phase 3 clinical trials appropriate with respect to dosing amounts and dosing frequency?

Yes. The Phase 3 program evaluated 20 and 30 mg BID dosing regimens for apremilast. These dosing regimens were selected on the basis of results from 2 Phase 2 dose-ranging studies. Study CC-10004-PSA-001 tested 20 mg BID and 40 mg QD dosing regimens of apremilast in PsA patients whereas study PSOR-005 tested 10, 20 and 30 mg BID dosing regimens of apremilast in PSOR patients.

Study CC-10004-PSA-001 indicated that as compared to placebo group, apremilast 20 mg BID treatment group achieved statistically better ACR 20 and ACR 50 responses at Week 12 (43.5% versus 11.8%, $p < 0.001$ and 17.4% versus 2.9%, $p = 0.012$, respectively) whereas apremilast 40 mg QD treatment group achieved statistical significance only for ACR 20 (35.8% versus 11.8%, $p = 0.002$) as compared to placebo (Figure 2 below). Further, from a PK perspective, it was noted that 20 mg BID dosing regimen produced exposure similar to 40 mg QD dosing regimen with a lower Cmax (by ~28%) and higher Cmin (by ~112%). In addition, it was noted that that the 20 mg BID dosing regimen was better tolerated than 40 mg QD dosing regimen in terms of frequency of gastrointestinal related adverse events.

Figure 2: ACR 20 and ACR 50 Responses at Week 12 (Study CC-10004-PSA-001)



Source: Figure 6 and Figure 7 in Clinical Study Report CC-10004-PSA-001

Study PSOR-005 indicated that there is a noticeable dose-response relationship in PSOR patients between the 3 doses tested, i.e., 10, 20 and 30 mg BID doses and the primary endpoint in that study which was the proportion of subjects achieving Psoriasis Area and Severity Index (PASI-75) response at Week 16 (Figure 3 below). The primary endpoint of the study, the proportion of subjects achieving PASI-75 response at Week 16, was achieved in the apremilast 20 mg BID and 30 mg BID treatment groups (28.7% and 40.9% PASI-75 responses, respectively, versus 5.7% with placebo; $p < 0.001$ for both comparisons), but not in the in the apremilast 10 mg BID treatment group (11.2%). The safety and tolerability profile of apremilast was acceptable and comparable in both the 20 mg BID and 30 mg BID treatment groups, with no clinically significant safety signals observed at either of these doses. Given the genetic and immunologic association between PSOR and PsA, it was considered reasonable to extrapolate that a similar safety and efficacy profile would also apply to the PsA population.

Based on the above 2 Phase 2 dose ranging studies, the 20 and 30 mg BID dosing regimes were further evaluated in Phase 3.

2.4.2 Is the proposed dose titration justified?

In the proposed package insert for apremilast, the sponsor has proposed to incorporate a 7 day dose titration in the PsA subjects to develop GI tolerability. This proposed titration was implemented in all Phase 2 and 3 trials for apremilast in PsA subjects. The main support for implementing this titration was provided by a PK study, CC-10004-PK-007. The dose titration schedule in this study was 10 mg QD on Days 1 - 3, 20 mg QD on Days 4 - 6, and 40 mg QD on Days 7 – 14. Comparing 40 mg QD dose without titration and 40 mg QD dose with titration, dose titration appeared to improve the safety profile as shown by total number of GI related adverse events (Table 5 below).

Table 5: Apremilast Adverse Events Comparison With and Without Titration (Study CC-10004-PK-007)

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: Table 15 and Table 16 in Clinical Study Report CC-10004-PK-007

In addition to this data, the PM reviewer Dr. Li Zhang in her review (Appendix 3), compared GI events in placebo vs. 20 and 30 mg BID dosing regimen in Phase 3 trials. She reports that diarrhea is the AE with highest frequency in PsA patients treated with apremilast. 60% diarrhea in APR arms occurred during the first week of treatment. In the first 3 days, both APR 20 and APR 30 cohorts received the same titrated dose, i.e., 10 mg to 30 mg, and have similar proportion (30%) of diarrhea events as that in placebo. From day 4 to day 7, APR 20 cohort received 40 mg daily dose while APR 30 cohort received titrated daily dose from 40 mg to 60 mg. The occurrence rate of diarrhea was 28.7% in APR 30 cohort but reduced to 6.3% in placebo and 13.3% in APR 20 cohort. After the first week, patient demonstrated tolerance to the drug and the occurrence rate of diarrhea in both apremilast cohorts was comparable to placebo. See her review for additional details.

2.4.3 Did the sponsor characterize the dose-response relationship for safety and efficacy variables?

The following information is extracted from PM review by Dr. Li Zhang (Appendix 3).

The sponsor characterized the dose-response relationship for both apremilast safety and efficacy.

Dose-Response in Efficacy

In each of the 3 pivotal studies, a statistically significantly greater proportion of subjects in both apremilast treatment groups achieved the primary endpoint of ACR 20 response at Week 16 compared with placebo, as shown in Table 6. Similar ACR 20 responses were seen across studies, with a dose effect observed in Studies PSA-002 and PSA-004.

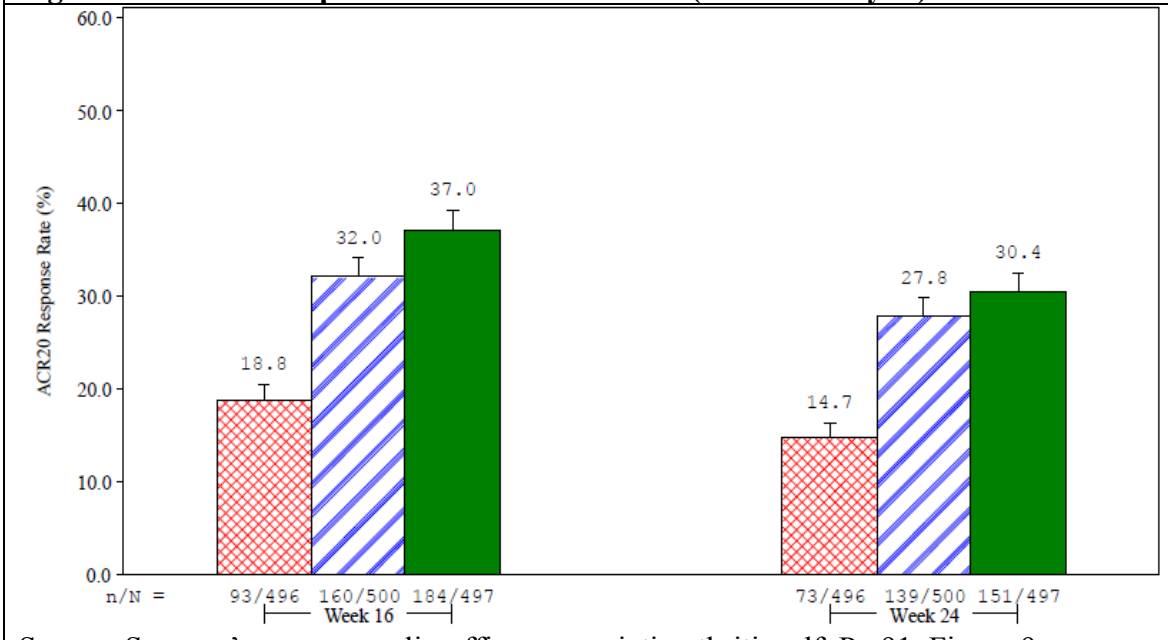
Table 6: Primary Endpoint: Proportion of Subjects Achieving ACR 20 at Week 16 in Studies PSA-002, PSA-003, and PSA-004

Study	Placebo n/N (%)[a]	APR 20 BID n/N (%)[a]	APR 20 BID Trt. Effect[b]	APR 20 BID P-value[c]	APR 30 BID n/N (%)[a]	APR 30 BID Trt. Effect[b]	APR 30 BID P-value[c]
PSA-002	32/168 (19.0)	51/168 (30.4)	11.3	**0.0166**	64/168 (38.1)	19.0	**0.0001**
PSA-003	30/159 (18.9)	61/163 (37.4)	18.7	**0.0002**	52/162 (32.1)	13.4	**0.0060**
PSA-004	31/169 (18.3)	48/169 (28.4)	9.8	**0.0295**	68/167 (40.7)	22.3	**< 0.0001**

Source: Sponsor's summary-clin-efficacy-psoriaticarthritis.pdf, Pg 40, Table 10

The pooled analysis demonstrated that a nominally significantly greater proportion of subjects in the APR 20 BID and APR 30 BID treatment groups achieved the primary endpoint of ACR 20 response at Week 16 compared with placebo. The treatment effects in ACR 20 response rates were maintained at Week 24. A dose effect was observed in the pooled analysis as well as shown in Figure 3.

Figure 3: ACR 20 Responses at Weeks 16 and 24 (Pooled Analysis)



Source: Sponsor's summary-clin-efficacy-psoriaticarthritis.pdf, Pg 91, Figure 9

Dose-Response in Safety

In the PsA phase 3 safety data pool, a dose-related safety relationship was observed. The adverse drug reactions with the highest frequency in subjects as treated for up to 16 weeks were diarrhea, nausea, and headache. A higher incidence of diarrhea (Placebo: 2.8%, APR 20: 9.3%, APR 30: 13.9%), nausea (Placebo: 4.4%, APR 20: 7.2%, APR 30: 11.7%), and headache (Placebo: 4.0%, APR 20: 6.3%, APR 30: 8.5%) were reported in the APR 30 BID group than in the APR 20 BID group and in placebo group.

In the PsA phase 3 safety data pool, the proportion of subjects who discontinued treatment due to any adverse drug reaction was higher in the apremilast-treated 30mg BID subjects (Placebo: 1.2%, APR 20: 2.5%, APR 30: 4.6%). The adverse drug reactions leading to drug withdrawal were nausea (Placebo: 0.6%, APR 20: 1.1%, APR 30: 1.8%), diarrhea (Placebo: 0.6%, APR 20: 0.8%, APR 30: 1.8%), and headache (Placebo: 0.4%, APR 20: 0.4%, APR 30: 1.2%).

2.4.4 Are there any covariates that influence the systemic exposure of apremilast that need dose adjustment?

Per the PM review by Dr. Li Zhang (Appendix 3), the final population PK model of apremilast identified disease status of having PsA, sex and body weight as statistically significant covariates on apremilast apparent clearance, while body weight and disease status of having PsA as statistically significant covariate on Vc/F. Typical apremilast steady-state AUC exposure in subjects with PsA (CC-10004-PSA-001-PK and CC-10004-PSA-002) is ~1.4 fold of that in healthy subjects (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008) (i.e., 3455.5 ng.h/mL versus 2490.4 ng.h/mL). Lower body weight and being female are associated with higher apremilast exposure. However, the exposure difference attributed to body weight and sex was generally less than 26% and well within the expected between subject variation. As such, no dose adjustment is warranted with any of these covariates.

2.4.5 Does this drug prolong QT/QTc Interval?

QT effect for apremilast was evaluated in a randomized, blinded, four-arm crossover group study, in 60 male healthy subjects who received apremilast 30 mg BID, apremilast 50 mg BID, placebo, and a single oral dose of moxifloxacin 400 mg.

No significant QT prolongation effect of apremilast (30 mg BID and 50 mg BID) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between apremilast (30 mg BID and 50 mg BID) and placebo of QTcF were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated indicating that assay sensitivity was established. For further details refer to QT/IRT review for this study in DARRTS dated 11/03/2009 (study report reviewed prior to NDA submission).

2.5 Pharmacokinetic Characteristics

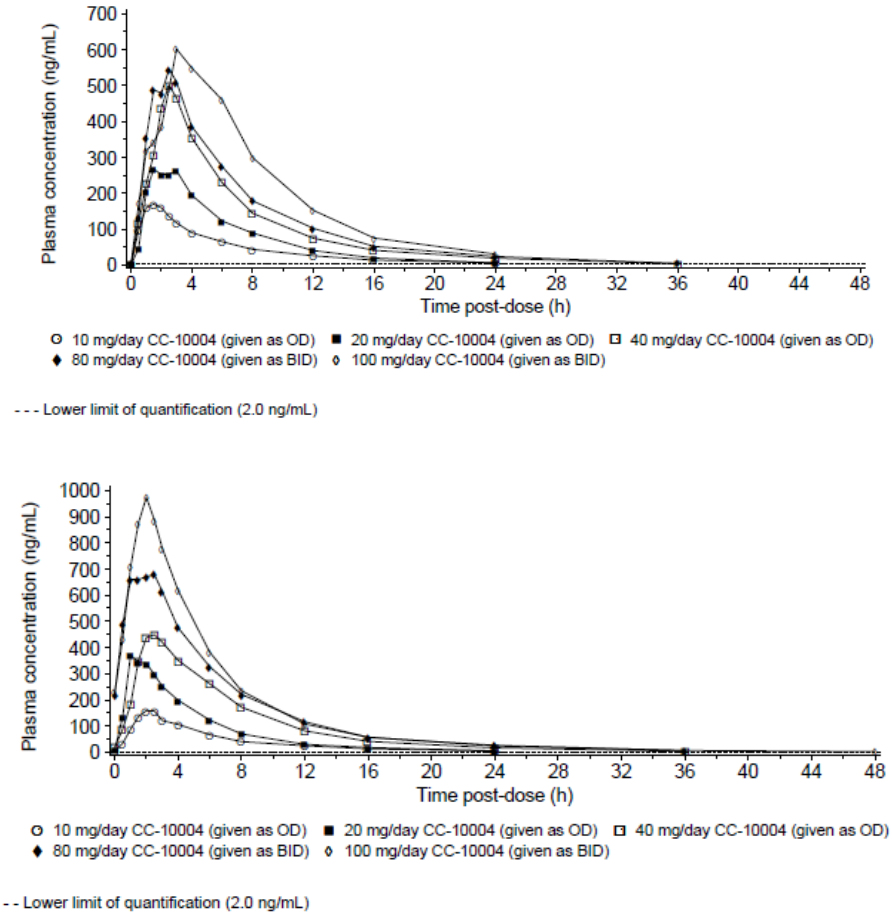
2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single and multiple dose PK of apremilast (parent, 42% of total plasma concentration) in healthy male subjects was characterized in studies CC-10004-PK-001 and CC-10004-PK-007. The metabolites of apremilast are not considered pharmacologically active (except for M7, N-deacetyl metabolite of apremilast which is potent but not present systemically in appreciable quantities) and are much less potent than apremilast. As such, their PK was not characterized in these studies. PK data for apremilast obtained from each of the studies is described below.

Study CC-10004-PK-001: This was a single-center, double-blind, placebo-controlled, sequential group, ascending single and multiple-dose study in healthy male subjects, aged 19 to 47 years inclusive. Five dose levels of apremilast as capsules (10, 20, and 40 mg given QD, and 80 mg [given as 40 mg BID] and 100 mg [given as 50 mg BID) were administered. At each of the planned dose levels, 6 subjects received apremilast, and 2 subjects received placebo in the fasted state. Each subject received a single oral dose followed by multiple oral doses over a period of 5 days. BID dosing regimen was administered at AM and PM at 12 hour intervals. PK was characterized up to 48 hours.

Cmax and AUC increased linearly with single and multiple ascending doses of apremilast (Figure 4 and Tables 7 and 8). Significant drug accumulation was not observed after multiple dosing for 5 days. Half life was found to be short (~5-7 h). Tmax was found to be ~1-3 h.

Figure 4: Geometric Mean Plasma Concentrations of CC-10004 on Day 1 and on Day 7/12 (Linear Scale)



Source: Figure 12.1-2 and Figure 12.1-4 in study report for CC-10004-PK-001

Table 7: Geometric mean (%CV) PK Parameters of Apremilast on Day 1

	10 mg	20 mg	40 mg	80 mg	100 mg
Cmax (ng/mL)	206 (32.3)	347 (36.6)	533 (35.9)	592 (49.0)	688 (43.4)
AUCinf (ng·h/mL)	1153 (18.0)	1908 (40.8)	3379 (47.1)	4106 (42.0)	5407 (32.4)
Half life (h)	6.54 (19.9)	4.45 (33.2)	6.04 (31.0)	5.56 (23.5)	5.56 (20.7)
Tmax (h)	1.00 (0.500-2.00)	1.75 (1.00 - 4.02)	2.05 (1.50 - 3.00)	2.25 (1.00 - 3.00)	3.00 (1.50 - 6.02)

Table 8: Geometric mean (%CV) PK Parameters of Apremilast on Day 12 (5 day dosing)

	10 mg (QD dosing)	20 mg (QD dosing)	40 mg (QD dosing)	80 mg Single dose of 40 mg on Days 1 and 7, BID dosing on Days 3 to 6.	100 mg Single dose of 50 mg on Days 1 and 7, BID dosing on Days 3 to 6.
Cmax (ng/mL)	180 (29.9)	419 (40.1)	490 (52.4)	881 (30.8)	994 (29.5)
AUCt (ng·h/mL)	998 (22.8)	1948 (42.0)	3289 (45.1)	4482 (34.7)	5164 (38.6)
Half life (h)	5.26 (33.7)	4.46 (28.7)	5.82 (47.2)	6.16 (22.1)	6.84 (18.7)
Tmax (h)	2.00 (1.50 - 2.50)	1.00 (1.00 - 2.50)	2.75 (2.00 - 3.00)	2.50 (1.00 - 3.00)	2.00 (1.50 - 2.03)
Source: Table 12.1-1 and Table 12.2-2 of report CC-10004-PK-001					

Study CC-10004-PK-007: This was a single-center, double-blind, randomized, placebo-controlled, ascending multiple dose study to assess the safety, PK, and PD of apremilast given to healthy male subjects for 14 days. Five dose levels of apremilast as capsules (40 mg QD, 60 mg QD, 80 mg QD, 40 mg BID, and 100 mg QD) were planned to be administered, however due to AEs that were considered dose limiting at the time of this study, observed at the 80-mg daily dose (both 40 mg BID and 80 mg QD), subjects in Group E (proposed 100 mg QD) were not dosed. In order to explore the possibility that dose titration would help to reduce the frequency and severity of gastrointestinal AEs, the dose in Group E was changed to 40 mg QD with a dose titration schedule. Subjects in Group E received 40 mg apremilast QD with a dose titration schedule as follows: 10 mg QD on Days 1 to 3, 20 mg QD on Days 4 to 6, and 40 mg QD on Days 7 to 14. In each dose group (Groups A to E), 9 subjects received apremilast and 2 subjects received placebo in the fasted state for 14 days.

Cmax and AUC increased linearly with multiple ascending doses of apremilast (Table 9). Significant drug accumulation was not observed after multiple dosing for 14 days. The half life was found to be ~6-9 h. Tmax was found to be ~1-4 h.

Table 9: Geometric mean (%CV) PK Parameters of Apremilast on Multiple Dosing (14 days)

	40 mg QD	60 mg QD	80 mg QD	**40 mg BID**	**40 mg QD with dose titration**
Cmax (ng/mL)	561 (29.5)	539 (37.1)	776 (28.9)	646 (25.0)	507 (28.2)
AUCt	4241	4347	6014	3828 (33.6)	3697 (56.2)

(ng·h/mL)	(43.6)	(39.5)	(37.3)		
Half life (h)	7.14 (24.8)	8.14 (28.9)	8.98 (43.3)	6.12 (27.5)	6.12 (27.5)
Tmax (h)	2.0 (1.5-4.0)	3.0 (3.0-3.0)	3.0 (3.0-4.0)	2.5 (1.0-3.0)	3.0 (2.0-4.0)

Source: Tables 14.2.16 through 14.2.24 of report CC-10004-PK-007

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Multiple dose PK of 30 mg BID apremilast administered for 5 days in PsA subjects was characterized in Study CC-10004-PK-010 (a DDI study with methotrexate) as shown in Table 10. In addition, the sponsor submitted a population PK model depicting PK in PsA subjects based on pooled sparse data from the phase 3 study CC-10004-PSA-002-PK, sparse and intensive data from the phase 2 study CC-10004-PSA-001-PK, and relevant data pooled from four phase 1 studies (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, and CC-10004-PK-010). To view data from this population PK report, refer to PM review by Dr. Li Zhang (Appendix 3).

Table 10: Summary of Apremilast Plasma Pharmacokinetic Parameters In PsA Subjects Following the Morning Dose on Day 7 (5 days BID dosing) (CC-10004-PK-010)

	Geometric Mean (Geometric %CV)			
Treatment	**t_{max}[a] (h)**	**C_{max} (ng/mL)**	**C_{min} (ng/mL)**	**AUC_{τ} (ng·h/mL)**
Apremilast Day 7 (N = 15)	2.00 (0.95 - 4.00)	554 (35.0)	207 (70.5)	3670 (53.8)

To be able to compare differences in apremilast PK in PsA subjects vs. healthy subjects at the same dose and dosing regimen (30 mg BID for 5 days), PK data from study CC-10004-PK-010 was compared to PK data in healthy subjects in study CC-10004-PK-008 which was a TQT study (Table 11). Apremilast steady state Cmax and AUC values are higher in PsA subjects vs. healthy subjects (Cmax increased by 57% and AUC by 38%).

Table 11: Summary of Apremilast Plasma Pharmacokinetic Parameters Following Multiple Oral Dose on Day 5 in Healthy Male Subjects (Geometric Mean, Geometric CV%)

Treatment	**Analyte**	**t_{max}[a] (h)**	**C_{max} (ng/mL)**	**AUC_{τ} (ng·h/mL)**	**$t_{1/2}$[b] (h)**
Apremilast 30 mg BID	Apremilast (N = 53)	2.0 (0.5 - 6.0)	351.8 (37.1)	2260 (36.1)	6.41 (24.3)

Source: Table 4 of report CC-10004-PK-008

2.5.3 What are the characteristics of drug absorption?

The absolute bioavailability of apremilast (S-enantiomer) following oral administration was assessed in Study CC-10004-CP-012. Following oral administration of 20 mg apremilast, the absolute bioavailability was approximately 73.2%. The mean (SD) plasma total clearance based on the IV administration was 169 (41.6) mL/min. PK parameters comparing oral and IV administration of apremilast are shown in Table 12.

Table 12: Summary of PK Parameters for Apremilast (Geometric Mean, Geometric CV%) After IV and Oral Administration

Treatment	t_{max}[a] (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{∞} (ng·h/mL)	CL (mL/min)	Vz (L)	F_{abs} (%)
Oral apremilast	2.29 (1.00 -4.00)	173 (27.2)	7.63 (1.14)	1480 (21.8)	230 (46.4)	NA	73.2 (12.5)
IV [^{14}C]-apremilast	0.25 (0.25 -0.33)	4.91 (27.2)	6.19 (1.21)	10.1 (22.8)	169 (41.6)	87.0 (22.5)	NA

Source: Table 5 of report CC-10004-CP-012

[redacted](b) (4) was not present in human plasma or urine in any quantifiable amount, indicating that there was no [redacted](b) (4) (Study CC-10004-PK-005).

2.5.4 What are the characteristics of drug distribution?

Apremilast is readily distributed with observed geometric mean (geometric CV%) for volume of distribution based on area, Vz, found to be 87 L (22.5%).

2.5.5 What are the characteristics of drug metabolism?

In study CC-10004-PK-002, a phase 1, open-label, single-center study, the total recovery of [14C]-apremilast and/or its radiolabeled metabolites in healthy male subjects following a 20 mg single oral suspension dose was characterized. Following a 20 mg single oral suspension dose, apremilast was extensively metabolized with up to 23 metabolites identified in plasma, urine and feces as shown in Figure 5.

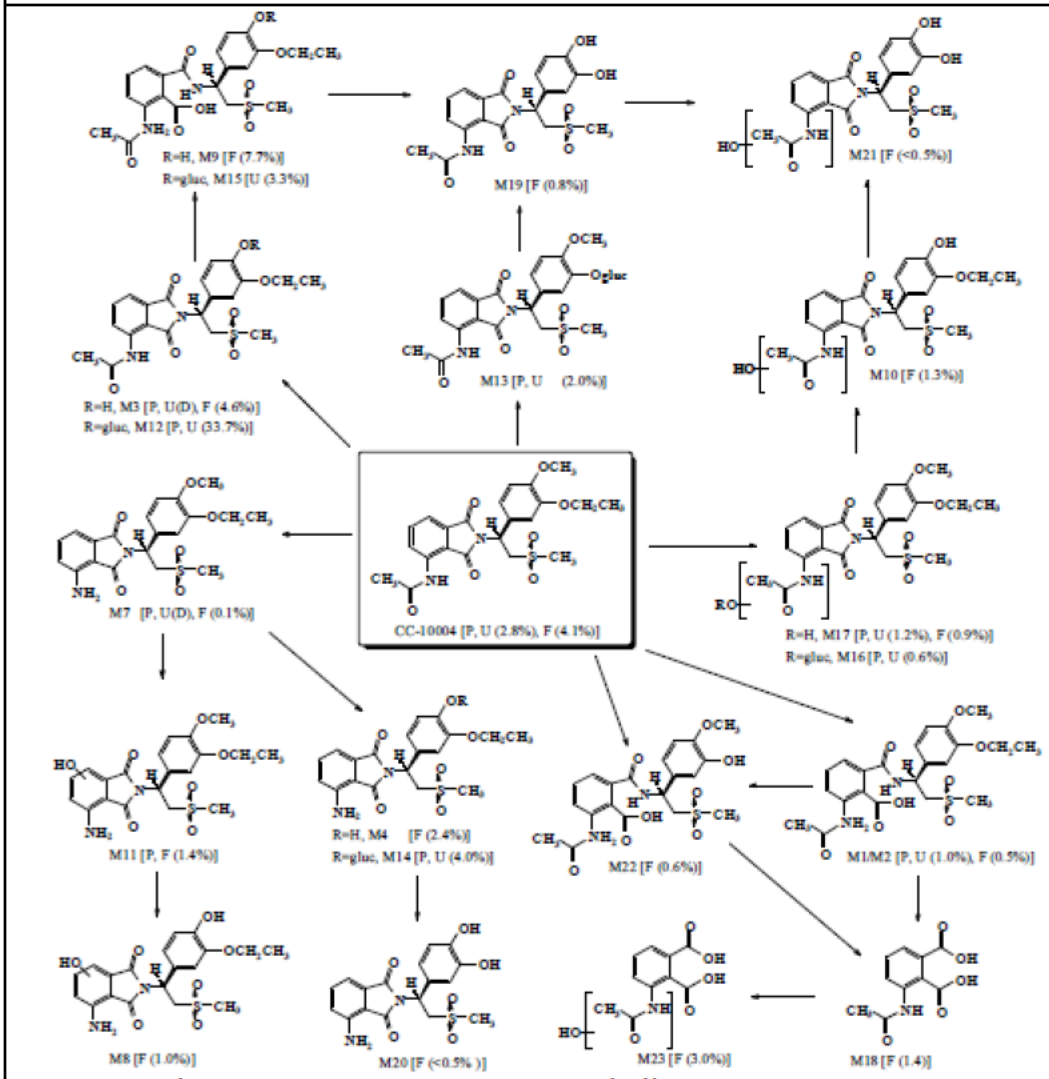
The major metabolic route of apremilast in humans is O-demethylation, with approximately 50% of the dose metabolized via this pathway (Table 13). Other minor metabolic routes included O-deethylation, N-deacetylation, hydroxylation (oxidative), hydrolysis of the imide ring, and a combination of these pathways. The O-demethylated and deethylated metabolites in the plasma and urine were predominantly glucuronide conjugates. The sponsor did not characterize glucuronide metabolism of apremilast *in vitro.*

The mean total urinary and fecal recovery of radioactive [14C]-apremilast and its metabolites was 97.1%, with mean contributions of 57.9% and 39.2% from urine and feces, respectively. Less than 3% of the dose was excreted renally as unchanged apremilast. Apremilast was eliminated by excretion of metabolites to a significant extent. A glucuronide conjugate of O-demethylated apremilast (M12) which is not considered pharmacologically active when compared to apremilast, was the major circulating metabolite and its urinary excretion represented approximately 34% of the total

administered dose. The circulating radioactivity, based on total radioactive equivalent AUC, was 45% for apremilast and 38% for M12. There were no unique human metabolites that were not found in one or more animal species.

In addition, Study CC-10004-PK-005 (DDI study with ketoconazole) showed that (b) (4) was not present in human plasma or urine in any quantifiable amount, indicating that there was no (b) (4)

Figure 5: Proposed Metabolic Pathways for Apremilast in Humans



Source: Study report CC-10004-PK-002-metabolite

Table 13: Composition of Circulating and Excreted Radioactivity in Humans Following a Single 20 mg Oral Dose of [14C]-apremilast to Healthy Male Subjects

			Percent of Radioactive Dose		
Transformation (Celgene compound number)	**Metabolite ID**	**% of Plasma TRA AUC**	**Urine**	**Feces**	**Total**
Apremilast (CC-10004)	Parent	44.80	2.82	4.06	6.88
Hydrolysis products (CC-15091)	M1/M2	detected	0.92	0.53	1.45
O-demethylated (CC-16085)	M3	detected	D	4.55	4.55
O-demethylated *N*-deacetylated	M4	ND	ND	2.36	2.36
O-deethylated (CC-10047)	M5	ND	ND	ND	ND
N-deacetylated (CC-10055)	M7	detected	D	0.11	0.11
Hydroxylated *O*-demethylated *N*-deacetylated	M8	ND	ND	0.97	0.97
Hydrolysis products of *O*-demethylated	M9	ND	ND	7.67	7.67
O-demethulated hydroxylated acetamide	M10	ND	ND	1.34	1.34
Hydroxylated *N*-deactylated	M11	2.50	ND	1.41	1.41
O-demethylated glucuronide (CC-16166)	M12	38.70	33.67	ND	33.67
O-deethylated glucuronide	M13	2.40	2.04	ND	2.04
N-deacetylated *O*-demethylated glucuronide	M14	4.90	4.04	ND	4.04
Hydrolysis products of *O*-demethylated glucuronide	M15	ND	3.32	ND	3.32
Hydroxylated acetamide glucuronide (CC-16557)	M16	6.60	0.64	ND	0.64
Hydroxylated acetamide (CC-16401)	M17	detected	1.16	0.86	2.02
3-Acetamide-phthalic acid	M18	ND	ND	1.38	1.38
O-demethylated *O*-deethylated	M19	ND	ND	0.78	0.78
N-deacetylated *O*-demethylated *O*-deethylated; *O*-demethylated *O*-deethylated hydroxylated acetamide	M20/M21	ND	ND	0.48	0.48
Hydrolysis products of *O*-deethylated	M22	ND	ND	0.59	0.59
Hydrolysis product of hydroxylated acetamide	M23	ND	ND	2.98	2.98

Source: Study report CC-10004-PK-002-metabolite

2.5.6 What are the characteristics of drug excretion in urine?

Mass balance study CC-10004-PK-002 suggested that less than 3% of the dose was excreted renally as unchanged apremilast. Apremilast was primarily eliminated by excretion of metabolites. A glucuronide conjugate of O-demethylated apremilast (M12) was the major circulating metabolite and its urinary excretion represented approximately

34% of the total administered dose. In addition, Study CC-10004-PK-005 (DDI study with ketoconazole) showed that [redacted] (b) (4)) was not present in human plasma or urine in any quantifiable amount, indicating that there was no [redacted] (b) (4)

2.6 Intrinsic Factors

2.6.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response?

- **Gender**

From study CC-10004-CP-024, apremilast systemic exposure as measured by AUC0-t and AUC0-inf was greater in female compared to male subjects by 28% and 31%, respectively. Between young female and young male subjects, AUC0-t and AUC0-inf were greater by about 13% in young female subjects, while Cmax was similar in both groups. Comparing elderly female and elderly male subjects, AUC0-t and AUC0-inf were greater by 46% and 50%, respectively, and Cmax was greater by 17% in elderly female subjects. See Tables 14 and 15.

Table 14: Plasma Pharmacokinetic Parameters of Apremilast by Age And Sex

Age/Sex	Young/Female N = 10	Young/Male N = 8	Elderly/Female N = 10	Elderly/Male N = 8
PK Parameter[a]	Geometric Mean (Geometric CV%)			
AUC_{0-t} (h*ng/mL)	2987 (32.5)	2649 (21.9)	3829 (40.6)	2620 (28.5)
$AUC_{0-\infty}$ (h*ng/mL)	3072 (32.9)	2698 (22.4)	3985 (41.7)	2648 (28.6)
C_{max} (ng/mL)	301 (33.7)	303 (17.5)	344 (33.6)	295 (16.8)
t_{max} (h)	2.25 (1.0-5.0)	2.50 (0.5-5.0)	4.00 (2.5-5.1)	2.25 (1.0-5.0)
$t_{½}$ (h)	10.1 (2.84)	8.5 (2.23)	10.4 (2.82)	7.63 (0.973)
CL/F (L/h)	9.77 (32.9)	11.1 (22.4)	7.53 (41.7)	11.3 (28.6)
Vz/F (L)	139 (45.8)	132 (31.8)	108 (38.7)	124 (31.5)

CV% = percent coefficient of variation; h = hour; N = number of subjects in each age/sex group; PK = pharmacokinetic
Elderly = Group 1 (65 to 85 years)
Young = Group 2 (18 to 55 years)
[a] Median (range) is presented for t_{max}; mean (standard deviation) is presented for $t_{1/2}$.
Source: Table 14.2.1.3 in study report for CC-10004-CP-024

Table 15: Plasma Pharmacokinetic Parameters of Apremilast by Age or Sex

Age or Sex	Young N = 18	Elderly N = 18	Male N = 16	Female N = 20
PK Parameter[a]	Geometric Mean (Geometric CV%)			
AUC_{0-t} (h*ng/mL)	2832 (28.1)	3235 (40.3)	2634 (24.5)	3382 (38.2)
$AUC_{0-\infty}$ (h*ng/mL)	2900 (28.7)	3323 (41.8)	2673 (24.8)	3499 (39.1)
C_{max} (ng/mL)	302 (26.8)	321 (27.8)	299 (16.6)	322 (33.5)
t_{max} (h)	2.50 (0.5-5.0)	2.50 (1.0-5.1)	2.50 (0.5-5.0)	2.75 (1.0-5.1)
$t_{½}$ (h)	9.41 (2.65)	9.15 (2.56)	8.06 (1.72)	10.3 (2.76)
CL/F (L/h)	10.4 (28.7)	9.03 (41.8)	11.2 (24.8)	8.57 (39.1)
Vz/F (L)	136 (38.9)	115 (35.3)	128 (30.7)	123 (43.4)

CV% = percent coefficient of variation; h = hour; N = number of subjects in each age/sex group; PK = pharmacokinetic
Elderly = Group 1 (65 to 85 years)
Young = Group 2 (18 to 55 years)
[a] Median (range) is presented for t_{max}; mean (standard deviation) is presented for $t_{1/2}$.
Source: Table 14.2.1.3 in study report for CC-10004-CP-024

- **Elderly**

From study CC-10004-CP-024, apremilast systemic exposure in elderly healthy subjects (70.5 ± 4.15 years of age [mean ± SD]) was ~13% higher than that in young healthy subjects (34.3 ± 7.17 years of age [mean ± SD]. See Tables 14 and 15 above.

- **Pediatric Patients**

In their proposed label, sponsor has included the following statement "*The safety and efficacy in pediatric patients have not been established*."

Since Juvenile Idiopathic Arthritis (JIA) is a rare diagnosis, and Juvenile Psoriatic Arthritis is a subset of JIA, studies in Juvenile Psoriatic Arthritis are deemed impossible or highly impractical. As such, pediatric study requirements will be waived for apremilast. See clinical review by Dr. Keith Hull for additional details.

- **Race/Ethnicity**

Apremilast PK is comparable across ethnic groups of Caucasian, Japanese and Chinese subjects based on study CC-10004-CP-018 (Figure 6). In addition, PK analyses from combined Phase 1 population including Hispanic Caucasians, non-Hispanic Caucasians, and African Americans showed that apremilast exposure is also similar among these groups (Figure 7).

Figure 6: Mean (+/- SD) Apremilast Plasma Profiles in Healthy Japanese, Chinese, and White Adult Males After a Single 20-mg Oral Dose of Apremilast (by Ethnic Group)

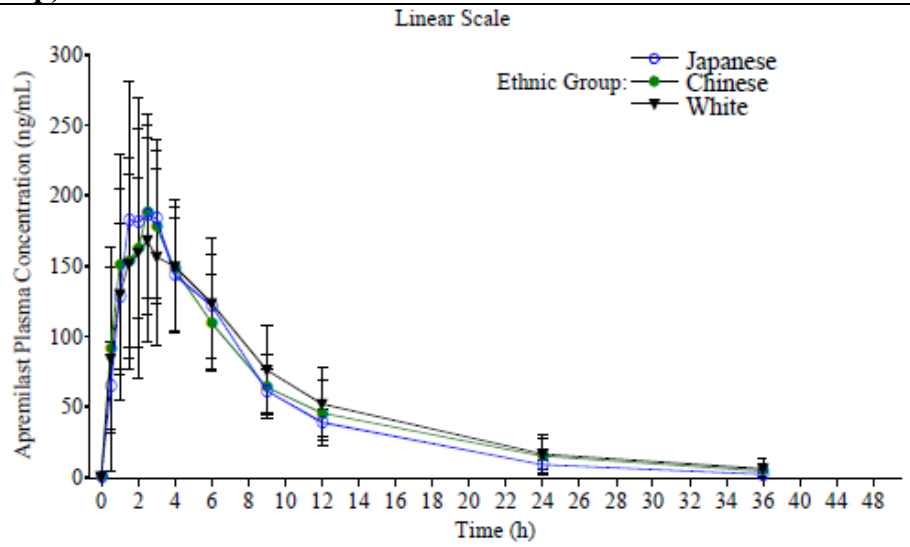
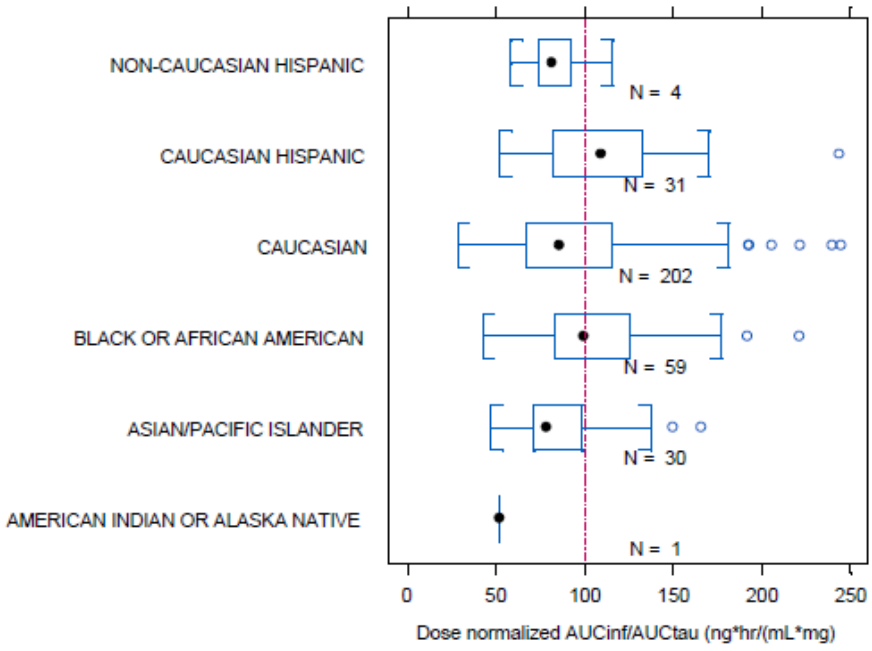


Figure 7: Apremilast AUC(0-inf)/AUC(0-tau) Exposure Comparison among Healthy Hispanic Caucasian, Non-Hispanic Caucasian, and African American Subjects



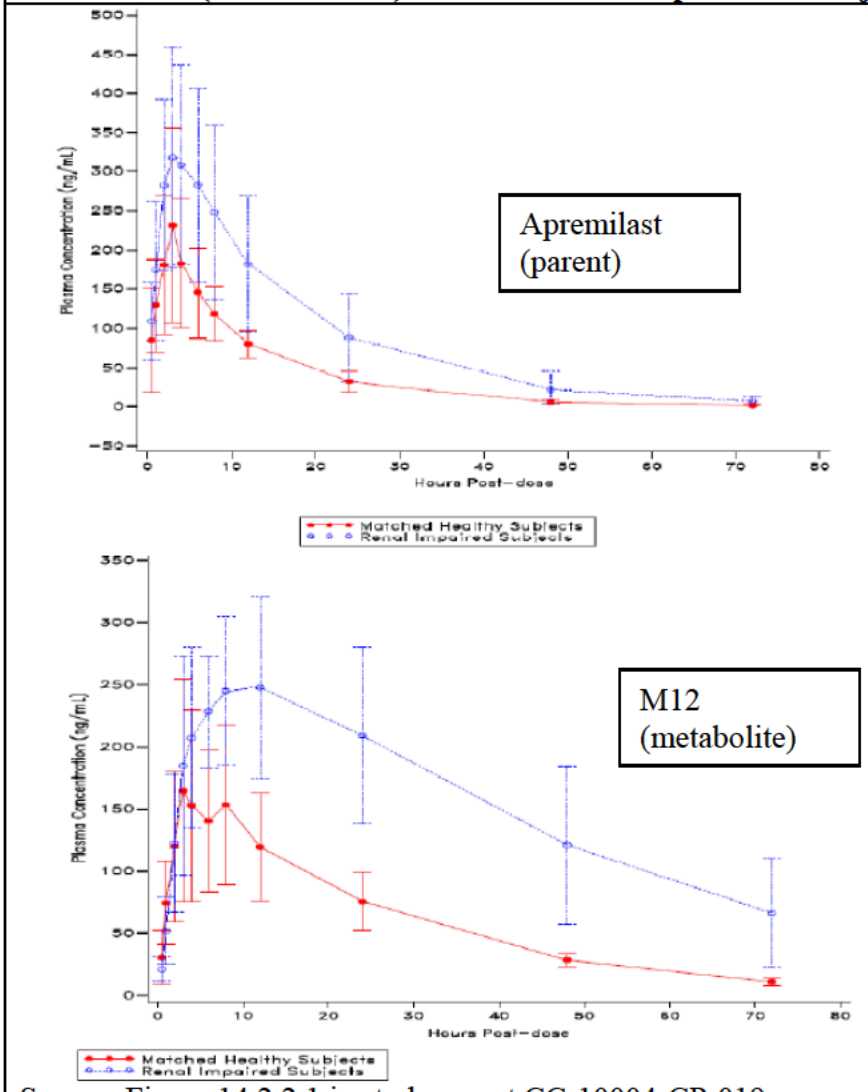
Source: Response to information request received 7/31/2013

- **Renal Impairment**

In subjects with severe renal impairment (RI), single-dose administration of 30 mg

apremilast resulted in an increase in overall mean exposure (AUCinf) of ~ 89% for apremilast and of ~145% for M12 (major metabolite) based on PK data obtained in study CC-10004-CP-019 (Figure 8). In addition, apremilast half life was prolonged by ~ 2.5 hours and clearance (CL/F) decreased approximately by 47% (Table 14). M12 half life was prolonged by ~10.5 hours and Tmax was delayed approximately 6.25 hours. The number of AEs in severe RI group was reported to be 4 (50%) vs. 2 (25%) in the healthy group. The sponsor conducted PK simulations that suggest that a 30 mg QD dose produces apremilast exposure in subjects with severe renal impairment comparable to 30 mg BID in subjects without renal impairment; thus, the dose should be reduced to 30 mg QD in subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/ min/1.73m2 or CLcr < 30 mL/min). See PM review by Dr. Li Zhang (Appendix 3) for further details.

Figure 8: Mean Apremilast and M12 (major metabolite) Plasma Concentration – Time Profile (Normal Scale) in Severe Renal Impairment Subjects



Source: Figure 14.2.2.1 in study report CC-10004-CP-019

Table 16: Summary of Plasma Apremilast and M12 Pharmacokinetic Parameters (Geometric Mean [CV%])

Group	Geometric Mean (Geometric %CV) [a]						
	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
Severe renal 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)

[a] T_{max} is summarized by median and range (minimum – maximum)

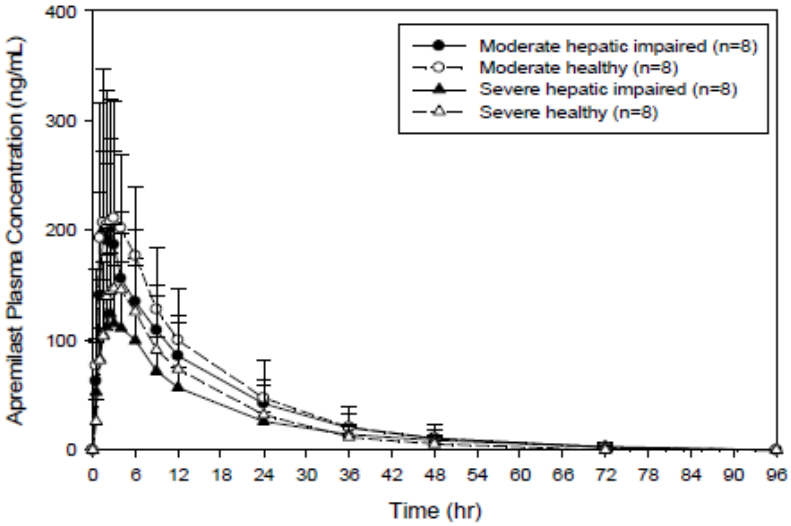
Group	**Geometric Mean (Geometric %CV)[a]**				
	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{1/2}$ (hr)
Severe renal impaired	10545.5 (34.8)[c]	13697.2 (49.5)[b]	267.7 (27.8)[c]	4 (3-24)[c]	27.393 (45.2)[b]
Matched healthy (n=7)	4308.4 (31.4)	4695.9 (25.0)	187.3 (38.5)	12 (3-8)	16.895 (21.7)

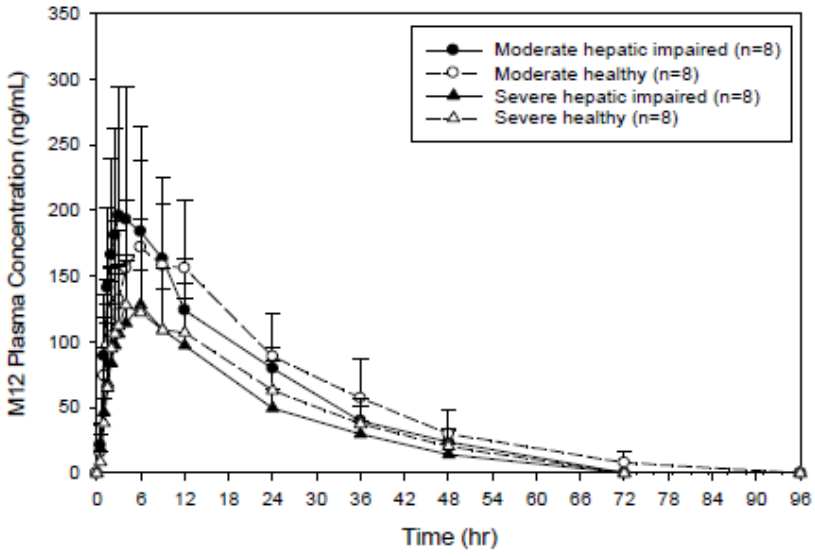
Source: Tables 5 and 10 in study report CC-10004-CP-019

- **Hepatic Impairment**

Mild, moderate and severe hepatic impairment did not affect apremilast or M12 exposure based on PK data obtained in study CC-10004-CP-011 (Figure 9); no dosage adjustment is necessary for subjects with hepatic impairment.

Figure 9: Mean Apremilast and M12 (major metabolite) Plasma Concentration – Time Profile (Normal Scale) in Hepatic Impairment Subjects





Source: Figures 14.2.2.1 and 14.2.2.2 in study report CC-10004-CP-011

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group (sex, elderly, pediatric, race/ethnicity, renal impairment, hepatic impairment)?

Population PK analyses (Pharmacometrics review by Dr. Li Zhang (Appendix 3)) identified sex and body weight as statistically significant covariates. Simulations based on extreme low and high body weights in males and females suggest that body weight and sex effects

combined were small relative to the intrinsic variability of apremilast. As such, no dosage regimen adjustments are recommended for these intrinsic factors.

Except for severe renal impairment, dosage regimen adjustments are not recommended for any other co-variates. In severe renal impairment, it is recommended that the dose be reduced to 30 mg QD (instead of 30 mg BID).

2.7 Extrinsic Factors

2.7.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of a high-fat, high-calorie meal on apremilast PK is discussed in section 2.8.3. Food did not affect apremilast PK or PD. The effect of co-administration of methotrexate as background therapy is discussed in section 2.7.2. All PsA patients are likely to take methotrexate in background therapy. Study CC-10004-PK-010 showed that multiple oral doses of 30 mg apremilast given BID do not significantly affect MTX (15 or 20 mg once a week) PK and neither is apremilast PK affected by MTX indicating that there is no PK interaction between the two drugs. Apremilast PD was not affected by MTX.

2.7.2 Drug-Drug Interactions

2.7.2.1 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

Yes. Apremilast is primarily eliminated as metabolites formed via both cytochrome P450 (CYP)-mediated oxidative metabolism (and subsequent glucuronidation) and non-CYP mediated hydrolysis. CYP3A4, CYP1A2, and CYP2A6 all participate in apremilast metabolism. Therefore, apremilast PK may be expected to be affected when inhibitors or inducers of CYP enzymes are co-administered. Sponsor conducted drug interaction studies with CYP3A4 substrate, CYP3A inhibitor and CYP inducer which are discussed further in this section.

- **Is the drug a substrate of CYP enzymes?**

In vitro, oxidative metabolism of apremilast is CYP metabolism of apremilast is mediated by CYP3A4 to a large extent, with minor contributions from CYP1A2 and CYP2A6.

- **Is the drug an inhibitor and/or an inducer of enzymes?**

Apremilast did not inhibit any relevant CYP enzymes in vitro, suggesting that it is unlikely to inhibit the metabolism of co-administered CYP substrates. Apremilast did not induce the activity of CYP1A2, CYP2C9, or CYP2C19 in vitro. At the highest concentration (100 μM or 46,000 ng/mL), apremilast increased the enzyme activity of CYP3A4 and CYP2B6 by approximately 3.7- and 1.7-fold, respectively. This concentration is more than 100-fold higher than the Cmax at steady-state of a 60 mg daily dose (given as 30 mg BID) in healthy subjects and PsA patients, respectively (Studies CC-10004-PK-008 and CC-10004-PSA-002-PK). Therefore, it is unlikely that co-administration of apremilast will result in

clinically significant decreases in the presence of CYP1A2, CYP2C9, CYP2C19, CYP3A4, or CYP2B6 substrates.

- **Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

In vitro study CC-10004-DMPK-017 showed that apremilast is a P-gp substrate. Efflux ratios (ER) of 10 microM apremilast in MDR1-LLC-PK1 cells were found to be 24 (60 minutes), 30 (90 minutes) and 27 (120 minutes), respectively, as compared to a positive control digoxin with an ER of 3. Co-incubation with 30 μM ketoconazole (a P-gp and CYP3A inhibitor), led to 92% inhibition of net efflux of apremilast, confirming its affinity for P-gp. The same study showed that apremilast is an inhibitor of P-gp (30% inhibition of digoxin transport at 50 microM) *in vitro*, however it is not expected to inhibit P-gp at expected systemic concentrations. The I1/IC50 and I2/IC50 values for P-gp inhibition for apremilast (calculated by this reviewer) were found to be 0.015 and 5 respectively; indicating that the drug will likely not inhibit P-gp *in vivo.*

The sponsor also submitted *in vitro* studies indicating apremilast is not a substrate for breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, or OATP1B3, and does not inhibit BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, multidrug resistance protein (MRP)1, MRP2, MRP3 and MRP4 (IC50 > 10 μM). Therefore, apremilast is not expected to cause DDIs at therapeutic doses when administered with substrates or inhibitors of these transporters.

- **What are the drug-drug interactions?**

Overall, 4 DDI studies were conducted with apremilast as described below:

- DDI studies with oral contraceptives (CYP3A4 substrates), ketoconazole (CYP3A inhibitor +P-gp inhibitor) and rifampin (CYP inducer) based on *in vitro* findings that it is a CYP (mainly CYP3A4) substrate and P-gp substrate.
- DDI study with methotrexate, a frequently co-administered drug in the PsA population.

DDI study with ketoconazole: Study CC-10004-PK-005 (Table 17) showed that co-administration with ketoconazole (400 mg QD for 7 days) increased apremilast (20 mg) mean AUC by ~36% and Cmax by 5%. The apparent clearance of apremilast was decreased from 9.7 L/h to 7.1 L/h. The number of subjects reporting AEs was higher when ketoconazole was co-administered (14, 78%) as compared to apremilast alone (5, 28%). This study also showed that M7 (N-acetylated metabolite of apremilast which is considered 2 fold less potent than apremilast) levels increased ~2 fold in the presence of ketoconazole. However, this metabolite is present in non-significant amounts in humans (AUC0-inf of M7 is ~4% of apremilast) and as such a ~2 fold increase in its exposure is not of clinical significance. Overall, ketoconazole, a P-gp and CYP3A inhibitor did not significantly affect apremilast exposure.

Table 17: Comparison of Apremilast Pharmacokinetics Following Administration with Ketoconazole (Treatment B) Versus Apremilast Alone (Treatment A) (Study CC-10004-PK-005)

Variable	LS Mean		% Ratio (Test/Reference)	90% Confidence Interval of Ratio	Intra individual CV%
	Treatment B (Test) apremilast With Ketoconazole	Treatment A (Reference) apremilast Alone			
Plasma PK					
C_{max} (ng/mL)	247.083	235.644	104.85	92.16; 119.30	22.5
AUC_t (h·ng/mL)	2795.405	2044.062	136.76	126.60; 147.73	13.4
AUC_∞ (h·ng/mL)	2827.492	2072.443	136.43	126.20; 147.49	13.5
$t_{1/2}$ (h)	8.140	7.644	106.49	100.30; 112.68	10.7
CL/F (L/h)	7.073	9.650	73.30	67.80; 79.24	13.5
Vz/F (L)	81.385	104.954	77.54	69.82; 86.12	18.2
Urine PK					
fe (µg)	886.285	650.776	136.19	113.12; 163.97	32.8
CL_r (mL/h)	317.051	318.374	99.58	83.47; 118.81	31.2

Source: Table 4 of report CC-10004-PK-005

DDI study with rifampin: Study CC-10004-CP-025 (Table 18) showed that multiple oral doses of rifampin (600 mg rifampin for 15 days), a potent inducer of CYP3A4 as well as other CYP enzymes and P-gp, resulted in a significant decrease in the exposure of apremilast (30 mg). There were 72%, 72%, and 43% decreases in mean AUCinf, AUCt, and Cmax, respectively, compared to the reference (apremilast alone). The labeling implications for this DDI were discussed in detail with the clinical review team. (b) (4) However, considering that apremilast AUC decreases by 72% in the presence of rifampin, which may lead to a total loss of efficacy, it was considered reasonable to include a recommendation of avoiding co-administration with CYP inducers in the product label.

Table 18: Summary of Plasma Apremilast Pharmacokinetic Parameters (Geometric Mean [Geometric CV%]

Parameter (unit)	Apremilast Alone Day 1 (Treatment A) n=21	MD Rifampin + Apremilast Day 20 (Treatment C) n=19
AUC_{∞} (ng·h/mL)	3120 (31.5)	869 (32.9)
AUC_t (ng·h/mL)	3070 (31.3)	850 (33.7)
C_{max} (ng/mL)	290 (24.5)	166 (23.2)
t_{max} (h)[a]	2.00 (0.50-5.00)	1.00 (0.50-5.00)
$t_{1/2}$ (h)	8.12 (14.1)	6.13 (24.8)
CL/F (L/h)	9.60 (31.5)	34.5 (32.9)
V_z/F (L)	112 (35.8)	305 (51.6)

DDI study with oral contraceptives: Study CC-10004-CP-020 showed that co-administration with Ortho Tri-Cyclen (OC) DIALPAKs (Ethinyl Estradiol (EE) + Norgestimate (NGM), CYP3A4 substrates), did not result in significant changes in apremilast PK nor of the 2 drugs (EE and NGM) including 17-NGM (primary metabolite for NGM) indicating that co-administration with other CYP3A4 substrates does not warrant a dose change for apremilast or for the co-administered drugs (Table 19).

Table 19: Plasma Pharmacokinetic Parameters of Ethinyl Estradiol, Norgestimate and 17-Deacetyl Norgestimate In the Presence and Absence of Apremilast Geometric Mean (Geometric CV%)

PK Parameter	Ethinyl Estradiol	Ethinyl Estradiol + Apremilast	Norgestimate	Norgestimate + Apremilast	17-Deacetyl Norgestimate	17-Deacetyl Norgestimate + Apremilast
	Treatment A (OC alone) N = 38	Treatment B (OC plus Apremilast) N = 35	Treatment A (OC alone) N = 38	Treatment B (OC plus Apremilast) N = 35	Treatment A (OC alone) N = 38	Treatment B (OC plus Apremilast) N = 35
AUC0–t (pg*hr/mL)	1336 (35.8)	1159 (35.0)	59.6 (38.7)	60.5 (39.7)	23404 (26.2)	20636 (22.6)

AUC0 – inf (pg*hr/mL)	1772 (40.7)	1449 (41.4)	76.3 (26.7)	76.9 (30.9)	39433 (38.6)	33161 (30.5)
Cmax (pg/mL)	132 (29.6)	121 (30.6)	45.7 (46.2)	42.1 (53.5)	2077 (22.2)	1861 (18.8)
tmax (hr)	1.18 (0.5-3.0)	1.50 (0.5-2.1)	1.00 (0.4-3.0)	0.98 (0.5-3.0)	1.50 (0.9-3.0)	1.50 (1.0-3.0)
t½ (hr)	15.8 (3.57)	13.8 (3.27)	0.78 (0.293)	0.85 (0.648)	24.7 (7.60)	22.5 (6.21)
CL/F (L/hr)	28.9 (34.8)	32.9 (34.0)	3883 (37.1)	3786 (37.6)	-	-
Vz/F (L)	640 (38.8)	640 (31.7)	3667 (43.6)	3705 (62.7)	-	-

DDI study with methotrexate (MTX): Study CC-10004-PK-010 showed that multiple oral doses of 30 mg apremilast given BID do not significantly affect MTX (15 or 20 mg once a week) PK (Table 20 below shows only MTX PK, no change in PK was observed for the major metabolite of MTX, 7-OH MTX as well) and the same is true vice-versa, i.e., MTX did not affect apremilast PK (Table 21).

Table 20: Summary of MTX Plasma Pharmacokinetic Parameters (Day 1 and Day 8) (CC-10004-PK-010)

		Geometric Mean (Geometric %CV)				
Treatment	**Day**	**t_{max}[a] (h)**	**C_{max} (ng/mL)**	**AUC_t (ng·h/mL)**	**AUC_∞ (ng·h/mL)**	**$t_{1/2}$ (h)**
MTX 15 mg	1 (N = 6)	1.27 (1.00-1.52)	411 (28.1)	1650 (40.2)	1520[b] (40.6)	3.5[b] (16.3)
MTX 15 mg + apremilast	8 (N =6)	1.25 (0.50-1.52)	396 (31.5)	1670 (31.6)	1660 (32.4)	3.3 (14.6)
MTX 20 mg	1 (N = 6)	1.50 (1.00-2.07)	593 (23.3)	2830 (31.0)	2840 (31.3)	5.1 (48.0)
MTX 20 mg + apremilast	8 (N = 6)	2.07 (1.00-2.08)	569 (26.4)	2700 (33.2)	2700 (33.5)	4.3 (30.1)

Source: Table 5 and Table 6 of report CC-10004-PK-010

Table 21: Summary of Apremilast Plasma Pharmacokinetic Parameters Following the Morning Dose on Day 7 and Day 8 (CC-10004-PK-010)

	Geometric Mean (Geometric %CV)			
Treatment	t_{max}[a] (h)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{τ} (ng·h/mL)
Apremilast Day 7 (N = 15)	2.00 (0.95 - 4.00)	554 (35.0)	207 (70.5)	3670 (53.8)
Apremilast + MTX Day 8 (N = 15)	2.00 (0.98 - 4.08)	526 (42.2)	195 (81.0)	3660[b] (56.5)

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Apremilast is classified as a BCS class IV drug, however the oral bioavailability of this drug is high (~70%). The sponsor determined an intrinsic apparent permeability value for apremilast across porcine kidney epithelial cell (LLCPK1) monolayers of 21 x 10^{-6} cm/sec. Since the drug is practically insoluble in water, and the *in vitro* permeability is low, a BCS Class 4 designation was assigned.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

Throughout the clinical development program for apremilast, the sponsor used 4 different formulations the compositions of which are described in Table 22 and the clinical development phases in which in one of these formulations were employed is shown in Table 23.

Table 22: Compositions of the Different Apremilast Formulations Employed in its Clinical Development Program

	Formula 1	Formula 2	Formula 3	Formula 4
Dosage Form	gelatin capsules 10 mg (white to off-white) 20 mg (white to off-white) 50 mg (white to off-white)	round film-coated tablets 10 mg (white to off-white) 20 mg (white to off-white) 30 mg (white to off-white) 40 mg (white to off-white)	modified diamond shape film-coated tablets 10 mg (pink) 20 mg (brown) 30 mg (beige)	modified diamond shape film-coated tablets 10 mg (pink) 20 mg (brown) 30 mg (beige)
Compositions	apremilast	apremilast	apremilast	apremilast
	silicified microcrystalline cellulose	microcrystalline cellulose	microcrystalline cellulose	microcrystalline cellulose
	lactose monohydrate	lactose monohydrate	lactose monohydrate	lactose monohydrate
	croscarmellose sodium	croscarmellose sodium	croscarmellose sodium	croscarmellose sodium
	magnesium stearate	magnesium stearate	magnesium stearate	magnesium stearate
	size 1 capsules	(b) (4)	(b) (4) (b) (4)	(b) (4)

Source: Table 3 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 23: Clinical Development Phase in which each Apremilast Formulation was Employed

Formulations	Clinical Studies
Drug substance	Toxicology studies
Formulated capsules (Formula 1)	Phase 1 and 2
White round film-coated tablets (Formula 2)	Phase 1 and 2
Phase 3 tablets (Formula 3)	Phase 2, 3 and stability studies
Commercial tablets (Formula 4)	Phase 1 (Clinical Pharmacology) and stability studies

The following information with respect to bridging different formulations used in apremilast clinical development program is extracted from Dr. Minerva Hughes's filing review in DARRTS dated 5/9/2013:

The proposed drug product is a diamond shaped tablet manufactured using (b) (4) (b) (4) *The phase 1 studies used a capsule formulation. During phase 2 studies, a white-round table was used. A comparative bioavailability study was conducted to compare the phase 2 tablets with the phase 1 capsule formulation. The tablet formulation was further modified for phase 3 studies* (b) (4) *The proposed commercial product has the same* (b) (4) *as the phase 3 material, however, the* (b) (4) *are different. The Applicant seeks to bridge the phase 3 and commercial product using in vitro dissolution. Comparative dissolution studies using the Phase 3 and commercial tablets have been conducted using media at 3 different pHs (1.2, 4.5 and 6.8).*

At the time of writing this review, no major concerns with regards to sponsor's proposed methods of bridging different formulations had been identified. For the final determination on this aspect, refer to Dr. Hughes's Biopharmaceutics review for apremilast.

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Study CC-10004-CP-022 evaluated the effect of a standard high fat breakfast on the PK of the commercial formulation of apremilast (30 mg tablet). Mean plasma apremilast concentration versus time profiles were similar after administration of a single 30 mg apremilast tablet under fasted (overnight for 10 hours) and fed conditions (Table 24).

Table 24: Summary of Plasma Pharmacokinetic Parameters of Apremilast by Treatment (Pharmacokinetic Population)

Parameter (Unit)	Single 30-mg Apremilast Tablet	
	Fasted (N = 45)	Fed (N = 44)
AUC_∞ (ng·h/mL)[a]	3157.96 (34.6)	3506.19 (33.9)
AUC_t (ng·h/mL)[a]	3083.05 (34.0)	3436.39 (33.0)
C_{max} (ng/mL)[a]	339.86 (26.5)	333.85 (30.0)
t_{max} (h)[b]	2.50 (0.62, 5.02)	3.00 (1.00, 8.00)
$t_{1/2}$ (h)[a]	8.88 (21.2)	7.99 (18.9)
CL/F (mL/h)[a]	9499.80 (34.6)	8556.28 (33.9)
Vz/F (mL)[a]	121735.96 (38.2)	98582.15 (28.0)

Source: Table 6 of report CC-10004-CP-022

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so, were they bioequivalent or not?

The proposed to be marketed formulation is different from the ones used in phase 1, 2 and 3 studies as indicated in section 2.8.2. A dose proportionality study with the 3 strengths of the final to be marketed formulation (10, 20 and 30 mg) was not conducted. However the sponsor has provided dissolution data with 10 and 30 mg tablets which will be reviewed by the Biopharmaceutics reviewer Dr. Minerva Hughes.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The sponsor indicates that apremilast (S enantiomer [CC-10004]), (b) (4) (racemate of apremilast (b) (4) and the metabolites of apremilast (CC-10055 [M7]; CC-16166 [M12]; CC-16793 [M14] and CC-16557 [M16]) were analyzed using validated high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods. In addition, the quantitative analysis of methotrexate (MTX), 7-hydroxy methotrexate (7-OH MTX), ethinyl estradiol (EE), norgestimate (NGM) and 17-deacetyl norgestimate (17-DNE) for DDI studies was also accomplished by validated LC-MS/MS methods.

The assay performance standards (range, accuracy and precision) for the various validation methods employed in the clinical development of apremilast for PsA are summarized below in Table 25. Only studies that were actually reviewed for this application are included. The performances of the assays seem acceptable.

Table 25: Summary of Bioanalytical Assay Performance for Apremilast (CC-10004), [redacted] (Racemate of CC-10004 [redacted]), Apremilast Metabolites (M7, M12, M14, and M16), [14C]-CC- 10004 and other Co-Medications from Clinical Studies

Clinical Study	Bioanalytical Report Celgene Study No. (CRO Study No.)	Validation Report Celgene Validation No. (CRO Validation No.) [matrix-anticoagulant stabilization]	Assay Performance[a]			
			Analyte (method utilized)	Calibration Range (ng/mL)	Quality Control	
					Precision (%CV)	Accuracy (%RE)
CC-10004-PSA-001	CC-10004-PSA-001-BA [redacted]155-0703)	CC-10004-DMPK-005 [redacted]155-0420) [Plasma–hep, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤10.9	-1.4 to 2.0
CC-10004-PSA-002	CC-10004-PSA-002-BA [redacted]155-1023)	CC-10004-DMPK-024 [redacted]155-0701) [Plasma-hep, citric acid][e]	CC-10004 (achiral LC-MS/MS)	1-1000	≤10.5	-4.4 to 2.7
CC-10004-PK-001	[redacted]1398/371	[redacted]1398/203-D0142) [Plasma–hep]	CC-10004 (achiral LC-MS/MS)	2-200	≤10.2	-0.3 to 4.0
	[redacted]1398/372	[redacted]1398/202-D0142) [Urine, 1:1 SB]	CC-10004 (achiral LC-MS/MS)	20-4000	NA	-7.3 to -5.2
CC-10004-PK-002	CC-10004-PK-002-BA [redacted]05801)	CC-10004-DMPK-015 [redacted]05083) [Plasma–hep, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	NA	-12.5 to 6.7
		CC-10004-DMPK-015 [redacted]05083) [Plasma–hep, 1:1 SB/A]	[redacted]	1-1000	NA	-10.4 to 7.7
CC-10004-PK-005	CC-10004-PK-005-BA-1 [redacted]155-0512A/B)	CC-10004-DMPK-005 [redacted]155-0420) [Plasma–hep, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤8.1	-1.7 to 4.2
		CC-10004-DMPK-005 [redacted]155-0420) [Plasma–hep, 1:1 SB/A]	[redacted]	1-1000	≤12.7	-0.7 to 3.7
		CC-10004-DMPK-010 [redacted]155-0507) [Urine, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤12.5	-2.4 to -0.5
		CC-10004-DMPK-010 [redacted]155-0507) [Urine, 1:1 SB/A]	[redacted]	1-1000	≤15.5[e]	-2.0 to 3.7
	CC-10004-PK-005-BA-2 [redacted]155-0512C)	CC-10004-DMPK-011 [redacted]155-0508) [Plasma–hep, 1:1 SB/A]	CC-10055 (M7) (achiral LC-MS/MS)	0.3-300	≤10.8	2.1 to 9.8
	CC-10004-PK-005-BA-3 [redacted]155-0512D)	CC-10004-DMPK-013 [redacted]155-0511) [Urine, 1:1 SB]	CC-10055 (M7) (achiral LC-MS/MS)	1-1000	≤11.7	-7.3 to 9.7
CC-10004-PK-007	CC-10004-PK-007-BA-01 [redacted]155-0604)	CC-10004-DMPK-010 [redacted]155-0507) [Urine, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤13.0	-3.2 to -1.8
	CC-10004-PK-007-BA-02 [redacted]06030)	CC-10004-DMPK-015 [redacted]05083) [Plasma–hep, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤8.97	-3.3 to -1.2
			[redacted]	1-1000	≤9.9	-3.3 to 0.8
CC-10004-PK-008	CC-10004-PK-008-BA [redacted]155-0816A/B)	CC-10004-DMPK-005 [redacted]155-0420) [Plasma–hep, 1:1 SB/A]	CC-10004 (chiral LC-MS/MS)	1-1000	≤12.2	-4.0 to 0.3
		CC-10004-DMPK-022 [redacted]155-0807) [Plasma–hep, 1:1 SB/A]	CC-16166 (M12) (achiral LC-MS/MS)	2-1000	≤9.5	-7.1 to 0.2
			CC-16793 (M14) (achiral LC-MS/MS)	1-100	≤10.6	-7.7 to 3.3
			CC-16557 (M16) (achiral LC-MS/MS)	1-100	≤5.5	-5.4 to -0.5
CC-10004-PK-010	CC-10004-PK-010-BA [redacted]155-0902A/B)	CC-10004-DMPK-024 [redacted]155-0701) [Plasma-hep, citric acid][f]	CC-10004 (achiral LC-MS/MS)	1-1000	≤7.2	-6.7 to 8.3
		[redacted]42-0822) [Plasma-hep]	Methotrexate (achiral LC-MS/MS)	1-500	≤4.8	0.5 to 3.2
			7-Hydroxy Methotrexate (achiral LC-MS/MS)	1-500	≤4.3	0.7 to 2.9

CC-10004-CP-011	CC-10004-CP-011-BA-1 (b) (4)155-1036A)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤4.2	-4.8 to 0.4
	CC-10004-CP-011-BA-2 (b) (4)155-1036B)	CC-10004-DMPK-037 (b) (4)155-0911) [Plasma-hep, citric acid][c]	CC-16166 (M12) (achiral LC-MS/MS)	5-1000	≤5.1	-9.0 to -2.4
CC-10004-CP-012	CC-10004-CP-012-BA-1 (b) (4)155-1016A)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤6.1	-6.0 to 1.7
	CC-10004-CP-012-BA-2 (b) (4)155-1016B)	CC-10004-DMPK-037 (b) (4)155-0911) [Plasma-hep, citric acid][c]	CC-16166 (M12) (achiral LC-MS/MS)	5-1000	≤2.6	-6.3 to 0.5
	CC-10004-CP-012-BA-3 (b) (4)109/US/004)	CC-10004-DMPK-033 (b) (4)109/US/003M) [Plasma-hep, citric acid][c]	[^{14}C]-CC-10004 (HPLC-AMS)[a]	0.05-20 (dpm/mL)	≤29.0[b]	NA
CC-10004-CP-018	CC-10004-CP-018-BA (b) (4)155-1035)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤4.5	-5.2 to 0.2
CC-10004-CP-019	CC-10004-CP-019-BA-1 (b) (4)155-1101A)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤4.3	-2.3 to 0.8
	CC-10004-CP-019-BA-2 (b) (4)155-1101B)	CC-10004-DMPK-037 (b) (4)155-0911) [Plasma-hep, citric acid][c]	CC-16166 (M12) (achiral LC-MS/MS)	5-1000	≤7.9	-7.9 to -0.3
CC-10004-CP-020	CC-10004-CP-020-BA-1 (b) (4)155-1107)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤7.8	-2.0 to 2.7
	CC-10004-CP-020-BA-2 (b) (4) CEL-R1833R1)	(b) (4)R1676 [Plasma-hep, citric acid][c]	Ethinyl Estradiol	2-1000 (pg/mL)	≤5.4	1.0 to 3.3
			Norgestimate	5-2500 (pg/mL)	≤8.9	0.0 to 2.7
			17-Desacetyl norgestimate	5-2500 (pg/mL)	≤6.4	-0.8 to 1.8
CC-10004-CP-022	CC-10004-CP-022-BA	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤4.5	-1.7 to 5.7
CC-10004-CP-024	CC-10004-CP-024-BA (b) (4)155-1203)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤5.1	-2.0 to 7.7
CC-10004-CP-025	CC-10004-CP-025-BA-1 (b) (4)155-1205A)	CC-10004-DMPK-024 (b) (4)155-0701) [Plasma-hep, citric acid][c]	CC-10004 (achiral LC-MS/MS)	1-1000	≤6.0	-3.3 to 5.3
	CC-10004-CP-025-BA-2 (b) (4)155-1205B)	CC-10004-DMPK-1232 (b) (4)155-1108) [Dry Blood Spot]	CC-10004 (achiral LC-MS/MS)	1-1000	≤4.3	-3.7 to 1.5

3. Detailed Labeling Recommendations

At the time of writing this review, the following relevant modifications were suggested to be made to the label from a clinical pharmacology perspective. In addition, the labeling language was modified in several places to reduce redundant information as well as include information that is considered important. As the label is not finalized at this time, the reader is referred to the post-approval labeling of this product for final recommendations made by the review team.

HIGHLIGHTS OF PRESCRIBING INFORMATION

i. Add under DOSAGE AND ADMINISTRATION: Dosage in Severe Renal Impairment: Reduce dose to 30 mg once daily (2.1)
ii. Add under WARNINGS AND PRECAUTIONS: Drug Interactions: Use of CYP P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with TRADE NAME is not recommended (5.2)
iii. Add under DRUG INTERACTIONS: Potent inducers of CYP enzymes (e.g., rifampin): Avoid co-administration as loss in efficacy may occur (5.2, 7.1)
iv. Add under USE IN SPECIFIC POPULATIONS: Severe renal impairment: Increased systemic exposure of TRADE NAME is observed, reduction in daily dose is recommended (2.2, 8.6)

SECTION 2, DOSAGE AND ADMINISTRATION, 2.2: Dosage Adjustment in Patients with Severe Renal Impairment

i. Add to section 2.2: For initial dosage titration in this group, it is recommended that TRADE NAME be titrated using only the AM schedule listed in Table 1 and the PM dose be skipped

SECTION 5, WARNINGS AND PRECAUTIONS

i. Add section 5.2: Drug Interactions: Co-administration of cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of TRADE NAME. Therefore, the use of cytochrome P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with TRADE NAME is not recommended. [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

SECTION 12, PHARMACOKINETICS

Add section 12.6: Cardiac Electrophysiology: At a dose 1.67 times the maximum recommended dose, DRUGNAME does not prolong QTc to any clinically relevant extent.

4. Appendices

4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

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

1.1.1 Did the sponsor characterize the dose-response relationship for safety and efficacy variables?

Yes. The sponsor characterized the dose-response relationship for both Apremilast safety and efficacy.

Dose-Response in Efficacy

In each of the 3 pivotal studies, a statistically significantly greater proportion of subjects in both apremilast treatment groups achieved the primary endpoint of ACR 20 response at Week 16 compared with placebo, as evaluated in Table 1. Similar ACR 20 responses were seen across studies, with a dose effect observed in Studies PSA-002 and PSA-004.

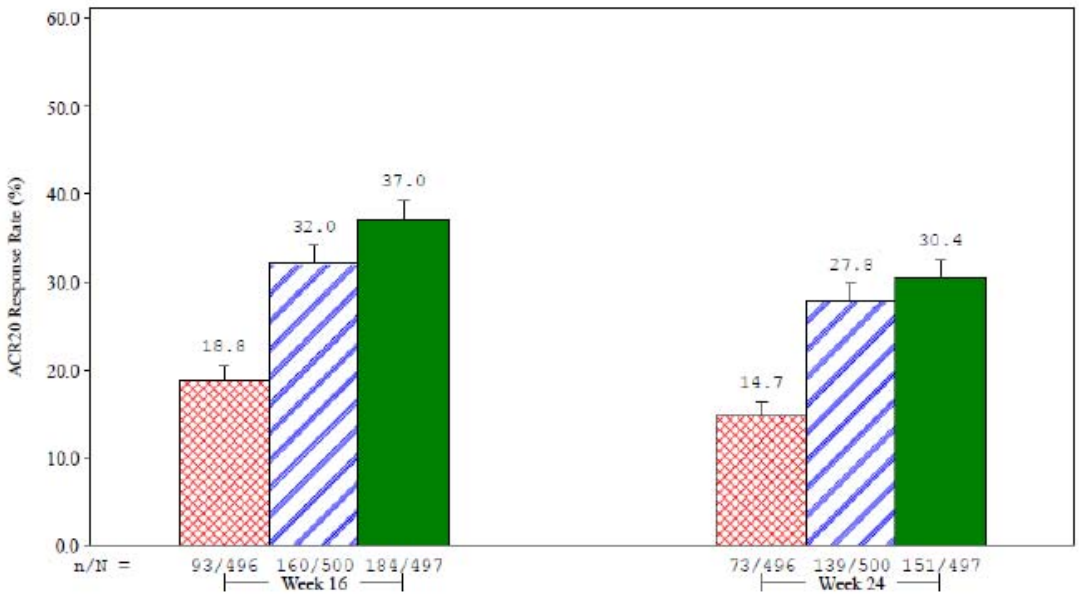
Table 1. Primary Endpoint: Proportion of Subjects Achieving ACR 20 at Week 16 in Studies PSA-002, PSA-003, and PSA-004

	Placebo	APR 20 BID			APR 30 BID		
Study	n/N (%)[a]	n/N (%)[a]	Trt. Effect[b]	P-value[c]	n/N (%)[a]	Trt. Effect[b]	P-value[c]
PSA-002	32/168 (19.0)	51/168 (30.4)	11.3	**0.0166**	64/168 (38.1)	19.0	**0.0001**
PSA-003	30/159 (18.9)	61/163 (37.4)	18.7	**0.0002**	52/162 (32.1)	13.4	**0.0060**
PSA-004	31/169 (18.3)	48/169 (28.4)	9.8	**0.0295**	68/167 (40.7)	22.3	**< 0.0001**

Source: Sponsor's summary-clin-efficacy-psoriaticarthritis.pdf, Pg40, Table 10

The pooled analysis demonstrated that a nominally significantly greater proportion of subjects in the APR 20 BID and APR 30 BID treatment groups achieved the primary endpoint of ACR 20 response at Week 16 compared with placebo. The treatment effects in ACR 20 response rates were maintained at Week 24. A dose effect was observed in the pool analysis as well (Figure 1).

Figure 1. ACR 20 Responses at Weeks 16 and 24 (Pooled Analysis)



Source: Sponsor's summary-clin-efficacy-psoriaticarthritis.pdf, Pg91, Figure 9

Dose-Response in Safety

In the PsA phase 3 safety data pool, a dose-related safety relationship was observed. The adverse drug reactions with the highest frequency in subjects as treated for up to 16 weeks were diarrhea, nausea, and headache. A higher incidence of diarrhea (Placebo: 2.8%, APR 20: 9.3%, APR 30: 13.9%), nausea (Placebo: 4.4%, APR 20: 7.2%, APR 30: 11.7%), and headache (Placebo: 4.0%, APR 20: 6.3%, APR 30: 8.5%) were reported in the APR 30 BID group than in the APR 20 BID group and in placebo group.

In the PsA phase 3 safety data pool, the proportion of subjects who discontinued treatment due to any adverse drug reaction was higher in the apremilast-treated 30mg BID subjects (Placebo: 1.2%, APR 20: 2.5%, APR 30: 4.6%). The adverse drug reactions leading to drug withdrawal were nausea (Placebo: 0.6%, APR 20: 1.1%, APR 30: 1.8%), diarrhea (Placebo: 0.6%, APR 20: 0.8%, APR 30: 1.8%), and headache (Placebo: 0.4%, APR 20: 0.4%, APR 30: 1.2%).

1.1.2 Is dose titration scheme appropriate?

Answer: *Yes. The dose titration scheme seems appropriate due to amelioration of GI AEs typically associated with PDE4 inhibitors.*

In the PsA clinical program, titration was implemented based on Phase 1 data (CC-10004-PK-007) in order to ameliorate GI AEs typically associated with PDE4 inhibitors. The dose titration schedule in study PK-007 was 10 mg QD on Days 1 - 3, 20 mg QD on Days 4 - 6, and 40 mg QD on Days 7 – 14. Comparing 40 mg QD dose without titration and 40 mg QD dose with titration, dose titration appears to improve the safety profile (Table 2). The proportion of subjects who reported nausea was lower by the dose group of 40 mg QD with titration (43%) than that by the dose group of 40 mg QD without titration. The dose titration group has fewer total number of AEs reported (34 AE

reported by the group of 40 mg QD with dose titration; 72 AEs reported by the group of 40 mg QD without titration).

Table 2. 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

In four PsA phase 3 studies, subjects with active PsA were randomized to receive APR 20 BID and APR 30 BID for the 24-week, placebo-controlled phase. All Apremilast arms were dose titrated over the first week of treatment. The dose titration strategies in PsA phase 3 studies are in table 3.

Table 3 Initial titration schedule in PsA phase 3 studies

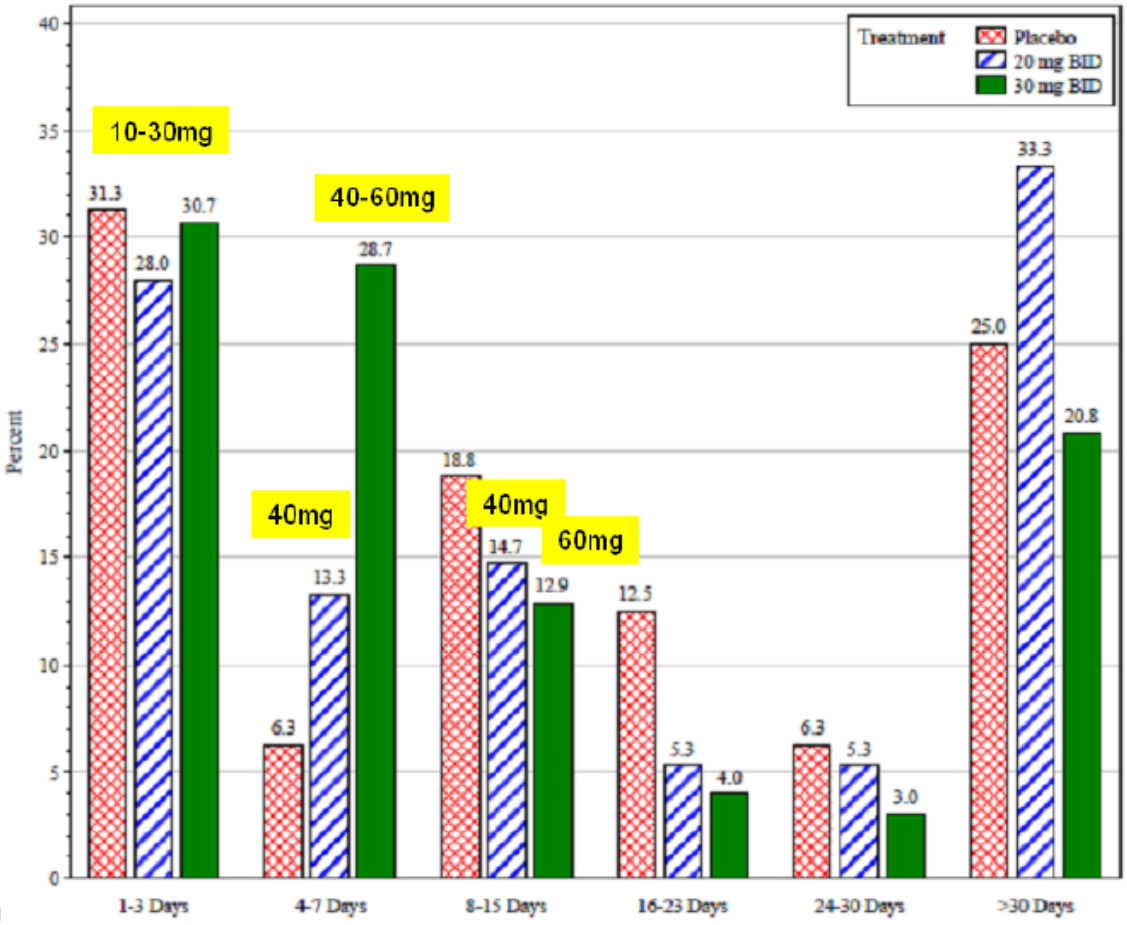
Study	Dose	Day1	Day2		Day3		Day4		Day5		Day6 & after	
		AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
PsA-002 PsA-003	20BID	10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
PsA-004 PsA-005	30BID	10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

In the PsA phase 3 safety data pool, the majority of diarrhea (Placebo: 56.3%, APR 20: 60.3%, APR 30: 72.5%), nausea (Placebo: 38.5%, APR 20: 70.7%, APR 30: 70.1%), headache (Placebo: 62.5%, APR 20: 50.8%, APR 30: 63.6%) events occurred within the first 15 days of drug exposure. Headache (Placebo: 75.0%, APR 20: 65.6%, APR 30: 56.1%), diarrhea (Placebo: 56.3%, APR 20: 47.4%, APR 30: 34.9%) and nausea (Placebo: 61.5%, APR 20: 55.2%, APR 30: 40.2%) resolved within 15 days.

Diarrhea is the AE with highest frequency in PsA patients treated with Apremilast. 60% diarrhea in APR arms occurred during the first week of treatment (Figure 2). At the first 3 days, both APR 20 and APR 30 received the same dose from 10mg to 30mg daily dose and have similar proportion (30%) diarrhea events as that in placebo. During day 4 to day

7, APR 20 received 40mg daily dose while APR 30 received titration daily dose from 40 mg to 60 mg. The occurrence rate of diarrhea was 28.7% in APR 30 but reduced to 6.3% in placebo and 13.3% in APR 20. After the first week, patient demonstrated tolerance to the drug and the occurrence rate of diarrhea in APR arms was comparable to placebo.

Figure 2. Diarrhea Events by Onset Day (Pooled Analysis)



Source: Reviewer's analysis

1.1.3 Is dose regimen for renal impairment population appropriate?

Answer: Yes. PK simulations indicate 30 mg QD dose in severe renal impairment patients leads to exposure similar to 30 mg BID in normal PsA patients. In addition, we propose an initial titration schedule for patients with severe renal impairment: 10mg QD on day 1-3, 20mg QD on day 4-5 and 30mg QD on day 6 and after.

We conducted simulations to compare the plasma concentration with various dosing regimens for 10 days in normal PsA patients and severe renal impairment PsA patients. Summary of plasma concentrations by scheduled time from subjects with severe renal impairment and matched healthy subjects was obtained from clinical study CC-10004-CP-019. By using a one-compartment PK model, clearance (CL/F), volume (V/F), and the rate constant of the initial ascending phase (K_a) for both severe renal impairment (CL/F=5.3 L/h; V/F=74.3 L; K_a=0.67 h^{-1}) and matched healthy subjects (CL/F=12.3 L/h;

V/F=93.4 L; K_a=0.72 h^{-1}) were obtained. The ratio of parameters for CL/F, V/F, and K_a between severe renal impairment and matched healthy subjects are the severe renal impairment factors. Clinical study PsA-002 is the only phase 3 study which collected PK samples. In PsA-002 PPK analysis, sponsor provided the final equation for CL/F, V/F, and K_a of apremilast by considering weight, gender and PsA disease status (Table 3). Multiplying table 3 parameters by the severe renal impairment factors (CL/F=0.43, V/F=0.80, and K_a =0.93), PK estimates for severe renal impairment patients with PsA disease were derived.

Table 3. Typical values of PK parameters derived with the final PK model of apremilast

Population PK Parameter	**Typical Values (RSE%)**
CL/F (L/h)	11.5 (6.8)
Disease status	
If PSA =	x 0.638 (6.6)
If other/missing =	x 0.761 (13.5)
Body weight	$x\ (WT/85.7)^{0.309\ (52.8)}$
Sex	
If Male =	x 1.18 (5.4)
Vc/F (L)	129 (3.4)
Disease status	
If PSA =	x 0.757 (6.6)
If other/missing =	x 0.722 (9.6)
Body weight	$x\ (WT/85.7)^{0.823\ (21.0)}$
Ka (h^{-1})	1.61 (13.8)

Source: Sponsor's PSA002PK.pdf, Pg 12

Typical values of PK parameters derived from a PsA female patient with 70kg weight and severe renal impairment condition are shown below:

$CL/F=11.5*(70/85.7)^{0.309}*0.638*0.43=7.38$

$V/F=129*(70/85.7)^{0.823}*0.757*0.8= 82.7$

$K_a=1.61*0.93=1.50$

Figure 3 shows the apremilast plasma concentrations for

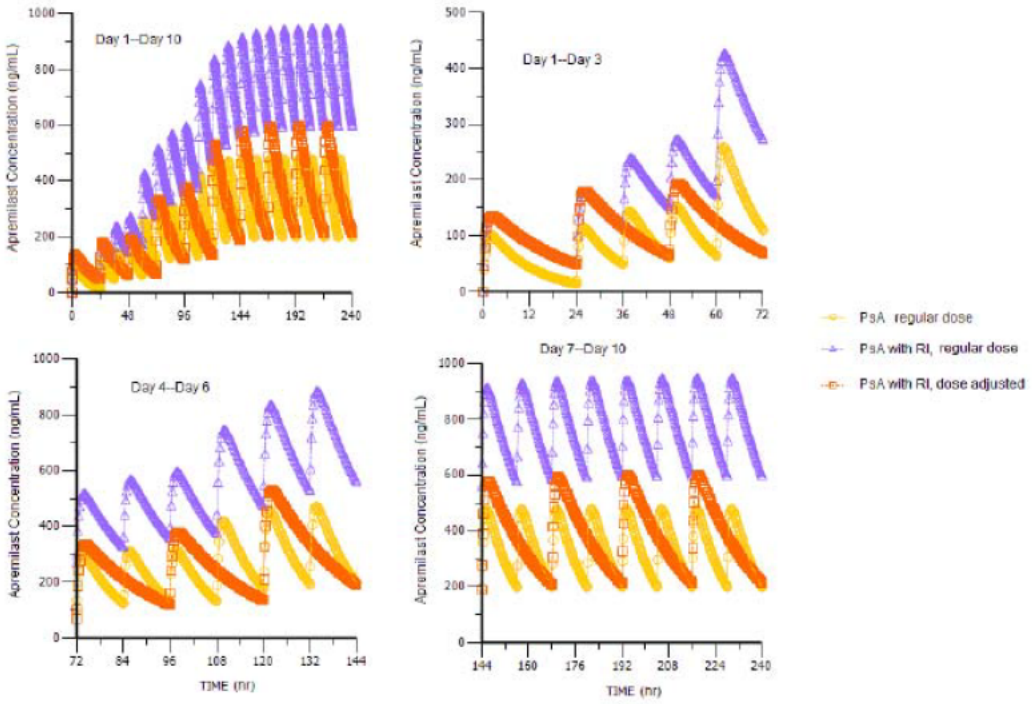
1) normal PsA patients with regular titration dose (10mg day 1, 20mg day 2, 30mg day 3, 40mg day 4, 50mg day 5 and 60 mg day 6 and after);

2) severe renal impairment PsA patients with regular titration dose (10mg day 1, 20mg day 2, 30mg day 3, 40mg day 4, 50mg day 5 and 60 mg day 6 and after);

3) severe renal impairment PsA patients with titration dose adjusted (10mg day 1, 10mg day 2, 10mg day 3, 20mg day 4, 20mg day 5 and 30 mg day 6 and after).

PK simulations indicate that the proposed titration dose in severe renal impairment leads to exposure similar to regular titration dose in normal PsA patients.

Figure 3. 10-day apremilast concentration for normal PsA patients and severe renal impairment PsA patients



Source: Reviewer's analysis

1.2 Recommendations

The proposed labeling guidelines for patients with severe renal impairment should be considered.

1.3 Label Statements

Section 2.2 Patients with Severe Renal Impairment

TRADE NAME dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CLcr) of less than 30 mL per minute estimated by the Cockroft–Gault equation) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. (b) (4)

(b) (4)

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

Apremilast is a novel, oral small molecule inhibitor of phosphodiesterase 4 (PDE4) that modulates pro- and anti-inflammatory mediators. It is developed for the treatment of adult patients with active psoriatic arthritis. 5 clinical studies (Table 4) include 1

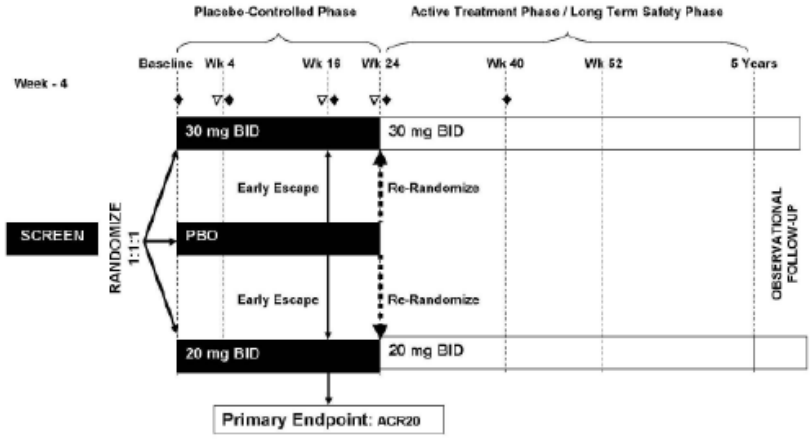
randomized, double-blind Phase 2 study (Study CC-10004-PSA-001) and 3 pivotal Phase 3 studies (Studies CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004). A fourth placebo-controlled Phase 3 PsA study (PSA-005) which used apremilast as monotherapy without background DMARDs is ongoing. Since the data are still blinded, efficacy results were not included in the submission.

Table 4: Description of Clinical Studies of Apremilast in Psoriatic Arthritis

Study #	Patients N (Dropout %)	Study Design	Apremilast Dosing	Primary Endpoint
Phase 2				
PSA-001	204 (19%)	R, DB, PC, PG	APR 40 mg QD APR 20 mg BID	ACR 20 @ Day 85
Phase 3				
PSA-002	504 (12%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-003	488 (11%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-004	505 (13%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-005	528 (n/a) R, DB, PC, PG	APR 20 mg BID	APR 30 mg BID	ACR 20 @ Week 16
	DMARD-naive, APR monotherapy Study---ONGOING			

The three global, pivotal Phase 3 studies of apremilast in PsA (Studies PsA-002, PsA-003, and PsA-004) studied 2 active treatment groups and consisted of 2 treatment phases: a 24-week, randomized, double-blind, placebo-controlled phase, and a 236-week active-treatment/long-term safety phase (Figure 4).

Figure 4: Study Design Schematic (Studies PSA-002, PSA-003, and PSA-004)



Source: Sponsor's Clinical-overview.pdf, Pg 23, Figure 1

3 RESULTS OF SPONSOR'S ANALYSIS

PK samples from a total of 258 subjects across 6 studies (CC-10004-PSA-002 and CC-10004-PSA-001-PK, as well as the data from 4 Phase 1 studies CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, and CC-10004-PK-010) who were given a dose of

apremilast and for which blood samples were collected after apremilast administration were available for the population PK analysis. The number of plasma samples collected after apremilast administration that were provided for the population PK analysis in the various treatment groups is presented in Table 5.

Table 5. Number of Plasma Samples for Population PK Analysis of Apremilast

Week	Number of Plasma Samples						
	20 mg - single dose	20 mg BID	30 mg BID	40 mg - single dose	40 mg QD	50 mg BID	Population PK Analysis
Single Dose	298	NA	NA	763	NA	NA	**1061**
Week 1	NA	17	819	NA	13	550	**1399**
Week 4	NA	110*	48	NA	45*	NA	**203**
Week 12	NA	150**	NA	NA	130**	NA	**280**
Week 16	NA	41	42	NA	NA	NA	**83**
Week 24	NA	53	51	NA	NA	NA	**104**
Total	**298**	**371**	**960**	**763**	**188**	**550**	**3130**

Source: Sponsor's PSA002PK.pdf, Pg 31, Table 3

Plasma concentration-time profiles of apremilast were modeled with a one-compartment model with first-order absorption (Ka) and lag time. The covariates tested were age, weight, height, body mass index (BMI), ideal body weight, lean body mass weight, creatinine clearance, sex, race, smoking status, and PsA disease status.

The conclusions are:

The final population PK model of apremilast identified disease status of having PSA, sex and body weight as statistically significant covariates on apremilast apparent clearance, while body weight and disease status of having PSA as statistically significant covariate on Vc/F.

1) Typical apremilast $AUC_{0-\tau,ss}$ exposure in subjects with PSA (CC-10004-PSA-001-PK and CC-10004-PSA-002) is ~1.4 fold of that in healthy subjects (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008) (i.e., 3455.5 ng.h/mL versus 2490.4 ng.h/mL).

2) Lower body weight and being female are associated with higher apremilast exposure. However, the exposure difference attributed to body weight and sex was generally less than 26% and well within the expected between subject variation.

Typical values (i.e., geometric means) of PK parameters derived with the final PK model of apremilast are presented in Table 6.

Table 6. Population PK Parameters of Apremilast Derived from the Final PK Model

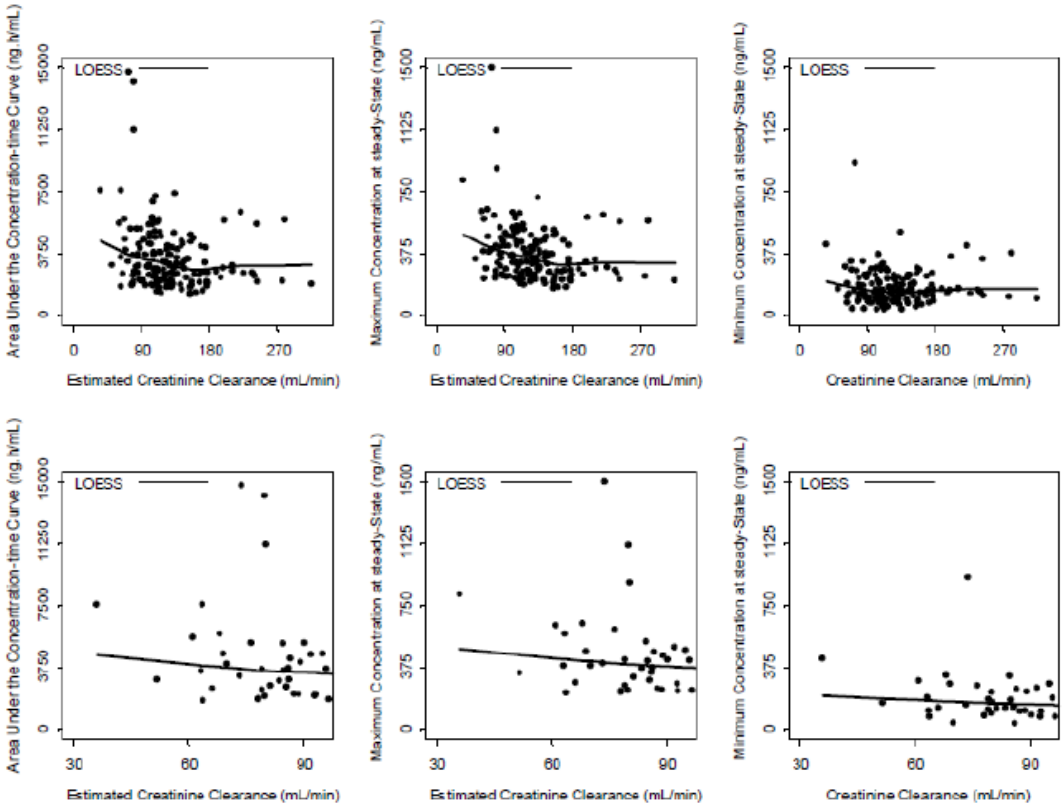
Population PK Parameter	Typical Values (RSE%)	Between Subject Variability (%) (RSE%)
CL/F (L/h)	11.5 (6.8)	39.1 (5.7)
Disease status		
If PSA =	x 0.638 (6.6)	
If other/missing =	x 0.761 (13.5)	
Body weight	x $(WT/85.7)^{0.309\ (52.8)}$	
Sex		
If Male =	x 1.18 (5.4)	
Vc/F (L)	129 (3.4)	28.4 (6.4)
Disease status		
If PSA =	x 0.757 (6.6)	
If other/missing =	x 0.722 (9.6)	
Body weight	x $(WT/85.7)^{0.823\ (21.0)}$	
Ka (h^{-1})	1.61 (13.8)	69.6 (12.3)
Lag (h)	0.272 (17.2)	0 Fix (NA)
Error Model		
Proportional Error (%)	36.7 (4.0)	NA

Source: Sponsor's PSA002PK.pdf, Pg 44, Table 10

Mild And Moderate Renal Impairment

Although the effect of mild and moderate renal impairment on apremilast PK was not directly assessed in the clinical study, population PK analyses in approximately 54 subjects with mild (n = 48) to moderate (n = 6) renal impairment (creatinine clearance [CLcr] of 60 to 89 mL/min and 30 to 59 mL/min, respectively) and PsA showed the predicted apremilast exposure does not appear to correlate with creatinine clearance, suggesting mild to moderate renal impairment may not meaningfully affect apremilast clearance (Figure 12.2.2.5). Thus, apremilast can be given to subjects with mild renal impairment without dose adjustment.

Figure 12.2.2.5 Relationship between Exposure Parameters of Apremilast at Steady-State and Creatinine Clearance (CC-10004-PSA-001-PK and CC-10004-PSA-002)



Source: Sponsor's PSA002PK.pdf, Pg 70, Figure 12.2.2.5

Reviewer's Comments: The population pharmacokinetic analysis conducted by the sponsor is reasonable.

4 REVIEWER'S ANALYSIS

See section 1

4.1 Introduction

N/A

4.2 Objectives

N/A

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in

Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
CP-019	cp019-csv.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Apremilast_NDA205437_LZ\Sponsor Data and Reports\Renal\datasets

4.3.2 Software

SAS 9.2, SPLUS 8.0 and Phoenix WinNonlin 6.3

4.3.3 Models

N/A

4.4 Results

N/A

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
RI.phxproj	Severe Renal Impairment Simulation	Reviews\Ongoing PM Reviews\Apremilast_NDA205437_LZ\ER Analyses\Final Model

4.2. Individual Study Reviews

Note –
In this review, early development name **CC-10004** is used to refer to apremilast, which is an S-enantiomer, [redacted] (b) (4) is used to refer to the racemic mixture of S-apremilast [redacted] (b) (4).

Unless otherwise noted, the data and the results (tables and figures) provided are extracted from sponsor provided reports and found to be generally acceptable by this reviewer. Thirteen *in vitro* and thirteen *in vivo* clinical pharmacology studies were reviewed. Reviewer's comments are included under 'Conclusion' for the *in vitro* studies and under 'Reviewer's Comments' for the *in vivo* studies.

ADME In-Vitro STUDIES

Absorption and Transporters

Report # CC-10004-DMPK-017
Title: Assessment of the Interaction of CC-10004 with Human P-g1ycoprotein

Objective: To determine the solubility of CC-10004 in assay buffer, and to determine if CC-10004 interacts with the xenobiotic transporter, human P-glycoprotein (P-gp), as a substrate and inhibitor.

Method: Part 1: Time Dependence of Permeability and Transport
The apparent permeability rate (P_{app} x 10^{-6} cm/sec) of CC-10004 was determined in control and P-gp-expressing cell monolayers, in the A (apical) to B (basolateral) and B to A directions. One concentration (10 µM), three incubation time points of 60, 90 and 120 minutes, and duplicate monolayers per condition were used. LC/MS/MS analysis was performed to quantify CC-10004 in the assay samples.

Method Part 2: Concentration Dependence of P-gp Mediated Transport
The A to B and B to A P_{app} of CC-10004 was determined in control and P-gp-expressing cell monolayers using a six point concentration range (1, 3, 10, 20, 35, 50 µM). Additionally, the effect of co-incubated 30 µM ketoconazole on the bi-directional P_{app} of 10µM CC-10004 was assessed. One time point of 90 minutes and duplicate monolayers per condition were used. LC/MS/MS analysis was performed to quantify CC-10004 in the assay samples. The rate of P-gp facilitated transport was calculated and the K_m and V_{max} were determined.

Method Part 3: P-glycoprotein Inhibition
The ability of CC-10004 to inhibit the P-glycoprotein transporter was assessed by measuring the A to B and B to A P_{app} of model P-gp substrate 5 µM [^{3}H]-digoxin in Pgp-expressing cell monolayers, in the presence and absence of CC-10004. Ten CC-10004 concentrations of 0.01, 0.03, 0.08, 0.20, 0.51, 1.3, 3.2, 8.0, 20 and 50 µM, one time point

of 90 minutes, and duplicate monolayers per condition were used. Analysis of [^{3}H]-digoxin in the assay samples was performed with liquid scintillation counting. The percent inhibition of P-gp mediated digoxin transport was determined.

Results and Conclusions Part 1: CC-10004 was assayed in the control and P-gp expressing cell monolayers using a donor concentration of 10 µM, and incubation times of 60, 90 and 120 minutes. Efflux ratios and net efflux ratios were calculated at each incubation time point to determine the extent of any P-gp mediated transport of CC-10004. The net efflux ratio for the positive control P-gp efflux substrate, digoxin, was 3, and the ratios for CC-10004 were 24 (60 minutes), 30 (90 minutes) and 27 (120 minutes), demonstrating that CC-10004 was transported by P-gp. The time dependence of P-gp facilitated transport of CC-10004 was linear over the time course tested. The intrinsic permeability of CC-10004 was determined from the P_{app} values measured in the A to B direction in the control cells. The determined P_{app} values were 26, 19 and 21 x 10^{-6} cm/sec at 60, 90 and 120 minutes respectively. Compared to P_{app} results of the permeability comparator drugs included in the assay and based on the US FDA Biopharmaceutics Classification System, CC-10004 was classified as a moderately permeable compound.

Results and Conclusions Part 2: Concentration-dependence of CC-10004 transport was determined over a range of 1 to 50 µM at one time point of 90 minutes, which was determined to be within the linear range of transport in Part 1. The net efflux ratios were > 3 at each concentration tested, and decreased with increasing concentration of CC-10004. These results demonstrate that CC-10004 was transported by P-gp in a concentration dependent manner. To further investigate the interaction of CC-10004 as a P-gp substrate, the ability of a known P-gp inhibitor, ketoconazole (30 µM) to inhibit P-gp mediated transport of CC-10004 (10 µM) was assessed. Ketoconazole inhibited CC-10004 by 92%.

Results and Conclusions Part 3: Inhibition of 5 µM [^{3}H]-digoxin efflux by increasing concentrations of CC-10004 (0.01, 0.03, 0.08, 0.20, 0.51, 1.3, 3.2, 8.0, 20, 50 µM) was measured in the P-gp-expressing cell line (22L1). No inhibition of digoxin activity was observed in the presence of 0.01 to 20 µM CC-10004. In the presence of 50 µM CC-10004, 31% inhibition of digoxin activity was determined. The results suggest that CC-10004 is not a P-gp inhibitor at concentrations < 20 µM, and could potentially be a weak inhibitor at > 50 µM. Results are shown below. This reviewer calculated the I1/IC50 and I2/IC50 values for P-gp inhibition by apremilast to be 0.015 and 5 respectively; indicating that the drug will likely not inhibit P-gp *in vivo.*

Report #CC-10004-DMPK-1347

Title: Evaluation of Substrate Potential of CC-10004 for Uptake (OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) and Efflux (BCRP) Transporters.

Objective: To assess the potential of CC-10004 to act as a substrate of the human organic anion transporter 1 (OAT1, SLC22A6), organic anion transporter 3 (OAT3, SLC22A8), organic cation transporter 2 (OCT2, SLC22A2), organic anion transporting polypeptide 1B1 (OATP1B1, SLCO1B1), organic anion transporting polypeptide 1B3 (OATP1B3, SLCO1B3) and human breast cancer resistance protein (BCRP, ABCG2)

transporters.

BCRP Method: The potential of CC-10004 to act as a substrate for human BCRP was measured using monolayers of porcine kidney epithelial LLC-PK1 cells transfected either with vector containing human BCRP cDNA or with vector only (control cells). The efflux ratios were measured for the transcellular transport of CC-10004 (1 and 10 μmol/L) across BCRP expressing cells and control cells in the absence and presence of the BCRP inhibitor, Ko143 (0.3 μmol/L). The net efflux ratios (R values) of CC-10004 were determined as Refflux-BCRP/Refflux-control.

BCRP Results and Conclusions: The efflux ratios of CC-10004 across BCRP expressing and control cells were determined to be 1.4 and 1.3 (1 μmol/L), 1.1 and 0.9 (10 μmol/L), respectively. The R values of CC-10004 were 1.1 (1 μmol/L) and 1.2 (10 μmol/L), indicating no BCRP mediated transcellular transport. In the presence of positive control inhibitor, Ko143 (0.3 μmol/L), the efflux ratio of CC-10004 was not changed in either BCRP expressing or control cells (both 1.3 for 1 μmol/L, 1.0 and 0.9 for 10 μmol/L). These results suggest that CC-10004 is not a substrate of BCRP. BCRP mediated transport of [3H] prazosin, the reference BCRP substrate, and the inhibition by Ko143 was observed as expected.

OAT1 and OAT3 Method: The potential of CC-10004 to act as a substrate for human OAT1 or OAT3 was measured using S2 cells transfected with vector containing human OAT1 cDNA or containing human OAT3 cDNA, as well as with vector only (control cells). The cleared volume was determined for CC- 10004 at 1 and 10 μmol/L in OAT1 expressing, OAT3 expressing, and control cells after 2- minute incubation. The cleared volume was also determined in the presence of OAT1 and OAT3 inhibitor, probenecid (100 μmol/L).

OAT1 and OAT3 Results and Conclusions: CC-10004 (1 and 10 μmol/L) showed comparable cleared volume into OAT1 expressing and control cell (29.6 and 34.7 μL/mg protein for 1 μmol/L, 40.5 and 42.1 μL/mg protein for 10 μmol/L). In the presence of positive control inhibitor, probenecid (100 μmol/L), the cleared volume of CC-10004 was not changed in either OAT1 expressing or control cells (48.4 and 52.2 μL/mg protein for 1 μmol/L, 43.2 and 44.5 μL/mg protein for 10 μmol/L). These results suggest that CC-10004 is not a substrate of OAT1. OAT1 mediated transport of [3H]p-aminohippuric acid, the reference OAT1 substrate, and the inhibition by probenecid was observed as expected.

CC-10004 (1 and 10 μmol/L) showed comparable cleared volume into OAT3 expressing and control cell (31.1 and 48.5 μL/mg protein for 1 μmol/L, 33.5 and 55.9 μL/mg protein for 10 μmol/L). In the presence of positive control inhibitor, probenecid (100 μmol/L), the cleared volume of CC-10004 was not changed in either OAT3 expressing or control cells (33.3 and 49.9 μL/mg protein for 1 μmol/L, 33.0 and 49.3 μL/mg protein for 10 μmol/L). These results suggest that CC-10004 is not a substrate of OAT3. OAT3 mediated transport of [3H]estrone sulfate, the reference OAT3 substrate, and the inhibition by probenecid was observed as expected.

OATP1B1 and OATP1B3 Method: The potential of CC-10004 to act as a substrate for human OATP1B1 or OATP1B3 was measured using HEK293 cells transfected with vector containing human OATP1B1 cDNA or containing human OATP1B3 cDNA, as well as with vector only (control cells). The cleared volume was determined for CC-10004 at 1 and 10 µmol/L in OATP1B1 expressing, OATP1B3 expressing, and control cells after 2-minute incubation. The cleared volume was also determined in the presence of OATP1B1 and OATP1B3 inhibitor, rifampicin (10 µmol/L).

OATP1B1 and OATP1B3 Results and Conclusions: CC-10004 (1 and 10 µmol/L) showed comparable cleared volume into OATP1B1 expressing and control cells (37.4 and 48.7 µL/mg protein for 1 µmol/L, 35.9 and 34.6 µL/mg protein for 10 µmol/L). In the presence of positive control inhibitor, rifampicin (10 µmol/L), the cleared volume of CC-10004 was not changed in either OATP1B1 expressing or control cells (27.0 and 38.4 µL/mg protein for 1 µmol/L, 30.6 and 27.0 µL/mg protein for 10 µmol/L). These results suggest that CC-10004 is not a substrate of OATP1B1. OATP1B1 mediated transport of [3H]estradiol 17β-D-glucuronide, the reference OATP1B1 substrate, and the inhibition by rifampicin was observed as expected.

The results of the OATP1B3 substrate assays for CC-10004 are summarized in Table 3. CC-10004 (1 and 10 µmol/L) showed comparable cleared volume into OATP1B3 expressing and control cell (39.1 and 50.9 µL/mg protein for 1 µmol/L, 37.7 and 42.1 µL/mg protein for 10 µmol/L). In the presence of positive control inhibitor, rifampicin (10 µmol/L), the cleared volume of CC-10004 was not changed in either OATP1B3 expressing or control cells (26.2 and 23.4 µL/mg protein for 1 µmol/L, 31.1 and 26.6 µL/mg protein for 10 µmol/L). These results suggest that CC-10004 is not a substrate of OATP1B3. OATP1B3 mediated transport of [3H]estradiol 17β-D-glucuronide, the reference OATP1B3 substrate, and the inhibition by rifampicin was observed as expected.

OCT2 Method: The potential of CC-10004 to act as a substrate for human OCT2 was measured using HEK293 cells transfected either with vector containing human OCT2 cDNA or with vector only (control cells). The cleared volume was determined for CC-10004 at 1 and 10 µmol/L in OCT2 expressing and control cells after 2-minute incubation. The cleared volume was also determined in the presence of OCT2 inhibitor, quinidine (300 µmol/L).

OCT2 Results and Conclusions: CC-10004 (1 and 10 µmol/L) showed comparable cleared volume into and OCT2 expressing and control cell (25.1 and 30.4 µL/mg protein for 1 µmol/L, 25.8 and 26.7 µL/mg protein for 10 µmol/L). In the presence of positive control inhibitor, quinidine (300 µmol/L), the cleared volume of CC-10004 was not changed in either OCT2 expressing or control cells (18.1 and 17.9 µL/mg protein for 1 µmol/L, 15.0 and 20.4 µL/mg protein for 10 µmol/L). These results suggest that CC-10004 is not a substrate of OCT2. OCT2 mediated transport of [14C]metformin, the reference OCT2 substrate, and the inhibition by quinidine was observed as expected.

Report # CC-10004-DMPK-036

Title: In Vitro Assessment of Inhibition Potential of CC-10004 for Efflux Transporters

Objective: To assess the potential for CC-10004 to inhibit BCRP-, MRP1-, MRP2-, MRP3-, MRP4-, and MRP8-mediated efflux transport of transporter-selective substrates in membrane vesicles prepared from transporter transfected or mock-transfected cells.

Method: The potential of CC-10004 to inhibit membrane efflux transporters (BCRP, MRP1-4, MRP8) mediated efflux transport of transporter-specific substrates was investigated using membrane vesicles prepared from transporter or mock transfected cells. The vesicular uptake of positive control substrates (with or without CC-10004 or positive control inhibitors) was measured in the presence of MgATP and MgAMP. The rate of ATP dependent transport was then determined by subtracting transport of compounds in the presence of MgAMP from transport in the presence of MgATP. The inhibition of ATP-dependent transport was assessed using probe substrates [methotrexate (100 μM) for BCRP and estradiol 17β-D-glucuronide (10, 50, 5, 50 and 10 μM, respectively), for MRP1-4, and MRP8] in the presence and absence of CC-10004 at 2 and 20 μM, or prototypical transporter inhibitors [sulfasalazine (5 μM) for BCRP; estrone-3-sulfate (100 or 200 μM) for MRP1, MRP3, MRP4, MRP8; and MK-571 (100 μM) for MRP2]. The probe substrates and CC-10004 or prototypical inhibitors were co-incubated with membrane vesicles at 1 mg/mL of protein for appropriate reaction time (3 min for BCRP, MRP4, and MRP8; 4 min for MRP1; 5 min for MRP2; 0.5 min for MRP3). Inhibition of ATP-dependent transport was assessed by comparing CC-10004-treated samples with substrate transport in the absence of positive control inhibitor or CC-10004.

Results and Conclusion: The employed positive control inhibitors demonstrated >50% inhibition in the transport of prototypical probe substrates in the tested vesicular systems. The results from this vesicular transport study indicate that CC-10004 did not inhibit ATP-dependent BCRP, MRP1, MRP2, and MRP4 mediated transport at the tested concentrations of 2 and 20 μM. Although CC-10004 exhibited modest inhibition of MRP3 mediated transport, this inhibition was concentration-independent with approximately 22% inhibition at 2 and 20 μM. CC-10004 inhibited MRP8 transport, with 42.7% and 59.8% inhibition, at 2 and 20 μM, respectively.

Report # CC-10004-DMPK-040

Title: CC-10004: Inhibition Potential in OCT2, OATP1B1 and OATP1B3 expressing HEK293 cells

Objective: To assess the inhibition potential of CC-10004 using OCT2, OATP1B1 and OATP1B3 expressing cells.

Method: The inhibitory effects of CC-10004 (2 and 20 μmol/L) on the uptake of [14C]-tetraethylammonium bromide into OCT2 expressing cells, and the uptake of [3H]-estradiol glucuronide into OATP1B1 and OATP1B3 expressing cells was investigated. The inhibitory effect of CC-10004 on the uptake into OCT2 expressing cells was evaluated as follows: After incubation of OCT2 expressing HEK293 cells with a buffer containing [14C]-tetraethylammonium bromide in the presence and absence of CC-10004 for 15 min,

the % of control was calculated from the ratios of cleared volumes into the OCT2 expressing cells in the presence of CC-10004 to those in the absence of CC-10004.

The inhibitory effects of CC-10004 on the uptake into OATP1B1 or OATP1B3 expressing cells were evaluated as follows: After incubation of OATP1B1 or OATP1B3 expressing HEK293 cells with a buffer containing [3H]-estradiol glucuronide in the presence and absence of CC-10004 for 2 min, the % of control was calculated from the ratios of cleared volumes into the OATP1B1 or OATP1B3 expressing cells in the presence of CC-10004 to those in the absence of CC-10004.

Results and Conclusion: CC-10004 (2 and 20 µmol/L) did not inhibit OATP1B3-mediated uptake of [3H]-estradiol glucuronide nor OCT2-mediated uptake of [14C]-tetraethylammonium bromide. CC-10004 (20 µmol/L) did show a small amount of inhibition (approximately 26%) of OATP1B1-mediated uptake of [3H]-estradiol glucuronide; no inhibition was observed at 2 µmol/L CC-10004. Verapamil and rifampicin showed substantial inhibition of OCT2-mediated uptake of [14C]- tetraethylammonium bromide and the OATP1B1 or OATP1B3-mediated uptake of [3H]-estradiol glucuronide, respectively, indicating these assay systems were functioning properly.

Report # CC-10004-DMPK-027

Title: Assessment of Interaction of CC-10004 with Human Organic Anion Transporters Using Influx Transporter cRNA Injected Xenopus laevis Oocytes

Objective: To determine if CC-10004 inhibits uptake of probe substrates into Xenopus laevis oocytes expressing human solute-linked carrier (SLC) uptake transporters hOAT1 and hOAT3.

Method: Uptake assays were performed in control (water-injected) and human OAT1 and OAT3-cRNA injected oocytes with transporter-specific probe substrates incubated in the presence of CC-10004 at concentrations of 2.0 µM and 10 µM. The uptake activity of the substrates in the absence and presence of CC-10004 was compared to assess inhibitory activity of CC-10004 with the transporters. The probe substrates were also incubated in the presence of known inhibitors, to serve as positive controls for inhibition of uptake.

Results and Conclusion: CC-10004 demonstrated weak inhibition (21%) of hOAT1-mediated uptake of PAH at 10 µM, and no inhibition of hOAT3-mediated uptake of estrone-3-sulfate at either concentration tested. The results suggest that CC-10004 is not an inhibitor of human OAT1 or OAT3 at the concentrations tested.

Distribution

Report #CC-10004-DMPK-026

Title: In Vitro Protein Binding Determination of CC-10004 in Mouse, Rat, Rabbit, Monkey, and Human Plasma Using Ultrafiltration and LC/MS/MS Analysis

Objective: To determine the extent of protein binding of CC-10004 in CD-1 mouse, Sprague-Dawley rat, New Zealand White rabbit, Cynomolgus monkey, and human plasma at room temperature using an ultrafiltration method. The spiked CC-10004 concentrations were 0.25, 0.75, and 2.5 µg/mL.

Methods: Spiked plasma sample (1 mL) for each matrix was loaded onto the Centrifree ultrafiltration device (30,000 MW cut-off) and centrifuged at 3000 rpm at room temperature for 15 minutes. At the end of centrifugation, an aliquot (200 µL) of the ultrafiltrate was collected into labeled polypropylene tubes containing an equal volume of a mixture of blank human plasma and 0.12 M citric acid to stabilize CC-10004. Also, an aliquot of 200 µL was taken from each spiked plasma preparation, mixed with 200 µL ultrafiltrate and 200 µL 0.12 M citric acid, and stored at -20°C until LC/MS/MS analysis.

Results and Conclusion: The overall mean CC-10004 percent bound was 88.6 ± 2.3% in mouse plasma, 90.6 ± 0.9% in rat plasma, 80.9 ± 1.2% in rabbit plasma, 84.3 ± 1.5% in monkey plasma, and 68.3 ± 0.9% in human plasma at the tested concentration range of 0.25 to 2.5 µg/mL. There was no concentration dependency in the extent of plasma protein binding within the tested concentration range.

In vitro Metabolism

Report # 1398/261-D1145

Title: Metabolism of (14C)-CC-10004 (b) (4) in microsomes isolated from mouse, rat, rabbit, dog, monkey and man.

Objective: To identify the number, proportions and possible structures of the metabolites generated following incubation of the enantiomers, (14C)-CC-10004 (b) (4), with male and female mouse, rat, rabbit, dog, monkey and human liver microsomes and to compare the species and sex specific metabolism.

Results and Conclusions: Two degradation products (b) (4) arising from (b) (4), were observed in all incubations. Additionally, hydrolysis of the N-acetyl group to the aryl amine (M7) was observed in some control incubations containing microsomal protein (but not cofactor). The major metabolite, M3, observed in all test incubations, with the notable exception of female rat, was identified spectroscopically as the O-desmethyl metabolite. This component was the only (P450 dependent) metabolite observed in dog, human and male rat. An additional metabolite, M5, was observed in mouse and monkey, which was not identified spectroscopically, but which co-chromatographed with the O-desethylmetabolite CC-10047. A number of other minor metabolites, M4, M8, M9 and M10, were observed in rabbit, in addition to the enzymic formation of M7. The metabolite, M7 was identified spectroscopically as the N-deacetyl metabolite CC-6070. The metabolite M4 gave a molecular ion consistent with the des-acetyl metabolite ofM3 while M8 was tentatively identified as ring hydroxylated M4. M4 and M6 were observed as minor metabolites in monkey microsomal incubations with (b) (4) At the concentration used in this study, the apparent rank order of extent ofmetabolism was rabbit>>monkey>mouse=male rat>human>dog>female rat. Human

metabolism was quantitatively and qualitatively most similar to dog and male rat. Results for metabolism in human liver microsomes are shown below.

Table 7
Metabolism of [redacted] (b) (4) and CC-10004 (10 µM) in male and female human liver microsomes to its respective metabolites

Males		Metabolite (% chromatogram radioactivity)			
Test compound	Time (min)	M1	M2	M3	M7
CC-10004	60	4.9	3.5	3.1	1.0
CC-10004	120	8.7	6.6	3.5	1.0
CC-10004 (NADPH control)	60	3.2	4.6	nd	0.7
CC-10004 (NADPH control)	120	12.1	11.3	nd	1.1
[redacted] (b) (4)	60	4.2	3.2	3.9	1.3
	120	7.1	5.3	3.7	1.3
	60	4.4	3.4	nd	1.4
	120	6.9	4.9	nd	1.8

Females		Metabolite (% chromatogram radioactivity)			
Test compound	Time (min)	M1	M2	M3	M7
CC-10004	60	5.0	3.9	7.9	1.1
CC-10004	120	9.4	7.1	8.4	1.0
CC-10004 (NADPH control)	60	5.4	4.9	nd	1.2
CC-10004 (NADPH control)	120	9.4	8.1	nd	1.1
[redacted] (b) (4)	60	3.9	2.7	8.9	1.3
	120	9.6	8.2	10.0	1.6
	60	3.9	3.0	nd	1.5
	120	8.3	5.9	nd	1.4

nd: not detected

Report # 1398-393-D1145

Title: Identification of the cytochrome P450 enzymes responsible for the in vitro metabolism of (14C)-CC-10004 in human liver microsomes

Objective: To determine the kinetic parameters Km and Vmax for the formation of the major metabolites of the test compound in human liver microsomes; to identify the major P450 isoenzymes responsible for the formation of the majormetabolites of the test compound by: (a) investigating which cDNA expressed isoenzymes (SupersomesTM) areresponsible for the formation of any given metabolite(s) of the test compound; (b) determining the effects of selective inhibitors of CYP450 activity on theformation of any metabolites of the test compound in human liver microsomes.

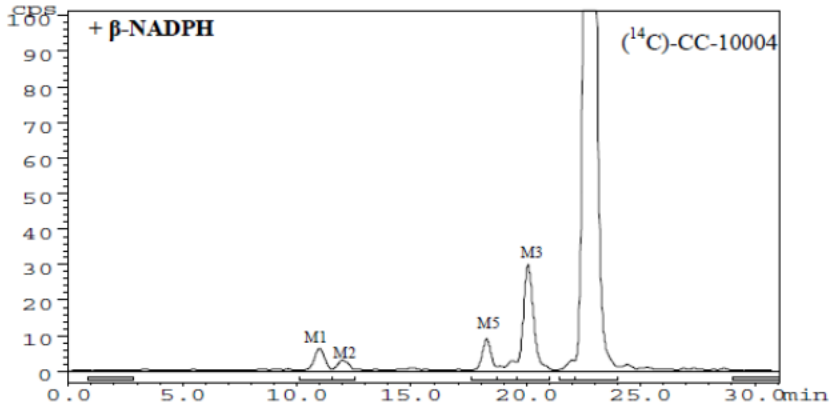
Method: Enzyme kinetic determination in human liver microsomes: Experiments to determine kinetic parameters (Km and Vmax) for the metabolism of(14C)-CC-10004 were conducted in duplicate using pooled human liver microsomes. Incubations comprised Tris buffer (50 mM, pH 7.4), varying (14C)-CC-10004concentrations (2, 5, 7.5, 10, 25, 50, 100, 250 and 500 µM) and microsomal protein (1.0 mg/mL). The incubation mixture was pre-incubated at 37°C for ca. 5 min prior toinitiation with pre-warmed β-NADPH (2 mM). Single blank incubations containing no β-NADPH were conducted at 2, 10 and 500 µM. An additional blank incubation was conducted in duplicate at 500 µM (14C)-CC-10004 containing no microsomes. The total incubation volume was 0.2 mL and incubations were terminated after 60 minutes.

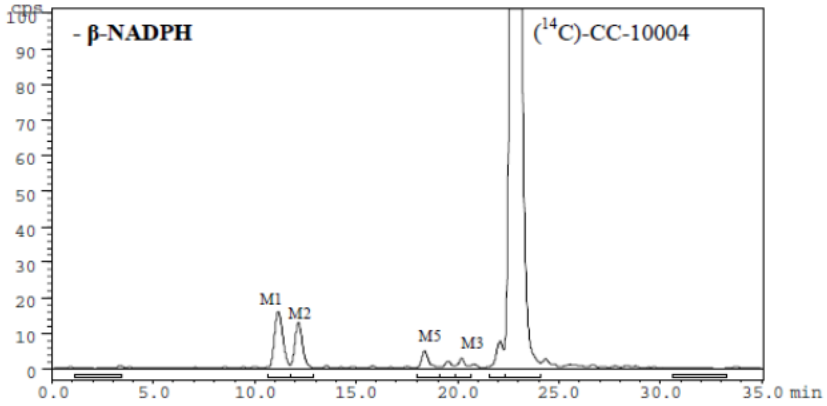
Method: Incubations with cDNA expressed isoenzymes (Supersomes™): Experiments to determine the degree of (14C)-CC-10004 metabolism were conducted in duplicate using microsomes obtained from insect cells transfected with over-expressed human CYP450 isozymes (Supersomes™). Incubations comprised Trisbuffer (50 mM, pH 7.4), (14C)-CC-10004 (200 µM) and Supersomes™ (either CYP1A2, CYP2A6, CYP2C8, CYP2C9 (Arg144), CYP2C19, CYP2D6 (Val374),CYP2E1 or CYP3A4 at a nominal concentration of 50 pmol CYP450/mL).

Method: Incubations with selective P450 inhibitors: Experiments to determine the inhibition of (14C)-CC-10004 metabolism by selective inhibitors were conducted in duplicate using pooled human liver microsomes. Incubations comprised Tris buffer (50 mM, pH 7.4), microsomal protein (1.0 mg/mL) and the selective inhibitors furafylline (CYP1A2; 50 µM), 8-methoxypsoralen(CYP2A6; 10 µM), sulphaphenazole (CYP2C8/9; 20 µM), tranylcypromine (CYP2C19; 20 µM), quinidine (CYP2D6; 3 µM), CYP2E1 inhibitory antibody (ratioAb: protein 1:10) and ketoconazole (CYP3A4; 2 µM), and (14C)-CC-10004 (200 µM). Reactions were stopped by the addition of ice-cold acetonitrile (100 µL) at the end of the appropriate incubation period. Following centrifugation (ca.13000 rpm; ca.5 min)to remove the protein precipitate, supernatants were transferred to a clean vial and analyzed immediately or stored at <-50°C (nominally -70°C) prior to HPLC analysis.

Results: (14C)-CC-10004 was metabolized by human liver microsomes to four main metabolites, namely M1, M2, M3 and M5. (b) (4) Incubations conducted in the absence of β-NADPH generated no other significant metabolites and indicated that the metabolism of (14C)-CC-10004 to M3and M5 was primarily mediated by CYP450. Results are shown below. The Km values for the metabolism of (14C)-CC-10004 to M3 and M5 were199 and 195 µM respectively, whilst the corresponding Vmax values were 141 and 30 pmoles/min/mg protein respectively. From the data presented by the sponsor, this reviewer believes that although CYP450 may be responsible for the generation of what seem like the major metabolites of apremilast in human liver microsomes, i.e., M3 and M5, but they don't seem to be present in very high concentrations indicating CYP metabolism may be one of the metabolizing routes for apremilast in addition to other routes.

Figure 2
Typical metabolic profile following a 60 minute incubation of (^{14}C)-CC-10004 (10 µM) in the presence and absence of β-NADPH





Two experiments were performed using cDNA expressed enzymes. In the first experiment, little or no metabolism of (14C)-CC-10004 was observed following incubation with any of the expressed enzymes. Given that the formation of M3 and M5 had already been confirmed as being predominantly mediated by CYP450, it was considered likely that the relatively high substrate concentration of 200 µM exceeded the limit of solubility of the compound (or its metabolites) in the incubation mixture. As such a second experiment was conducted to increase solubility of apremilast.

In the second experiment with cDNA expressed enzymes, the incubations were repeated in the presence of heat-inactivated rat microsomal protein (ca. 1 mg/mL).This inactivated microsomal protein had no metabolic capacity but was added as an aid to compound solubility and was indeed found to enhance the amount of metabolism of(14C)-CC-10004 observed. The metabolism of (14C)-CC-10004 to M3 was found to be mediated exclusively by CYP3A4. No other CYP450 enzymes mediated in the formation of this metabolite to any appreciable extent. The enhanced production of M5 was observed following incubations with cDNA expressed CYP3A4 and, to a lesser extent, with CYP2A6. Based on the Supersome™ data alone, CYP3A4 was the predominant CYP450involved in the formation of each of the metabolites with notable contributions fromCYP2A6 for M5. Other CYP450's (namely CYP1A2, CYP2C8, CYP2C19 andCYP2E1) participated in the formation of low levels of M5, although none was considered to have any major involvement. Results are shown below.

Experiment 2 (fortified with heat-inactivated rat microsomal protein):

Supersomes™	Rate (pmoles/min/nmole P450)	
	Metabolite	
	3	5
CYP1A2	ND	80.0
CYP2A6	ND	200.0
CYP2C8	ND	46.7
CYP2C9	ND	ND
CYP2C19	ND	6.7
CYP2D6	ND	ND
CYP2E1	ND	6.7
CYP3A4	613.3	396.7

All values are the mean of two determinations
Rates calculated following subtraction of corresponding peak areas in blank incubations
ND: Not detected

The metabolism of (14C)-CC-10004 to M3 was inhibited mainly by 8-methoxypsoralen (CYP2A6; 58.7%), ketoconazole (CYP3A4; 57.8%) and furafylline (CYP1A2; 56.2%),

although some inhibition was observed with sulphaphenazole (CYP2C9; 30.6%) and tranylcypromine (CYP2C19; 19.2%).

With the exception of sulphaphenazole and quinidine, the metabolism of(14C)-CC-10004 to M5 was inhibited by all of the inhibitors to varying extents, with ketoconazole (104.1%) displaying the most potent inhibition.

Conclusion: In human liver microsomes (14C)-CC-10004 was metabolized to 4 products, designated as M1, M2, M3 and M5. [redacted] (b) (4) metabolites (M3 and M5) were not produced to an appreciable extent in the absence of β-NADPH, indicative of the involvement of CYP450 enzymes. Following incubations with cDNA expressed human CYP450 isoforms (Supersomes™), the metabolism of (14C)-CC-10004 was found to be mediated predominantly by CYP3A4. Potent inhibition of the formation of M3 and M5 was observed following incubation in the presence of the selective CYP3A4 inhibitor ketoconazole. Notable inhibition was also observed with furafylline (CYP1A2), 8-methoxypsoralen (CYP2A6), monoclonalanti-CYP2E1, sulphaphenazole (CYP2C9) and tranylcypromine (CYP2C19). The sponsor concludes that as CYP2A6 is not a major human hepatic isozyme (ca. 4% of constitutively expressed CYP's, on average, in humans; Shimada et al., 1994) and, although metabolism of (14C)-CC-10004 was observed to a minor extent with expressed CYP2A6 cDNA, it is unlikely that this isozyme would contribute significantly to the overall metabolism of (14C)-CC-10004. This reviewer agrees.

The apparent inhibitory action of furafylline, monoclonal anti-CYP2E1, tranylcypromine and sulphaphenazole may indicate the involvement of other CYP's in the metabolism of (14C)-CC-10004. The observed inhibition with ketoconazole, however, supports the data obtained with the cDNA expressed CYP3A4. Therefore, the sponsor concludes that the results of the present study indicate that the metabolism of (14C)-CC-10004 is mediated predominantly by CYP3A4, although other isozymes may contribute to a lesser extent to the overall metabolism.

Report # CC-10004-DMPK-023

Title: *In Vitro* Metabolism of [^{14}C]-CC-10004 in Hepatocytes from the Mouse, Rat, Rabbit, Dog, Monkey, and Human

Objective: To determine the *in vitro* metabolite profiles of [^{14}C]-CC-10004 in hepatocytes from the mouse, rat, rabbit, dog, monkey and human.

Methods: [^{14}C]-CC-10004, at 5 and 25 μM, was incubated with mouse, rat, rabbit, dog, monkey and human hepatocytes for 4 hr. Metabolite radio-profiling was accomplished by HPLC radio-chromatography.

Results: After a 4-hr incubation without hepatocytes, only 69.0-73.2% of [^{14}C]-CC-10004 remained unchanged. Significant hydrolysis products M1/M2 and M18 were observed, accounting for 13.3-13.9% and 11.6-13.0%, respectively. [^{14}C]-CC-10004 was metabolized extensively by rabbit hepatocytes, and moderately by rat hepatocytes and to a limited extent

by hepatocytes from the mouse, dog, monkey and human. Unchanged [^{14}C]-CC-10004 and twelve metabolites (M1/M2, M3, M4, M7, M11, M12, M14, M15, M16, M17, M18, and M23), were characterized and/or identified. Overall, all the metabolites formed in vitro by human hepatocytes were formed by hepatocytes from one or more animal species.

Report #CC-10004-DMPK-038

Title: *In Vitro* Metabolism of CC-10004 in Adult and Juvenile Human Cryopreserved Hepatocytes, Human Microsomes and CD-1 Mouse Microsomes

Objective: To investigate the in vitro comparative metabolic profiles of [14C]-CC-10004 in cryopreserved adult and juvenile male and female human hepatocytes, adult and juvenile human liver microsomes, as well as adult and juvenile CD-1 mouse liver microsomes.

Methods: [14C]-CC-10004 (1 and 10 microM) was incubated with liver microsomes of adult human (pooled mixed gender) and juvenile human male (6 and 10 yr) and juvenile human female (7 and 11 yr), adult male CD-1 mouse and juvenile male CD-1 mouse (14 day), and cryopreserved hepatocytes of adult human (pooled mixed gender) and juvenile human male (14 yr) and juvenile human female (6 yr) donors. Positive control incubations with [14C]-7EC at a concentration of 10 μM for 30 min were also performed in parallel to verify the metabolic capacity of the microsomes or cryopreserved hepatocytes used in this study. Metabolite profiling was performed by HPLC in conjunction with radioactive monitoring (RAM). Metabolites were identified by LC-MS/MS product ion scans in multiple reaction monitoring (MRM) or selected reaction monitoring (SRM) mode.

Results: Only human microsomes and hepatocytes data presented: Metabolites identified in human microsomes and hepatocytes included M3 (O-demethylated), M7 (N-deacetylated; microsomes only), M11 (hydroxylated N-deacetylated), M12 (O-demethylated glucuronide), M13 (O-deethylated glucuronide), M14 (N-deacetylated- O-demethylated glucuronide), M15 (hydrolysis product of O-demethylated glucuronide) and M17 (hydroxylated acetamide). There were no notable qualitative differences between the metabolite profiles in the adult human liver microsomes (pooled mixed gender) versus the juvenile male and juvenile female liver microsomes. Similarly, for human cryopreserved hepatocytes, there were no notable differences observed between the adult (pooled mixed gender) versus juvenile male and female hepatocytes.

Conclusion: The results of this study suggest that the metabolite profiles are comparable in adult and juvenile humans.

In vitro CYP Enzyme Induction and Inhibition reports

Report # CC-10004-DMPK-012

Title: In vitro Evaluation of CC-10004 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Objective: To investigate the effect of treating primary cultures of human hepatocytes with CC-10004 on the activity of microsomal cytochrome P450 (CYP) enzymes.

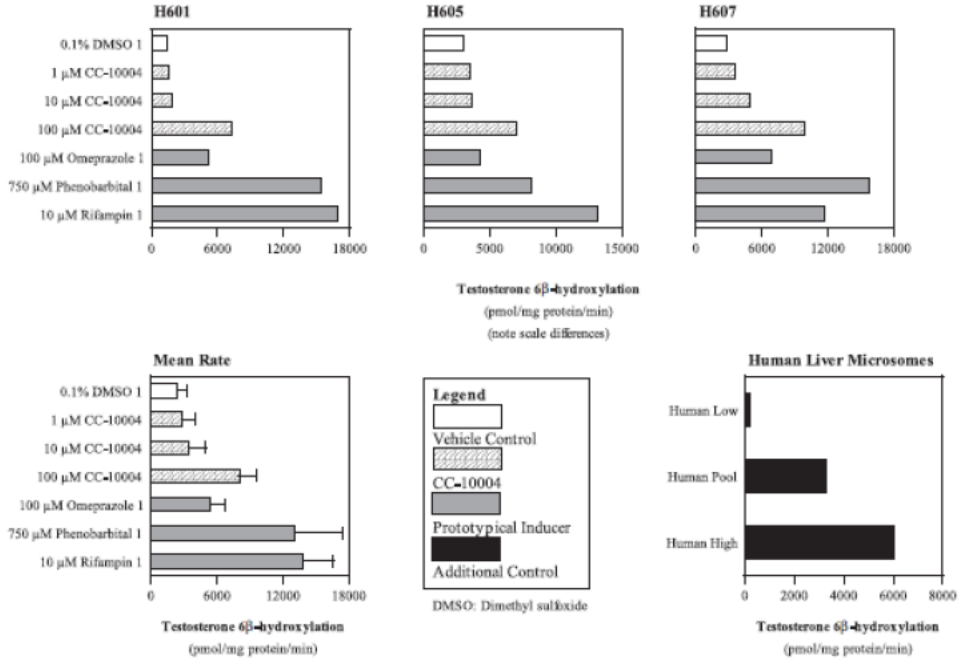
Methods: Three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with dimethyl sulfoxide (vehicle, 0.1%, v/v), one of three concentrations of CC-10004 (1, 10 or 100 µM), or one of three known human CYP inducers namely omeprazole (100 µM) phenobarbital 750 µM) or rifampin (10 µM). Treatment schedule was once daily for three consecutive days. After last treatment, cells were harvested to prepare microsomes for the analysis of 7-ethoxyresorufin O-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6), diclofenac 4′-hydroxylation (marker for CYP2C9), S-mephenytoin 4′-hydroxylation (marker for CYP2C19) and testosterone 6β-hydroxylation (marker for CYP3A4/5.

Results: Treatment of cultured human hepatocytes with CC-10004 had little or no effect on CYP2B6 and CYP2C19. It had no effects on CYP1A2 and CYP2C9 at 1 µM; treatment at higher concentrations caused ~35% (10 µM) and up to 70% (100 µM) decreases in CYP1A2 and CYP2C9 activities. There was no effect on CYP3A4 activities at 1 and 10 µM CC-10004. A 3.7-fold induction of CYP3A4 (to roughly half the extent induced by rifampin) was observed at 100 µM (results for CYP3A4/5 induction shown below). All the positive controls exhibited expected induction effects.

(b) (4) Study Number: (b) (4) 053017

Celgene Study Number: CC-10004-DMPK-012

Figure 9: **The effect of treating cultured human hepatocytes with CC-10004 on the rate of microsomal testosterone 6β-hydroxylation (a marker of CYP3A4/5 activity)**



Report # CC-10004-DMPK-039

Title: In Vitro Evaluation of CC-10004 as an Inhibitor of Human Cytochrome P450 Enzymes CYP2A6, CYP2B6 and CYP2C8

Objective: To evaluate the potential of CC-10004 to act as a direct or time-dependent inhibitor of cytochrome P450 (CYP) activities in pooled human liver microsomes. In this study, inhibition of three cytochrome P450 activities, namely CYP2A6, CYP2B6 and CYP2C8 were investigated.

Methods: To examine the ability of CC-10004 as a direct inhibitor of CYP enzymes, pooled human liver microsomes were incubated with probe substrates, at concentrations approximately equal to their apparent Km, in the presence of CC-10004 (0.1 to 100 μM) and NADPH. In addition, CC-10004 was evaluated for its ability to function as a time-dependent inhibitor at the same concentrations mentioned above, in which case CC-10004 was pre-incubated with human liver microsomes and NADPH for 30 minutes to generate possible metabolites that might inhibit CYP activity prior to the addition of the probe substrate. Known direct inhibitors as well as time-dependent inhibitors of CYP isoforms were included as positive controls in addition to appropriate vehicle controls.
Following the incubation, the levels of probe substrate metabolites were quantified using established LC-MS/MS methods.

Results: Under the experimental conditions used to examine direct inhibition, CC-10004 (up to 100 μM) caused little to no (<20%) inhibition of CYP2A6 and CYP2B6 activities. CC-10004 exhibited concentration-dependent inhibition of CYP2C8-catalyzed paclitaxel 6a-hydroxylation with an estimated IC50 value of 56.1 μM. Under the conditions used to test time-dependent inhibition, in the presence of CC-10004 the inhibition profiles for CYP2A6 and CYP2C8 were similar (<20% difference) following a 30 minute pre-incubation with or without NADPH. CC-10004 was not observed to be a time-dependent inhibitor of CYP2A6, CYP2B6 and CYP2C8.

Report # 1398-227-D1145

Title: Effects of CC-10004 on selected cytochrome P450 activities in human liver microsomes: Prediction of drug interactions

Objective: To determine the effects of the test compound on selected cytochrome P450 activities(CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) in microsomes isolated from human liver; and to assess the time dependency of inhibition.

Methods: Phenacetin O-deethylase was used as a marker enzyme for CYP1A2, tolbutamidemethyl-hydroxylase for CYP2C9, S-mephenytoin 4-hydroxylase for CYP2C19, bufuralol 1-hydroxylase for CYP2D6, lauric acid 11-hydroxylase for CYP2E1 andtestosterone 6β-hydroxylase, midazolam 1-hydroxylase and nifedipine oxidase for CYP3A4. Investigations were carried out in the presence of known inhibitors or the test compound. CC-10004 was tested at nominal concentrations of 1, 10 and 100 μM. In order

to assess the time dependent inhibition, CC-10004 (10 µM) was pre-incubated for 15 minutes prior to initiation of each substrate assay.

Results: CC-10004 did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 at any concentration evaluated. Results for CYP3A4 are shown below as representative and relevant enzyme for this drug.

Table 7
CC-10004: Effects on CYP3A4 (midazolam 1-hydroxylase) activity in human liver microsomes

Test substance	Nominal concentration (µM final)	Enzyme activity (pmol/mg/min)	% Inhibition from relative control
Control	-	278 ± 9.9	-
CC-10004	1	230 ± 10.4	30.2
	10	254 ± 13.3	22.9
	100	249 ± 25.2	24.4
Ketoconazole	1	44.9 ± 5.6	86.4
Acetonitrile 1%*v/v*	-	330 ± 8.2	0.0
Time dependent Control	-	712 ± 29.9	-
Time dependent Acetonitrile vehicle	-	640 ± 21.4	10.1
Time dependent CC-10004	10	606 ± 30.2	5.4

- = Not Applicable
Values are expressed as mean ± SD of three determinations
CC-10004 and ketoconazole were dissolved in acetonitrile
Time dependent samples were pre-incubated for 15 mins at 37°C prior to initiation with midazolam

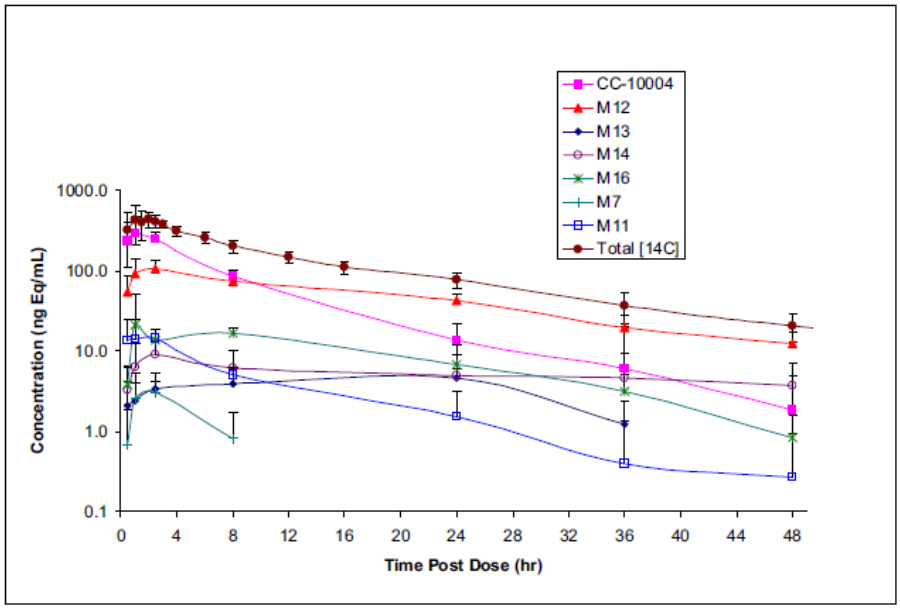
PHARMACOKINETICS

Mass Balance Study

Study # CC-10004-PK-002 (Also report RPT01329)

Study Title	An Open-Label Study to Evaluate the Absorption, Distribution, Metabolism, and Excretion of [14C]-CC-10004 Following a Single Oral 20 mg Suspension Dose in Healthy Male Subjects
Clinical Site and Principal Investigator	MDS Pharma Services, 621 Rose Street, Lincoln, Nebraska 68502 James C. Kisicki, MD
Study Period	(Date of first enrollment) 18 April 2005 (Date of last completed) 28 April 2005
Objectives	To characterize the metabolic profile, the routes and rates of excretion, and the total recovery of [14C]-CC-10004 and/or its radiolabeled metabolites in healthy male subjects following a 20 mg single oral suspension dose. The secondary objectives were to characterize the pharmacokinetics and safety of [14C]-CC-10004/CC-10004 and its major metabolites, if identified, following a 20 mg single oral suspension dose.
Study Design and Population	Open-label, single-center design. N=6 healthy males 19-55 years enrolled, completed, included in PK analysis
Dosing and Administration	Single oral dose of 20 mg CC-10004 (manufactured by (b) (4) (b) (4) Re-test date: (b) (4) which consisted of 100 µCi of total radioactivity in each vial.
Results	The following table summarizes the cumulative radioactivity recovery (percent) and whether excreted in urine or feces:

Subject	Urine Excretion	Fecal Excretion	Total Excretion
1	71.15	27.58	98.73
2	48.51	50.77	99.28
3	56.58	40.78	97.37
4	55.18	41.82	97.00
5	47.42	46.71	94.13
6	68.45	27.74	96.19
Mean	57.88	39.23	97.11
SD	9.94	9.66	1.85
CV (%)	17.17	24.61	1.91

	Figure 2 Mean (± SD) Plasma Equivalent Concentration-Time Profile of CC-10004, Metabolites M12, M13, M14, M16 and Total Radioactivity (ngEq/mL) (Concentrations measured by radioprofiling) 
Reviewer's Comments	Apremilast was extensively metabolized by humans. The observed metabolic routes of apremilast (CC-10004) in humans included 1) O-deacylation (demethylation and deethylation), 2) N-deacetylation, 3) hydroxylation, 4) hydrolysis, and 5) glucuronidation. The major metabolic route of CC-10004 in humans was O-demethylation, with approximately 50% (mean value) of the dose metabolized by this particular pathway. The O-demethylated and deethylated metabolites in plasma and urine are predominantly glucuronide conjugates. CC-10004 is primarily eliminated by metabolism, renal excretion of unchanged drug is a very minor (less than 3% of the dose) elimination route. Unchanged apremilast and M12 (a glucuronide conjugate of O-demethyl apremilast) were the predominant radio-components, accounting for 68% to 83% of the plasma radioactivity, with similar AUC values.

Single Dose Ascending (SAD)

Trial # CC-10004-PK-001

Study Title	A Phase I, Double-Blind, Placebo-Controlled Ascending Single and Multiple Oral Dose, Safety and Pharmacokinetic Study in Healthy Subjects
Clinical Site and Principal Investigator	Covance Clinical Research Unit Ltd., Leeds, UK E Engmann, MBChB
Study Period	20 March 2003 to 22 July 2003
Objectives	To determine the safety of ascending single then multiple oral doses of CC-10004 in healthy subjects. To determine the single and multiple oral dose pharmacokinetics of CC-10004 in healthy subjects.
Study Design and Population	Double-Blind, Placebo-Controlled design. N=40 healthy males and females 18-55 years enrolled, completed, included in PK analysis
Dosing and Administration	Dose levels of CC-10004 were 10 mg/day, 20 mg/day and 40 mg/day (given as once daily), and 80 mg/day and 100 mg/day (given as twice daily [BID]) (Groups A to E, respectively). Doses were administered as CC-10004 capsules (10 and 50 mg); lot numbers 0129U and 0130U, respectively. Placebo capsules; lot number 0108U. Each subject received a single oral dose following by multiple oral doses over a period of 5 days. During the multiple dose phase, the OD doses were given in the morning (am) at 24-hourly intervals and the BID doses were given in the morning and evening (am and pm) at 12-hourly intervals.

Results

The pharmacokinetic parameters of CC-10004 (OD doses) are summarised in the following table:

	Total Daily Dose of CC-10004 (OD)					
	10 mg		20 mg		40 mg	
Parameter	Day 1 (N=6)	Day 12 (N=6)	Day 1 (N=6)	Day 7 (N=6)	Day 1 (N=6)	Day 7 (N=6)
AUC(0-τ) (ng.h/mL)	1085 (16.6)	998 (22.8)	1854 (39.2)	1948 (42.0)	3225 (47.8)	3289 (45.1)
AUC(0-∞) (ng.h/mL)	1153 (18.0)	NC	1908 (40.8)	NC	3379 (47.1)	NC
C_{max} (ng/mL)	206 (32.3)	180 (29.9)	347 (36.6)	419 (40.1)	533 (35.9)	490 (52.4)
t_{max}† (h)	1.00 (0.500-2.00)	2.00 (1.50-2.50)	1.75 (1.00-4.02)	1.00 (1.00-2.50)	2.05 (1.50-3.00)	2.75 (2.00-3.00)
C_{trough} (ng/mL)	5.95 (64.1)	4.30 (92.6)	5.22 (222)	4.94 (117)	18.5 (54.2)	15.9 (104)
$t_{½}$ (h)	6.54 (19.9)	5.26 (33.7)	4.45 (33.2)	4.46 (28.7)	6.04 (31.0)	5.82 (47.2)
CL/F (mL/min)	145 (18.0)	167 (22.8)	175 (40.8)	171 (42.0)	197 (47.1)	203 (45.1)
V_z/F (L)	81.8 (25.2)	76.1 (51.1)	67.3 (33.6)	66.1 (51.0)	103 (73.4)	102 (48.2)
RA_1	1.06 (3.82) [a]	0.920 (18.4)	1.03 (2.05) [a]	1.05 (7.40)	1.05(1.66) [a]	1.02 (10.9)
RA_2		0.876 (18.8)		1.21 (32.2)		0.920 (25.8)
RL	NA	0.866 (21.5)	NA	1.02 (7.66)	NA	0.973 (10.2)

The pharmacokinetic parameters of CC-10004 (BID doses) are summarised in the following table:

	Total Daily Dose of CC-10004 (BID)			
	80 mg/day#		100 mg/day~	
Parameter	Day 1 (N=6)	Day 7 (N=6)	Day 1 (N=6)	Day 7 (N=6)
AUC(0-τ) (ng.h/mL)	3270 (45.6)	4482 (34.7)	4315 (29.3)	5164 (38.6)
AUC(0-∞) (ng.h/mL)	4106 (42.0)	NC	5407 (32.4)	NC
C_{max} (ng/mL)	592 (49.0)	881 (30.8)	688 (43.4)	994 (29.5)
t_{max}† (h)	2.25 (1.00-3.00)	2.50 (1.00-3.00)	3.00 (1.50-6.02)	2.00 (1.50-2.03)
C_{trough} (ng/mL)	102 (44.4)	116 [a] (91.0)	152 (33.2)	107 (66.7)
$t_{½}$ (h)	5.56 (23.5)	6.16 [a] (22.1)	5.56 (20.7)	6.84 (18.7)
CL/F (mL/min)	162 (42.0)	149 [a] (34.7)	154 (32.4)	161 (38.6)
V_z/F (L)	78.2 (57.4)	79.3 [a] (46.3)	74.2 (28.5)	95.5 (43.7)
RA_1	1.26 (9.82) [b]	1.36 (24.1) [a]	1.25 (4.35) [b]	1.20 (9.76)
RA_2		1.49 (25.4)		1.44 (15.9)
RL	NA	1.08 (16.9) [a]	NA	0.955 (9.75)

	The urinary excretion of CC-10004, assessed at the 10 mg/day OD dose level only, is summarised in t following table: 10 mg/day CC-10004 (OD) Parameter: Day 1 (N=6) / Day 12 (N=6) Ae(0-τ) (μg): 129 (42.6) / 187 (25.9) Ae(0-48 h) (μg): 130 (42.2) / NA fe(0-τ) (%): 1.29 (42.6) / 1.87 (25.9) fe(0-48 h) (%): 1.30 (42.2) / NA CL_R(0-48 h) (mL/min): 1.89 (43.7) / 3.12 (37.0) CL_R(0-τ) (mL/min): 1.98 (41.9) / NA
Reviewer's Comments	Median tmax of 1 to 3 hours post-dose indicated quick absorption. Cmax and AUC values increased linearly with increase in dose. The mean apparent elimination half-life of apremilast was estimated to be between approximately 5 and 7 hours, and was similar for all doses and days. Steady-state plasma concentrations of apremilast were achieved by 24 hours after the start of multiple dosing. There was no accumulation of apremilast following OD multiple dosing (from 10 to 40 mg/day) and only slight accumulation following BID multiple dosing from 80 to 100 mg/day. The urinary excretion of CC-10004, assessed at the 10 mg/day OD dose level, was very low, with <2% being eliminated as unchanged drug over the dosing interval, suggesting that apremilast is subject to non-renal clearance mechanisms.

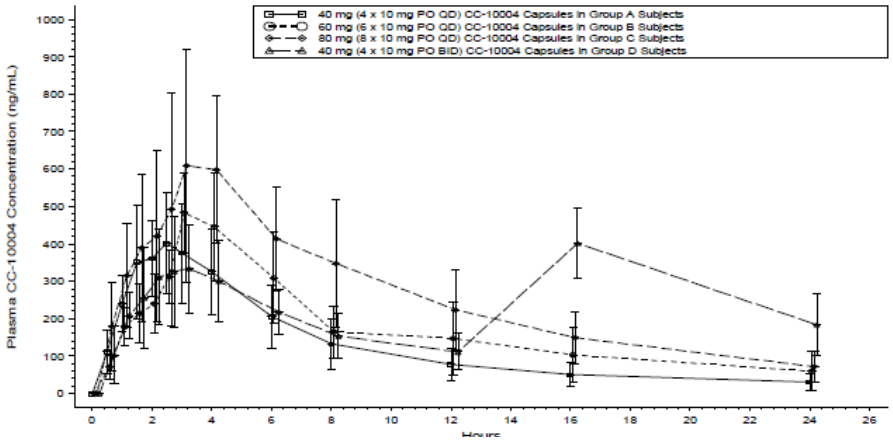
Multiple Ascending Dose (MAD) and Dose Titration Effects

Trial # CC-10004-PK-007

<table>
<tr><td>Study Title</td><td>A Phase I Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of Ascending Multiple Oral Doses of CC-10004 in Healthy Subjects</td></tr>
<tr><td>Clinical Site and Principal Investigator</td><td>MDS Pharma Services, 22-24 Lisburn Road, Belfast, Northern Ireland BT9 6AD
Dr Brendan Colgan, MB, BCH, MRCGP</td></tr>
<tr><td>Study Period</td><td>19 Jan 2006 to 17 Aug 2006</td></tr>
<tr><td>Objectives</td><td>To determine the safety of multiple oral daily doses of 40, 60, 80, and 100 mg of CC-10004 in healthy subjects
To determine the multiple oral dose pharmacokinetics (PK) of CC-10004 in healthy subjects
To determine effect of apremilast on ex vivo whole blood lipopolysaccharides (LPS) stimulated TNF-α production and TNF-α inhibition</td></tr>
<tr><td>Study Design and Population</td><td>Single-center, double-blind, placebo-controlled, randomized design. N=55 healthy males 18-55 years enrolled, N=53 completed, N=44 included in PK analysis</td></tr>
<tr><td>Dosing and Administration</td><td>The test product was CC-10004 10-mg capsules (Lot No. 0293X).
Matching placebo capsules for CC-10004 (Lot No. 0247X).
<table>
<tr><th>Groups</th><th>Doses</th></tr>
<tr><td>A</td><td>40 mg CC-10004 or placebo QD x 14 days</td></tr>
<tr><td>B</td><td>60 mg CC-10004 or placebo QD x 14 days</td></tr>
<tr><td>C</td><td>80 mg CC-10004 or placebo QD x 14 days</td></tr>
<tr><td>D</td><td>40 mg CC-10004 BID (80 mg daily dose) or placebo x 14 days</td></tr>
<tr><td>E</td><td>10 mg QD on Days 1 - 3, 20 mg QD on Days 4 - 6, and 40 mg QD on
Days 7 - 14.</td></tr>
</table>
</td></tr>
</table>

Results

Figure 2: Mean CC-10004 Plasma Concentration vs. Time profile following single oral administration on Day 1(Groups A Through D) – Linear



Plasma CC-10004 PK parameters for Day 1 are presented in the following table:

Mean (SD) Plasma CC-10004 Pharmacokinetic Parameters on Day 1

Pharmacokinetic Parameter	Arithmetic Mean (SD) Group A 40 mg QD N = 9	Group B 60 mg QD N = 9	Group C 80 mg QD N = 9	Group D 40 mg BID (AM Dose) N = 9
C_{max} (ng/mL)	436 (131)	520 (132)	690 (275)	375 (116)
AUC_{tau} (ng.hr/mL)	3037.9 (1199.1)	4230.0 (1627.4)	6183.0 (2174.0)	2410.1 (635.42)
AUC_{∞} (ng.hr/mL)	3088.6 (942.72)	4844.8 (2564.2)	6996.8 (2574.1)	ND
t_{max} (hr)[a]	2.50 (1.50, 3.99)	3.00 (2.00, 4.00)	3.99 (1.50, 8.00)	3.00 (2.01, 6.00)
$t_{1/2}$,z (hr)[b]	6.97 (1.68)	8.27 (2.15)	7.04 (2.04)	ND
CL/F (mL/min)[b]	237.7 (87.31)	240.8 (81.99)	218.1 (87.26)	ND
Vz/F (L)[b]	143.7 (63.29)	168.3 (66.78)	124.5 (36.46)	ND

Plasma CC-10004 PK parameters for Day 14 are presented in the following table:

Mean (SD) Plasma CC-10004 Pharmacokinetic Parameters on Day 14

Pharmacokinetic Parameter	Arithmetic Mean (SD)					
	Group A 40 mg QD N = 9	Group B 60 mg QD N = 9	Group C 80 mg QD N = 9	Group D 40 mg BID N = 9		Group E 40 mg QD N = 8
				AM Dose	PM Dose	
C_{max} (ng/mL)	582 (162)	571 (208)	806 (253)	662 (154)	475 (111)	525 (148)
C_{trough} (ng/mL)	50.4 (37.0)	52.2 (38.5)	66.2 (29.5)	126 (49.6)	178 (83.7)	41.3 (39.0)
AUC_{tau} (ng.hr/mL)	4587.3 (1975.1)	4667.9 (2078.4)	6362.0 (2235.9)	4004.8 (1214.6)	3576.6 (1015.3)	4173.2 (2257.5)
t_{max} (hr)[a]	2.00 (1.50, 4.00)	3.00 (3.00, 3.01)	2.99 (2.99, 4.00)	2.50 (0.969, 3.00)	3.04 (2.03, 7.99)	2.99 (2.00, 3.99)
$t_{1/2}$,z (hr)	7.34 (1.90)	8.46 (2.65)	9.74 (4.49)	ND	6.31 (1.53)	9.21 (3.74)
CL/F (mL/min)	169.3 (66.67)	243.6 (78.02)	235.1 (88.01)	ND	201.1 (60.62)	202.3 (102.6)
Vz/F (L)	103.6 (39.57)	176.4 (79.22)	204.0 (133.8)	ND	105.8 (30.25)	178.8 (182.7)
RA1 (AUC_{tau})	1.50 (0.150)	1.07 (0.176)	1.04 (0.181)	ND	1.53 (0.475)	ND
RA2 (C_{max})	1.35 (0.219)	1.08 (0.192)	1.26 (0.375)	ND	1.33 (0.365)	ND

Urine PK parameters are presented in the following table:

Urinary Excretion of CC-10004 (Mean [SD]) on Days 1 and 14

Group	% Dose Excreted Unchanged Per Dosing Interval (tau)*		CLr (mL/min)	
	Day 1	Day 14	Day 1	Day 14
A (40 mg QD)	1.66 (0.7)	2.94 (1.2)	3.98 (1.58)	4.83 (2.44)
B (60 mg QD)	1.31 (0.2)	1.61 (0.4)	3.32 (1.14)	3.75 (1.03)
C (80 mg QD)	1.94 (0.6)	2.45 (0.8)	4.73 (1.96)	5.53 (2.14)
D (40 mg BID)	1.93 (0.7)	3.46 (0.8)	5.47 (1.76)	6.73 (1.72)
E (40 mg QD on a dose titration schedule)	ND	3.94 (3.1)	ND	6.39 (2.92)

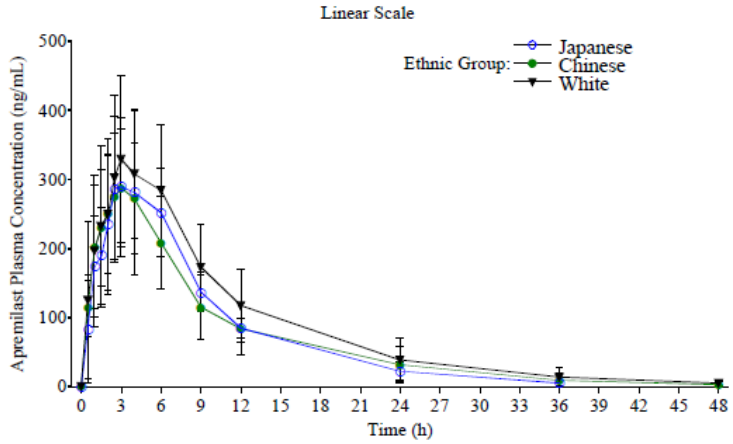
PD data: Variability was large, no confirmatory analysis.

Reviewer's Comments

Median Tmax of 2 to 3 hours on all study days and appeared to be consistent with daily dosing. For doses in the ratio of 1:1.5:2 from 40 to 80-mg QD, geometric mean Cmax and AUC ratio increased in less than dose proportional manner. The PK of CC-10004 on Day 14 behaved similarly to that observed on Day 1. Mean T-half appeared to be similar (6-9 hrs) across all doses (QD and BID) and dosing days (no trends observed in CL/F or Vz/F). Overall renal clearance was low (less than 4% unchanged apremilast recovered in urine on days 1 and 14). This study also established benefits of dose titration. The proportion of subjects who reported nausea was lower by Group E (40 mg QD with dose titration) than that by other dose groups (40 mg QD, 60 mg QD, 80 mg QD, and 40 mg BID). Also, dose titration group had fewer total number of AEs reported (34 AE reported by the group of 40 mg QD with dose titration; 72 AEs reported by the group of 40 mg QD).

Effect of Race

Trial # CC-10004-CP-018

Study Title	A Phase 1, Double-blind, Placebo-controlled Study to Compare the Pharmacokinetics of Apremilast (CC-10004) in Healthy Japanese, Chinese, and Caucasian Subjects
Clinical Site and Principal Investigator	▪ Covance Clinical Research Unit Inc., One Waterfront Plaza, 500 Ala Moana Boulevard, Suite 400, Honolulu, Hawaii 96813 USA Thomas Murtaugh, MD ▪ California Clinical Trials Medical Group, 1560 East Chevy Chase Drive, Suite 140, Glendale, California 91206 USA Hakop Gevorkyan, MD, MBA
Study Period	30 Nov 2010 to 16 Jun 2011
Objectives	To compare the pharmacokinetics (PK) of 2 single doses (20 and 40 mg) of apremilast in healthy Japanese, Chinese, and Caucasian subjects.
Study Design and Population	Randomized, double-blind, placebo-controlled, single-dose, 3-period, 3-sequence, 3-way crossover study design. A washout period of 7-10 days between each dose administration. N=36 healthy males 20-50 years enrolled, N=35 completed, N=36 included in PK analysis. N=12 each Japanese, Chinese and White. Japanese and Chinese were age and BMI matched to White.
Dosing and Administration	Single oral doses of 20- and 40-mg apremilast (Lot number 10F0291) were administered to subjects under fasted conditions.
Results	**Mean (+/- SD) Apremilast Plasma Profiles in Healthy Japanese, Chinese, and White Adult Males After a Single 40-mg Oral Dose of Apremilast (by Ethnic Group)** 

Geometric Mean (Geometric CV%) Apremilast Plasma Pharmacokinetic Parameters Data When Administered as a Single 20- or 40-mg Oral Dose in Healthy Japanese, Chinese, and White Adult Males (All Subjects)

	Apremilast Dose					
	20 mg			40 mg		
PK Parameter	Japanese	Chinese	White	Japanese	Chinese	White
AUC_{0-t} (ng*hr/mL)	1515 (21.9)	1593 (35.9)	1686 (42.1)	2921 (17.2)	2914 (29.2)	3601 (40.9)
AUC_{0-inf} (ng*hr/mL)	1532 (21.2)	1619 (35.9)	1723 (42.8)	2943 (17.1)	2944 (29.6)	3655 (41.2)
C_{max} (ng/mL)	211 (31.3)	201 (34.5)	201 (23.5)	343 (25.9)	322 (23.4)	377 (23.2)
t_{max}[a] (hr)	2.50 (1.00, 6.00)	2.50 (1.00, 4.00)	2.50 (0.500, 6.00)	3.50 (2.00, 6.00)	2.50 (1.00, 6.00)	3.00 (1.00, 6.00)
$t_{1/2}$ (hr)	5.44 (15.8)	5.85 (26.6)	6.83 (28.4)	5.32 (16.3)	6.11 (21.3)	7.05 (26.0)
CL/F (L/hr)	13.1 (21.2)	12.3 (35.9)	11.6 (42.8)	13.6 (17.1)	13.6 (29.6)	10.9 (41.2)
Vz/F (L)	102 (27.2)	104 (20.9)	114 (30.7)	104 (28.4)	120 (22.8)	111 (34.0)

Table 12: Statistical Comparison of Apremilast Systemic Exposure Pharmacokinetic Parameters in Healthy Japanese and Chinese Males Relative to Healthy White Males (All Subjects)

Pharmacokinetic Parameter (unit)	Apremilast Dose Levels	Ethnic Group	N	Geometric Mean	Comparison	Ratio (%) of Geometric Means	90% CI of Ratio (%) of Geometric Means	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	20 mg	Japanese	12	1514.5	Jpn vs. White	89.81	(71.88, 112.21)	9.6
		Chinese	12	1592.8	Chi vs. White	94.45	(75.59, 118.01)	--
		White	12	1686.4	--	--	--	--
	40 mg	Japanese	12	2921.1	Jpn vs. White	81.12	(64.92, 101.35)	--
		Chinese	12	2913.9	Chi vs. White	80.92	(64.76, 101.11)	--
		White	12	3601.0	--	--	--	--
AUC_{0-inf} (ng*hr/mL)	20 mg	Japanese	12	1532.4	Jpn vs. White	88.94	(71.08, 111.29)	9.5
		Chinese	12	1619.4	Chi vs. White	94.00	(75.12, 117.62)	--
		White	12	1722.8	--	--	--	--
	40 mg	Japanese	12	2942.7	Jpn vs. White	80.51	(64.34, 100.73)	--
		Chinese	12	2943.9	Chi vs. White	80.54	(64.36, 100.77)	--
		White	12	3655.3	--	--	--	--
C_{max} (ng/mL)	20 mg	Japanese	12	210.8	Jpn vs. White	104.86	(87.57, 125.55)	17.9
		Chinese	12	201.4	Chi vs. White	100.16	(83.65, 119.93)	--
		White	12	201.0	--	--	--	--
	40 mg	Japanese	12	343.2	Jpn vs. White	91.01	(76.01, 108.98)	--
		Chinese	12	321.6	Chi vs. White	85.29	(71.23, 102.12)	--
		White	12	377.1	--	--	--	--

Reviewer's Comments	Apremilast systemic exposure is comparable between Japanese and White subjects and Chinese and White subjects as reflected by inclusion of unity (i.e., 1) in the 90% confidence intervals around the mean exposure ratios for Cmax, AUC0-t and AUC0-inf.

SPECIFIC POPULATIONS

Age/Gender Effect

Trial # CC-10004-CP-024

Study Title	An Open-label, Single-dose Study to Evaluate the Effect of Age and Sex on the Pharmacokinetics of Apremilast (CC-10004) in Healthy Subjects
Clinical Site and Principal Investigator	▪ PRA, 9755 Ridge Drive, Lenexa KS 66219; Marisa Leonardelli, MD ▪ Covance Clinical Research Unit Inc, 1341 W Mockingbird Lane, Suite 300 E & 400E, Dallas TX 75247; William Lewis, MD
Study Period	Date first subject enrolled: 03 February 2012 Date last subject completed: 16 April 2012
Objectives	To evaluate the effect of age and sex on the pharmacokinetics (PK) of apremilast in healthy subjects after a single 30-mg dose
Study Design and Population	Open-label, parallel-group study. N=36 total, N=18 healthy males and females 18-55 years of age and N=18 elderly males and females 65-85 years of age. N=36 completed, included in PK analysis.
Dosing and Administration	Apremilast (CC-10004; Lot 11F2065) was supplied by the sponsor in 80-count stock bottles containing 30-mg oral tablets.
Results	**Plasma Pharmacokinetic Parameters of Apremilast by Age and Sex**

Age/Sex	Young/Female N = 10	Young/Male N = 8	Elderly/Female N = 10	Elderly/Male N = 8
PK Parameter[a]	Geometric Mean (Geometric CV%)			
AUC_{0-t} (h*ng/mL)	2987 (32.5)	2649 (21.9)	3829 (40.6)	2620 (28.5)
$AUC_{0-\infty}$ (h*ng/mL)	3072 (32.9)	2698 (22.4)	3985 (41.7)	2648 (28.6)
C_{max} (ng/mL)	301 (33.7)	303 (17.5)	344 (33.6)	295 (16.8)
t_{max} (h)	2.25 (1.0-5.0)	2.50 (0.5-5.0)	4.00 (2.5-5.1)	2.25 (1.0-5.0)
$t_{½}$ (h)	10.1 (2.84)	8.5 (2.23)	10.4 (2.82)	7.63 (0.973)
CL/F (L/h)	9.77 (32.9)	11.1 (22.4)	7.53 (41.7)	11.3 (28.6)
Vz/F (L)	139 (45.8)	132 (31.8)	108 (38.7)	124 (31.5)

	Plasma Pharmacokinetic Parameters of Apremilast by Age or Sex

Age or Sex	Young N = 18	Elderly N = 18	Male N = 16	Female N = 20
PK Parameter[a]	Geometric Mean (Geometric CV%)			
AUC_{0-t} (h*ng/mL)	2832 (28.1)	3235 (40.3)	2634 (24.5)	3382 (38.2)
$AUC_{0-\infty}$ (h*ng/mL)	2900 (28.7)	3323 (41.8)	2673 (24.8)	3499 (39.1)
C_{max} (ng/mL)	302 (26.8)	321 (27.8)	299 (16.6)	322 (33.5)
t_{max} (h)	2.50 (0.5-5.0)	2.50 (1.0-5.1)	2.50 (0.5-5.0)	2.75 (1.0-5.1)
$t_{½}$ (h)	9.41 (2.65)	9.15 (2.56)	8.06 (1.72)	10.3 (2.76)
CL/F (L/h)	10.4 (28.7)	9.03 (41.8)	11.2 (24.8)	8.57 (39.1)
Vz/F (L)	136 (38.9)	115 (35.3)	128 (30.7)	123 (43.4)

Reviewer's Comments	Mean systemic exposure of apremilast as measured by AUC 0-t and AUC0-inf was greater in elderly compared to young subjects by about 13%. Systemic exposure as measured by AUC0-t and AUC0-inf was greater in female compared to male subjects by 28% and 31%, respectively. Comparing elderly female and elderly male subjects, AUC0-t and AUC0-inf were greater by 46% and 50%, respectively, and Cmax was greater by 17% in elderly female subjects. This data will be reflected in the product labeling.

Renal Impairment

Trial # CC-10004-CP-019

Study Title	A Multi-Center, Open-Label, Single-Dose Study to Assess the Pharmacokinetics of Apremilast and its Major Metabolite M12 in Subjects with Severe Renal Impairment and Normal Renal Function.
Clinical Site and Principal Investigator	▪ New Orleans Center for Clinical Research –Knoxville (NOCCR) 1928 Alcoa Highway, Suite G-50 Knoxville, TN 37920 William B. Smith, MD ▪ Orlando Clinical Research Center (OCRC) 5055 South Orange Ave Orlando, FL 32809-3017 Thomas Marbury, MD
Study Period	18 Apr 2011 to 27 Dec 2011
Objectives	To assess the pharmacokinetics (PK) of apremilast and its major metabolite M12 in patients with severe renal impairment and normal renal function.
Study Design and Population	Two-center, open-label, single dose. N=8 severe renal impairment (Group 1; eGFR <30 mL/min) and N=8 age, gender and weight matched healthy subjects (Group 2; eGFR >90 mL/min). N=8 severe RI and N=7 healthy subjects included in PK analysis. Male or female of any race between 18 to 80 years of age, inclusive, with a body mass index (BMI = weight [kg] / [height {m2}]) between 18 and 36 kg/m2 (inclusive) and body weight >50 kg were eligible for study participation.
Dosing and Administration	A single oral dose of 30 mg apremilast tablet on Day 1, batch number 10F0655, was administered.

Results

Table 1: Summary of Plasma Apremilast Pharmacokinetic Parameters (Geometric Mean [CV%])

Group	Geometric Mean (Geometric %CV) [a]						
	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{1/2}$ (hr)	CL/F (L/hr)	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)

[a] T_{max} is summarized by median and range (minimum – maximum)

Table 2: Summary Pharmacokinetic Parameters of Primary Metabolite (M12)

Group	Geometric Mean (Geometric %CV)[a]				
	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{1/2}$ (hr)
Severe renal impaired (n=7-8)	10545.5 (34.8)	13697.2 (49.5)	267.7 (27.8)	4 (3-24)	27.393 (45.2)
Matched healthy (n=7)	4308.4 (31.4)	4695.9 (25.0)	187.3 (38.5)	12 (3-8)	16.895 (21.7)

Reviewer's Comments

Apremilast and M12 exposure increased by ~89% and ~192% respectively in severe RI subjects. Clearance of these 2 moieties also decreased significantly in the severe RI subjects. These changes in overall exposure did not correlate with the AEs observed, probably because a single dose was administered. In the product labeling, a dose reduction of apremilast in severe RI subjects as compared to the general population is included by the sponsor which seems reasonable. However, additional analysis will be conducted by the Pharmacometrics reviewer for this application, Dr. Li Zhang to support the dose reduction.

Hepatic Impairment

Trial # CC-10004-CP-011

Study Title	An Open-Label, Single-Dose Study to Assess the Pharmacokinetics of Apremilast in Moderate And Severe Hepatic Impaired Subjects
Clinical Site and Principal Investigator	▪ University of Miami – Division of Pharmacology (UM-DCP) Richard A. Preston, MD, M.S.P.H., M.B.A. ▪ Orlando Clinical Research Center (OCRC) Thomas C. Marbury, MD
Study Period	Date first subject enrolled: 15 Dec 2010 Date last subject completed: 22 Jul 2011
Objectives	To assess the effect of moderate and severe hepatic impairment on the pharmacokinetics (PK) of apremilast and its major metabolite M12
Study Design and Population	N=32 male or female adult subjects with different degrees of chronic hepatic impairment matched with healthy subjects (with respect to age [±5 years], gender and weight [± 30 pounds (±13.61 kg)] enrolled. Group 1 (moderate hepatic impairment) were required to have confirmation of the diagnosis of cirrhosis made by biopsy or laparoscopy with a Child-Pugh score of 7 to 9, inclusive. For Group 2 (severe hepatic impairment), if biopsy or laparoscopy was not performed prior to Screening, subjects were included only if they had chronic liver disease and objective evidence of portal hypertension (ascites diagnosed by imaging or varices), with a Child-Pugh score ≥10 and ≤13.
Dosing and Administration	1 x 30 mg CC-10004 tablet, fasting, orally, lot number 10F0187 1 x 20 mg CC-10004 tablet, fasting, orally, lot number 10F0186 Regimen A: 8 moderate hepatic impaired subjects [1 x 30 mg CC-10004 tablet, fasting] Regimen B: 8 moderate matched healthy subjects [1 x 30 mg CC-10004 tablet, fasting] Regimen C: 8 severe hepatic impaired subjects [1 x 20 mg CC-10004 tablet, fasting] Regimen D: 8 severe matched healthy subjects [1 x 20 mg CC-10004 tablet, fasting]
Results	**Summary of CC-10004 Plasma Pharmacokinetic Parameters**

Group	T_{max}[a] (hr)	Geometric Mean (Geometric %CV) $AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
Moderate hepatic impaired (n=8)	2.50□ (1.0 – 9.0)	2897.07 (30.0)	206.92 (42.6)	10.04 (38.7)	10.35 (29.9)	149.98 (42.6)
Moderate matched healthy (n=8)	2.25 (1.0 – 6.0)	3063.51 (55.2)	246.14 □(39.8)□	9.14 (22.9)	9.79 (55.2)	129.21 (36.0)
Severe hepatic impaired (n=8)	2.50 (1.0 – 6.0)	1967.83 (31.8)	125.74 (61.6)	12.36 (49.6)	10.16 (31.6)	180.94 (66.6)
Severe matched healthy (n=8)	2.25 (1.5 – 6.0)	2000.19 (56.4)	193.08 (28.7)	8.01 (24.4)	10.00 (56.5)	115.42 (38.7)

Summary of M12 Plasma Pharmacokinetic Parameters

Group	T_{max}[a] (hr)	Geometric Mean (Geometric %CV)		
		$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)
Moderate hepatic impaired (n=8)	3.50 (2.0 – 9.0)	4440.31 (22.5)	198.35 (45.9)	12.09 (22.7)
Moderate matched healthy (n=8)	6.00 (2.5 – 12.0)	4805.65 (39.8)	184.22 (36.3)	13.07 (22.6)
Severe hepatic impaired (n=8)	□6.00 (2.0 – 12.0)	2993.65 (27.5)	127.36 (48.1)	14.07 (24.2)
Severe matched healthy (n=8)	3.50 (2.0 – 12.0)	3407.88 (27.0)	142.84 (29.6)	12.26 (25.8)

Reviewer's Comments

Mean AUC0-inf and Cmax for apremilast were 5.4% and 15.9% lower in moderate hepatic-impaired group as compared to moderate healthy-matched group; mean AUC0-inf and Cmax were 1.6% and 34.9% lower in the severe hepatic group as compared to the severe matched healthy group. For M12, the overall results observed were similar to those for apremilast. Although apremilast is significantly metabolized (more than 50%) as observed in the mass balance study, it is possible that severe HI does not impair its metabolism to a significant extent as many metabolic pathways are involved in its metabolism. The sponsor has not included any dose modifications for the severe HI group in the proposed product labeling which seems reasonable.

DRUG-DRUG INTERACTIONS

DDI with Ketoconazole

Trial # CC-10004-PK-005

Study Title	An open-label 2-period study to evaluate the influence of multiple oral doses of ketoconazole (NIZORAL) on the single dose pharmacokinetics of CC-10004 in healthy adult male subjects
Clinical Site and Principal Investigator	PAREXEL Clinical Pharmacology Research Unit (CPRU), Level 7, Northwick Park Hospital, Watford Road, Harrow HA1 3UJ, United Kingdom Dr David Wessels, MBChB, MBA
Study Period	Date first subject enrolled: 02 Apr 2005 Date last subject completed: 11 May 2005
Objectives	To evaluate the influence of multiple doses of ketoconazole on the single-dose pharmacokinetics of: ▪ CC-10004 ▪ (b) (4) ▪ CC-10055 (an active metabolite of CC-10004, Celgene code M7)
Study Design and Population	Single-center, open-label, 2-period. N=18 healthy males 18-55 years enrolled and included in PK analysis. Subjects were not permitted to: ▪ take any prescribed systemic or topical medication within 30 days of the first dose administration or any nonprescribed systemic or topical medication within 7 days of the first dose administration (with the exception of vitamin/mineral supplements). ▪ use any medications known chronically to alter drug absorption or elimination processes within 30 days of the first dose administration. ▪ to consume grapefruit or grapefruit juice from 2 weeks prior to first dose until the last PK sample was taken.
Dosing and Administration	Single 20 mg (2 x 10 mg) oral dose of CC-10004 given on the fifth of 7 days of once daily oral dosing with ketoconazole (NIZORAL) 400 mg. Batch number of CC-10004: 0293X Batch number of ketoconazole: 04KL836 Subjects received a single dose of CC-10004 followed by a 1-week washout and then 7 consecutive days of dosing with ketoconazole 400 mg QD with a single dose of CC-10004 on Day 5.

Results	**Summary Pharmacokinetics of CC-10004** **Variable** | **LSMean: Treatment B (Test)** | **LSMean: Treatment A (Reference)** | **% Ratio (Test /Reference)[a]** | **90% Confidence Interval[b]** | **Intra CV%** **Plasma PK** C_{max} (ng/mL) | 247.083 | 235.644 | 104.85 | 92.16; 119.30 | 22.5 $AUC_{(0-t)}$ (h*ng/mL) | 2795.405 | 2044.062 | 136.76 | 126.60; 147.73 | 13.4 $AUC_{(0-\infty)}$ (h*ng/mL) | 2827.492 | 2072.443 | 136.43 | 126.20; 147.49 | 13.5 $t_{½}$ (h) | 8.140 | 7.644 | 106.49 | 100.30; 112.68 | 10.7 Cl/F (L/h) | 7.073 | 9.650 | 73.30 | 67.80; 79.24 | 13.5 V_z/F (L) | 81.385 | 104.954 | 77.54 | 69.82; 86.12 | 18.2 t_{max} (h) | 3.975 | 2.525 | 0.74 | 0.06; 1.10 | - **Urine PK** fe (µg) | 886.285 | 650.776 | 136.19 | 113.12; 163.97 | 32.8 CL_r (mL/h) | 317.051 | 318.374 | 99.58 | 83.47; 118.81 | 31.2 [a] For t_{max}, the median difference (Test B-Reference A) is presented [b] For t_{max}, the CI is the B – A median difference. For all other variables the CI is of the ratio. **Summary Pharmacokinetics of CC-10055 (M7)** **Variable** | **LSMean: Treatment B (Test)** | **LSMean: Treatment A (Reference)** | **% Ratio (Test /Reference)[1]** | **90% Confidence Interval[2]** | **Intra CV%** **Plasma PK** C_{max} (ng/mL) | 13.541 | 8.756 | 154.65 | 131.08; 182.46 | 29.1 $AUC_{(0-t)}$ (h*ng/mL) | 135.228 | 67.208 | 201.21 | 177.81; 227.69 | 21.6 $AUC_{(0-\infty)}$ (h*ng/mL) | 144.079 | 73.659 | 195.60 | 173.41; 220.63 | 21.0 $t_{½}$ (h) | 8.527 | 7.241 | 117.77 | 96.79; 138.74 | 36.2 Cl/F (L/h) | 138.813 | 271.522 | 51.12 | 45.32; 57.67 | 21.0 V_z/F (L) | 1642.219 | 2490.842 | 65.93 | 54.73; 79.42 | 32.9 t_{max} (h) | 4.000 | 3.033 | 1.00 | 0.09; 1.31 | - **Urine PK** fe (µg) | 12.121 | 8.850 | 136.96 | 115.19; 162.85 | 30.5 CL_r (mL/h) | 89.637 | 131.683 | 68.07 | 56.44; 82.10 | 33.2
Reviewer's Comments	Ketoconazole co-administration increased mean apremilast AUC0-inf by 36% and mean Cmax by 5%, in addition CC-10055 (M7) AUC0-inf and Cmax increased by 96% and 55%, respectively. However, M7, the N-deacetyl active metabolite of apremilast was present in very low quantities in the plasma (AUC0-inf of M7 is ~4% of apremilast), as such a ~2 fold increase in its exposure is not considered significant enough to warrant a dose modification in this scenario. The t1/2 values for both apremilast and M7 did increase and CL/F values decreased, in the presence of ketoconazole indicating there is some effect of this P-gp/CYP inhibitor on apremilast disposition. The sponsor has not proposed to include a dose modification of apremilast when co-administered with ketoconazole, in the proposed product labeling, which seems reasonable. The data will be described in the product labeling.

DDI with Rifampin

Trial # CC-10004-CP-025

Study Title	A Phase 1, Open-label, 3-Period, Fixed-sequence Study to Evaluate the Effects of Rifampin on the Pharmacokinetics of Apremilast (CC-10004) in Healthy Subjects
Clinical Site and Principal Investigator	Quintiles Phase I Services, 6700 W. 115th Street, Overland Park, KS 66211 Philip T. Leese, MD
Study Period	Date first subject enrolled: 10 Feb 2012 Date last subject completed: 24 Apr 2012
Objectives	To evaluate the effect of multiple oral doses of rifampin as well as a single IV dose of rifampin on the pharmacokinetics (PK) of apremilast)
Study Design and Population	Single-center, open-label, 3-treatment period, fixed-sequence. N=20 male and female subjects 18-55 years of age planned, N=21 enrolled and included in PK analysis.
Dosing and Administration	Apremilast 30 mg oral tablets: Batch number 11F2066. Rifampin 600 mg for IV infusion: Batch number 7005369. Rifampin 300 mg oral capsules: Batch number 3083315. The 3 treatment periods in this study included: • Treatment Period 1 (Day 1): A single oral dose of 30 mg apremilast (Treatment A) • Treatment Period 2 (Day 5): A single oral dose of 30 mg apremilast followed 5 minutes later by a 30-minute IV infusion of 600 mg rifampin (Treatment B) • Treatment Period 3 (Day 7 to Day 21): Once daily oral doses of 600 mg rifampin for 15 days (from Day 7 to Day 21) with a single oral dose of 30 mg apremilast coadministered with the rifampin dose on Day 20 (Treatment C)
Results	**Table 1: Summary of Plasma Apremilast Pharmacokinetic Parameters (Geometric Mean [CV%]) (Subject 0011107 Excluded from Treatments B and C)**

	Apremilast alone (A, Day 1) (n=21)	Apremilast + IV Rifampin (B, Day 5) (n=19)	MD Rifampin + Apremilast (C, Day 20) (n=19)
AUC_{∞} (ng·h/mL)	3120 (31.5)	2980 (31.2)	869 (32.9)
AUC_t (ng·h/mL)	3070 (31.3)	2940 (31.3)	850 (33.7)
C_{max} (ng/mL)	290 (24.5)	331 (25.1)	166 (23.2)
T_{max} (h)[a]	2.00 (0.50-5.00)	1.50 (0.50-5.00)	1.00 (0.50-5.00)
$t_{1/2}$ (h)	8.12 (14.1)	7.35 (18.5)	6.13 (24.8)
CL/F (L/h)	9.60 (31.5)	10.1 (31.2)	34.5 (32.9)
V_z/F (L)	112 (35.8)	107 (43.4)	305 (51.6)

Table 2: Statistical comparisons of Apremilast exposure parameters (Subject 0011107 Excluded from Treatments B and C)

Parameters	Treatments	N	Geometric LS Mean	Pair	Pairwise Comparisons (test/reference)[a]		Intra-Subject CV%
					Ratio (%)	90% CI	
AUC_∞ (ng·h/mL)	A	21	3123	--	--	--	15.5
	B	19	2989	B/A	95.71	(87.99, 104.12)	
	C	19	873.2	C/A	27.96	(25.70, 30.41)	
AUC_t (ng·h/mL)	A	21	3066	--	--	--	15.6
	B	19	2954	B/A	96.35	(88.56, 104.82)	
	C	19	854.9	C/A	27.88	(25.63, 30.34)	
C_{max} (ng/mL)	A	21	289.5	--	--	--	17.0
	B	19	327.4	B/A	113.07	(103.18, 123.91)	
	C	19	164.5	C/A	56.80	(51.84, 62.25)	

Reviewer's Comments

There were no significant changes to the exposure of apremilast in presence of a single IV dose of rifampin. This confirms that inhibition of hepatic transports such as OATP1B1 and OATP1B3 would unlikely affect PK of apremilast which was not found to be a substrate for these transporters. Mean AUCinf, AUCt, and Cmax of apremilast decreased by 72%, 72%, and 43% respectively, in the presence of rifampin indicating that multiple oral doses of rifampin, a potent inducer of CYP3A4 as well as other CYP enzymes as well as P-gp, resulted in a significant decrease in the exposure of apremilast. Based on the data observed in this study, a recommendation to avoid co-administration of rifampin with apremilast is recommended to be included in the product labeling by this reviewer (b) (4)

DDI with Ortho Tri-Cyclen® DIALPAKs® (CYP3A4 substrates)

Trial # CC-10004-CP-020

Study Title	A Phase 1, Open-label, Randomized, 2-way Crossover Study to Investigate the Effects of Apremilast (CC-10004) on the Pharmacokinetics of an Oral Contraceptive in Healthy Female Subjects
Clinical Site and Principal Investigator	▪ PRA International, Clinical Pharmacology Center, 9755 Ridge Drive, Lenexa KS 66219; Sandra K. Willsie, DO, MA ▪ QPS Bio-Kinetic Clinical Applications, 1816 W Mt. Vernon, Springfield, MO 65802; Christopher W. Billings, DO
Study Period	Date first subject enrolled: 01 JUL 2011 Date last subject completed: 15 DEC 2011
Objectives	To assess the effects of apremilast on the pharmacokinetics (PK) of an oral contraceptive (OC), containing ethinyl estradiol (EE) (0.035 mg) and norgestimate (NGM) (0.180 mg/0.215 mg/0.250 mg per phase, respectively. Both EE and NGM are extensively metabolized by first-pass mechanisms in the GI tract and/or liver and 17-DNE is an active metabolite of NGM. It has been reported that one of the major metabolic pathways for EE is CYP3A4.
Study Design and Population	Open-label, multi-center, randomized, 2-sequence, 2-way crossover. N=40 healthy females 18-42 years of age had to be using a combination OC for a minimum of 2 consecutive, complete dosing cycles prior to screening, planned and enrolled, N=35 completed study, N=38 included in PK anaylsis.
Dosing and Administration	Apremilast (CC-10004; Lot 11F0327) were supplied by the sponsor in bulk bottles containing 30-mg oral tablets. Commercially available DIALPAKs® of Ortho Tri-Cyclen® (Ortho-McNeil-Janssen Pharmaceuticals, Inc; Lot 1EM154), each containing 28 oral tablets (21 active; 7 inactive) were supplied by the study center. At the beginning of the run-in phase, subjects were given either one or 2 Ortho Tri-Cyclen® DIALPAKs®, each containing 28 tablets (21 active, 7 inactive). The treatment phase consisted of 2 consecutive cycles (Cycle 1 and Cycle 2; each cycle = 28 days) to ensure steady state is reached with both the drugs. Prior to the first treatment administration, eligible subjects were randomized to one of the following 2 sequences: Sequence 1: Treatment A → Treatment B or Sequence 2: Treatment B → Treatment A The treatment sequence determined the order in which each subject received each of the 2 treatments: Treatment A: OC QD (Days 1 to 28) or Treatment B: OC QD (Days 1 to 28) plus apremilast 30 mg BID (Days 12 to 21)

Results

Plasma Pharmacokinetic Parameters of Ethinyl Estradiol (PK Population)

Treatment	Treatment A (OC alone) N = 38	Treatment B (OC plus Apremilast) N = 35
PK Parameter[a]	Geometric Mean (Geometric CV%)	Geometric Mean (Geometric CV%)
AUC_{0-t} (pg*hr/mL)	1336 (35.8)	1159 (35.0)
AUC_{0-tau} (pg*hr/mL)	1213 (34.8)	1063 (34.0)
$AUC_{0-\infty}$ (pg*hr/mL)	1772 (40.7)	1449 (41.4)
C_{max} (pg/mL)	132 (29.6)	121 (30.6)
t_{max} (hr)	1.18 (0.5-3.0)	1.50 (0.5-2.1)
$t_{½}$ (hr)	15.8 (3.57)	13.8 (3.27)
CL/F (L/hr)	28.9 (34.8)	32.9 (34.0)
Vz/F (L)	640 (38.8)	640 (31.7)

Plasma Pharmacokinetic Parameters of 17-Deacetyl Norgestimate (PK Population)

Treatment	Treatment A (OC alone) N = 38	Treatment B (OC plus Apremilast) N = 35
PK Parameter[a]	Geometric Mean (Geometric CV%)	Geometric Mean (Geometric CV%)
AUC_{0-t} (pg*hr/mL)	23404 (26.2)	20636 (22.6)
AUC_{0-tau} (pg*hr/mL)	20497 (25.2)	18149 (21.5)
$AUC_{0-\infty}$ (pg*hr/mL)	39433 (38.6)	33161 (30.5)
C_{max} (pg/mL)	2077 (22.2)	1861 (18.8)
t_{max} (hr)	1.50 (0.9-3.0)	1.50 (1.0-3.0)
$t_{½}$ (hr)	24.7 (7.60)	22.5 (6.21)

Statistical Analysis of Ethinyl Estradiol and 17-Deacetyl Norgestimate Parameters: AUC_{0-tau} and C_{max} (PK Population)

Analyte	PK Parameter	Treatment	N	Geometric Mean	Ratio (%) of Geometric Means (B/A)	90% CI of Ratio of Geometric Means	Intra-subject CV%
EE	AUC_{0-tau} (pg*hr/mL)	B	35	1077	88.8	(83.6, 94.3)	14.9
		A	38	1213			
	C_{max} (pg/mL)	B	35	121	91.3	(86.1, 96.9)	14.8
		A	38	132			
17-DNE	AUC_{0-tau} (pg*hr/mL)	B	35	18295	89.3	(85.9, 92.8)	9.5
		A	38	20497			
	C_{max} (pg/mL)	B	35	1869	90.0	(85.0, 95.3)	14.3
		A	38	2077			

Reviewer's Comments

NGM concentrations were very low, so only its metabolite concentrations are presented here. Co-administration of apremilast did not have an effect on the PK of either EE or 17-DNE (metabolite of NGM) indicating these CYP3A4 substrates can be co-administered with apremilast without any metabolic drug- drug interaction concerns.

DDI with Methotrexate (Frequently Co-Administered Drug in PsA Subjects)

Trial # CC-10004-PK-010

Study Title	Apremilast: A Multi-center, Open-label, 1-Sequence, 3-Period Study to Investigate the Effects of Multiple Doses of Apremilast on the Pharmacokinetics of Methotrexate in Subjects
Clinical Site and Principal Investigator	▪ Altoona Clinical Research Center, 175 Meadowbrook Lane, Duncansville, PA 16635; Alan Kivitz, MD ▪ Metroplex Clinical Research Center, 5939 Harry Hines Blvd., Suite 411, Dallas, TX 75235; Roy M. Fleischmann, MD
Study Period	Date first subject enrolled: 17 June 2009 Date last subject completed: 30 July 2009
Objectives	To assess the effects of multiple oral doses of apremilast on the pharmacokinetics (PK) of methotrexate (MTX) and its metabolite 7-OH MTX, given once a week (single administration). To assess the effect of MTX given once a week (single administration) on the steady-state pharmacokinetics of apremilast.
Study Design and Population	Open-label, multi-center, 3-treatment period, 1-sequence. N=15 male and female subjects 18-65 years of age, having psoriasis, psoriatic arthritis (PsA), or rheumatic arthritis (RA) and receiving weekly stable oral MTX therapy (between 7.5 and 20 mg once a week) for at least 3 months and not taking any other disease-modifying antirheumatic drugs (DMARDs) and/or immunosuppressive medication were enrolled in the study. N=15 completed study and were included in PK analysis.
Dosing and Administration	Apremilast 30 mg tablets batch number B080093, expiration Oct 2010. Methotrexate ((b) (4) Lot number 857861B, expiration Oct 2010). **The 3 treatment periods in this study included:** • Treatment Period I (Days 1 to 2): Subjects received a single oral dose of MTX on Day 1 morning. The MTX dose was the same dose that the subject had received as maintenance dose between 7.5 and 20 mg given once a week during the last 3 months. • Treatment Period II (Days 3 to 7): Subjects received apremilast 30 mg twice daily (BID) orally from Day 3 to Day 7. The Day 3 morning dose, Day 6 afternoon dose, and Day 7 doses were administered on-site. The remaining doses of apremilast from Day 3 afternoon to Day 6 morning were given to subjects to take home for self-administration. • Treatment Period III (Days 8 to 9): Subjects received a single oral dose of MTX between 7.5 and 20 mg along with apremilast 30 mg on Day 8 morning, followed by additional doses of apremilast alone BID (Day 8 evening and Day 9 morning and evening).

Results

Table 6: Summary of MTX Plasma Pharmacokinetic Parameters (Day 8)

		Geometric Mean (Geometric %CV)[a]					
Treatment	**t_{max}[b] (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (hr*ng/mL)**	**$AUC_{0-\infty}$ (hr*ng/mL)**	**$t_{1/2}$ (hr)**	**CL/F (mL/min)**	**Vz/F (mL)**
MTX 10 mg + apremilast	0.98 (NA-NA)	427 (NA)	1300 (NA)	1300 (NA)	3.5 (NA)	129 (NA)	39400 (NA)
N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1
MTX 12.5 mg + apremilast	2.07 (NA-NA)	669 (NA)	3020 (NA)	3010 (NA)	3.2 (NA)	69 (NA)	19100 (NA)
N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1
MTX 15 mg + apremilast	1.25 (0.50-1.52)	396 (31.5)	1670 (31.6)	1660 (32.4)	3.3 (14.4)	150 (32.5)	42800 (29.1)
N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6
MTX 17.5 mg + apremilast	1.00 (NA-NA)	565 (NA)	2270 (NA)	NC (NA)	NC (NA)	NC (NA)	NC (NA)
N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1	N = 1
MTX 20 mg + apremilast	2.07 (1.00-2.08)	569 (26.4)	2700 (33.2)	2700 (33.5)	4.3 (30.1)	124 (33.7)	45800 (11.9)
N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6

Table 7: Statistical Analysis of MTX Plasma Pharmacokinetic Parameters – AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}

PK Parameter	Treatment Received	N	Ratio of Geometric Means	90% CI of Ratio of Geometric Means	Intra-subject CV%
AUC_{0-t} (h•ng/mL)	MTX+Apremilast	15	99.90	(93.35, 106.90)	10.57
	MTX	15			
$AUC_{0-\infty}$ (h•ng/mL)	MTX+Apremilast	14	100.39	(92.89, 108.50)	11.19
	MTX	14			
C_{max} (ng/mL)	MTX+Apremilast	15	99.49	(92.67, 106.81)	11.07
	MTX	15			

Table 13: Summary of CC-10004 Plasma Pharmacokinetic Parameters

		Geometric Mean (Geometric %CV)[a]			
Treatment	**t_{max}[b] (hr)**	**C_{max} (ng/mL)**	**C_{min} (ng/mL)**	**AUC_{0-tau} (hr*ng/mL)**	**CL_{ss}/F (mL/min)**
Apremilast Day 7	2.00 (0.95-4.00)	554 (35.0)	207 (70.5)	3670 (53.8)	136 (53.8)
N = 15	N = 15	N = 15	N = 15	N = 15	N = 15
Apremilast + MTX Day 8	2.00 (0.98-4.08)	526 (42.2)	195 (81.0)	3660[c] (56.5)	137[c] (56.5)
N = 15	N = 15	N = 15	N = 15	N = 13	N = 13

	Table 14: Statistical Analysis of Apremilast Plasma Pharmacokinetic Parameters - AUC_{tau} and C_{max} **Pharmacokinetic Parameter** / **Treatment** / **N** / **Ratio of Geometric Means** / **90% CI of Ratio of Geometric Means** / **Intra-subject CV%** AUC_{tau} (ng*hr/mL) / MTX + Apremilast / 13 / 99.30 / (92.84, 106.20) / 9.66 Apremilast / 15 C_{max} (ng/mL) / MTX + Apremilast / 15 / 95.00 / (87.93, 102.65) / 12.07 Apremilast / 15
Reviewer's Comments	Given that patients with PSOR, PsA and RA are likely to receive concomitant MTX, this was an important DDI study to assess DDI of apremilast with a frequently co-administered background drug for the indications that the sponsor is developing apremilast for. Methotrexate did not affect the steady-state PK of apremilast. Multiple doses of apremilast did not affect the PK of MTX or 7-OH MTX. As such, the doses of neither of the 2 drugs need to be altered when co-administered.

BIOPHARMACEUTICS

Absolute Bioavailability

Trial # CC-10004-CP-012

Study Title	A Phase 1, Single-Center, Partly Randomized, Open-label Study to Investigate the Absolute and Regional Bioavailability of Apremilast (CC-10004) in Healthy Subjects
Clinical Site and Principal Investigator	Quotient Bioresearch Ltd, Mere Way, Ruddington, Nottingham, UK Sharan Sidhu, MB, ChB, BAO, MRCS
Study Period	Date first subject enrolled: 21 Jun 2010 Date last subject completed: 17 Aug 2010
Objectives	To evaluate the absolute bioavailability of apremilast following a single dose of a 20-mg immediate release (IR) tablet by using a [14C]-apremilast microtracer intravenous (IV) dose.
Study Design and Population	Single center, open-label, 5-period, partly randomized (fixed treatment for Period 1, and randomized treatment sequences for Periods 2 to 5), 5-way crossover study. N=12 healthy males 18-50 years of age, N=9 completed and analyzed for PK.
Dosing and Administration	Apremilast 20 mg tablets for oral administration in Regimen A (batch no. 10F0185) [14C]-labeled apremilast microdose solution for IV administration in Regimen A (batch nos. 1252/C/01 and 1252/C/03). Regimen A: 20 mg apremilast tablet administered orally followed by an IV infusion of 100 µg apremilast containing ~210 nCi of [14C]-apremilast (max 270 nCi or 10 kBq), starting at 1 hour 45 minutes after the oral dose (approximately the time to reach maximum concentration [Tmax] of the oral dose). The IV infusion was given over 15 minutes in approximately 5 mL of vehicle. Other regimens are not included and not discussed, as not relevant for discussion.
Results and Reviewer's Comments	Only absolute BA data is presented here. This study explored other objectives that are not included here as they are not relevant for discussion. The absolute bioavailability (CV) following oral administration of 20 mg apremilast was 73.2 (12.5)% compared with the IV dose. The mean plasma total CL was low compared to liver plasma flow, which suggests that apremilast is not a high extraction drug. Apremilast volume of distribution exceeds the value for total body water, which suggests that there was significant distribution into the tissue space.

Food Effect

Trial # CC-10004-CP-022

<table>
<tr><td>Study Title</td><td>A Phase 1, Open-Label , Randomized, Two-Period, Two-Sequence Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a Single 30-mg Tablet of Apremilast (CC-10004) in Healthy Subjects</td></tr>
<tr><td>Clinical Site and Principal Investigator</td><td>PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, TX 78744; Theresa T. Pham, MD</td></tr>
<tr><td>Study Period</td><td>Date first subject enrolled: 25 Feb 2012
Date last subject completed: 21 Mar 2012</td></tr>
<tr><td>Objectives</td><td>To evaluate the effect of food on the pharmacokinetics (PK) of a single oral 30-mg dose of apremilast in healthy subjects</td></tr>
<tr><td>Study Design and Population</td><td>Single-center, open-label, randomized, 2-period, 2-sequence crossover. N=46 healthy males 18-65 years of age planned and enrolled, N=44 completed, N=45 in PK analysis.</td></tr>
<tr><td>Dosing and Administration</td><td>A single 30-mg apremilast tablet administered orally, lot number 11F 2064. Subjects in the fasted group (Treatment A) did not receive breakfast before dosing, and subjects in the fed group (Treatment B) were dosed 30 minutes after starting a high-fat breakfast (~150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively).</td></tr>
<tr><td>Results</td><td>Summary of Plasma Pharmacokinetic Parameters of Apremilast by Treatment (Pharmacokinetic Population):
<table>
<tr><th rowspan="2">Parameter (unit)</th><th colspan="2">Single 30-mg Apremilast Tablet</th></tr>
<tr><th>Fasted
(N = 45)</th><th>Fed
(N = 44)</th></tr>
<tr><td>$AUC_{0-\infty}$ (ng•hr/mL)[a]</td><td>3157.96 (34.6)</td><td>3506.19 (33.9)</td></tr>
<tr><td>AUC_{0-t} (ng•hr/mL)[a]</td><td>3083.05 (34.0)</td><td>3436.39 (33.0)</td></tr>
<tr><td>C_{max} (ng/mL)[a]</td><td>339.86 (26.5)</td><td>333.85 (30.0)</td></tr>
<tr><td>t_{max} (hr)[b]</td><td>2.50 (0.62, 5.02)</td><td>3.00 (1.00, 8.00)</td></tr>
<tr><td>$t_{1/2}$ (hr)[a]</td><td>8.88 (21.2)</td><td>7.99 (18.9)</td></tr>
<tr><td>CL/F (mL/hr)[a]</td><td>9499.80 (34.6)</td><td>8556.28 (33.9)</td></tr>
<tr><td>Vz/F (mL)[a]</td><td>121735.96 (38.2)</td><td>98582.15 (28.0)</td></tr>
</table></td></tr>
<tr><td>Reviewer's Comments</td><td>No effect of a high-fact, high-calorie mean on apremilast PK was observed.</td></tr>
</table>

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/s/

SHEETAL S AGARWAL
11/20/2013

VENKATESH A BHATTARAM
11/20/2013

SATJIT S BRAR
11/20/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205437
Submission Date	21 March 2013
Product name, generic name of the active	Otezla (proposed), apremilast
Dosage form and strength	Film-coated Tablets (10, 20 and 30 mg)
Applicant	Celgene
Clinical Division	Pulmonary, Allergy and Rheumatology Products
Type of Submission	505(b)1, NME, QbD
Primary Biopharmaceutics Reviewer	Minerva Hughes, Ph.D.
Secondary Biopharmaceutics Reviewer	John Duan, Ph.D. (QbD Liaison)
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Assignment Date	10 April 2013
Filing Date	20 May 2013
Filing Review Date	**9 May 2013**

I. SUBMISSION OVERVIEW

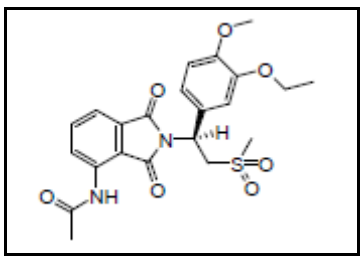
NDA 205437 was submitted in accordance with section 505(b)1 of the FDC act for the use of apremilast in the treatment of adult patients with active psoriatic arthritis (PsA). The proposed drug product is a film-coated tablet supplied in 10, 20, and 30 mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and [redacted] (b) (4) Film Coating [redacted] (b) (4) Pink/Brown/Beige. The recommended dose is 30 mg twice daily without regard to food; however, an initial dose titration up to 30 mg is required.

Data from three pivotal Phase 3, double-blind, placebo-controlled, parallel-group studies in approximately 1500 subjects with active PsA are submitted in support of the proposed indication. Also, the pharmacokinetic (PK) disposition of apremilast was characterized in 16 clinical pharmacology studies.

II. BIOPHARMACEUTICS SUMMARY INFORMATION

The drug substance apremilast (USAN) is a selective phosphodiesterase 4 (PDE4) inhibitor, which works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic disease.

Apremilast has the molecular formula $C_{22}H_{24}N_2O_7S$ and the following chemical structure.



The S-enantiomer was used in clinical studies and is the proposed form for marketing. The Applicant determined an intrinsic apparent permeability value for apremilast across porcine kidney epithelial cell (LLC-PK1) monolayers of 21 x 10-6 cm/sec. Since the drug is practically insoluble in water, and the in vitro permeability is low, a BCS Class 4 designation was assigned. That being said, the absolute oral bioavailability is around 70%.

(b) (4) The proposed drug substance specification includes tests for appearance, identification, assay, residual solvents, related impurities, chiral purity, heavy metals, residue on ignition, and particle size distribution (by laser diffraction).

The proposed drug product is a diamond shaped tablet manufactured using (b) (4) The Phase 1 studies used a capsule formulation. During phase 2 studies, a white-round table was used. A comparative bioavailability study was conducted to compare the phase 2 tablets with the phase 1 capsule formulation. The tablet formulation was further modified for phase 3 studies (change to diamond shape, (b) (4)). The proposed commercial product has (b) (4) . The Applicant seeks to bridge the phase 3 and commercial product using in vitro dissolution. Comparative dissolution studies using the Phase 3 and commercial tablets have been conducted using media at 3 different pHs (1.2, 4.5 and 6.8).

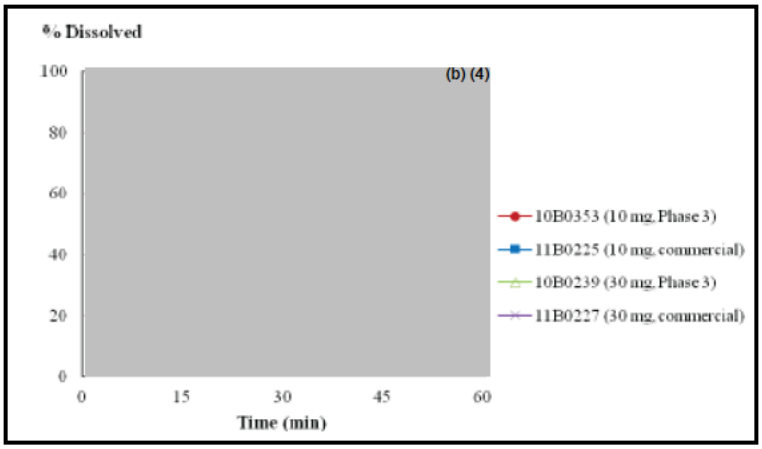
The commercial manufacturing process was evaluated and optimized using a QbD approach. Multivariate DoE studies were carried out on potentially medium/high risk process parameters that need to be controlled to ensure conformance to critical quality attributes (CQAs) at scale. The specified CQAs are drug substance particle size distribution, assay, content uniformity, and dissolution. A comparative bioavailability study was also completed to evaluate the effects of micronized and milled drug substance on bioavailability.

This Biopharmaceutics review will evaluate the adequacy of the proposed dissolution method and acceptance criterion for its intended use. The proposed dissolution method and acceptance criterion are as follows.

- USP Apparatus II, 0.3% SLS in 25 mM Sodium Phosphate Buffer, pH 6.8, 900 mL, 75 rpm
- Q = (b) (4) at (b) (4) minutes

A representative dissolution profile is illustrated below.

Dissolution Profile, 10 mg Tablet, Commercial and Phase 3



The review will also evaluate the following.

- DOE studies that used dissolution as a response variable to assure that target operating ranges are appropriately validated. These studies include the following.

(b) (4)

- Dissolution stability and product expiry
- Comparative dissolution data to bridge the to-be-marketed product with the phase 3 material.

III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The Applicant denotes dissolution as a CQA and relies on dissolution performance as an assessment of product quality and response factor for various DoE studies. However, there is no information justifying the selection of the proposed method parameters or information showing the method's ability to detect meaningful manufacturing changes. The following comments should be addressed by the Applicant to support a complete review.

(1) Provide the complete dissolution method development report for review. The report should include the following:

a. The complete drug substance pH solubility profile.

b. *A detailed description of the testing done to select the proposed dissolution method as optimal for your product (e.g., equipment, medium, agitation speed, pH, assay, sink conditions, etc.). We note that* (b) (4) *is proposed and data supporting* (b) (4) *should be provided.* (b) (4) *. For each variable tested, clearly specify the testing conditions. Complete dissolution data (individual values, mean, RSD, and profiles) should be provided for all variables tested. Also, the sampling time points should be sufficient to characterize the complete dissolution profile, which means sampling at early time points (i.e., 5, 10, 15 and 20 minutes) in the event of rapid product dissolution. The data in the NDA do not include complete dissolution profile information.*

c. *Testing conducted to demonstrate the discriminating capability of the selected dissolution test. Your proposed assessment of* (b) (4) *is inadequate. The optimal dissolution method should be able to distinguish between micronized and nonmicronized drug substance (i.e., similarity f2 values <50) owing to the significant effect of drug substance particle size on bioavailability, as observed in Study CC-10004-BA-001 and the designation of drug substance particle size distribution as a critical quality attribute. Further, a dissolution method that achieves* (b) (4) *dissolution in* (b) (4) *minutes for a poorly soluble drug substance is generally not sufficiently robust to detect meaningful manufacturing changes.*

d. *The complete dissolution method validation report.*

(2) Provide the complete dissolution data (individual values, mean, RSD, and profiles) for all DOE studies supporting the proposed commercial manufacturing process and site changes that used dissolution as a response factor and the results of similarity f2 testing, using a clinical batch as a reference, where appropriate.

(3) FDA understands that the proposed dissolution method (USP 2, 75 rpm, 0.3% SLS pH 6.8 sodium phosphate buffer) was not used for testing any clinical supplies or the primary registration stability lots. Please confirm.

(4) FDA recommends adding dissolution sampling at 10 and 20 minutes to the ongoing stability studies and including the complete dissolution data in your next stability update.

IV. FILING REVIEW CHECKLIST

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Proposed: USP II, 0.3% SLS in pH 6.8 Sodium Phosphate, 75 rpm Q = (b) (4) at (b) (4) minutes
3.	Does the application contain the dissolution method development report?		x	A tabular summary of method development changes was found in 3.2.P.5.1 Batch Analysis-AAI, but this is inadequate.
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Summary validation data were in Section 3.2.P.5, the report was not found. There was no method validation package either.
5.	Does the application include a biowaiver request?		x	No formal biowaiver request, but comparative dissolution is used to bridge the commercial and Phase 3 product, which is an implied biowaiver.
6.	Does the application include a IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		BCS 4 designated
8.	Is information on mixing the product with foods or liquids included?		x	Product will be taken without regards to food.
9.	Is there any in *vivo* BA or BE information in the submission?	x		CC-10004-BA-001 – particle size evaluation (not BE under fasting) CC-10004-BA-002 – capsule vs. tablet and food effect (not BE under fasting)

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping? c.) Is there a site comparability protocol?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See above list.

{See appended electronic signature page}
Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
John Duan, Ph.D.
Biopharmaceutics Team Leader (Acting)/ QbD Liaison
Office of New Drug Quality Assessment

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

/s/

MINERVA HUGHES
05/09/2013

JOHN Z DUAN
05/09/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 205437**	**Proposed Brand Name**	**None**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Apremilast**
Medical Division	**DPARP**	**Drug Class**	**PED4 inhibitor**
OCP Reviewer	**Sheetal Agarwal**	**Proposed Indication(s)**	**Psoriatic arthritis**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**IR tablets**
Date of Submission	**3/21/2013**	**Dosing Regimen**	**30 mg BID (titrate for 1 week with 10 and 20 mg tablets for better GI tolerability)**
Estimated Due Date of OCP Review		**Route of Administration**	**Oral**
Medical Division Due Date		**Sponsor**	**Celgene**
PDUFA Due Date	**4/21/2014**	**Priority Classification**	**S**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	**16**	**16**	**Includes PK, ADME, food effect, renal and hepatic impairment, race and gender effects and DDI studies**
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**	**2**	
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	
multiple dose:	**X**	**2**	**2**	
Patients-				
single dose:				
multiple dose:	**X**			**Pop PK**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**	**2**	
In-vivo effects of primary drug:	**X**	**1**	**1**	
In-vitro:	**X**	**12**	**12**	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Subpopulation studies -				
ethnicity:	**X**	**1**	**1**	
gender:	**X**	**1**	**1**	
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**	**1**	
hepatic impairment:	**X**	**1**	**1**	
PD -				
Phase 2:	**X**			
Phase 3:	**X**			
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**	**2**	**Pop PK data submitted to be reviewed by Pharmacometrics reviewer**
Phase 3 clinical trial:	**X**	**4**	**4**	**To be reviewed by medical officer, pop PK data to be reviewed by Pharmacometrics reviewer**
Population Analyses -				
Data rich:				
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**	**1**	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**30**	**30**	**Includes 16 human, 12 in vitro and 2 bioanalytical reports**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		x		Dissolution data comparing Phase 2 and 3 formulations and to be marketed formulations has been submitted, to be reviewed by Biopharmaceutics reviewer
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic	x			

	requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None so far.

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

/s/

SHEETAL S AGARWAL
04/28/2013

SURESH DODDAPANENI
04/28/2013