CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

Date:	March 13, 2014
From:	Timothy J. McGovern, PhD, ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA:	205437
Agency receipt date:	March 21, 2013
Drug:	Otezla (Apremilast)
Sponsor:	Celgene Corporation

Indication: Treatment of adult patients with active psoriatic arthritis (PsA)

Reviewing Division: Division of Pulmonary, Allergy, and Rheumatology Products

Introductory Comments: The primary pharmacology/toxicology reviewer and supervisor concluded that the nonclinical data support approval of apremilast for the indication listed above.

The recommended pharmacologic class for apremilast is a phosphodiesterase 4 (PDE4) inhibitor.

A complete nonclinical program was conducted including pivotal general toxicology studies in mice and monkeys, a genetic toxicology battery, two-year carcinogenicity studies in rats and mice, and a battery of reproductive and developmental toxicology studies. In the general toxicology studies the primary toxicities included arteritis, perivascular inflammation of the lung, hepatocyte hypertrophy, and gastrointestinal pathology. The identified NOAELs provided exposure margins of ~ 1- to 5-fold compared to the anticipated clinical exposure at the recommended dose.

The carcinogenicity studies did not produce any significant findings and apremilast was negative in the genetic toxicity battery.

Fertility, embryo-fetal development (EFD) and pre/postnatal development studies of apremilast were conducted in mice and an EFD study was conducted in monkeys. Apremilast prolonged the estrus cycle and increased the interval to mating in female mice. Apremilast was not teratogenic in mice or monkeys but was associated with dystocia, reduced viability, fetal weight and litter size, and increases in abortion and embryo-fetal death. The Division recommended a Pregnancy Category "C" for this product.

Conclusion: I agree with the Division pharmacology/toxicology conclusion that apremilast can be approved from the pharmacology/toxicology perspective. I have discussed and am in agreement with labeling revisions proposed by the Division and the sponsor has indicated agreement with the revisions as well.

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/s/

TIMOTHY J MCGOVERN
03/13/2014

Secondary Pharmacology and Toxicology Review for NDA 205-437

TO: NDA 205-437 (Celgene Corp.)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Drug Products

DATE: November 27, 2013

Overview: I concur with the recommendation of Dr. L. Steven Leshin (detailed in a nonclinical review dated November 20, 2013) that the pharmacology and toxicology of OTEZLA (apremilast) have been adequately studied and the drug product should be approved from a nonclinical perspective.

Background: Apremilast (Code name: CC-10004) is a NME phosphodiesterase type IV (PDE4) inhibitor. It is indicated for chronic, twice-daily, oral treatment of psoriatic arthritis. The proposed maximum clinical dose is 30 mg b.i.d. (60 mg/day).

Pharmacology: The pharmacodynamic effects of apremilast were investigated both *in vitro* and *in vivo*. In primary pharmacodynamic studies, apremilast had an IC_{50} of 74 nM for PDE4 isolated from U937 monocytic cells. Apremilast was also approximately 279- to 40,000-fold more selective for PDE4 inhibition than for other PDE subtypes, but was non-selective for subtypes A1A, B1, B2, C1, and D2 within the PDE4 group. The applicant conducted numerous in vitro and in vivo pharmacology studies to demonstrate that apremilast modulates both pro- and anti-inflammatory mediators. Many of these studies are summarized in Dr. Leshin's review and will not be discussed here.

Safety Pharmacology: In a CNS study in mice, lacrimation and pitosis were observed after single oral doses of 1000 mg/kg and greater. Findings at the high-dose of 2000 mg/kg included apathy (sluggish movement) and death of one animal on the day following dosing. Findings at the high dose (e.g. lacrimation, pitosis, and apathy) were judged to be possibly due to autonomic effects of apremilast. In a hERG assay, apremilast inhibited hERG channel current with an IC_{50} of 184 µM. In a combined cardiovascular and respiratory safety study in anesthetized dogs, a dose-related increase in dP/dt_{max} and heart rate were observed after single oral doses of 0.5 mg/kg and above, but QT prolongation was not observed. Dose-related increases in peak inspiratory and expiratory flow were also observed at 0.5 mg/kg and above. There were no gastrointestinal effects noted in mice at single oral doses up to 1000 mg/kg.

Toxicology: Pivotal oral toxicology studies were conducted in the mouse and monkey up to 6 months and 12 months, respectively. The major apremilast-related finding across mouse studies was arteritis. Arteritis was usually noted within the thoracic organs, particularly prominent at the junction of the aortic root and the heart, and less prevalent in the thymus. Perivascular inflammation of the lung was also observed. Other findings included centrilobular hepatocyte hypertrophy, likely due to extensive apremilast metabolism. High doses also resulted in gastrointestinal effects, such histopathological changes in the stomach (distension, thickening, irregular surface and raised foci) and associated reduction in food consumption and weight loss. As expected, incidence or severity of findings generally increased with dose. The NOAEL of the 6-month mouse study was determined to be 10 mg/kg/day,

primarily due to arteritis at higher doses. The AUC exposure margin for the maximum recommended human dose of 30 mg b.i.d. at the NOAEL is 0.8.

Arteritis was also observed in shorter duration, high dose monkey studies, including a 14-day study with doses up to 1000 mg/kg and a 28-day study at doses up to 650 mg/kg, but not in a 13-week study with doses up to 300 mg/kg or the chronic, 12-month study with doses up to 600 mg/kg. When arteritis was observed, it was generally found in the myocardium and other locations that included connective tissue of the sciatic nerve and kidney. Other findings at higher doses included emesis or retching or excessive salivation, and thin body condition. The NOAEL of the 12-month monkey study was identified as 600 mg/kg/day. The AUC exposure margin for the maximum recommended human dose of 30 mg b.i.d. at the NOAEL is 4.7.

Although the animal:human exposure margin in the chronic mouse study was slightly less than 1 as noted above (AUC exposure margins of 1 or greater are generally preferred), systemic exposure at the NOAEL of 10 mg/kg was previously judged to be adequate to support clinical development. Therefore, this review concludes that the NOAELs of both chronic mouse and monkey studies provide adequate systemic safety margins on an AUC basis (approximately 1 for the mouse and approximately 5 for the monkey) for the proposed maximum dose of apremilast. See Dr. Leshin's review for further exposure margin details.

Genotoxicity: Apremilast was negative in the *in vitro* bacterial mutagenicity test (Ames assay), the in vitro chromosomal aberration assay, and the in vivo mouse micronucleus assay.

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

Reproductive and Developmental Toxicology: Pivotal reproductive and developmental toxicity studies of apremilast were completed in mice and monkeys via the oral route of administration. These studies evaluated the effects of apremilast on fertility in mice, teratogenicity in mice and monkeys, and pre- and post-natal development in mice. In a male mouse fertility study, apremilast had no effects on male fertility at doses up to 50 mg/kg/day. In a separate female mouse fertility study, however, apremilast treatment prolonged estrus cyclicity and increased time to mating, though there was no difference in pregnancy rate between control and apremilast-treated groups. Apremilast also caused an increase in early resorptions and a decrease in fetal body weights. Both the maternal and fetal NOAELs were identified as 10 mg/kg/day.

In embryofetal development studies in mice, no treatment-related teratogenic findings were observed; however, a dose-dependent reduction in litters and litter sizes due to postimplantation loss occurred at doses greater than or equal to 20 mg/kg/day. Increases skeletal variations were also noted at doses greater than or equal to 20 mg/kg/day. The NOAEL for embryofetal effects was identified as 10 mg/kg/day. In an embryofetal development study in monkeys, apremilast treatment resulted in a dose-dependent increase in fetal losses (abortions). Although a NOAEL for teratogenic effects was identified as the low-dose of 20 mg/kg/day, it was not possible to adequately assess teratogenic effects at doses greater than 20 mg/kg/day (50 mg/kg/day and above) due to the high incidence of fetal loss and lack of examination of aborted fetuses.

In a pre- and postnatal development study in mice, premature delivery, dystocia, reduced viability, and reduced birth weights occurred at doses greater than or equal to 80 mg/kg/day. The NOAEL was identified as 10 mg/kg/day.

Labeling: Section 8.1 (Pregnancy Category C), Section 8.3 (Nursing Mothers), Section 12.1 (Mechanism of Action), and Section 13.1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility) have been revised. Revisions to Section 8.1 resulted in hybrid labeling that incorporates currently required CFR labeling with formatting expected to arise from a new pregnancy and lactation labeling rule that is expected to be established in 2014. Section 8.1 revisions were made in consult with Dr. Carrie M. Ceresa of the Maternal Health Team. See Dr. Leshin's review for complete product labeling details.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/

MARCIE L WOOD
11/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205437
Supporting document/s:	(b) (4)
Applicant's letter date:	March 20 2013, July 31 2013
CDER stamp date:	March 21 2013, July 31 2013
Product:	Otezla (apremilast)
Indication:	Psoriatic Arthritis
Applicant:	Celgene Corp
Review Division:	DPARP
Reviewer:	L. Steven Leshin, D.V.M., Ph.D.
Supervisor/Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Michelle Jordan Garner

Disclaimer

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1 Executive Summary

1.1 Introduction

Apremilast (identified as CC-10004 in study reports) is a small molecular new molecular entity indicated for the treatment of psoriatic arthritis. It has pharmacological properties of a phosphodiesterase IV (PDE4) inhibitor. The nonclinical development program was initially reviewed for the indication of psoriasis in DDDP under (b) (4), but the NDA was submitted to DPARP for psoriatic arthritis following development under IND 101761. The applicant provided evidence in nonclinical studies that apremilast increases intracellular cyclic adenosine monophosphate (cAMP) levels in numerous types of cells including peripheral mononuclear blood cells. They postulate that elevated cAMP, in turn, alters the secretion of pro- and anti-inflammatory modulators attenuating the symptoms and course of psoriatic arthritis.

Apremilast is formulated for oral administration as 10, 20 and 30 mg tablets, with a maximum proposed human dose of 30 mg, b.i.d. (60 mg/day).

1.2 Brief Discussion of Nonclinical Findings

Pharmacology

CC-10004 (apremilast) is a new molecular entity that inhibits phosphodiesterase 4 (PDE4) enymes. In primary pharmacodynamic studies, CC-10004 had a IC_{50} of 74 nM for PDE4 isolated from U937 monocytic cells (b) (4) CC-10004 was approximately 279- to 40,000-fold more selective for PDE4 inhibition than for other PDE subtypes, but was non-selective for subtypes A1A, B1, B2, C1, and D2 within the PDE4 group. From published studies, it is known that inhibition of PDE4 results in increased levels of intracellular cAMP, initiation of an intracellular signaling pathway that involves the activation of protein kinase A, and activation of cAMP responsive element binding protein (CREB/ATF-1) family of transcription factors, as well as downregulation of nuclear factor kappaB (NF-κB) transcriptional activity. The functional result is alteration of both inflammatory and anti-inflammatory mediators. The applicant demonstrated that CC-10004 alters many mediators in numerous in vitro and in vivo conditions (animal studies), including various animal models of arthritis. Some of the mediators assessed by the applicant were inducible nitric oxide synthase, tumor necrosis factor-alpha (TNF-α), and interleukins (IL-17, IL-23, and IL-10).

Safety Pharmacology

Following single oral doses of CC-10004 to rats, there were findings of initial concern in studies of neurobehavioral and cardiovascular function, but not respiratory function, or gastroinstestinal transport. In CNS evaluations, one high dose animal died the day after neurological testing. CC-10004 produced sympathetic activation responses. In the hERG assay, an IC_{50} of 184 μM for CC-10004 inhibition of I_{Kr} was identified, which is

greater than 100-times the human C_{max} at 30 mg BID dose. Lack of QT prolongation was confirmed in a follow-up study in anesthetized dogs, however, an increase in left ventricular pressure with increasing doses was observed. Further studies were conducted in monkeys as part of the general toxicology assessments. They were also negative for QT prolongation, but there was insufficient information provided to assess the validity of these studies and minimal data listings were provided. A tQT evaluation in humans was negative for inducing QT prolongation (refer to the Medical Officer's Review).

General Toxicology

Pivotal GLP studies were conducted in the mouse and cynomolgus monkey.

Mouse: Studies in the mouse (up to 6 months in duration) covered a range of doses from 2000 mg/kg down to 1 mg/kg. The 6-month mouse study identified a NOAEL at 10 mg/kg/day, slightly greater than the NOAEL of shorter-term studies (4-6 mg/kg/day).

The major effect of CC-10004 in the mouse was arteritis. Arteritis was usually noted within the thoracic organs, particularly prominent at the junction of the aortic root and the heart, and less prevalent in the thymus. These were accompanied by perivascular inflammation of the lung. Other findings included centrilobular hepatocyte hypertropy which was probably related to the extensive metabolism of CC-10004. High doses resulted in gastrointestinal effects, such histopathological changes in the stomach (distension, thickening, irregular surface and raised foci) and associated reduction in food consumption and weight loss. The hemological profile consisted of an inflammatory profile in which there was an increase in total white cells due to an increase in neutrophils, along with a reduction in lymphocytes. Increases in total protein and globulin and a reduction in albumin were also observed. Usually, serum enzymes were not affected. As expected, incidence or severity of findings generally increased with dose.

Monkey: In the monkey, studies were conducted up to 12 months in duration. The 12-month monkey study identified a NOAEL at 600 mg/kg/day.

At high doses in the monkey, emesis/retching or excessive salivation were common findings, along with thin body condition. As with mice, there was an inflammatory hemotology profile in which there was an increase in total white cells due to an increase in neutrophils and a simultaneous reduction in lymphocytes. Arteritis occurred at doses of 1000 mg/kg/day for 14 days, and at 180 and 650 mg/kg/day for 28 days, but not at 25, 85 or 300 mg/kg/day for 13 weeks or at 60, 180 or 600 mg/kg/day for 12 months. Arteritis was observed within the myocardium (differing from the common observed aortic root location in the mouse), as well as other locations that included the connective tissue of the sciatic nerve and kidney.

Genetic Toxicology

CC-10004 was negative in the standard series of genetic toxicology assay that included the bacterial reverse mutation assay, in vitro chromosomal aberration assay using

human peripheral blood lymphocytes pooled from 3 individuals, and the in vivo mouse micronucleus assay.

Carcinogenicity
CC-10004 was not carcinogenic in 2-year oral dosing studies in mice at doses up to 1000 mg/kg/day or in rats at dose levels up to 20 mg/kg/day in males and 3 mg/kg/day in females.

Reproductive and Developmental Toxicology
Reproductive and developmental toxicology GLP studies were conducted with either the mouse or the monkey. The rabbit had negligible exposure to CC-10004 after oral administration and low doses administered intravenously were lethal.

Fertility: Studies in the mouse found no effect of CC-10004 on sperm motility or sperm counts and no effect on mating parameters or resultant pregnancies and embryo-fetal survival. Fertility studies in females found that estrous cyclicity was prolonged due to an increase in diestrus period and resulted in a longer time until mating. CC-10004 resulted in an increase in early resorptions, and a reduction in fetal body weights. The NOAEL was the high dose of 50 mg/kg/day for males and the low dose of 10 mg/kg/day in females.

Embryofetal Development: Pregnant mice administered CC-10004 had reduced body weight gain that was due to reduced uterine weight. There were reductions in litters and litter size due to postimplantation losses in all CC-10004 dose groups. Fetal weight was also reduced in a dose dependent manner in both males and females. There was no dose-related effect on malformations, although skeletal variations were increased. The NOAEL was 10 mg/kg/day.

In the monkey, there were dose-related fetal losses, mostly occurring during weeks 3 and 4 of gestation. The teratogenic effects of CC-10004 in the monkey were not adequately evaluated due to the high incidence of dose-related fetal abortions, coupled with the absence of examination of these fetuses. There was an increased incidence of skeletal variations, most related to a reduced number of ossification sites and misaligned tail vertebrae. A NOAEL for embryofetal development was 20 mg/kg.

Pre- and Post-Natal Development: There was difficulty in delivery in the high dose group that resulted in the death of one dam. The high dose group also had reduced maternal body weight. There was no effect on late pregnancy administration of CC-10004 on pregnancy duration or number of dams that delivered. In the F1 generation, postnatal pup mortality was increased, with reduced pup weights of survivors until day 21 of lactation. There were no effects of F_0 treatment with apremilast on the F_1 generation for clinical or necropsy observations after weaning; body, testes or epididymis weights; sexual maturation; passive avoidance; motor activity; mating; fertility or F2 embryofetal parameters. The maternal NOAEL was 10 mg/kg/day. The NOAEL for the F_1 generation was 10 mg/kg/day due to early postnatal mortality. There

were no adverse findings in surviving pups through during evaluations at stages of physical developement, fertility, and in various behavior and learning tests.

Apremilast was detected in the milk of lactating mice at levels at levels approximately 1.5-times that of simultaneously collected blood plasma samples at 1 and 6 hours, and not detectable in either milk or plasma at 24 hours.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, the application may be approved.

1.3.2 Additional Non Clinical Recommendations

There are no additional nonclinical recommendations.

1.3.3 Labeling

The sponsor's label was submitted in SD-6 June 24 2013. A consult with Carrie M. Ceresa, Pharm D, MPH of the Maternal Health Team for recommended wording in Pregnancy Section 8 was requested on Oct 30, 2013. The recommendations from Dr. Ceresa (email of the draft consult on Nov 14 2013) are included in the reviewer's revised labeling for pregnancy. Labeling negotiations with the sponsor will occur after the finalization of this review. The maximum recommended human dose (MRHD) is 30 mg twice daily.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Sponsor's proposed label

(b) (4) *Pregnancy Category C:*

(b) (4)

(b) (4)

Reviewer's Recommendation

Pregnancy Category C

Risk Summary

Adequate and well-controlled studies with TRADE NAME have not been conducted in pregnant women. In animal embryofetal studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximal recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. Although no teratogenic effects were observed in monkeys at doses corresponding 2.1-times MRHD, the study was insufficient to thoroughly evaluate the teratogenic risk due to abortion/embryofetal loss at higher doses. In mice, there were no ampreilast-induced malformations up to exposures (b) (4)-times MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for TRADE NAME. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. TRADE NAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Labor or delivery

The effects of TRADENAME on labor and delivery in pregnant women are unknown. In mice, premature delivery and dystocia were noted at doses corresponding to ≥ (b) (4) times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data

Monkey embryofetal development: In an embryofetal developmental study, cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during weeks 3 to 4 of dosing during the first trimester, at doses approximately 2.1 times the MRHD and greater (on an AUC basis at doses ≥ 50 mg/kg/day). No abortifacent effects were observed at a dose approximately 1.4 times the MRHD (on an AUC basis at a dose of 20

mg/kg/day). Although there was no evidence for a teratogenic effect at 20 mg/kg/day, there were insufficient numbers of fetal monkeys to adequately address teratogenic risk at doses approximately 4.5 times the MRHD and greater (on an AUC basis at doses ≥50 mg/kg/day).

Mouse embryofetal development: In an embryofetal study, apremilast was administered at dosages of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation day 6 through 15). In a combined fertility and embryofetal development study, apremilast was administered at dosages of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of (b) (4) -times the MRHD (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately (b) (4) -times the MRHD (10 mg/kg/day).

Mouse pre- and postnatal development: In a pre- and post-natal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from day 6 of gestation through day 20 of lactation, with weaning at day 21. Premature delivery, dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥(b) (4) -times the MRHD (on an AUC basis at doses ≥80 mg/kg/day). No adverse effects occurred at a dose (b) (4) -times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to approximately (b) (4) -times the MRHD (up to 300 mg/kg/day).

8.3 Nursing mothers

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

It is not known whether TRADENAME or its metabolites are present in human milk; however, apremilast was detected in milk of lactating mice. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Caution should be exercised when TRADENAME is administered to a nursing woman.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, affecting numerous cellular functions in PDE4 responsive cells. The specific mechanism(s) by which TRADE NAME exerts its therapeutic action in psoriatic arthritis patients is not well defined

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to (b) (4)-times the MRHD on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD in males and females, respectively (3 mg/kg/day in females and 20 mg/kg/day in males).

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

Sponsor's proposed label

(b) (4)

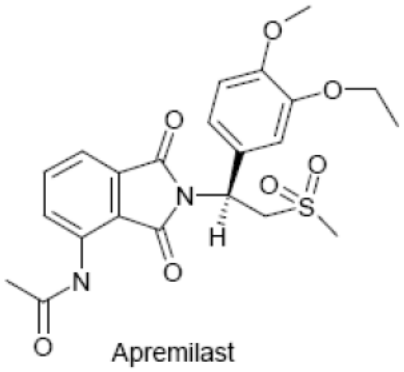
Reviewer's Recommendation

In a fertility study of male mice, apremilast at oral dosages up to approximately 3-times the MRHD based AUC (up to 50 mg/kg/day) produced no effects on male fertility.

In a fertility study of female mice, apremilast was administered at oral dosages of 10, 20, 40, and 80 mg/kg/day. At dosages ≥(b) (4)-times the MRHD (20 mg/kg/day), estrous cycles were prolonged and time to mating was decreased. There was no effect of apremilast at approximately (b) (4)-times the MRHD (10 mg/kg/day).

2 Drug Information

2.1 Drug

Generic Name	**Apremilast**
Code Name	**CC-10004** (S-enantiomer)
CAS Registry Number	608141-41-9
Chemical Name	(b) (4) [redacted]
Molecular Formula	$C_{22}H_{24}N_2O_7S$
Molecular Weight	460.5 Daltons
Structure	 Apremilast CC-10004 (S enantiomer)
Pharmacologic Class	Phosphodiesterase type IV (PDE4) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1: Relevant IND's

IND	Status	Division	Indication	Received Date
(b) (4)	Active	DDDP	Treatment of psoriasi	July 29, 2004
101,761	Active	DPARP	Behcet's disease and psoriatic arthritis	Dec 16, 2008

2.3 Drug Formulation

There are 3 dosage forms of the immediate release film-coated tablets: 10, 20 and 30 mg tablets. The composition is listed in the following table:

Table 2: Composition of Apremilast Tablets: 10 mg, 20 mg, and 30 mg

			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)

2.4 Comments on Novel Excipients

There are no novel excipients used in the apremilast tablet formulations. All excipients were listed in the FDA Inactive Ingredient database and do not exceed the maximum potency limits.

2.5 Comments on Impurities/Degradants of Concern

There are currently no toxicological concerns with the type of impurities or degradants at the levels detected (refer to the CMC Review).

Three different processes with different manufacturing sites were used during development and the certificates of analysis in the nonclinical reports indicated that not all impurities were found for all manufacturing methods. This difference appears to depend on (b) (4) The major impurities of apremilast drug substance are the (b) (4) both of which have

specifications of NMT (b) (4) The measured concentrations in the drug product are (b) (4) for (b) (4) and (b) (4) for (b) (4) The specification for unspecified impurities is (b) (4), and for total impurities is (b) (4). In stability studies, the impurities appear to be reasonably stable with time.

The original characterization of the amount of (b) (4) in CC-10004 batches found levels up to (b) (4) Therefore a specific study for potential mutagenicity of (b) (4) was conducted (Report CC-10004-TOX-015) in which CC-10004 was spiked with (b) (4) The findings were negative for mutagenicity of (b) (4) Later batch analysis of (b) (4), found that the original amounts in the batches were (b) (4) Batches of the API were reanalyzed as described in the submission of Oct 15, 2009 of IND 101761 and subsequently a corrective impurity level amendment was submitted to the appropriate nonclinical toxicology reports. The acceptance criteria was also reduced for (b) (4) to the current level of NMT (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The indicated patient population is adults with active psoriatic arthritis. The recommended oral dosage is 30 mg twice daily.

2.7 Regulatory Background

The apremilast development program for psoriasis originated under (b) (4) in DDDP (July 29, 2004). The apremilast development program for rheumatologic conditions was intiated later under IND 101761 (December 16, 2008), with cross-reference to (b) (4) for nonclinical support. However, the opening clinical studies under IND 101761 were for the treatment of Behcet's disease and not psoriatic arthritis.

The first US clinical protocol that included patients with psoriatic arthritis was a small Phase 1 trial, Protocol CC-10004-PK-010, submitted April 14 2009, to study the effects of apremilast (30 mg BID for 10 days) in patients on a background of methotrexate. Patients (n=15) included those with psoriasis, psoriatic arthritis, or rheumatic arthritis.

This was followed with a request on Oct 20, 2009, for an End of Phase 2 meeting to discuss the Phase 3 clinical development program for psoriatic arthritis. The EOP2 meeting was held on March 25, 2010 as a teleconference. Pertinent to nonclinical development, the applicant was informed the previously submitted nonclinical studies were adequate to initiate Phase 3 clinical trials in psoriatic arthritis and that nonclinical phototoxicity studies were not necessary.

During development, issues regarding the interpretation of reproductive and developmental toxicology studies and the implications for contraceptive use in future clinical studies were also addressed. Upon review of the monkey embryofetal developmental study, reviewers for (b) (4) and IND 101761 (Dec 6, 2010) concurred that there was an inadequate assessment of teratogenicity due to fetal

demise and abortion. However, after consultation with Dr. Abby Jacobs, it was agreed that this could be addressed through labeling and repeat of the study was unnecessary. The Maternal Health Team reviewed the past and present contraceptive protocols and provide clarification for Phase 3 and future contraceptive use for apremilast trials in their consult of Oct 28 2010. The reproductive and developmental toxicology findings are reviewed in Section 9, Reproductive and Developmental Toxicology

A pre-NDA meeting for the psoriatic arthritis indication was held on December 19 2012. The applicant was informed the submitted nonclinical studies were sufficient to support the NDA.

3 Studies Submitted

3.1 Studies Reviewed

Report Number	Title	Review Date
Pharmacology		
Primary Pharmacology		
8611	In Vitro Pharmacology and ADMR-Tox: Diversity Profile + CYP450 + HERG, Study of Four Compounds	current
PDE 0801	Phosphodiesterase (PDE) Inhibitor Assays Enzymatic Study of 4 compounds	current
PDE4-1001	Phosphodiesterase (PDE) Inhibitor Assays: Enzymatic Study of Six Compounds	current
SSBK8217_23649	SelectScreen Biochemical Kinase Profiling of CC-220 and CC-10004 (Apremilast)	current
CC10004ET151	In Vitro Pharmacology Study of CC0010004	current
5424-11	Multiple Cytokine profiling for PDE4 inhibitors CC-10004, (b) (4) CC-11050, (b) (4) in LPS-stimulated human PBMCs	current
5042-107	Anti-Inflammatory Activities of the Novel PDE4 Inhibitor CC-10004 Against Human Leukocytes in Vitro	Sept 7, 2005
Phamacology of Metabolites		
5275-179	PDE4 and TNF-α Inhibitory Activity of CC-10004 Metabolites M1, M2, M3 (Racemate), M5 (Racemate), and M7	Nov 2 , 2006
5347-137	PDE4 and TNF-α Inhibitory Activity of CC-10004 Metabolite M12 ([^{14}C]O-desmethyl glucuronide)	current
5424-75	Phosphodiesterase 4 and Tumor Necrosis Factor-alpha Inhibitory Activity of CC-10004 S-isomer Metabolites M3, M12 (Synthesized), M16, and M17	current
5638-96	Phosphodiesterase 4 and Tumor Necrosis Factor-alpha Inhibitory Activity of CC-10004 (Apremilast) Metabolite M14 (N-deacetylated O-desmethylated glucuronide)	May 13, 2011
Effects on Cytokines and Inflammation		
5673-140	In Vitro Effects of CC-10004 and CC-11050 alone and in Combination with Anti-Rheumatic Agents on Synovial Markers in Primary Chondrocytes and Rheumatoid Arthritis Synovial Fibroblasts	May 13 2011
5265-117	Effect of the PDE4 inhibitors CC-10004, (b) (4) (cilomilast), CC-11050 and (b) (4) (roflumilast), and the IMiD CC-5013	Sept 7, 2005

	on IL-6 production by human, rat, mouse and monkey whole blood stimulated with LPS *in vitro*.	
7600-043	Effect of Apremilast on Cytokine and Chemokine Production in LPS Stimulated Human Whole Blood Using the TruCulture System	current
5478-159	Multiple Cytokine Profiling for Phosphodiesterase Type 4 Inhibitors CC-10004 and CC-11050 in Anti-CD3 Monoclonal Antibody Stimulated Human T cells	current
AP279R AP284R AP291R	Effect of Pretreatment with CC-11050 or CC-1000rum TNF-α in Female CD Rats	current
7600-011	Effect of Apremilast on Transcriptional Regulation and Gene Expression in Monocytes, Peripheral Blood Mononuclear Cells, Jurkat T Cell Leukemia and THP-1 Monocytic Leukemia Cells	current
In Vivo Models		
WEL 01-027	Mouse Type II Collagen Arthritis Model	current
AP707 RAP830R	Effect of CC-11050, CC-10004, (b) (4) on Mouse Collagen Induce Arthritis	current
CLG/001/EM	Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model	current
CLG/001/EM Histoloogy	Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model	current
CLG/002/EM;	Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model	current
CLG/002/EM Histology	Effects of Enbrel and/or CC-10004 in Antibody-Induced Arthritis in Mice	current
CLG/003/EM	Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model	current
CLG/003/EM Histology	Histological Analysis of Hind Limb Ankle Joints from Murine Arthritogenic Model	current
KIR-P03604	Therapeutic Effect of CC-10004 and CC-11050 in Collagen-Induced Arthritis	current
MD320051220	Evaluation of the effect of apremilast treatment on the TH-17 cells in the murine model of collagen induced arthritis	Apr 4, 2012 May 13,-2011
MDCG6	CC-10004: Evaluation of CC-10004 of CC-10004 in Combination with Methotrexate and Indomethacin in the Collagen-Induced Arthritis Model	current
5589-97	Effects of Phosphodiesterase 4 Inhibitors CC-10004 and CC-11050 in Combination with Cyclosporine A, Methotrexate and Etanercept on Rheumatoid Arthritis and Psoriasis Associated Cytokine Production in Stimulated T Cells.	current
Secondary Pharmacology		
2744121	CC-10004 (Apremilast) Does Not Bind Human Cereblon	current
qsk121001	A final summary report of the in vivo pharmacokinetic and ADME data generated on five Celgene PDE-4 inhibitors in the rat and ferret	current
121401	Therapeutic Index of SelCIDs in Ferret Lung Neutrophilia and Emesis Model	current
MDCG5	Evaluation fo CC-10004 in the T and B cell Transfer Model in Mice	current
7645-001	Effect of Apremilast on Primary Human Osteoclasts and Osteoblasts In Vitro	current
5299148	The effect of thalidomide and IMiDs including lenalidomide (CC-5013), CC- 11006, and CC10015, and the PDE4 inhibitors CC-10004 and CC-11050 on thromboxane B2 and prostacyclin	Dec 2, 2005

	production in endothelial cell/platelet co-cultures	
5197130	Effect of IMiDs, PDE4 inhibitors, and tubulin inhibitors on COX-2 expression and PGE2 production by human PBMC.	Dec 2, 2005
52260865265012	Effect of CC-10004 +/- 16.16-diemthyl PGE2 and CC-4047 on cell adhesion molecules in TNF-α stimulated human umbilical vein endothelial cells (HUVEC)	Dec 2, 2005
TECH10282009	Treatment of Psoriasiform with Methotrexate in Combination with Apremilast	May 13, 2013
558997	Effects of Phosphodiesterase 4 Inhibitors CC-10004 and CC-11050 in Combination with Cyclosporine A, Methotrexate and Etanercept on Rheumatoid Arthritis and Psoriasis Associated Cytokine Production in Stimulated T Cells.	current
5299-148	The Effect of Thalidomide and IMiDs including lenalidomide (CC-5013), CC-11006, and CC-10015, and the PDE4 inhibitors CC-10004 and CC-11050 on Thromboxane B2 and Prostacyclin Production in Endothelial Cell/Platelet Co-Cultures	current
5570-044	Effect of PDE4 Inhibitors and IMiDs® on Human Dermal Fibroblast Proliferation and PAI-1 Production	current
5279-153	Effect of the PDE4i's CC-10004 and CC-11050 on proliferation and Akt phosphorylation in HUVEC	
md220051168	Evaluation of Two Test Items, CC-10004 and CC-11050 in the Air Pouch Gout-like Inflammation Model in Mice	May 13, 2013
md220051169	Evaluation of Two Test Items, CC-10004 and CC-11050 in the Gout-like Peritonitis Model in Mice	May 13, 2013
TECH1102006	CC-11050 and CC-10004 in Treatment of Psoriasiform	Nov 2, 2006
3252910	Effect of PDE4 Inhibitors CC-11050 and Apremilast and JNK Inhibitor CC-930 on Type I Interferon Pathophysiology in Cellular Models of Cutaneous Lupus	May 13 2011
Safety Pharmacology		
1398-443	CC-10004: Effects on General Activity and Behaviour in the Mouse Following Oral Administration	Sept 7 2005
031206.DFN	Effects of CC-10004 on Cloned hERG Channels Expressed in Mammalian Cells	Sept 7 2005
1398-264-D6146	CC-10004: Cardiovascular and Respiratory Effects in the Anaesthetised Dog Following Intravenous Administration	Sept 7 2005
CC-10004-TOX-1171	CC-10004: Gastrointestinal Motility Assessment Following Oral Administration to Male CD-1 Mice	current
Absoprtion, Distribution, Metabolism, Elimination		
Methods of Analysis (Mouse, Rat, Rabbit, Monkey)		
CC-10004-DMPK-001	Determination of CC-10004 and (b) (4) in Heparinized Mouse Plasma by LC/MS/MS	current
CC-10004-DMPK-016	Determination of CC-16085 (Desmethyl CC-10004) and CC-16166 (Desmethyl CC-10004 Glucuronide) in Heparinized CD1 Mouse Plasma by LC/MS/MS	current
CC-10004-DMPK-041	Validation of a Method for the Determination of CC-10004 in Lithium Heparinized Mouse Plasma by LC-MS/MS	current
1398/251-D0142	Validation of an Analytical Procedure for the Determination of (b) (4) and/or its enantiomers CC-10004 and (b) (4) in Mouse Plasma (Heparin) using Solid Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometric Detection	current
1398/136-D0142	Validation of an Analytical Procedure for the Determination of (b) (4) in Rat Plasma (Heparin Anticoagulant) using Solid Phase Extraction for Sample Preparation and Liquid	current

	Chromatography with Mass Spectrometric Detection	
CC-10004-DMPK-002	Determination of CC-10004 and (b) (4) in Heparinized Rat Plasma by LC/MS/MS	current
1398/347-D0142	Validation of an Analytical Procedure for the Determination of CC-10004 in Rabbit Plasma (Heparin) using Solid Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometric Detection	current
1398/362-D0142	Investigation into the Storage Stability of CC-10004 in Rabbit Plasma using Solid Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometric Detection	current
CC-10004-DMPK-004	Determination of CC-10004 and (b) (4) in Heparinized Rabbit Plasma by LC/MS/MS	current
CC-10004-DMPK-003	Determination of CC-10004 and (b) (4) in Heparinized Monkey Plasma by LC/MS/MS	current
CC-10004-DMPK-025	Determination of CC-16085 (Desmethyl CC-10004) and CC-16166 (Desmethyl CC-10004 Glucuronide) in Heparinized Monkey Plasma by LC/MS/MS	current
1398/135-D0142	Validation of an Analytical Procedure for the Determination of (b) (4) in Monkey Plasma (Heparin Anticoagulant) using Solid Phase Extraction for Sample Preparation and Liquid Chromatography with Mass Spectrometric Detection	current
ADME		
Mouse		
1398/376-D1145	(^{14}C)-CC-10004: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the mouse	Sept 7, 2005
Rat		
1398/215-D1140	Determination of the oral pharmacokinetics and bioavailability of racemic (b) (4) and its enantiomers in the male and female rat a	Sept 7, 2005
1398/259-D1145	Investigation into the pharmacokinetics, excretion and metabolism of [^{14}C]-CC-10004 in the male and female rat following single and repeated oral administrations	Sept 7, 2005
QSK121001	A final summary report of the in vivo pharmacokinetic and ADME data generated on five Celgene PDE-4 inhibitors in the rat and ferret	current
Rabbit		
1398/387-D1145	(^{14}C)-CC-10004: A pilot study of plasma pharmacokinetics following oral administration to the rabbit	Sept 7, 2005
Monkey		
1398/399-D1145	(^{14}C)-CC-I0004: A study of absorption, excretion and metabolism following oral and intravenous administration to the cynomolgus monkey	Sept 7, 2005
Protein Binding		
CC-10004-DMPK-026	"In Vitro Protein Binding Determination of CC-10004 in Mouse, Rat, Rabbit, Monkey, and Human Plasma Using Ultrafiltration and LC/MS/MS Analysis"	Sept 7, 2005 Dec 10 2007 July 21, 2009
Milk		
CC-10004-DMPK-034	Determination of Lacteal Transfer of CC-10004 following a Single Oral Dose to Lactating CD-1 Mice	May 13, 2011
Placental Transfer		
CC-10004-TOX-012 Refer to the Toxicology Section	Placental Transfer Pregnant CD-1 mice	current

CC-10004-TOX-013 Refer to the Toxicology Section	Placental Transfer – Monkey Pregnant monkeys	current
Metabolism		
In Vitro		
1398/261-D1145	Metabolism of (^{14}C)-CC-10004 and (^{14}C)-[redacted] (b) (4) in microsomes isolated from mouse, rat, rabbit, dog, monkey and man	Sept 7, 2005
1398/393-D1145	Identification of the cytochrome P450 enzymes responsible for the in vitro metabolism of (^{14}C)-CC-10004 in human liver microsomes	Sept 7, 2005
CC-10004-DMPK-023	In Vitro Metabolism of [^{14}C]-CC-10004 in Hepatocytes from the Mouse, Rat, Rabbit, Dog, Monkey, and Human	July 21, 2009
CC-10004-DMPK-012	In vitro Evaluation of CC-10004 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes	Nov 2, 2006
CC-10004-DMPK-038	In Vitro Metabolism of CC-10004 in Adult and Juvenile Human Cryopreserved Hepatocytes, Human Microsomes and CD-1 Mouse Microsomes	April 4 2012
In Vivo		
1398/393-D1145	Identification of the cytochrome P450 enzymes responsible for the in vitro metabolism of (^{14}C)-CC-10004 in human liver microsomes	Sept 7, 2005
CC-10004-DMPK-031	Metabolite Radio-Profiling and Identification after A Single Oral and IV Dose of [^{14}C]CC-10004 in Male Intact and BDC Mice	July 21, 2009
Excretion		
CC-10004-DMPK-030	Elimination of Radioactivity in Bile, Urine, and Feces Following Oral and Intravenous Administration of ^{14}C-CC-10004 to Mice	July 21, 2009
1398/227-D1145	Effects of CC-10004 on selected cytochrome P450 activities in human liver microsomes: Prediction of drug interactions	Sept 7, 2005
CC-10004-DMPK-039	In Vitro Evaluation of CC-10004 as an Inhibitor of Human Cytochrome P450 Enzymes CYP2A6, CYP2B6 and CYP2C8	May 13, 2011
CC-10004-DMPK-017	Assessment of the Interaction of CC-10004 with Human P-glycoprotein	
CC-10004-DMPK-027	Assessment of Interaction of CC-10004 with Human Organic Anion Transporters Using Influx Transporter cRNA Injected Xenopus laevis Oocytes	July 21, 2009
CC-10004-DMPK-036	In Vitro Assessment of Inhibition Potential of CC-10004 for Efflux Transporters	May 13, 2011
CC-10004-DMPK-040	CC-10004: Inhibition Potential in OCT2, OATP1B1 and OATP1B3 expressing HEK293 cells	May 13, 2011
CC-10004-DMPK-1347	Evaluation of Substrate Potential of CC-10004 for Uptake (OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) and Efflux (BCRP) Transporters	current
General Toxicology		
Single-Dose Toxicity		
Mouse		
1398/278	CC-10004: Single Dose Oral Toxicity Study in the Mouse	Sept 7 2005
1398/279	CC-10004: Single Dose Intravenous Toxicity Study in the Mouse	Sept 7 2005
Rat		
1398/276	CC-10004: Single Dose Oral Toxicity Study in the Rat	Sept 7 2005
1398/277	CC-10004: Single Dose Intravenous Toxicity Study in the Rat	Sept 7 2005
Repeat-Dose Toxicity		
Mouse		

1398/262	CC-10004: 14 Day Oral (Gavage) Administration Range-finding Study in the Mouse	Sept 7 2005
1398/289	CC-10004: 28 Day Oral (Gavage) Administration Toxicity Study in the Mouse	Sept 7 2005
1398/297	CC-10004: 4 Week Oral (Gavage) Administration Toxicity Study in the Mouse	Sept 7 2005
1398/333	CC-10004: 4 Week Oral (Gavage) Administration Toxicity Study in the Mouse	Sept 7 2005
1398/373	CC-10004: 13 Week Oral (Gavage) Administration Toxicity Study in the Mouse	Sept 7 2005
CC-10004-TOX-002	CC-10004: A 90-Day Oral Toxicity Study in Mice	Sept 25, 2007
CC-10004-TOX-004	CC-10004: A 6-Month Oral Toxicity Study in Mice	Dec 10, 2007 April 30, 2008
CC-10004-TOX-008	CC-1004: Oral Toxicity Study in Mice to Investigate the Time Course for Development and Recovery of Inflammatory Lesions in Multiple Tissues	Dec 10, 2007 Aug 26, 2010
Rat		
1398/213	CC-10004 and (b) (4) Oral (Gavage Administration) Comparative Toxicity Study in the Female Rat	Sept 7 2005
10004-TOX-003	CC-10004: 90-Day Oral Toxicity Study in Rats	Sept 25, 2007
Monkey		
1398/283	CC-10004: Maximum Tolerated Dose (MTD) followed by a 14 Day Fixed Dose Oral (Gavage) Administration Toxicity Study in the Monkey	Sept 7 2005
CC-10004-TOX-010	14-day oral (gavage) pilot study with CC-10004 in cynomolgus monkeys	
1398/296	CC-10004: 28 Day Oral (Gavage Administration) Toxicity Study in the Monkey	Sept 7 2005
1398/368	CC-10004: 13 Week Oral (Gavage) Administration Toxicity Study in the Monkey	Sept 7 2005
CC-10004-TOX-005	CC-10004: A 12-Month Oral Toxicity Study in Cynomolgus Monkeys	Dec 10, 2007 April 30, 2008
Genetic Toxicology		
398/282	CC-10004: Reverse Mutation in five Histidine requiring strains of Salmonella typhimurium	Sept 7 2005
1398/280	CC-10004: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes	Sept 7 2005
1398/281	CC-10004: Induction of micronuclei in the bone marrow of treated mice	Sept 7 2005
Impurity		
CC-10004-TOX-015	Bacterial Reverse Mutation Assay Apremilast (CC-10004) spiked with (b) (4) (an impurity)]	Aug 26, 2010
Carcinogenicity		
Mouse		
CC-10004-TOX-006	A 104-Week Oral Carcinogenicity Study of CC-10004 in Mice	
Rat		
CC-10004-TOX-007	CC-10004: A 104-Week Oral Carcinogenicity Study in Rats	
Reproductive and Developmental Toxicity		
Fertility		
CC-10004-TOX-001	CC-10004: Oral (Gavage) Fertility and General Reproduction Toxicity Study in Mice	July 21, 2009
CC-10004-TOX-011	Oral (Gavage) Fertility and General Reproduction Toxicity Study of CC-10004 in Male Mice	July 21,2009 Aug 26, 2010

CC-10004-histoexpertreport	Histopathology Expert Report	July 21, 2009
CC-10004-TOX-012	Combined Oral (Gavage) Fertility and Developmental Toxicity Study of CC-10004 in Female Mice	Aug 26, 2010
Embryo-Fetal Development		
Mouse		
1398/308	CC-10004: Oral (Gavage) Range-Finding Study of Embryo-Foetal Development in the Mouse	Sept 7,2005
1398/309	CC-10004: Oral (Gavage) Study of Embryo-Foetal Development in the Mouse	Sept 7, 2005
Rabbit		
CC-10004-TOX-009	Intravenous Dosage-Range Finding Developmental Toxicity Study of CC-10004 in Rabbits	Aug 26, 2010
1398/290	CC-10004: Oral (Gavage) Preliminary Study in the Non-Pregnant Rabbit	Sept 7, 2005
1398/291-D6154	CC-10004: Oral (Gavage) Range-Finding Study of Embryo-Foetal Development in the Rabbit	Sept 7, 2005
1398/292	CC-10004: Oral (Gavage) Study of Embryo-Foetal Development in the Rabbit	Sept 7, 2005
Monkey		
CC-10004-TOX-013	Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey	Aug 26, 2010 Nov 24, 2010
Pre- and Postnatal Development		
Mouse		
CC-10004-TOX-1139	Oral (Gavage) Developmental and Perinatal/Postnatal Reproduction Toxicity Study of CC-10004 in Mice, Including Maternal Function and Postnatal Behavioral/Functional Evaluation	
CC-10004-TOX-014	Two-Week Oral (Gavage) Dosage Range Finding Repeated-Dose Toxicity Study of CC-10004 in Neonatal Mice	April 4, 2012
Special Toxicology		
Local Tolerance and Phototoxicity		
CC-10004-TOX-500	An Acute Dermal Irritation Study in Rabbits of CC-10004 in Ethanol:Propylene Glycol	
CC-10004-TOX-501	A Skin Sensitization Study (Buehler Method) in Guinea Pigs of CC-10004 in Ethanol:Propylene Glycol	
CC-10004-TOX-1170	Neutral Red Uptake Phototoxicity Assay of CC-10004 in Balb/c 3T3 Mouse Fibroblasts	
Biomarkers		
AP1012R	CC-10004:Evaluation of Biomarkers for Predicting Toxicity of CC-10004 in Rat	Sept 7, 2005

3.2 Studies Not Reviewed

The following reports were not reviewed since they did not directly pertain to the proposed indication of the NDA or did not provide additional useful safety information. A few studies were not interpretable due to insufficient information.

Report Number	Title	Previous Review Date
Pharmacology		
BSK-1073	BioMAP Profiling Study	
5448-74	Inhibition of Ultraviolet Light B Induced TNF-alpha Production by Thalidomide (CC-2001), Pomalidomide (CC-4047), Lenalidomide (CC-5013), Apremilast (CC-10004), CC-10015, CC-11006, CC-11050, CC-13097, CC-15965, (b) (4) CC-16057, (b) (4) in Primary Human Neonatal Epidermal Keratinocytes and Primary Mouse Epidermal Keratinocytes	
5638-35	Effect of Phosphodiesterase 4 Inhibitors, CC-11050 and Apremilast (CC-10004) on Interferon-alpha and Tumor Necrosis Factor-alpha Production by CpG-A Oligodeoxynucleotide Stimulated Human Peripheral Blood Mononuclear Cells and Plasmacytoid Dendritic Cells	
ap576ap600ap1025	Effect of CC-10004 on LPS-Induced Lung Neutrophilia in the Rat.	
ap998rap1036r	Effect of CC-10004 in a Murine Ovalbumin-Induced Asthma Model.	
ap1217rap1356r	Effect of CC11050 and CC-10004 in a Murine Ovalbumin-induced Asthma Model	
dlxj1000	Effects of CC-10004 and CC-11050 on Allergen-Induced Bronchospasm in Actively Sensitised, Anaesthetised, Ventilated Guinea-Pigs	
1270RC35-001	Effect of CC-2001, CC-4047, CC-5013, CC-11006, CC-10004, CC-11050, CC-401, and (b) (4) on Carrageenan-Induced Hyperalgesia in Rats	
drxl001cc10004	CC-10004: Changes in Disease Onset and Life Span in the G93A SOD1 Mouse Model of ALS	
epistem06218c	The Efficacy of CC-10004, CC-11050 and Tetomilast in a TNBS-Induced Colitis Model	
epistem07163	The Efficacy of CC-10004, CC-11050 and Tetomilast in a TNBS-induced Colitis Model: Further Gene Expression Analysis	
s07059	Analgesic assessment of test articles in the Bennett (CCI) model of neuropathic pain	
5196-141-155	Anti-Proliferative Activity of CC-4047, CC-5013, CC-5079, and CC-10004 against the Non-Hodgkins B Lymphoma Cell line Farage *in vitro*.	
AP343R	Effect of Pretreatment with CC-11050, CC-10004, (b) (4) or (b) (4) on Carrageenan-Induced Paw Edema in the Rat	
AP352R	Effect of Pretreatment with CC-11050, CC-10004 or (b) (4) on Neutrophil Infiltration and TNF-alpha Production in the Airpouch of Rats	
AP2599	Anti-apoptotic Effects of Phosphodiesterase 4 Inhibitors Apremilast and CC-11050 to Ultraviolet Light B Exposure in SKH-1 Female Mouse Skin	
1016668	Pharmacology Data Report On Compounds (b) (4), CC-10004 To (b) (4), CC-11050	
5127-132	Screening of IMiDs® and PDE4 inhibitor compounds for anti-angiogenic activity in the human umbilical cord vessel ring assay	
5478100	Ulcerative colitis biomarker profiling for Phosphodiesterase-4 inhibitors CC-10004, CC-11050 and tetomilast, and cyclosporine A in human peripheral blood mononuclear cells.	

1016668	Pharmacology Data Report On Compounds (b) (4), CC-10004 To (b) (4), CC-11050	
538708	Investigation of the Anti-angiogenic Potential of CC-10004 and CC-11050 in Endothelial Cells	
5369006041	The Effect of PDE4 inhibitors and IMiDs on GM-CSF Production by Normal Human Lung Fibroblasts	
ADME		
CC-10004-DMPK-007	CC-10004: Oral Pharmacokinetics and Dosing Formulation (milled versus Micronized) Evaluation in Fasted Male Rats	
CC-10004-DMPK-009	Report for "Intravenous and Oral (Stomach Tube) Pharmacokinetic Study of CC-10004 in Pregnant Rabbits"	
CC-10004-DMPK-028	Vehicle Tolerance and Pharmacokinetic Study for CC-10004 in Rabbits via Oral (Stomach Tube), Intravenous and Subcutaneous Routes	
Toxicology		
CC-10004-TOX-010	14-day oral (gavage) pilot study with CC-10004 in cynomolgus monkeys	

3.3 Previous Reviews Reference

The pharmacology-toxicology reviews for (b) (4) and IND 101761 were referenced with review dates indicated below. (b) (4) is an active program in DDDP for the treatment of psoriasis and DDDP was the initial review Division. The program for psoriatic arthritis under IND 101761 was initiated later, after the majority of nonclinical studies were reviewed. The nonclinical reviews for (b) (4) are provided in the Appendices.

Review Date	Appendix Number
(b) (4)	
Sep 7, 2005	2
Dec 2, 2005	3
Nov 2, 2006	4
June 19, 2007	5
Sep 25, 2007	6
Dec 10, 2007	7
Apr 30, 2008	8
Jul 21, 2009	9
Aug 26, 2010	10
Nov 4, 2010	11
May 13, 2011	12
Apr 4 2012	13
IND 101761	
Apr 3, 2009	-
Dec 6, 2010	-

4 Pharmacology

4.1 Primary Pharmacology

A number of primary pharmacology studies were previously reviewed under (b) (4) and are provided in the Appendices (Appendix 2, September 7, 2005 Review; Appendix 3, December 2, 2005 Review; Appendix 4 November 2, Review 2006; and Appendix 12, May 13, 2011 Review). Additional studies are summarized below.

PHOSPHODIESTERASE ACTIVITY

Study Title: In Vitro Pharmacology and ADMR-Tox: Diversity Profile + CYP450 + HERG, Study of Four Compounds

Report 8611

Key Study Findings:

- This was an in vitro pharmaceutical screening assay for 68 cell surface receptors, 17 enzymes, metabolism, and hERG channel activity (QT prolongation).
- CC-10004 (batch 5121-134-D) at 10 μM was a potent inhibitor of phophodiesterase (PDE) 4.

Table 3: Summary of PDE inhibition

PDE	IC_{50} % inhibition
PDE1	12%
PDE2	30%
PDE3	26%
PDE4	95%

- These four PDE reactions all used cAMP as a substrate. The source of PDE enzyme was U-937 cells (PDE1 and PDE4), bovine brain (PDE1) or human platelets (PDE2 and PDE5)
- These tests were followed up in Report 5042-107 (below) with multiple dose response curves to determine more precisely the selectivity of toward PDE types.
- There was a 52% enhancement of agonist binding to the L-type (verapamil) calcium channel receptor, but this was not confirmed in a follow-up assay (Report CC-10004-ET-151)
- Based on the hERG assay, CC-10004 was classified as having a borderline moderate to high potency for affecting the I_{Kr} current with 51% inhibition when tested at 1 μM (A GLP Safety Pharmacology study of hERG was conducted later, refer to Report 031206.DFN in Appendix 2)

Study Title: Phosphodiesterase (PDE) Inhibitor Assays Enzymatic Study of 4 compounds

Report PDE 0801

Key Study Findings:

- In a screening in vitro enzymatic assay, the effect of 10 µM CC-10004 was studied on the enzymatic activities of recombinant human PDEs.
- CC-10004 exhibited >91% inhibition of PDE4 subtypes A1A, B1, B2, C1, and D2.

Study Title: Phosphodiesterase (PDE) Inhibitor Assays: Enzymatic Study of Six Compounds
Report PDE4-1001

Key Study Findings:

- The effect of 1 nM to 10,000 nM of CC-10004 in 10% DMSO on the enzymatic activities of seven recombinant human PDE4 enzymes was assessed in an in vitro enzymatic assay. The mean IC_{50} values of the compounds are summarized in the table below.
- Dose-dependent responses were obtained for all subtypes. The activity toward C1 inhibition was the least potent with an IC_{50} of 118 nM. CC-10004 reactivity with the other subtypes produced IC_{50} values ranging from 14 to 43 nM.

Table 4: IC_{50} of the compounds against PDE4 enzymes

Compound	IC50 (nM) on each PDE4 Enzyme						
	A1A	B1	B2	C1	D2	D3	D7
#1 CC-10004	14	43	27	118	33	28	30
Rolipram[a]	188	418	135	847	858	825	913

[a] Rolipram is used as a positive control.

Study Title: SelectScreen Biochemical Kinase Profiling of CC-220 and CC-10004 (Apremilast)
Report: SSBK8217_23649

Key Study Findings:

- CC-10004 at 10 µM was tested for its ability to inhibit 255 kinases in Invitrogen's SelectScreen® Profile.
- CC-10004 did not significantly inhibit any of the 255 kinases tested. One kinase that was initially positive was retested with additional doses and was negative in this follow-up assay.

EFFECT ON GENE REGULATION

Study title: Effect of Apremilast on Transcriptional Regulation and Gene Expression in Monocytes, Peripheral Blood Mononuclear Cells, Jurkat T Cell Leukemia and THP-1 Monocytic Leukemia Cells
Report 7600-011

Key Study Findings:

- Jurkat T cells and THP-1 monocytic cells were incubated with CC-10004 (0.1 - 1 μM) alone, or with forskolin (10 μM each), or with IκB kinase (IKK) inhibitor VII followed by stimulation with recombinant human TNF-α (rhTNF-α) or LPS, respectively
- CC-10004 activated the PKA-CREB pathway, resulting in enhancement of cAMP responsive element (CRE)-driven gene transcription and inhibited NF-κB-driven gene transcription.
- A second study was conducted with human peripheral blood mononuclear cells and monocytes incubated with 1 μM CC-10004 and stimulated by LPS.
- CC-10004 inhibited the expression of numerous chemokine-, chemokine receptor-, and Th1 cytokine- genes and enhanced genes associated with anti-inflammatory factors, such as the suppressor of cytokine signaling 3 (SOCS3), chemokine epithelial-derived neutrophil-activating peptide 78 (ENA-78), and growth factors amphiregulin and bone morphogenic protein 6 (BMP-6).

PHARMACOLOGY OF METABOLITES

There is extensive metabolism of CC-10004 as described in Section 5.1 of the NDA Review. Metabolites were evaluated for potential pharmacodynamic activity of PDE4 inhibition and by the suppression of LPS-stimulated production of TNFα. M7 and M17 were both nearly as potent as the parent CC-10004 in these assays. However, since the levels of these metabolites in blood are very low in all species, it is unlikely they would contribute substantially to the pharmacology or toxicological findings.

Refer to Appendix 4 for the Nov 2, 2006 review of Report 5275-179 and to Appendix 12 for the May 13 2011 review of Report 5638-96 by Dr. Barbara Hill.

Study Titie: PDE4 and TNF-α Inhibitory Activity of CC-10004 Metabolite M12 ($[^{14}C]$O-desmethyl glucuronide
Report 5347-137

Key Findings:

- The M12 metabolite (CC-10004-O-desmethyl glucuronide) of CC-10004 was isolated from urine samples from a previous human pharmacokinetic study (Report 5275-179) and tested for PDE4 enzyme activity and for bioactiivity by quantifying TNFα release from lipopolysaccharide (LPS)-stimulated peripherial blood mononuclear cells, compounds added prior to LPS stimulation. CC-10004 was used as a comparative positive control.

- M12 inhibited PDE4 with an IC_{50} of 5.5 µM. CC-10004 had an IC_{50} of 0.080 µM.
- M12 inhibited TNFα release IC_{40} of 10 µM. The maximal dose was 10 µM, and this reach IC_{40}, thus an IC_{50} was not determined. CC-10004 had an IC_{50} of 0.011 µM.

Study Titie: Phosphodiesterase 4 and Tumor Necrosis Factor-alpha Inhibitory Activity of CC-10004 S-isomer Metabolites M3, M12 (Synthesized), M16, and M17

Report 5424-75

Key Findings:

- Four metabolites of CC-10004 were tested for PDE4 enzyme activity and for bioactivity by quantifying TNFα release from lipopolysaccharide (LPS)-stimulated peripherial blood mononuclear cells. These were the S entaniormers of M3 (CC-16085, *O*-desmethyl), M12 (CC-16166, *O*-desmethyl glucuronide), M16 (CC-16557, acetamide hydroxyl-glucuronide) and M17 (CC-16401, acetamide-hydroxy). All compound were synthesized. M12 used in the above Report 5347-137 was a urine-isolated radioisotope.CC-10004 was used as a comparativer positive control.
- For PDE4 activity, M17 resulted in an IC_{50} = 0.094 µM, which was reasonably similar to that of parent CC-10004 (IC_{50} = 0.047 µM). The others in potency rank order of potency were M16 (IC_{50} = 6.5 µM) M3 (IC_{50} = 8.3 µM), and M12 (IC_{50} > 100 µM).
- All metabolites had inhibitory effects on TNFα activity. M17 had an IC_{50} = 0.021 µM similar to parent CC-10004 (IC_{50} = 0.036 µM). M3 had an IC_{50} = 5.6 µM. Both M12 and M16 produced ≈ 24% inhibition of TNFα production at 10 µM, and therefore could be considered IC_{24} = 10 µM.

Table 5: Summary of PDE4 and TNF-α inhibitory activity of CC-10004 and its metabolites.

(b) (4)

EFFECTS ON CYTOKINES AND ANTI-INFLAMMATORY ACITIVITY

The applicant conducted numerous studies examining the effects of CC-10004 in various paradigms of cytokine release or production, and in which cellular activity associated with inflammation was induced. These effects of CC-10004 are summarized in the table below. The applicant focused on known major inflammatory mediators, and for the most part, CC-10004 was effective in inhibiting release or expression in paradigms in which inflammatory compounds are used to stimulate the cells. Less consistent and less robust effects of CC-10004 occurred under basal or resting conditions, and in in vivo studies.

Study Title: Multiple Cytokine profiling for PDE4 inhibitors CC-10004, CC-10082, CC-11050, CC-14046 and CC-14064 in LPS-stimulated human PBMCs
Report 5424-11

Key Study Findings:

- The anti-inflammatory activity of CC-10004 was examined by assessing its effect in vitro on the level of 10 cytokines and chemokines. Luminex technology was used to determine the 50% inhibitory or enhancement concentration, IC_{50} or EC_{50}, for CC-10004 effects on pro-inflammatory cytokines and IL-10 (anti-inflammatory cytokine) from LPS-stimulated healthy human donor PBMCs.
- The cytokines and chemokines evaluated were tumor necrosis factor-alpha (TNF-α), interleukins IL-12 and IL-1β, granulocytemacrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1 alpha (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), and secreted (RANTES), IL-8, IL-6, and IL-10.
- The effects of CC-10004 are indicated in the Figure and Table below.
- Correlation analysis showed that inhibition of TNF-α production positively correlated with the IC_{50} for IL-12, GM-CSF, MIP-1α, and MCP-1. There was no correlation between the TNF-α IC_{50} and IL-1β and RANTES IC_{50}, or with IL-6 and IL-10 enhancement, EC_{50}.

Figure 1: Concentration-Inhibition Response Curves for Cytokine Production

Figure 1: CC-10004 Cytokine Profile

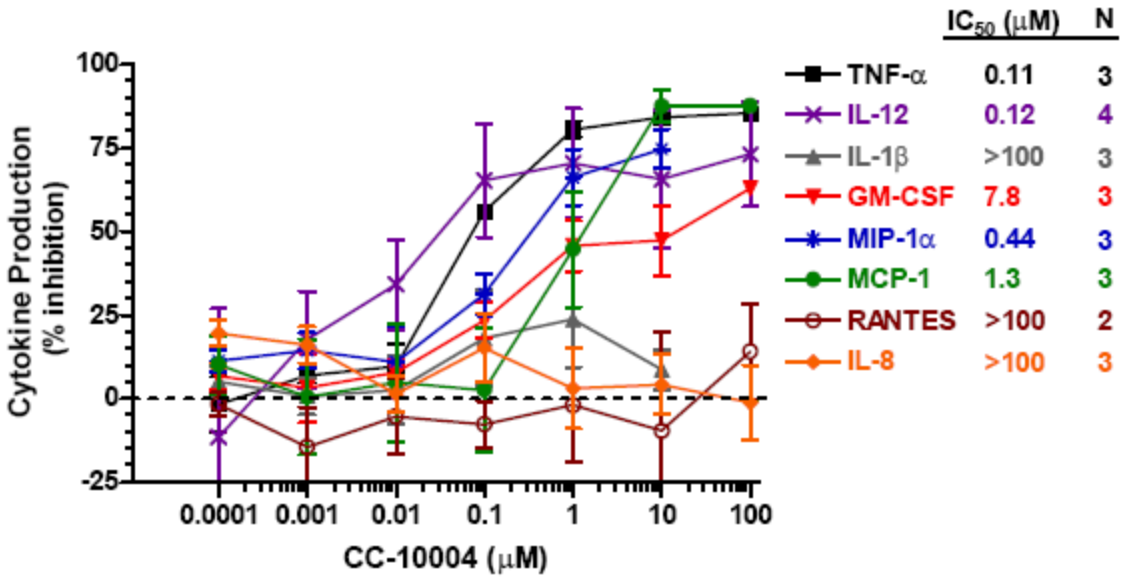


Table 6: Summary of IC_{50} and EC_{50} values

Table 1: Phosphodiesterase-4 Inhibitors Cytokine Profile Summary

	Luminex IC_{50} (µM)									
CC	TNF-α	IL-12	IL-1β	GM-CSF	MIP-1α	MCP-1	RANTES	IL-8	IL-6 EC_{50} (µM)	IL-10 EC_{50} (µM)
10004	0.11	0.12	>100	7.8	0.44	1.3	>100	>100	11	0.080

Study Title: Effect of Apremilast on Cytokine and Chemokine Production in LPS Stimulated Human Whole Blood Using the TruCulture System
Report 7600-043

Key Study Findings:

- Human whole blood, ex vivo, was pre-treated for 1 hour with CC-10004 (0.5 and 1.5 μM), then stimulated with LPS for 18 hours. Supernatants were analyzed using the Luminex multiplex assay.
- CC-10004 at both doses inhibited cytokine release/production stimulated by LPS. The inhibited cytokines were TNF-α, IL-12/IL-23 p40, interferon gamma inducible protein 10 (IP-10), and MCP-1.
- IL-23 p19 and total IL-23 was inhibited only by the higher dose of CC-10004.
- There was no effect on IL-10.
- IFN-γ, IL-12 p70, IL-17A, and IL-22 were below the limit of quantitation.

Study title: Multiple Cytokine Profiling for Phosphodiesterase Type 4 Inhibitors CC-10004 and CC-11050 in Anti-CD3 Monoclonal Antibody Stimulated Human T cells
Report 5478-159

Key Study Findings:

- Apremilast was profiled for cytokine immunomodulatory activity in plate-bound anti-CD3 mAb-stimulated (18 hours) primary human T cells.
- Anti-CD3 mAb was used to stimulate primary human T cells in an in vitro plate-bound antibody assay.
- After incubation for 2 days, CC-10004 inhibited levels of cytokines of the Th1 and Th2 groups, and also IL-17 representative of Th17.
- The rank order of apremilast inhibitory potency for the T cell-derived cytokines indicating greater inhibition of Th2 cytokine production than Th1 cytokine production was: IL-5 (IC_{50} = 0.03 μM) > IL-17 (IC_{50} = 0.09 μM) > IL-10 (IC_{50} = 0.19 μM) > IL-13 (IC_{50} = 0.28 μM) > TNF-α (IC_{50} = 0.93 μM) > GM-CSF (IC_{50} = 1.0 μM) > IFN-γ (IC_{50} = 1.3 μM) > IL-2 (IC_{50} = 2.4 μM) > RANTES (IC_{50} = 4.1 μM)
- The applicant determined that at the maximum plasma concentrations in healthy human volunteers (Clinical Report CC-10004-PK-001, with a C_{max} = 420 ng/mL on day 7 of a 40 mg once daily regimen) CC-10004 at a dose of 420 ng/mL inhibited Th1 cytokine production within a range of 40% (IL-2 and RANTES) to 50% (TNF-α) and Th2 cytokine production within a range of 65% (IL-13) to 100% (IL-5).

Study Title: Therapeutic Effect of CC-10004 and CC-11050 in Collagen-Induced Arthritis
Report KIRP03604

Key Study Findings:

- This report contained two studies: one on the effects of CC-10004 in the collagen-induced arthritis model which is presented in the collagen induced arthritis section later in the section, and an in vitro study of the effects of CC-10004 in dissociated synovial membrane tissue samples from rheumatoid arthritis subjects.
- Freshly obtained synovial tissue was dissociated and cultured in the presence of CC-10004 for 48 hours. Cytokine levels in the supernatant were measured by ELISA. There was no effect on cell viability.
- CC-10004 inhibited TNF-α production both with an IC_{50} of 100 nM. There was no effect on IL-6 or IL-10 levels.

Study Title: Effects of Phosphodiesterase 4 Inhibitors CC-10004 and CC-11050 in Combination with Cyclosporine A, Methotrexate and Etanercept on Rheumatoid Arthritis and Psoriasis Associated Cytokine Production in Stimulated T Cells.

Report 5589-97

Key Study Findings:

- The effect of CC-10004 in combination with a second drug (cyclosporine A, methotrexate, or etanercept) in the reducing the concentrations of a number of assayed cytokines was studied in vitro in anti-CD3 monoclonal antibody-stimulated T cells obtained from rheumatoid arthritis patients with either low or high cytokine levels.
- Altered patterns of cytokines were found depending on the donor status (low or high cytokine levels), the combination of drugs, and the doses utilized.
- Synergistic effects were infrequently observed with CC-10004 and methotrexate (IL-2 and IL-10, high cytokine donors), but was more common with CC-10004 and etanercept or cyclosporine (INFγ,IL-10, IL-13, IP-10, MIP-1α, MIP-1β, and TNFα from high cytokine donors; and also for IL-4 from low cytokine donors).
- In a separate series of studies with Staphylococcal enterotoxin B (SEB)-treated peripheral blood mononuclear cells, there was no synergistic effects on cytokine levels with the CC-10004 methotrexate combination, but there was synergism with CC-10004 with either etanercept or cyclosporine (IL-10, IP-10, MIP-1α, MIP-1β, and TNFα).
- Generally, the effects of CC-10004 and Methotrexate were non additive.

IN VIVO ANTIARTHRITIC AND ANTI-INFLAMMATORY ACTIVITY OF CC-10004

Anti-Inflammatory Activity

A number of animal models were used to demonstrate the anti-inflammatory effects of CC-10004, summarized in the applicant's table below. Various stimuli were used to induce inflammation as measured usually by an increase in TNFα or some other inflammatory mediator. CC-10004 was used to demonstrate a dose-dependent inhibition in TNFα levels. Studies listed in the table below found that CC-10004 inhibited TNFα production or levels in a dose dependent manner when stimulated by LPS in mice and 1% carrageenan in rats. Other models included subdermal air-pouch and nociceptive stimuli to induce both pain and inflammation. CC-10004 appeared to be beneficial in pain associated models when the dose was increased over those paradigms in which there was an absence of apparent pain.

CC-10004 Antiarthritic and Anti-inflammatory Activity In Vivo

Study Number	Treatment Duration	Stimulus	Dose/ Route of Administration	Study Type Species/Sex	Major Findings
Acute TNF-α Production, Inflammation, and Hyperalgesia					
5042-107	3.5 hours	LPS	0.01 - 1 mg/kg, PO	In vivo BALB/c mice Females	Apremilast inhibited LPS-induced serum TNF-α levels with an ED_{50} of 0.05 mg/kg.
AP279R, AP284R, AP291R	2.5 hours	LPS	0.01 - 10 mg/kg, PO	In vivo CD rats Females	Apremilast inhibited LPS-induced plasma TNF-α levels > 80% (ED_{50} = 0.018 mg/kg).
AP352R	5 hours	carragee-nan	10 mg/kg, PO	In vivo CD rats Females	Apremilast pretreatment reduced airpouch TNF-α levels by 82%.
1270RC35.001	3 days	carragee-nan	50 mg/kg (10 mg/mL, IP)	In vivo Sprague-Dawley Rats Males	Apremilast produced significant reductions in paw edema and biologically relevant increases in the 3-hour postdose threshold for both mechanical and thermal hyperalgesia.
AP343R	4 hours	carragee-nan	10 mg/kg, PO	In vivo CD Rat Females	Apremilast had no effect on paw edema following carrageenan injection.

Collagen Induced Arthritis:

Two variations of the collagen induced arthritis mouse model were studied with generally similar findings, summarized here as an adjunct to the applicant's table below.

The model is subject to inconsisitency in the development of arthritic disease which hampers the interpretation of the effectiveness of drug treatments. Overall CC-10004 reduced paw edema and thickness, signs of acute inflammation, and reduced the severity of joint (ankle) disease that correlated with histological findings. Quantifying the observations by numerical scoring, coupled with statistical analysis, however, did not always reflect the supposed effectiveness of CC-10004, and this was attributed to the less severe disease indicators in the comparison control groups.

Study Title: Mouse Type II Collagen Arthritis Model

Report WEL01027

Key Study Findings:

- Mice were immunized against collagen with an intradermal injection at the base of the tail of fetal calf type II collagen incomplete Freund's adjuvant. At day 21 postimmuniztion, mice were injected with liopolysaccharide (LPS, 50 µg, sc). CC-10004 (5 or 25 mg/kg/day) or vehicle (0.5% methylcellulose) was administered once daily from day 21 (1 hour after LPS) to day 34. There were 20-30% nonresponding control collagen-treated mice in the study (those that failed to show joint disease).
- Paw edema (considered an acute inflammatory response) was assessd 4 days after LPS injection (day 25 postimmunization). CC-10004 treated mice (10 mg/kg, po) had a 28% reduction in edema score compared to collagen treated controls, and similar to prednisolone (1 mg/kg, po).
- Joint stiffnes and deformity (considered a measure of T-cell mediated inflammation) was assessed on day 28 (8 days after LPS administration).
- At day 35, CC-10004 treated mice had a reduction of mean severity score of 49% compared to the collagen control group.

Study Title: Effect of CC-11050, CC-10004, (b) (4) on Mouse Collagen Induce Arthritis
Report AP707R-AP830R

Key Study Findings:

- This was similar in experimental methodology and design as the above study, with the exception that nonresponding mice (those without signs of arthritis) were culled. CC-10004 (1, 5 or 25 mg/kg/day, po) was administered from day 26 to including day 42. The vehicle was 0.5% carboxymethylcellulose/0.25% Tween 80.
- CC-10004 (5 and 25 mg/kg/day) inhibited disease severity only on day 42.

Study Title: Therapeutic Effect of CC-10004 and CC-11050 in Collagen-Induced Arthritis
Report KIR-P03604

Key Study Findings:

- This was similar in experimental methodology and design as the above studies, CC-10004 (5 or 25 mg/kg/day, ip) or vehicle (0.5% carboxymethylcellulose/0.25% Tween 80) was administered daily from the onset of arthritis for 10 days. Culling of nonresponders was not mentioned.
- CC-10004-treatment group had reduced the clinical severity scores and reduced histological evidence of arthritic severity compared to the control group.

- In vitro cultures of the draining inguinal lymph node cells from untreated collagen-immunized mice were stimulated by the addition of collagen or anti-CD-3 monoclonal antibodies in the presence of CC-10004 had reduced T cell proliferation and reduced TNFα and IFNγ production. There was no effect on Th2 cytokine or IL-5.
- In cultures from mice treated daily with CC-10004 compared to control treatment, there was no effect on basal levels of anti-collagen IgG1 or IgG2, IFN, IL-5, or IL10.

Study Title: Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model
Reports CLG/001/EM and CLG/001/EM-Histology

Key Study Findings:

- Arthritis was induced by an intravenous injection of a cocktail of 4 monoclonal antibodies followed 72 hours later by an injection of LPS (2.5 mg/kg, ip). CC-10004 (1, 5, or 25 mg/kg/day, po) or vehicle (0.5% carboxymethylcellulose/0.25% Tween 80) was administered once daily for 5 days starting on the day of LPS injection (day 3 from the administraion of the antibody cocktail and animals were monitored for 9 days in total from the administration of the anitbody cocktail). A number of animals were administered Talwin (pentazocine) on day 7-9 for animal welfare concerns. This had no apparent effect on arthritic scoring.
- Paw thickness and hind-paw arthritic reactions were dose-dependently reduced with CC-10004 treatment of 5 and 25 mg/kg/day.
- Histological scoring of 8 parameters of the tissue of the hind-limb ankles (not mentioned but assumed a day 9 termination) indicated the control group were a grade 3 or moderate severity on day 9, and there was essentially no signs of arthritis in the 25 mg/kg CC-10004 treatment group (grade 0), the only dose group examined.

Study Title: Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model
Reports CLG/002/EM and CLG/002/EM-Histology

Key Study Findings:

- The paradigm of the above study was repeated with doses of CC-10004 (5 and 25 mg/kg/day, po) administered for 11 days.
- CC-10004 treatment reduced hind-paw thickness and arthritic scores.
- Quantitative histological assessments found the control animals had a minimal to moderate severity in total score. The effects of CC-10004 were not different from controls.
- Included in the study was a positive control group treated with Embrel (6.25 mg/kg/day, po) that exhibied similar responses as CC-10004 treatment, with the exception that this group had significant inhibition of inflammation and cartilage

damage. Another group consisting of the combination treatment Embrel (5 mg/kg/day) with CC-10004 (5 mg/kg/day) had histological findings similar to Embrel (6.25 mg/kg/day) group. The histological analysis of this group was also not different from the controls.
- The applicant suggests these lack of differences were due to control group having a minimal to moderate severity of disease, rather than a more severe condition to make comparisons.
- The "Table 1. Histopathology Summary Sheet" was not present in the report and the actual numbers and animal variation is therefore unknown.

Study Title: Evaluation of Anti-Arthritic Activity in the mAb/LPS-induced Experimental Murine Arthritogenic Model
Report CLG/003/EM Report CLG/003/EM-Histology

Key Study Findings:

- Study GLG/002/EM was repeated without the combination treatment group, but included another applicant compound under development.
- CC-10004 (5 or 25 mg/kg/day, po) administered for 11 days produced a similar reduction in hind-paw thickness and arthritic scores as found previously.
- Histological analysis found the control animal severity to be minimal to mild, with no siginifcant inhibition in the other groups including CC-10004 treatment.
- The applicant estimated the control animal's disease severity was about 50% less than occurred in study CLG/002/EM.

Study Title: Evaluation of CC-10004 in combination with methotrexate (MTX) and indomethacin in the collagen induced arthritis model
Report MDCG6

Key Study Findings:

- Arthritis was induced in DBA/1 mice (n=10/group) by an intradermal injection of collagen in complete Freund's adjuvant on day 1 and boosted with a second injection on day 21.
- Signs of arthritis were first observed on day 17. Once daily from day 17 onward, CC-10004 (5 mg/kg) was administered PO either alone or in combination with indomethacin (3 mg/kg PO) or methotrexate (1 mg/kg IP).
- CC-10004 had no effect on clinical score or mean paw thickness compared with vehicle-treated group.
- From day 29 onward, methotrexate-treated mice had lower scores than the vehicle treated group. From day 34 onward, indomethacin-treated mice had lower scores than the vehicle treated group.
- The combination of CC-10004 with either methotrexate or indomethacin did not further reduce arthritis scores.

Table 7: Summary of CC-1000 Effects in Collagen Induced Arthritis

Study Number	Treatment Duration	Stimulus	Dose/ Route of Administration	Study Type Species/Sex	Major Findings
(b) (4)					
(b) (4)					
(b) (4)					

CLG/001/EM; CLG/001/EM-Histology	5 days	collagen mAB and LPS	1, 5, and 25 mg/kg, PO, QD	In vivo BALB/c mice Males	Apremilast, at 25 mg/kg for 5 days, demonstrated significant antiarthritic activity in the combined mAb cocktail and LPS-induced experimental arthritis mouse model. Apremilast treated mice had minimal histopathologic indications of arthritis. The antiarthritic activity of apremilast at 25 mg/kg was similar to dexamethasone at 1 mg/kg.
CLG/002/EM; CLG/002/EM-Histology	11 days	collagen mAB and LPS	5 or 25 mg/kg, PO, QD	In vivo BALB/c mice Males	Apremilast, at 5 and 25 mg/kg for 11 days, demonstrated significant antiarthritic activity in the combined mAb/LPS arthritis model. However, apremilast-treated mice had reduced histopathologic signs of arthritis, but these changes were not statistically significant. The antiarthritic activity of apremilast at 5 and 25 mg/kg, PO was similar to that of etanercept at 5 mg/kg, IP (8% to 28% reductions; Days 5 to 9).
CLG/003/EM; CLG003EM-Histology	11 days	collagen mAb and LPS	5 mg/kg, PO, QD	In vivo BALB/c mice Males	Apremilast demonstrated significant antiarthritic activity in the mAb/LPS arthritis model. The histopathologic assessment did not validate the arthritis inhibition resulting from apremilast treatment due to the minimal-to-moderate arthritis disease level observed in control animals.

CIA = collagen-induced arthritis; ED50 = median effective dose; IP = intraperitoneal; LPS = lipopolysaccharide; mAb = monoclonal antibody; PO = oral; QD =daily; TNF-α = tumor necrosis factor-alpha.

Other Arthritis and Psoriasis Models

4.2 Secondary Pharmacology

With the exception of a few studies reviewed below, the majoriy of animal model studies were not reviewed because they mostly pertain to studies of CC-10004 under conditions or in animals models other than those pertinent to psoritic arthritis, and the general effects on inflammatory mediators were previously reviewed.

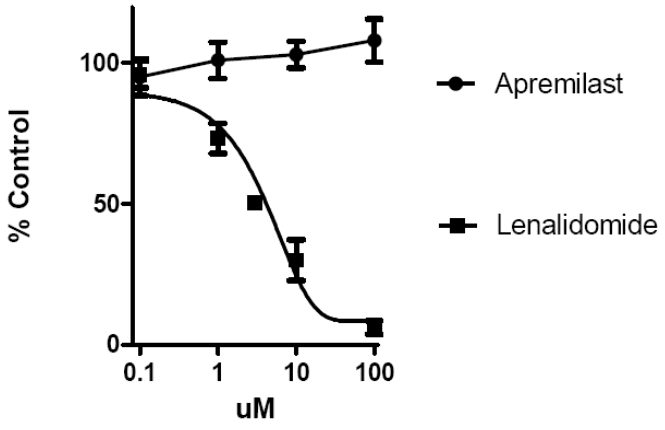
Refer to Appendix 3 for the Dec 2, 2005 review of Secondary Pharmacology studies by Dr. Paul Brown. Additional studies are summarized below.

CC-10004 was created by modifications to thalidomide. The study summarized here is important for distinquishing CC-10004 from thalidomide and related analogs that have a known toxicity during fetal development.

Study Title: CC-10004 (Apremilast) Does Not Bind Human Cereblon
Report 2744-121

- Apremilast does not bind appreciably to endogenous human cereblon (CRBN), and therefore has a different pharmacodynamic profile than thalidomide and its related approved and marketed drugs thalidomide (CC-2001), and its analogs lenalidomide (CC-5013) and pomalidomide (CC-4047). CRBN is a component of the E3 ubiquitin ligase complex, the binding target of thalidomide, lenalidomide and pomalidomide.
- CC-10004 (up to 100 µM) was tested in a competition assay for the binding of human U266 CRBN to the thalidomide analog affinity beads.

Figure 2: Competition Assay of Thalidomide Analog Beads Binding to Human U266 Cereblon



Study Title: Therapeutic Index of SelCIDs in Ferret Lung Neutrophilia and Emesis Model
Report 121401

Key Study Findings:

- Male ferrets (Mustela Pulorius Furo, weighing 1 – 2kg) were orally (gavage) administered a single dose of CC-10004 ranging from 0.1 to 30 mg/kg. Thirty minutes after dosing, animals were exposed in a closed chamber to an aerosol of LPS (100 ug/mL) for 10 minutes, then returned to theri cages and observed for at least 2.5 hours. At 6 hours after CC-10004 treatment, animals were killled and bronchoalveolar fluid was obtained by lavage and examined for neutrophil numbers.

- Since there were no control animals without LPS, it is unknown if LPS exposure contributed to an emetic reaction, but CC-10004 produced a dose-responsive emetic reaction in ferrets.
- Retching without emesis was observed at 10 mg/kg in 2 of 6 animals.
- Moderate to marked emesis occurred at 30 mg/kg in 3 of 4 animals.

Study Title: Evaluation of CC-10004 in the T and B cell Transfer Model in Mice
Report MDCG5

Key Study Findings:

- This study tested the effect of CC-10004 on the adaptive immune response following IV injections in IgHb mice of antigen specific T-cells (which recognize hen egg lysozyme, HEL antigens) and B-cells (which recognize ovalbumin, OVA, antigens).
- Mice were orally administered 5 mg/kg CC-10004 once daily for 12 days, from one day -1, before the day of T cell or B cell injection, until 12 day. On Day 0, mice were immunized SC with OVA-HEL.
- There were no effects on the following: T cell activation markers CD69 or CD25 or on expression of B cell co-stimulatory molecules CD86, CD40 or MHC II.
- CC-10004 prevented down regulation of CD62L on activated T cells and increased CD80 expression on the transgenic B cells.
- CC-10004 did not alter the relative in vitro proliferative ability of Tg T cells.
- CC-10004 did not have any significant effects on the production of OVA-specific IgG1, IgG2a or IgMa.
- The effects of apremilast on the adaptive immune responses of T and B cells were minimal.

Study Title: Effect of PDE4 Inhibitors and IMiDs® on Human Dermal Fibroblast Proliferation and PAI-1 Production
Report 5570-044

Key Study Findings:

- Human dermal fibroblasts (HDFs) were treated for 1 hour with CC-10004 (0.00001 - 10 µM). Cells were then stimulated by the addition of IL-1β (1 ng/mL), TNF-α (5 ng/mL), or IFN-γ (20 ng/mL) and incubated for 72 hours. ^{3}H-thymidine was added and allowed to incorporate into dividing cells for 6 hours.
- CC-10004 had no anti-proliferative effect on HDF or HDF survival.

Study Title: Effect of Apremilast on Primary Human Osteoclasts and Osteoblasts In Vitro
Report 7645-001

Key Study Findings:

- Bone marrow mononuclear cells and normal human osteoblasts and were incubated with CC-10004 (0.1 - 1 μM) for 7 days.
- In both culture types, oteroclastogenesis was inhibited in association with a decrease in form of soluble RANKL (sRANKL) protein expression and an increase in BMP-6 gene expression.
- CC-10004 decreased the sRANKL/OPG protein ratio in both osteoclast and osteoblast cultures, and the effect was more pronounced in the osteoblasts.
- Positive controls rolipram, alendronate, and sulphasalazine had no effect on the sRANKL/OPG protein ratio, indicating that CC-10004 acts by a distinct mechanism.

Study Title: The Effect of Thalidomide and IMiDs including lenalidomide (CC-5013), CC-11006, and CC-10015, and the PDE4 inhibitors CC-10004 and CC-11050 on Thromboxane B2 and Prostacyclin Production in Endothelial Cell/Platelet Co-Cultures
Report 5299-148

- CC-10004 was added to human peripheral blood mononuclear cells at doses up to 100 μM, and COX-2 expression and PGE_2 formation was measured.
- CC-10004 increased COX-2 and PGE2 production by LPS- or phytohemagglutinin (PHA)-stimulated HPBMCs by 50% to 100%,
- CC-10004 added to human umbilical vein endothelial cells or platelets did not affect either prostacyclin or thromboxane production.
- The lack of effect on eicosanoids in HUVEC was use to suggest that apremilast would not present a risk of vascular thrombemobolic events by this mechanism, differing from COX-2 inhibitors.

4.3 Safety Pharmacology

Refer to Appendix 2 for the Sept 7, 2005 review of Safety Pharmacology studies by Dr. Paul Brown. These included neurobehavioral evaluations in mice (Report 1398-443), hERG channel assay for I_{Kr} (Report 031206.DFN), and a combined cardiovascular and respiratory evaluation in anesthetized dogs (Report 1390-264-D6146). The results of a gastrointestinal safety study are presented below.

Study Title: CC-10004: Gastrointestinal Motility Assessment Following Oral Administration to Male CD-1 Mice
Report CC-10004-TOX-1171

Key Study Findings:

- Oral administration (gavage) of CC-10004 at doses up to 1000 mg/kg to male mice had no effect on intestinal mobility (distance traveled of an oral gavage administered charcoal suspension).

5 Pharmacokinetics/ADME/Toxicokinetics

Pharmacokinetics/ADME studies were previously reviewed under [redacted] (b) (4) and are provided in the Appendices (Appendix 2, review of September 7, 2005; Appendix 6, review of Dec 10, 2007; Appendix 9, review of July 21, 2009; Appendix 12, review of May 13, 2011; and Appendix 12, April 4 2012. The major findings from these studies are summarized below.

5.1 PK/ADME

ADME STUDIES

The main studies for characterizing the absorption, distribution, metabolism, and elimination of CC-10004 were conducted under GLP regulations. Radiolabeled [^{14}C]-CC-10004 was administered both orally by gavage and intravenously. Although studies were conducted in the mouse, rat, rabbit, and monkey, the emphasis of the review will be on the mouse and monkey studies since species were used in the majority of the toxicology studies.

MOUSE

Key ADME Findings in the Mouse:

- CD-1 Mice (n/3/sex/dose/timepoint/) were administered [^{14}C]-CC-10004 (apremilast) intravenously (IV) at 10 mg/kg or orally at 500 mg/kg.
- With IV dosing, detectable levels of radioacitivity were present in whole blood and plasma at the last sampling time point (48 h after dosing) in both sexes due to the presence of metabolites.
- With IV dosing, [^{14}C]-CC-10004 had a shorter elimination time, 1.7 hours in males and 2.3 hours in females, compared to total radioactivity in plasma approximately 19 hours in males and 30 hours in females. This was slightly longer in whole blood indicating possible cellular penetration.
- With oral dosing, the terminal elimination half life of [^{14}C]-CC-10004 was approximately 15 hours in males and 22 hours in females with similar values for plasma and blood.
- Oral bioavailability ranged from approximately 20% to 33% (average 27%).
- There was no significant sex-related difference in toxicokinetic parameters of CC-10004.
- The exposure to parent-derived radioactivity (i.e., metabolites) was about 2-fold higher than that of the parent.
- There was no detectable chiral conversion of CC-10004 (S-enantiomer) to [redacted] (b) (4) in mice (Reports CC-10004-TOX-002 and CC-10004-TOX-004).

Mouse Tissue Distribution of [^{14}C]-CC-10004

- The mean (n = 3) concentrations of radioactivity were measured by quantitative whole-body autoradiography in the tissues of albino mice up to 24 hours after dosing.
- Absorbed radioactivity was rapidly distributed into the tissues.
- The highest levels of radioactivity were generally associated with the principal organs of biotransformation and excretion (ie the liver and kidney), and the pancreas, and gall bladder (billiary elimination).
- Concentrations measured in the central nervous system were consistently low. indicating that penetration of the blood/brain barrier was limited.
- Males and females had similar patterns of tissue distribution.
- Radioactivity with not associated with melanin-containing tissues (ie uveal tract and pigmented skin) in pigmented male mice.
- By the 72 h sampling time levels were below the lower limit of quantification of 0.71 µg eq/g, except for the liver and, for males only, the kidney (cortex and medulla), skin, uveal tract, nasal mucosa and gastrointestinal mucosa.
- Radioactivity was not detected in any tissues at 168 h after dosing or later.

MONKEY

Key ADME Findings in the Cynomolgus Monkey:

- Bioavailibility of total administered radioactivity was approximately 78% in plasma for a 10 mg/kg oral dose. However, it was not possible to calculate the bioavailability of [^{14}C]-CC-10004 due to the lack of detection of [^{14}C]-CC-10004 from the low dose from intravenous dosing.
- In multiple-dose toxicity studies with monkeys, there was a dose-related increase in exposure but this was less than dose proportional (refer to Reports 1398/296, 1398/368, and CC-10004-TOX-005).
- There was slight accumulation of apremilast following multiple dosing at high doses, but this finding was inconsistent across studies.
- There were no sex-related differences in pharmacokinetics parameters.
- CC-10004 (S-enantiomer) did not convert to (b) (4) in monkeys (Report CC-10004-TOX-005).

RAT

Due to substantial differences toxicokinetics between the male and female rat in early single dose (Reports1398/276 and 1398/277) and short term repeated dose studies in the rat (Reports 1398/213), only a 2-year carcinogenicity bioassay study (Report CC-10004-TOX-007) along with its 3-month repeated dose range-finding study (Report 10004-TOX-003) were conducted.

An ADME study(Report 1398/259-D1145) found that males more extensively metabolized [^{14}C]-CC-10004 than females. In males, plasma total radioactivity was 25-96 times greater than for [^{14}C]-CC-10004 parent, but in females total radioactivity was 2-3 times grater than for the [^{14}C]-CC-10004 parent. In another study (Report 1398/215),

there was greater systemic exposure to CC-10004 in females than males, following either oral administration (10 or 50 mg/kg, 32-85-fold greater in females) or intravenous administration (5 mg/kg dose, 4-6-fold greater in females). The bioavailability following oral dosing for CC-10004 was approximately 11.5% in males and 63% in females.

RABBIT

Preliminary studies in the rabbit indicated that adequate systemic exposure of CC-10004 could not be obtained due to poor bioavailability (Reports 1398/290, 1398/291, and 1398/292) and an intravenous infusion repeated dose range-finding study resulted in early termination due to moribundity. Therefore, the rabbit was not an appropriate species for CC-10004 study Report 1398/292 mentioned that possible causes of poor bioavailability (e.g., absorption, metabolism) or instability in frozen samples stored prior to analysis were being investigated. Report 1398/261 found that the metabolism of CC-10004 by rabbit microsomes under in vitro conditions occurred faster than the other species examined (rabbit>>monkey>mouse=male rat>human>dog>female rat), but it is doubtful this would explain why samples were not detectable at the first sampling timepoint.

Also, the applicant mentioned that stability data for CC-1004 stored frozen for an extended period of time will be available in October 2003 as Report 1398/366. However, since this report was not submitted the stability question is unanswered. It is possible the study was not completed since an alternative species, cynomolgus monkey, was utilized in another developmental toxicology study.

BRAIN UPTAKE

Study Title: A final summary report of the in vivo pharmacokinetic and ADME data generated on five Celgene PDE-4 inhibitors in the rat and ferret
Report QSK121001

Key Study Findings:

- Although the applicant states that brain:plasma ratio of CC-10004 was low in the rat and ferret, <10%, there were ratios in the 30% range. The data were not clearly presented and some tables appear to be mislabeled, therefore this study was not useful for assessing brain uptake and possible CNS-mediated emetic responses.

PROTEIN BINDING

Key Study Finding:

- Less protein binding occurs in human plasma (68%) than in mouse (89%), rat (91%) and monkey (84%), the main toxicology study species.

DISTRIBUTION INTO MILK

Key Study Findings:

- Lactating CD-1 mice, on approximately 13 days post-partum, were administered a single oral dose of 10 mg/kg CC-10004 in 1% sodium carboxymethylcellulose vehicle (~10 to 11 weeks of age when mated).
- Milk and plasma was collected from 5 animals/time point at approximately 1, 6 and 24 h post-dose.
- The peak average concentration of CC-10004 occurred at 1 h postdose, and were 984 and 1441 ng/mL in plasma and milk, respectively.
- Concentrations were below the limit of quantitation (3 ng/mL) by 24 h post-dose.
- The average milk to plasma concentration ratios were 1.46 and 1.62 at 1 and 6 h postdose

PLACENTAL TRANSFER INTO THE FETUS

In the mouse and monkey embryofetal developmental studies, assessments were made of CC-10004 concentrations in the fetus (mouse) or umbilical cord blood (monkey) at the end of the study prior to necrospy and fetal examination. In both species, CC-10004 was detected in the fetal compartments. Refer to Section 9.2 of this NDA review for Reports CC-1004-TOX-012 (mouse) and CC-10004-TOX-013 (monkey) for additional information and specific findings.

METABOLISM

Table 8: Nomenclature of CC-10004 Metabolites

	MW	Human	Mouse	Mouse	Rat	Monkey
Transformation (Celgene compound number)	daltons	(Report CC-10004-PK-002)	(Report CC-10004-DMPK-031)	(Report 1398/376-D1145)	(Report 1398/259-D1145)	(Report 1398/399-D1145)
Apremilast (CC-10004)	460	Parent	Parent	MuU22, MuF22, MuP22	RP20, RU20, RF20	MkP24, MkF24
Hydrolysis products (CC-15091)	478	M1/M2		MuP10/P11, MuU11[a], MuF10/F11	RP10/P11, RU10/U11, RF10/F11	MkP13, MkP14, MkU11
O-Demethylated (CC-16085)	446	M3	M3	MuF20	RP18, RU18, RF18	MkU22, MkF22
O-Demethylated *N*-deacetylated	404	M4				MkF21
O-Deethylated (CC-10047)	432	M5[b]	M5	MuU17	RP16, RU16, RF16	
N-Deacetylated (CC-10055)	418	M7	M7		RP14, RF14	
Hydroxylated *O*-demethylated *N*-Deacetylated	420	M8			RF15	
Hydrolysis products of M3	464	M9		MuF8, MuF9	RP7/P8, RU7/U8, RF7/F8	MkU9/U10, MkF9/F10
O-Demethylated hydroxylated acetamide	462	M10				MkF20
Hydroxylated *N*-deactylated	434	M11	M11			
O-Demethylated glucuronide (CC-16166)	622	M12	M12	MuU12	RP12, RU12, RF12	MkP15, MkU14
O-Deethylated glucuronide	608	M13	M13	MuU11[a]		MkU13[a]
N-Deacetylated M12	580	M14	M14			
Hydrolysis products of M12	640	M15	M15	MuP3, MuU2		MkP6, MkP7, MkU4, MkU5
Hydroxylated acetamide glucuronide (CC-16557)	652	M16	M16			
Hydroxylated acetamide (CC-16401)	476	M17	M17			
3-Acetamide-phthalic acid	223	M18	M18			
O-Demethylated *O*-deethylated	418	M19	M19	MuF14		MkF16
N-Deacetylated *O*-demethylated *O*-deethylated	376	M20	M20			
O-Demethylated *O*-deethylated hydroxylated acetamide	434	M21	M21			
Hydrolysis products of M5	450	M22		MuF6, MuF7		
Hydrolysis product of hydroxylated acetamide	239	M23	M23			

MW = molecular weight.

[a] MuU11 and MkU13 peaks contained hydrolysis product of apremilast and *O*-Deethylated glucuronide

[b] M5 was not detected in humans

IN VITRO METABOLISM

Key Study Findings

Liver Microsome Metabolism (Report 1398/261-D1145)
All the metabolites formed by human liver microsomes were formed by microsomes of one or more animal species.
The order of the extent of metabolism from greatest least was rabbit >> monkey > mouse = male rat > human > dog > female rat.
The rat was the only species with sex differences in the metabolism of CC-10004.
Incubation of [^{14}C]-CC-10004 with liver microsomes resulted in both enzymatic (CYP-mediated) and non-enzymatic means (hydrolysis, forming M1/M2 and M7).
The major metabolite, M3, was formed in all species except the female rat.
M5 was formed in the mouse and monkey.

Heptocyte Metabolism **(Report CC-10004-DMPK-023)**
[^{14}C]-CC-10004 was metabolized most extensively by rabbit hepatocytes, moderately by rat hepatocytes, and to a limited extent by hepatocytes from the mouse, dog, monkey, and human.
Twelve metabolites (M1/M2, M3, M4, M7, M11, M12, M14, M15, M16, M17, M18 and M23) were characterized or identified.
All metabolites formed in vitro by human hepatocytes were formed by hepatocytes from one or more animal species, although the amounts differed among the species.

CYP Isozyme Induction by CC-10004 (Report CC-10004-DMPK-012)
CC-10004 treatment of cultured human hepatocytes produced a concentration dependent (1, 10, and 100 µM) increase in CYP3A4 activity, a decrease in CYP1A2 and CYP2C9 activity, and no effect on CYP2B6 or CTP2C19 activity.
There was no hepatocyte cytotoxicity determined by LDH release in the culture medium.

Metabolism of Adult and Juvenile Microsome (Report CC-10004-DMPK-038)
There was no qualitative differences in studies of hepatocytes or microsomes in the types of metabolites and amounts formed betweeen human adults and juveniles.
There was also no diference between male mouse adults and juveniles.

The table below indicates that a number of metabolites are formed (M1, M2, and M7) in the absence of NADPH, implying the absence of CYP isozyme activity.

Table 9: Summary of In Vitro Metabolism of [^{14}C]-CC-10004 by Liver Microsomes

Percent of Sample Radioactivity after 120-minute Incubation with 10 µM Apremilast													
		Mouse		Rat		Rabbit		Dog		Monkey		Human	
Met.	Sex	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o
M1	M	10.3	8.2	7.4	8.2	4.8	5.8	4.1	3.9	7.0	7.4	8.7	12.1
	F	6.9	7.0	6.4	7.5	4.0	4.8	3.1	4.2	7.0	7.3	9.4	9.4
M2	M	9.2	7.9	5.6	6.5	2.1	4.2	3.0	2.9	5.4	6.2	6.6	11.3
	F	5.4	5.3	5.0	5.9	3.1	4.3	2.6	3.5	5.9	5.8	7.1	8.1
M3	M	4.9	ND	9.4	ND	36.2	ND	2.8	ND	11.2	ND	3.5	ND
	F	1.5	ND	ND	ND	28.5	ND	4.0	ND	12.8	ND	8.4	ND
M4	M	ND	ND	ND	ND	21.2	ND	ND	ND	ND	ND	ND	ND
	F	ND	ND	ND	ND	12.0	ND	ND	ND	ND	ND	ND	ND
M5	M	4.6	ND	ND	ND	ND	ND	ND	ND	1.9	ND	ND	ND
	F	0.7	ND	ND	ND	ND	ND	ND	ND	2.7	ND	ND	ND
M7	M	0.8	2.1	ND	ND	4.8	51.4	3.0	3.0	ND	ND	1.0	1.1
	F	2.5	3.1	ND	ND	13.4	32.6	2.8	3.9	ND	ND	1.0	1.1
M8	M	ND	ND	ND	ND	4.1	ND	ND	ND	ND	ND	ND	ND
	F	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M9	M	ND	ND	ND	ND	4.1	ND	ND	ND	ND	ND	ND	ND
	F	ND	ND	ND	ND	2.1	ND	ND	ND	ND	ND	ND	ND
M10	M	ND	ND	ND	ND	4.2	ND	ND	ND	ND	ND	ND	ND
	F	ND	ND	ND	ND	1.9	ND	ND	ND	ND	ND	ND	ND

F = female; M = male; ND = not detected; Met. = metabolite assignment; with = with NADPH; w/o = without NADPH.

In Vivo Metabolism

Key Study Findings

Metabolism in the Mouse (Report 1398/376-D1145)
A single dose of [^{14}C]-CC-10004 was administered either orally by gavage (500 mg/kg) or intravenously (10 mg/kg) to mice.
The metabolite profiles obtained from plasma, urine, and feces were qualitatively similar for both routes and both sexes.
Hydrolysis products M1 and M2 were the major components of plasma radioactivity.
Metabolites detected in urine and feces included M1/M2, M3, M9, M12, M15, M19 and M22 in approximately similar amounts between males and females for each of metabolite.

Metabolism in the Mouse (Report CC-10004-DMPK-031)
Male mice (intact or bile duct cannulated, BDC) were administered a single 10-mg/kg oral dose or 5- or 10-mg/kg IV dose of [^{14}C]-CC-10004.

Unchanged [^{14}C]-CC-10004 and M12 (glucuronide conjugate of O-demethylated CC-10004) were the major components in mouse plasma, with minor amounts of M13 and M14, and trace amounts of M7, M16, M17 and M18 present.
Bile was a major excretion route of [^{14}C]-CC-10004., with 53.9% of the oral dose and 59.1% of the IV dose found in bile with M12 and M13 accounting for 30% and 10% of the dose during the first 48 hours.
An average of 15.1% (oral) and 17.8% (IV) of the dose was recovered in male BDC mouse urine from the oral and IV groups during the 0-48 h time period, with M12 comprising 4.01%and M13 comprising 7.14% of the dose.

Metabolism in the Rat (Report 1398/259-D1145)
[^{14}C]-CC-10004 was administered orally, either as a single dose at 10 mg/kg or as a single dose preceded by 6 daily doses of non-radiolabeled apremilast (10 mg/kg/day), in order to assess the effect of repeated dosing.
There was little to no [^{14}C]-CC-10004 detected in plasma.
The major metabolites in male plasma was an unidentified, early eluting (ie polar) component (RP1) and M12, whereas in females [^{14}C]-CC-10004, RP1, M1/M2, and M12 were detected.
The principal metabolite in urine was M12 with similar amounts in males and females.
The amounts of [^{14}C]-CC-10004 parent and M1/M2 were greater in females than males.
The principle metabolite in feces was M3, with higher concentrations in males than females. Unchanged [^{14}C]-CC-10004 and M1/M2 were higher in females

Metabolism in the Rabbit (Report 1398/387-D1145)
A preliminary study was conducted in female rabbits in which they were orally administered by gavage 1000 mg/kg (100 µCi/kg) of [^{14}C]-CC-10004.
The rabbit had negligible drug CC-10004 exposure in the embryofetal development toxicology studies (Reports 1398/290, 1398/291, and 1398/292) and a different species (monkey) was selected for study.
Due to the relatively low specific activity of [^{14}C]-CC-10004 by the time this metabolite study was conducted, metabolite profiling by HPLC with radioactive detection could not be conducted and few metabolites could be detected.
One animal contained a glucuronic acid conjugate of O-desmethyl-CC-10004, (M12) which was interpreted to probably be a major metabolite.

Metabolism in the Monkey (Report 1398/399-D1145)
Cynomolgus monkeys were administered [^{14}C]-CC-10004, an IV dose of 1 mg/kg and an oral dose of 10 mg/kg in a crossover design with a 28 day period between treatments.
The metabolites observed in plasma include M1, M2, and M12, in addition to two polar metabolites (MkP2 and MkP3), which could not be identified due to interference from high levels of [^{14}C]-CC-10004.
The metabolites observed in plasma include M1, M2, and M12, in addition to two polar metabolites (MkP2 and MkP3), which could not be identified due to interference from high levels of endogenous material. Two minor metabolites were identified as the two isomers of M15 (*O*-desmethyl hydrolyzed apremilast glucuronide).

Little or no [^{14}C]-CC-10004 parent was excreted in urine and feces. The major urinary metabolite was M12 with small amounts of M15, M9, M1/M2, M13, and M3 also detected.
The principal metabolites in feces were (M3), and two possible isomers of M19 and M10 at low levels.

Major metabolites and Interspecies Comparison of Metabolism

In the clinical study of CC-10004-PK-002 (refer to the Clinical Pharmacology review), the major metabolite was M12, (CC-16166, O-demethylated glucuronide comprising about 86%of the total radioactive dose of [^{14}C]-CC-10004.
Although the levels of this metabolite were much greater than in the toxicologcal study species, M12 was a glucuronide conjugate and it was not necessary to conduct further toxicological assessments, since glucuronides are pharmacologically and probably toxicologically inactive.

The applicant's table below summarizes the plasma levels of metabolites following oral administration of [^{14}C]-CC-10004 in humans and the toxicological study species.

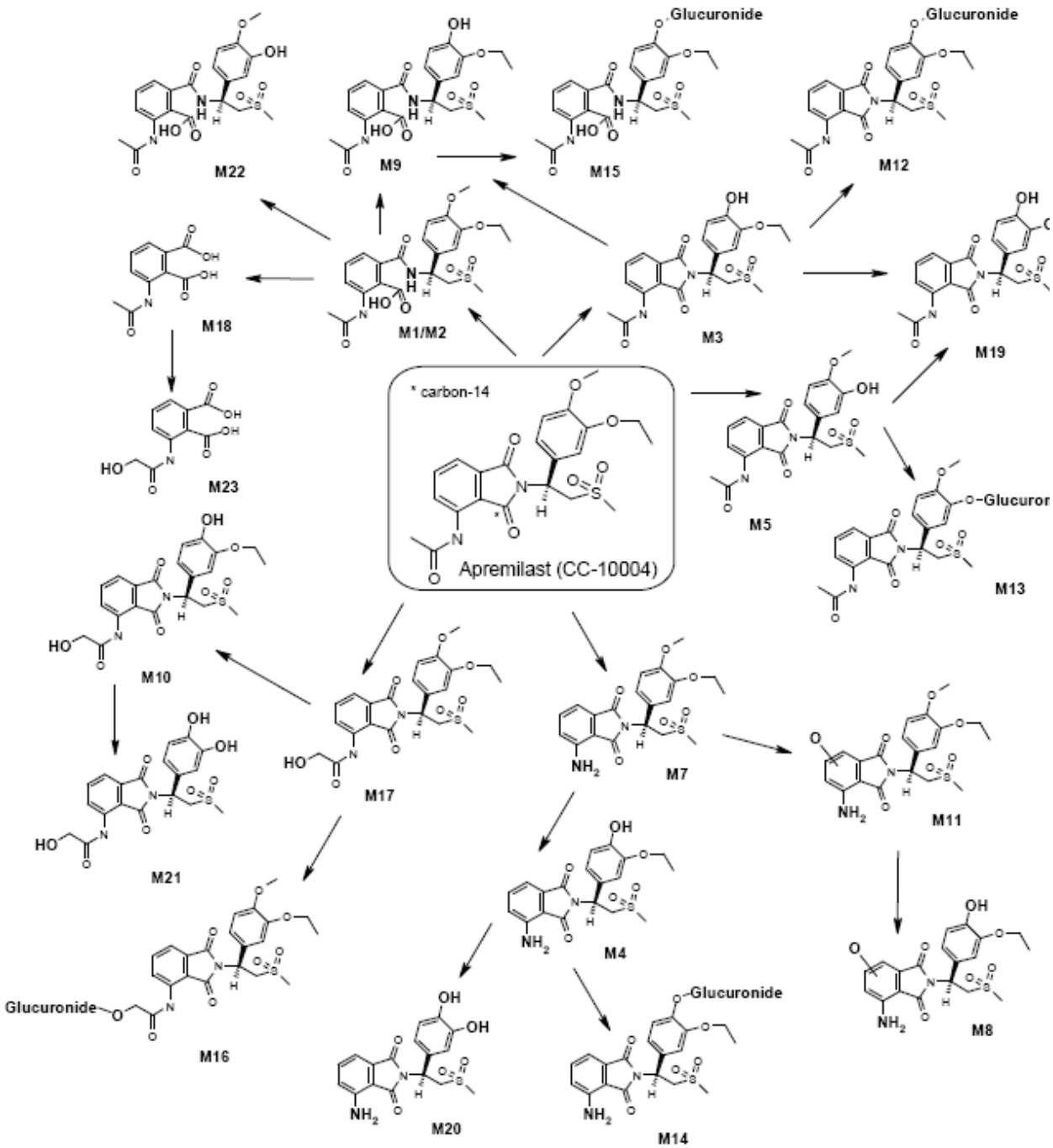
Table 10: Estimated Exposure Ratios of Apremilast (CC-10004) and Metabolites M3, M7, M12, and M17 in Mouse and Monkey to Human

Analyte	AUC_{24h} in human at 30 mg BID (ng•h/mL)	6 month mouse (10 mg/kg/day) [a]		Mouse carcinogenicity (1000 mg/kg/day) [b]		12 month monkey (600 mg/kg/day) [c]	
		AUC (ng•h/mL)	Ratio to human	AUC (ng•h/mL)	Ratio to human	AUC (ng•h/mL)	Ratio to human
Apremilast	7308 [d]	5614/ 5842 [e]	0.77/ 0.80	52856/ 75049	7.2/ 10	42608/ 26936	5.8/ 3.7
M3	Trace [f]	5.29/ 15.2	NC	Not assayed	NC	2768/ 1065	NC
M12	12700 [g]	1459/ 1856	0.11/ 0.15	Not assayed	NC	90035/ 63662	7.1/ 5.0
M7	260 [h]	56/ 58	0.21/ 0.22	530/ 750	2.0/ 2.9	ND	NA
M17	Trace [f]	67/ 70	NC	630/ 900	NC	ND	NA

AUC = area under the plasma concentration-time curve; BID = twice daily dosing; NA = not applicable; NC = not calculated, but presumed to be > 1 based on available data; ND = not detected.
[a] AUC values for M3 and M12 in the 6 month mouse study (Report CC-10004-TOX-004) were determined using a validated bioanalytical assay and are from the NOAEL of 10 mg/kg/day. M7 and M17 AUC values in the 6 month mouse study were estimated based on the apremilast AUC in the study multiplied by the metabolite to apremilast ratio observed in plasma from the mouse metabolism study: 0.01 for M7 and 0.012 for M17 (Report CC-10004-DMPK-031)
[b] M7 and M17 AUC values at the highest dose in the mouse carcinogenicity study (Report CC-10004-TOX-006) were estimated based on the apremilast AUC in the study multiplied by the metabolite to

apremilast ratio observed in plasma from the mouse metabolism study: 0.01 for M7 and 0.012 for M17 (Report CC-10004-DMPK-031)
[c] AUC vlues for M3 and M12 in the 12 month monkey study (Report CC-10004-TOX-005) were determined using a validated bioanalytical assay and are from the NOAEL of 600 mg/kg/day. M7 and M17 were not detected in monkey plasma.
[d] Apremilast arithmetic mean total drug exposure (steady state AUC_{24h}; population-based estimates) at the highest therapeutic dose of 30 mg twice daily obtained in clinical Phase 2 Study: CC-10004-PSOR-005.
[e] All animal data are presented as male/female
[f] Data for human exposures to M3 and M17 are from a single 20 mg dose in the human AME study (CC-10004-PK-002), which indicated they were trace metabolites in human plasma.
[g] Human plasma exposure to M12 was collected using a validated bioanalytical assay following 30 mg twice daily dosing on Day 5 in clinical study CC-10004-PK-008. The AUC value in the table is calculated based on the M12 to apremilast AUC ratio in clinical study CC-10004-PK-008 multiplied by the steady state apremilast exposure in psoriasis patients at 30 mg BID (7308 ng•h/mL).
[h] Human plasma exposure to M7 was collected using a validated bioanalytical assay following a single 20 mg dose in clinical study CC-10004-PK-005. The AUC value in the table is calculated based on the M7 to apremilast AUC ratio in clinical study CC-10004-PK-005 multiplied by the steady state apremilast exposure in psoriasis patients at 30 mg BID (7308 ng•h/mL).

Table 11: Proposed Metabolic Pathways of Apremilast (CC-10004)



Ring-hydrolyzed metabolites M1 and M2 are represented as one structure.

EXCRETION

Biliary excretion with fecal elimination is the major route of CC-10004 excretion in the mouse and monkey. This was demonstrated in studies comparing samples from intact and bile duct cannulated mice. Although there were no bile duct cannulated monkeys, intravenous administration of [^{14}C]-CC-10004 resulted in high amounts of radioactive

fecal elimination which is only explained by biliar excretion, if there were no gastrointestinal lesions resulting in direct gastrointestinal leakage.

CC-10004 is extensively metabolized. Except for the mouse, there is less unchanged CC-10004 excreted in the animal studies than for humans. The major excreted form in humans is M12 the O-demethylated glucouronide (34%) and M3 the O-demethylated product (5-8%), with 7% unchanged CC-10004. In the monkey, M9 the hydrolysis products of O-demthylation (28-40%), and M3 (9-17%) are the major excretion forms, with very little up to 0.05% unchanged CC-10004. In the mouse, M12 (37% in one study), M13 the O deethylated glucuronide (13%), M9 (13-14%), and M3 (6-8%) were the major excretion forms, with unchanged CC-10004 parent comprising 4% or 16-23% depending on the study.

5.2 Toxicokinetics

Refer to the individual species studies in Section 6.2 Repeated Dosing of this NDA review for toxicokinetic values and interpretation.

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose oral and intravenous toxicity studies were conducted in mouse and rat. Refer to the review of Septempter 5 2007 for (b) (4) by Dr. Paul Brown, located in Appendix 2.

6.2 Repeat-Dose Toxicity

MOUSE

Repeat-dose oral toxicity studies in mice were conducted for durations of 14 days (Reports 1398/262), 4 weeks (Reports 1398/289, 1398/297, and 1398/333), 3 months (Report 1398/373 and CC-10004-TOX-002), and 6-months (Report CC-10004-TOX-004) and were previously reviewed under (b) (4) Refer to Appendix 2 for the Sept 7 2005 review, Appendix 6 for the Sept 25, 2007 review, Appendix 7 for the Dec 10, 2007 review, Appendix 8 for the April 30 2008 review.

A repeat-dose oral toxicity study in mice was also conducted to investigate the recovery from adverse findings (Report 1398/262 in the Dec 10 2007 and Aug 26 2010 reviews located in Appendices 7 and 10, respectively). See Pharmacology/Toxicology review to (b) (4) dated Auguest 26, 2010 for complete details.

Salient results from these studies are presented in Section 11 Integrated Summary and Safety Evaluation of this NDA Review.

RAT

A 13-week rat oral toxicity study (Study no. 1398/213) was conducted for the purpose of identifying doses for a 2-year carcinogenicity bioassay in the rat. Pronounced sex differences in toxicokinetics and associated toxicities were observed in the rat. In females, smaller doses resulted in a much larger drug exposure and toxicity was evident at doses lower much lower than for male induced toxicity. Females were more sensitive to CC-10004 than males. Refer to Appendix 6 for the review Sept 25, 2007 of (b) (4) by Dr. Barbara Hill that was conducted to select doses for the 2-year carcinogenicity bioassay..

MONKEY

Repeat-dose oral toxicity studies of 14 days (Study nos. 1398/283), 3-months (Study nos. 1398/368), and 12-months (Study no. CC-10004-TOX-005) were previously reviewed under (b) (4) Refer to Appendix 2 for the September 7, 2005 review, Appendix 7 for the Dec 10, 2007 review, and Appendix 8 for the April 30, 2008 review. Salient study results are discussed in Section 11 Integrated Summary and Safety Evaluation of this NDA Review.

Although the pilot study in monkeys below was not previously reviewed, it did help define a maximally tolerated dose, which was incorporated into determining doses in the longer duration studies. It is reviewed here to present the toxicological findings at high doses of CC-10004.

Study title: 14-day oral (gavage) pilot study with CC-10004 in cynomolgus monkeys

Study no.:	CC-10004-TOX-010
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 28, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, Batch 59275-06 (Phase 1 study), Purity 99.9%, (Impurity (b) (4) Batch 59692-07 (Phase 2 study), Purity 99.6%, (Impurity (b) (4)

Amendment 1, signed Feb 6 2013
At the applicant's request, additional histopathological examiniations were conducted of the heart lesions of 3 females monkeys, #14023 in the 200 mg/kg/day dose group, and #14037 and #14145 in the 1000 mg/kg/day dose group. Tissue were examined at (b) (4) This report is Attachement 2 to the Final Report.

Key Study Findings

- CC-10004 was administered by oral gavage to female cynomolgus monkeys (3/sex/group, 2.7 to 3.4 kg,>4 years of age, purpose bred of Chinese/Vietnamese origin) once or twice daily for 14 days to determine doses for doses for a future embryo-fetal toxicity study. The study was conducted in 2 phases as indicated in the study design tables below.
    - Phase 1

Group Number	Group [a] Description	Dose Level (mg/kg)	Total Daily Dose (mg/kg/day)	Dosing Frequency	Duration (Days)	Dose Volume (mL/kg)	Animals/ group Females
1	control	0	0	twice daily	14	5	3
2	low	50	100	twice daily	14	5	3
3	intermediate 1	200	200	once daily	14	5	3
4	intermediate 1	200	200	once daily	14	5	3
5	intermediate 2	250	500	twice daily	14	5	3
6	high	1000	1000	once daily	14	5	3

a - vehicle for groups 1, 2, 3, 5, and 6 was 1.0% carboxymethylcellulose; vehicle for group 4 was 1.0% carboxymethylcellulose with 0.25% polysorbate 80 (Tween 80)

Phase 2

Group Number	Group [b] Description	Dose Level (mg/kg)	Total Daily Dose (mg/kg/day)	Dosing Frequency	Dose Volume (mL/kg)	Animals /group Females
7	Phase 2	200	200	once	5	3

b - vehicle was 1.0% carboxymethylcellulose

- There were no mortalities, and no effects on body weight or food consumption, although animals appeared thin in the high dose group (1000 mg/kg/day, QD). There were no clinical pathology or macroscopic effects
- Emesis occured in all groups and the incidences most common in the first week was dose related.
- Histopathological findings in the heart consisted of myocardium degeneration/necrosis with acute to subacute inflammation and hemorrhage.
    - Outside peer review of the heart tissue confirmed the original findings but added additional information that the two females in the 1000 mg/kg/day dose group had acute eosinophilic inflammation with associated with the lesions which is usually indicative of a hypersensitivity reaction, hypersensitivity myocarditis.

  - The female in the 200 mg/kg/day group also had similar heart findings with lymphocytic and neutrophilic infiltrates, a more common background finding.
  - There were no vascular changes in the heart tissue.
- There was a marked difference in exposure betweent the two batches of CC-10004 (Phase 1 batch vs Phase 2 batch). The applicant stated that a direct comparison was not made since the extent of accumulation following multiple dosing was not determined in this study.
- The NOAEL was 100 mg/kg/day (50 mg BID) initially, but after peer review reevaluation, the NOAEL was revised to 500 mg/kg/day (250 mg BID). It is unknown to this reviewer if there were any decisions concerning clinical doses that were affected by either NOAEL determination. If in fact this is a hypersensitivy reaction, if may not be predictive of the drug's effect in humans, in which case the NOAEL could be the high dose. However, since this study and the previous study were conducted simultaneously and were the initial monkey studies, a consevative NOAEL would be prudent until additional information is obtained.

Heart Lesion Descriptions
Heart lesions in the animal at 200 mg/kg/day (14023F) were further characterized by moderate to marked karyomegaly, cytoplasmic vacuolation, and minimal mononuclear cell infiltrates (mainly neutrophils), with a predisposition for the endocardial surface.

In the 1000 mg/kg/day group, acute myocardial inflammation was observed in the hearts of two females (14037F, 14145F). Although multifocal in distribution, the lesions were temporally uniform, extending from the endocardium midway through the ventricular wall or septum. They had characteristics of moderate accumulations of eosinophils and occasional mixed cell infiltration and moderate myofiber degeneration, hemorrhage, and slight interstitial edema, fibrin deposition and/or minimal fibroplasia, and myodegeneration. Special staining was used to determine that almost all of the inflammatory cells were granulocytes and almost all of the granulocytes were eosinophils. In the animal from the 200 mg/kg/day group (14023F), the inflammatory cell infiltration in the heart was much lower, and they consisted of mononuclear (lymphocytes) and granulocytes. In the section examined, only one of the granulocytes was clearly an eosinophil; the remainder granulocyes were neutrophils.

Table 12: Toxicokinetic Summary on Day 14 of the Phase 1 Study:

Group	Dose (mg/kg/day)	Dose Freq,	Cmax (ng/mL)	Tmax (h)	AUC_{0-24} (ng-h/mL)
2[a]	100	50 BID[c,d]	2417	10	33754
3[a]	200	200 QD[c]	4991	4	67853
4[b]	200	200 QD[c]	3554	4	44506
5[a]	500	250 BID[c,d]	5938	10	93755
6[a]	1000	1000 QD[c]	8494	8	92975

[a] Vehicle was 1% carboxymethylcellulose.
[b] Vehicle was 1% carboxymethylcellulose with 025% polysorbate 80.

[c] Administered for 14 consecutive days.
[d] Doses were administered approximately 8 hours apart.

7 Genetic Toxicology

The genotoxic potential of apremilast was assessed in an adequate battery of genetic toxicology tests that included the bacteria reverse mutation assay, in vitro chromsomal aberration assay, and the in vivo micronucleus assay. In addition, an early identified synthesis impurity was tested in an adequately conducted bacteria reverse mutation assay. All assays yielded negative results for either mutagenicity or clastogenicity. The assays are summarized in the table below. Evaluations of these studies are located in Appendix 2 (review of Sept 7 2005) and Appendix 10 (review of Aug 26 2010).

Summary of Genetic Toxicology Studies

Assay	Dose	Result
Bacterial Reverse Mutation Assay (Report 398/282)		
Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537, and TA102	156.25, 312.5, 625, 1250, 2500, 5000 µg/plate ±S9	Negative
Bacterial Reverse Mutation Assay spike with [redacted] (b) (4) (Report CC-10004-TOX-015) [redacted] (b) (4) is both a process impurity detected up to [redacted] (b) (4) but eventually was controlled at [redacted] (b) (4) It is also the same as [redacted] (b) (4)		
Salmonella typhimurium strains: TA98, TA100, TA1535, and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A	50, 150, 500, 1500 and 5000 µg/plate ±S9	Negative
In Vitro Chromosomal Aberration Assay (Report 1398/280)		
Isolated and cultured human peripheral blood lymphocytes	up to 488 µg/mL ±S9	Negative
In Vivo Micronucleus Assay (Report 1398/281)		
CD-1 mice	500, 1000, and 2000 mg/kg	Negative

8 Carcinogenicity

MOUSE

Study title: A 104-Week Oral Carcinogenicity Study of CC-10004 in Mice

Study no.:	CC-10004-TOX-006
Study report location:	Module 4.2.3.4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Nov 27, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, Batch 54560-05, Purity 99.9% (b) (4) (statement indicated that levels previously reported were incorrect; correct values are: (b) (4) in Batch no. 54560-05, used for dosing animals (b) (4) in Batch no. 53625-04, used for bioanalytical assay
CAC concurrence:	Yes, Dose and Protocol Recommendation at the Meeting of Sept 26 2006 (refer to Appendix 14) Concurrence on Study Results and Conclusions at the Meeting of July 2, 2012 (refer to Appendix 15)

Key Study Findings

- Crl:CD-1 (ICR) Mice (n=70/sex/dose) were dosed once daily by gavage with CC-10004 at doses of 0 (vehicle:1.0% sodium carboxymethylcellulose in deionized water), 100, 300, and 1000mg/kg/day. Due to morbidity and deaths in the latter part of the study, during week 73, dosing of the high dose males was terminated, and dosing of the high dose females was reduced to 500 mg/kg/day. Also the dose of 300 mg/kg/day group was lowered to 200 mg/kg/day and maintained through weeks 98 and 96, respectively, at which time dosing was stopped and the remaining animals were maintained without receiving test article until the scheduled necropsy (study weeks 103 and 102, respectively).
- Satellite animals (25/sex/group) were dosed on a comparable regimen for 47 weeks for clinical pathology and toxicokinetic evaluation. There were small effects indicative of anemia (reduced RBC, hemoglobin, hematocrit), increases in

neutrophils and reduction in lymphocytes. The changes were relatively small and not toxicologically important, but may reflect ongoing and vascular inflammation related to CC-10004 treatment.

- Analysis by the sponsor did not reveal any CC-10004-related neoplastic findings. However, internal analysis revealed statistically significant findings in female mice for the combination of osteomas and osteosarcomas yielding a trend test p-value of 0.0128. These tumors were only present in the high dose group, though, and pairwise comparison with the control group was not significant due to the low incidences in the control and high dose groups (0 and 3, respectively; p= 0.0918). Therefore, the ECAC concurred with the conclusion there were no definitive CP-10004-related malignancies in either male or female rats.
- Non-neoplastic findings included fibrosis and vascular changes in the heart, hemorrhage of skeletal muscle in the lower limbs, increased prominence of perivascular and/or peribronchiolar lymphocyte and plasma cell infiltrates in the lung, and an increased incidence and severity of vaginal and cervical mucification in females treated with CC-10004.
- Based on the approximate human exposure of 7440 ng-h/mL for a MRHD of 30 mg BID, (refer to Clinical Study CC-10004-RA-002 and CC-10004-RA-005), there is an 8.6-times exposure margin in the high dose group (average of male and female AUC values).

Adequacy of Carcinogenicity Study

The study was adequate, although the mid and high doses were reduced for last 25 weeks and eventually stopped weeks prior to necropsy due to drug related mortality. In retrospect, the 3-month dose-determining study did not allow an adequate prediction of survival toxicity for this drug in the mouse.

Appropriateness of Test Models

The 2-year lifetime treatment in mice is a standard and acceptable carcinogenicity study.

Evaluation of Tumor Findings

The sponsor's analysis concluded there was no drug-related carcinogenicity. FDA analysis by Dr. Jackson resulted in statistically significant findings in female mice for the combination of osteomas and osteosarcomas. For osteomas and osteosarcomas, tumors were only present in the high dose females with a p value of 0.0918 compared to the control group but yielded a trend test p-value of 0.0128. Refer to Appenidix 15 for ECAC conconcurence of these results at the meeting on July 2 2013.

Table 13: Summary of Significant Combined Endpoints in Female Mice*

Table of tumors reported significant (alpha < 0.05) in at least one arm - Mouse Study
NDA 205437
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Osteomas and osteosarcomas	P-value of test of trend or comparison	.0128			.0918
	Number of animals reported with tumor	0	0	0	3
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	7.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,8.6)	(0,10.0)	(1.62,21.4)
	Poly-3 adjusted number of animals at risk	45.0	41.2	35.7	38.1

* The analysis was conducted by Dr. Matthew Jackson, PhD, (CDER/OTS/OB/DBVI), refer to the Biometric Review of Nov 15 2013.

Methods

Doses:	0, 100, 300/200, 1000/500 mg/kg/day, On day 514 (week 73, ~month 18) the 300 mg/kg/day dose was reduced to 200 mg/kg/day for both males and females. The 1000 mg/kg/day dose for males was stopped, and in females this dose was reduced to 500 mg/kg/day; refer to dosing tables below.
Frequency of dosing:	Once daily
Dose volume:	10mL/kg
Route of administration:	Oral (by gavage)
Formulation/Vehicle:	1.0% aqueous carboxymethylcellulose (CMC)
Basis of dose selection:	MTD in the 3-month repeated dose mouse study (b) (4)-553002)
Species/Strain:	Crl:CD-1 (ICR) mice
Number/Sex/Group:	70/sex/dose
Age:	7 weeks old at start of dosing
Animal housing:	All animals were housed individually
Paradigm for dietary restriction:	Ad libitum feeding, no dietary restriction
Dual control employed:	No
Interim sacrifice:	Only for satellite groups for hematology and serum chemistry evaluations, with no histopathology of these animals
Satellite groups:	Toxicokinetic and Clinical Pathology assessment groups (Groups 1A to 4A n=25/sex/dose)

	Hematology and serum chemistry parameters (up to 10 animals/sex/group) were evaluated from blood samples obtained in weeks 8, 21, and 47.
Deviation from study protocol:	Dose adjustments and animal necropsy times are described below. Other than these changes, there were no deviations that would be expected to affect data interpretation and conclusions.

Table 14: Dosing Protocol Adjustments

	Dose, (mg/kg/day)	
Doses Proposed by	**Males**	**Females**
Sponsor	**0, 100, 300, 1000**	**0, 100, 300, 1000**
ECAC	**0, 100, 300, 1000**	**0, 100, 300, 1000**
Duration and Reduction during study	0 and 100 for 103 wks 300 for 73 wks, then 200 until wk 98, then dosing stopped and animals terminated wk 103 1000 for 73 wks, then dosing stopped and animals terminated wk 103	0 and 100 for 99 wks, then dosing stopped and animals terminated in wk 102 300 for 73 wks, then 200 until wk 96, then dosing stopped and animals terminated wk 102 1000 for 73 wks, then 500 until animals terminated at wk 102

Observations and Results

Sentinel animals

Sentinel animals (15/sex) from the same shipment of animals as used for the main study were housed in the same main study room but were not treated. They were observed for mortality and moribundity twice daily and detailed physical observations were conducted weekly. Body weights were recorded weekly through study week 14 and then biweekly. Sentinel animals that survived to the end of the study or were euthanized in extremis were euthanized by carbon dioxide inhalation. Blood and a full set of tissues were collected and stored for possible analysis.

There was no analysis of sentinel animals since there was no evidence of disease outbreak in the animal room

Mortality

Animals were checked at least twice daily.

There was a significant dose-related increase in mortality for males but not females. As indicated from Table 4, the reduction or stopping of dosing prevented the rapid loss of animals in those groups prior to the dose adjustment. The cause of the majority of deaths in males and females was not determined. Of the causes of mortality that were able to be determined, the most common in males were urogenital inflammation and malignant lymphoma, while in females, mortality was mainly due to malignant lymphoma, gavage injury, undifferentiated sarcoma of the skin, and skeletal muscle hemorrhages.

Table 15: Survivors and Mortalities in Relationship to Dose Adjustments

	Males				Females			
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
n, Day 1	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
n, wk 52	**62**	**61**	**57**	**50**	**63**	**60**	**59**	**50**
n, wk 73*	50 (74%)	48 (69%)	46 (66%)	**31 (46%)**	54 (78%)	53 (77%)	45 (67%)	42 (62%)
wk 73 dose adjustment (mg/kg)	-	-	**200**	**0**	-	-	**200**	**500**
n, wk 90 (% alive)	38 (54%)	37 (53%)	29 (41%)	**20 (29%)**	39 (76%)	37 (67%)	**27 (39%)**	33 (47%)
n wk 96*	27 (39%)	31 (44%)	24 (34%)	**17 (25%)**	29 (43%)	24 (35%)	**20 (30%)**	26 (38%)
wk 96 dose adjustment (mg/kg)	-	-	-	-	-	-	**0**	-
n, wk 98	27 (36%)	31 (37%)	**24 (27%)**	**17 (25%)**	29 (37%)	24 (30%)	**20 (27%)**	26 (37%)
wk 98 dose adjustment (mg/kg)	-	-	**0**	-	-	-	-	-
n, wk 99	24 (34%)	24 (34%)	18 (26%)	16 (24%)	25 (37%)	**18 (26%)**	**16 (24%)**	21 (34%)
wk 99 dose adjustment (mg/kg)	-	-	-	-	-	**0**	-	-
n, wk 102	-	-	-	-	25 (36%)	**18 (26%)**	**15 (21%)**	20 (29%)
n wk 103	20 (29%)	18 (26%)	**15 (21%)**	**15 (21%)**	-	-	-	-

- not applicable
*** dosing accidental deaths were removed from the total animals treated to determine percentages (Male: 1000 n=3; Female: 0 n=1, 100 n=1, 300 n=3, 1000 n=2)**

Table 16: Common Causes of Unscheduled Deaths

	Males				Females			
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
n, Day 1	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
n found dead or euthanized in extremis	**50**	**52**	**55**	**55**	**45**	**52**	**55**	**50**
Cause of Death								
Undetermined	10	32	29	22	10	19	16	27
Gavage error	0	0	0	3	2	1	3	2
Urogenital inflammation	15	4	5	7	0	0	0	0
Urinary tract obstruction	2	3	3	1	0	0	0	0
Amyloidosis	0	0	5	0	1	2	1	1
Liver, adenoma or carcinoma	2	4	0	1	0	1	2	0
Lung carcinoma	3	0	0	4	2	3	0	1
Skeletal muscle hemorhage	0	1	2	8	0	0	4	4
Lymphoma, malignant	12	4	4	2	8	13	9	7

Table 17: Survival (%) Curves, males (above) and females (below); (from sponsor's analysis, also refer to the Biometric Review of Nov 15, 2013 by Dr. Jackson)

(b) (4)

(b) (4)

Clinical Signs

Observations were conducted at least twice daily, and detailed physical examinations were conducted weekly.

There was no effect of CC-10004 treatment on clinical observations or the incidence of palpable masses.

Table 18 : Palpable Masses (from applicants's table 13 and 14)

	Males				Females			
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
n	70	70	70	70	70	70	70	70
Animals with masses	6	8	12	14	10	7	18	7
Animals with multiple masses	0	0	3	2	1	2	2	0
Mean number of days to first mass	583	427	372	392	615	616	498	492

Body Weights

Body weights were recorded weekly through week 14, then monitored biweekly until study termination.

There was a small increase (<5%) in body weights in all male CC-10004 treated groups during the first 13 weeks of the study compared to the control group. Except for the high dose group, there were no consistent differences after this time due to greater variation between groups as the number of survivors within groups decreased. At week 72, for the high dose males, the mean body weight was 6.3% lower than the control group. The high dose male group dosing was stopped during week 73, and mean body weights became similar or greater than the control group.

For females, body weights were greater in CC-10004 treated groups compared to controls throughout the study, except for the high dose females starting at week 32. In this group, body weight was not different from control, until after dosing was reduced at week 73. When dosing was stopped in the weeks prior to termination, body weights were similar to the controls.

Table 19: Body Weights (g) at Selected Time Points

Gender	Males				Females			
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
n	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
Mean Body Weight (g)								
week 0	31.1	31.2	30.8	**29.9**	24.5	24.5	24.1	24.2
2	31.9	**33.3**	**34.1**	**33.5**	25.3	**27.2**	**28.5**	**27.7**
4	34.2	**36.0**	**35.4**	34.7	27.5	**30.1**	**30.6**	**29.4**
12	37.9	**40.2**	**39.7**	38.4	30.2	**34.0**	**34.2**	**32.3**
16	39.0	39.9	40.3	39.4	30.6	**35.0**	**35.4**	**34.0**
24	41.3	41.9	41.2	40.2	31.7	**35.7**	**36.9**	**34.6**
52	42.1	42.3	42.0	41.0	34.3	**38.2**	**37.7**	**36.3**
(n)	(62)	(61)	(57)	(50)	(63)	(60)	(59)	(50)
68	42.1	41.8	41.5	**39.9**	34.7	**38.5**	**38.1**	**36.7**
72	42.6	41.5	42.6	**39.9**	35.2	**38.5**	**37.9**	36.8
(n)	(51)	(50)	(46)	**(32)**	(55)	(54)	(47)	(44)
74	42.1	41.2	41.9	39.9*	34.6	**38.0**	**37.1**[#]	**36.6**[#]
76	42.1	41.9	41.6	41.6*	35.4	**39.3**	**38.6**[#]	**37.6**[#]
102	40.7	39.6	40.3	40.9*	34.7	36.8[##]	36.4[##]	36.4[#]
(n)	(23)	(23)	(18)	(16)	(25)	(18)	(15)	(20)

* dosing was stopped in this dose group in week 73
[#] dosing was reduced from 300 to 200 and from 1000 to 500 in females in week 73
dosin g was stopped for 100 in week 99, and for 200 in week 96.
Bolded values, p<0.05 compared with controls

Table 20: Body Weights of Males (above) and Females (below)

(b) (4)

(b) (4)

Feed Consumption

Food consumption was recorded weekly, through study week 14, then biweekly. thereafter. Food intake was calculated as g/animal/day for the corresponding body weight intervals.

In general, the higher body weights of males and females correlated to the higher food consumption in the CP-10004-treated animals during the corresponding time periods.

Hematology

Blood samples were obtain at the end of the 2nd, 5th, and 11th months (study weeks 9, 21, and 47, respectively) from the retro-orbital sinus of satellite animals (Groups 1A-4A, up to 10 animals/sex/group) under isoflurane anesthesia. Parameters examined were:

Total leukocyte count (White Cells)
Erythrocyte count (Red Cells)
Hemoglobin
Hematocrit
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count (Platelet)
Reticulocyte count
  Percent (Reticulocyte)
  Absolute (Retic Absolute)
Differential leukocyte count -
  Percent and absolute
  -Neutrophil
  -Lymphocyte
  -Monocyte
  -Eosinophil
  -Basophil
  -Large unstained cell
Platelet estimate[a]
Red cell morphology (RBC Morphology)[a]

( ) = Designates tabular abbreviation.
[a] = Presented on individual tables if a manual differential was performed, and the manual data were accepted and reported instead of the automated differential data.

CC-10004-related hematology effects included an increase in neutrophil counts and a decrease in lymphocytes in males and females, although there were variable responses over time. Compared to the control mean, there was also a small (up to 8%) reduction in red blood cells, hemoglobin and hematocrit, and an increase (16%) in absolute reticulocytes in females. The responses fluctuated and were not always dose dependent, particularly for the high dose. During week 21, elevated levels of white blood cells at the 200 mg/kg/day dose level were attributed to one female (#5412) that was suspected of having malignant lymphoma, although this was verified only by the cursory gross pathology conducted for the satellite animals. Overall the observed changes were relatively mild and unlikely to be toxicologically significant.

Table 21: Summary of Hematology Findings [absolute or %, and (% of control)]

Dose (mg/kg/day)	0		100		200		1000	
	M	F	M	F	M	F	M	F
n	10	10	10	10	10	10	10	10
WBC (10^3/µL)								
week 9	6.62	4.83	5.68	5.64	6.65	5.19	5.85	5.84
week 21	6.48	6.21	5.65	6.35	6.42	**16.90 (272%)**	5.07 (78%)	**8.62 (139%)**
week 47	6.33	6.46	6.37	6.81	6.64	5.86	6.11 (96%)	5.66 (88%)
Neutrophils (%)								
week 8	13.2	15.0	16.8	26.3	**27.9 (211%)**	26.9	22.7 (172%)	29.4 (196%)
week 21	24.5	16.4	20.4	24.7	35.0 (143%)	28.6	24.4 (100%)	33.2 (202%)
week 47	22.9	24.2	26.3	31.4	36.9 (161%)	29.1	30.9 (135%)	36.3 (150%)
Lymphocytes (%)								
week 9	82.4	80.1	78.3	67.1	68.1	69.6	71.8 (87%)	66.4 (83%)
week 21	69.1	78.3	74.4	69.2	60.4	66.5	70.8 (102%)	62.0 (79%)
week 47	71.1	69.2	67.7	64.7	58.0	65.8	63.7 (90%)	59.3 (86%)
RBC (10^6/µL)								
week 9	9.94	9.92	9.95	9.40	9.86	9.40	9.92 (100%)	9.43 (95%)
week 21	9.32	9.42	9.24	**8.68 (92%)**	8.85	**8.55 (91%)**	9.35 (100%)	**8.71 (92%)**
week 47	8.94	8.75	8.59	8.62	8.66	8.13	8.93 (100%)	8.11 (93%)
Hematocrit (%)								
week 9	40.0	40.8	40.4	39.5	39.6	39.3 (96%)	40.8 (102%)	39.0 (96%)
week 21	41.8	42.9	41.8	**39.4 (92%)**	40.5	**39.7 (92%)**	42.9 (103%)	**40.3 (94%)**
week 47	41.6	40.5	40.0	40.6	40.3	40.2	41.9 (101%)	40.1 (99%)
Hemoglobin (g/dL)								
week 9	15.6	15.9	15.7	15.1	15.2	15.2	15.6 (100%)	**15.1 (95%)**
week 21	14.8	15.3	14.8	**14.1 (92%)**	14.0	**14.3 (93%)**	14.9 (101%)	**14.2 (93%)**
week 47	14.4	13.5	13.6	13.8	13.6	13.5	14.0 (97%)	13.1 (97%)

Reticulocytes (10^3/µL)								
week 9	218	167	231	153	207	158	220 (101%%)	158 (95%)
week 21	190	143	200	142	212	155	197 (104%)	166 (116%)
week 47	220	156	198	161	179	162	216 (98%)	174 (112%)
Reticulocytes (%)								
week 9	2.5	2.5	2.5	3.1	2.8	2.8	2.5	3.6
week 21	3.2	2.9	3.1	2.8	4.4	3.9	3.2 (100%)	3.6 (112%)
week 47	2.9	4.5	3.5	2.8	3.5	4.4	3.4 (117%)	5.5 (122%)
Bolded values, p<0.05 compared with controls								

Serum Chemistry

Blood samples were obtained at the end of the 2nd, 5th, and 11th months (study weeks 8, 21, and 47, respectively) from the retro-orbital sinus of satellite animals (Groups 1A-4A) under isoflurane anesthesia. Parameters examined were:

Albumin
Total protein
Globulin [by calculation]
Albumin/globulin ratio (A/G Ratio) [by calculation]
Total bilirubin (Total Bili)
Urea nitrogen [a]
Creatinine
Alkaline phosphatase (AlkalinePhos'tse)
Alanine aminotransferase (Alanine Transfer)
Aspartate aminotransferase (AspartatTransfer)
Gamma glutamyltransferase (GlutamylTransfer)
Glucose
Total cholesterol (Cholesterol) [a]
Calcium [a]
Chloride [a]
Phosphorus [a]
Potassium [a]
Sodium [a]
Triglycerides (Triglyceride)

( ) = Designates tabular abbreviation.
[a] = Analyzed only if a sufficient sample was available after completion of other analyses.

The serum chemistry changes that occurred with CC-10004 administration included elevations in total protein, mainly due to an increase in globulin levels, a reduction in alkaline phosphatase activity in females but not males, and elevated blood urea nitrogen levels also in females but not males. Many of these effects were not obviously dose-dependent, and fluctuated with time. The effects were not considered toxicologically significant due to the small changes and variability in the control values, the basis for comparisons.

Serum Chemistry Summary [absolute, and (% of control)]

Dose (mg/kg/day)	0		100		200		1000	
	M	F	M	F	M	F	M	F
n	10	10	10	10	10	10	10	10
Protein (g/dL)								
week 9	5.4	5.5	**5.9**	5.6	**5.8**	5.6	**5.8 (107%)**	5.4 (98%)
week 21	5.3	5.1	**6.0**	**5.5**	**6.0**	**5.5**	**5.8 (109%)**	**5.7 (111%)**
week 47	5.5	5.6	**6.0**	6.0	**6.2**	5.6	**5.9 (107%)**	6.0 (107%)
Albumin (g/dL)								
week 9	3.3	3.6	**3.5**	3.5	3.3	3.6	3.2 (97%)	3.4 (94%)
week 21	3.0	3.2	**3.4**	3.4	3.1	3.3	3.1 (103%)	3.3 (103%)
week 47	3.1	3.3	3.4	3.3	3.1	3.3	2.9 (94%)	3.1 (94%)
Globulin (g/dL)								
week 9	2.1	1.9	2.4	2.1	**2.5**	2.0	**2.6 (124%)**	2.1 (110%)
week 21	2.3	1.9	**2.6**	2.2	**2.9**	2.2	**2.7 (118%)**	**2.5 (132%)**
week 47	2.4	2.3	2.6	2.6	**3.1**	2.4	**3.0 (125%)**	**2.9 (126%)**
A/G ratio								
week 9	1.57	1.97	1.47	1.76	1.35	1.76	**1.28 (82%)**	**1.62 (82%)**
week 21	1.36	1.75	1.34	1.66	**1.08 (79%)**	1.56	1.16 (85%)	1.36 (78%)
week 47	1.32	1.44	1.31	1.35	**1.04 (79%)**	1.37	**1.01 (76%)**	1.12 (77%)
Alk Phos (U/L)								
week 9	65	97	71	78	71	81	66	79
week 21	43	67	51	64	49	51	44	60
week 47	42	84	53	**59 (70%)**	52	**57 (68%)**	38 (90%)	**56 (67%)**
BUN (mg/dL)								
week 9	26.1	20.3	26.7	22.6	26.6	23.4	22.8	24.2
week 21	23.7	21.8	22.9	25.8	23.6	23.5	22.7	24.2
week 47	22.6	20.6	22.1	**28.1 (136%)**	22.8	25.5	22.5 (100%)	**27.4 (133%)**

Bolded values, $p<0.05$ compared with controls

Gross Pathology

Animals were euthanized by carbon dioxide inhalation. Complete necropsies, including palpable masses, were performed on animals (Groups 1-4) found dead, euthanized in extremis, or at the scheduled necropsy. Satellite group animals (Groups 1A-4A) found dead or euthanized in extremis received only a brief examination of the thoracic cavity, lungs, esophagus, and trachea to look for potential signs of intubation errors. Identified tumors were graded according to their likelihood of having caused death or moribundity as indicated in the table below:

Tumor Grade	**Meaning**	
1	incidental	not causing death
2	probably incidental	not causing death
3	probably fatal	cause of death
4	fatal	cause of death
only for scheduled necropsy:		
6*	incidental, scheduled sacrifice)	not causing death
*** grade 5 is not used**		

In early mortality animals, there were some tissues that had dose-related gross findings of white areas in the heart of females, and signs of hemorrhage in the liver of females, skeletal muscle of males and females, and stomach of males and females as indicated in the table below. Relative to the total number of animals within each dose group examined, these findings comprised a small percentage of animals.

Table 22: Toxicologically Relevant Gross Necropsy Observations (Unscheduled Deaths)

	Males				Females			
	0	**100**	**300 / 200**	**1000**	**0**	**100**	**300 / 200**	**1000 / 500**
n	**50**	**52**	**55**	**55**	**45**	**52**	**55**	**50**
week dosing reduced	-	-	73	73	-	-	73	**73**
week dosing stopped	103	103	98	73	99	99	96	**102**
week group terminated	103	103	103	103	102	102	102	**102**
Heart								
white areas	0	6	5	3	0	0	3	**3**
Liver								
dark red areas	1	0	0	0	0	0	1	**1**
Skeletal muscle								
discoloration, dark red	0	0	1	1	0	0	0	**2**
Stomach								
dark red areas	1	2	2	2	1	3	5	**4**

Histopathology

Peer Review: Yes. Slides were examined by (b) (4) This consisted of examination of tissues as follows:

Adrenals (2)
Aorta
Bone with marrow
  Sternum
  Femur with distal articular surface
Bone marrow smear[a]
Brain
  Cerebrum (2 levels)
  Cerebellum with pons/medulla
Cervix
Clitoral/Preputial glands
Epididymides (2)[b]
Eyes with optic nerves (2)[c]
Exorbital lacrimal glands (2)
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum[d]
  Ileum[d]
  Cecum
  Colon
  Rectum
Harderian glands
Heart
Kidneys (2)
Larynx
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph node
  Mandibular
  Mesenteric
Mammary gland (females only)
Nasal cavity[e]
Ovaries (2) with oviducts[f]
Pancreas
Peripheral nerve (sciatic)
Pharynx
Pituitary
Prostate
Salivary glands [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin
Spinal cord (cervical, thoracic, lumbar)
Spleen
Testes (2)[b]
Thymus
Thyroids (2) with parathyroids[f]
Tongue
Trachea
Urinary bladder
Uterus
Vagina
Zymbal's glands (2)
All gross lesions
All tumors

[a] = Obtained from all animals euthanized in extremis and at the scheduled necropsy; not placed in formalin.
[b] = Fixed in Bouin's solution.
[c] = Fixed in Davidson's solution.
[d] = Peyer's patches were collected with the jejunum or ileum.
[e] = Sectioning of the nasal cavity was performed according to the method of Young (1981).
[f] = Examined histopathologically if in the plane of section and in all cases when a gross lesion was present.

Neoplastic Findings

The sponsor's analysis concluded there was no drug-related carcinogenicity. FDA analysis by Dr. Jackson (refer to the Biometrics Review of Nov 15 2013) resulted in statistically significant findings in female mice for the combination of osteomas and osteosarcomas. These tumors were present only in the high dose female group located in the mandible, cavarium, and near the ear canal. One female was euthanized in extremis at 1 year (day 363) with an osteosarcoma of the clavaria; the other findings were identified at the scheduled necropsy a year later. All were from non-protocol tissues that were noted for further examination upon gross examination at necropsy.

There was a statistically significant trend analysis of increasing incidence with dose (p = 0.0128). However, pairwise comparison with the control group was not significant due to the low incidences in the control and high dose groups (0 and 3, respectively; p= 0.0918). Therefore, there were no definitive CP-10004-related malignancies in either male or female mice.

Malignant lymphomas had a fairly high incidence level, but there was a reduction in incidence with increasing dose in both males and females. The (b) (4) for carcinogenicity studies (version 2.2) indicated a 7.6% (83/1097) incidence of malignant lymphoma in male CD-1 mice; therefore, the number of cases in the control group males from this study was atypically high.

Fibrosarcoma of the skin occurred in 12 animals with 6 involving the subcutaneous placement of the identification chip. The sponsor noted that this association had been previously described in mice (Blanchard, 1999 and LeCalvez, 2006).

Table 23: Neoplastic Findings

	Males				Females			
	0	100	300 / 200	1000	0	100	300 / 200	1000 / 500
n	70	70	70	70	70	70	70	70
week dosing reduced	-	-	73	73	-	-	73	73
week dosing stopped	103	103	98	73	99	99	96	102
week group terminated	103	103	103	103	102	102	102	102
Bone n	1	5	3	2	14	5	1	4
osteoma	0	0	1	0	0	0	0	1
osteosarcoma	0	0	0	0	0	0	0	2

Table 24: Summary of Significant Combined Endpoints in Female Mice

Table of tumors reported significant (alpha < 0.05) in at least one arm - Mouse Study
NDA 205437
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Osteomas and osteosarcomas	P-value of test of trend or comparison	.0128			.0918
	Number of animals reported with tumor	0	0	0	3
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	7.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,8.6)	(0,10.0)	(1.62,21.4)
	Poly-3 adjusted number of animals at risk	45.0	41.2	35.7	38.1

Non-Neoplastic Findings

Non-neoplastic changes occurred in the heart, skeletal muscle, and other random sites of focal hemorrhage (skin, abdominal soft tissue and bone; not tabulated below) and the cervix/vagina.

Table 25: Incidence of Selected Nonneoplastic CC-10004-Related Findings

	Males				Females			
Group (mg/kg/day):	**0**	**100**	**300/200**	**1000**	**0**	**100**	**300/200**	**1000/500**
Heart [a]	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
Fibrosis	3	21	22	29	3	15	22	26
Minimal	3	16	9	25	3	11	12	18
Mild	0	3	12	3	0	4	8	8
Moderate	0	2	1	1	0	0	2	0
Arteriopathy, chronic	0	1	2	12	0	0	2	3
Minimal	-	0	2	5	-	-	2	2
Mild	-	1	0	5	-	-	0	1
Moderate	-	0	0	2	-	-	0	0
Cardiomyopathy	26	37	30	33	12	29	22	25
Minimal	20	27	27	27	10	23	16	20
Mild	5	8	3	6	2	6	6	5
Moderate	1	2	0	0	0	0	0	0
Skeletal muscle [a]	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
Hemorrhage [b]	0	1	3	12	0	0	4	5
Mild	-	0	1	2	-	-	0	0
Moderate	-	0	0	4	-	-	1	0
Severe	-	1	2	6	-	-	3	5

Skeletal muscle (continued) [a]	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
Arteriopathy, chronic [c]	0	0	1	1	0	0	0	1
Mild	-	-	1	0	-	-	-	1
Moderate	-	-	0	1	-	-	-	0
Lung [a]	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
Infiltrate, lymphocyte	9	18	25	20	9	15	20	28
Minimal	8	17	19	18	8	10	15	21
Mild	1	1	5	2	1	5	4	6
Moderate	0	0	1	0	0	0	1	1
Vagina [a]	**NA**	**NA**	**NA**	**NA**	**69**	**69**	**69**	**70**
Mucification	-	-	-	-	11	33	36	31
Minimal	-	-	-	-	10	28	31	26
Mild	-	-	-	-	1	5	5	5

NA = Not Applicable
[a] = Number of tissues examined from each group.
[b] = Found only in FD or EE mice.
[c] = Found only in FD (found dead) or EE (euthanized in extremis) mice within the first 12 months of study.

Heart: Fibrosis and vascular changes were common findings in the heart. The fibrosis tended to be of the epicardium at the base of the heart or along the left ventricle and often surrounded the intra- and/or extra-mural coronary vessels. This was the most frequent histologic correlation to the necropsy finding of white area(s) of the heart, observed at necropsy.

A form of vasculitis known as chronic arteriopathy of coronary vessels occurred in mice with early mortality (<18 months). The affected vessels were at or near the base of the heart and the condition and the condition began as a minimal to moderate chronic active arteritis. A later chronic (end-stage) condition developed as subintimal proliferation of spindle cells as well as an overall thickening of the vessel wall. Inflammation at the base of the heart and centered on the root of the aorta was diagnosed as inflammation (either as chronic or chronic active inflammation) under the tissue category ‘aorta’. Vasculitis was used if inflammation was associated with vessels within the myocardium in areas.

The incidences of spontaneously developing cardiomyopathy were higher in CC-10004 treated animals than the control groups. The sponsor claims these cardiac effects were indirect drug effects due to the minimal severity and lack of progression with time. However, dose reductions and dose stoppage characterized the latter aspects of this study, and the lack of progression is more likely a stabilization or recovery due to dose reduction or withdrawal.

Skeletal muscle: Hemorrhage occured in the skeletal muscle and was judged by the pathologist to contribute to the animal's death. These tissues also had an associated arteriopathy that was morphologically similar to the findings described above for the

heart, as well as muscle inflammation and necrosis. The hemorrhage was encapsulated, and the region exhibiting signs of chronic active inflammation, granulation tissue, or fibroplasia. The most common site of this hemorrhage was the hind limb musculature, with bone or abdominal soft tissue as a less common location.

Lungs: There was an increased prominence of perivascular and/or peribronchiolar lymphocyte and plasma cell infiltrates in the lung at doses ≥ 100 mg/kg/day in both sexes. Control animals generally had very few lymphocytes associated with the larger airways and blood vessels.

Vagina: In the vagina, and to a lesser extent the cervix, there was an increased incidence and severity of mucification in the CC-10004-treated females. Mucification was characterized by the presence of mucus-containing epithelial cells (stratum mucification) diffusely within the vagina or cervix.

Toxicokinetics

Blood samples from the retro-orbital sinus were collected on days 22 and 175 (weeks 3 and 25) prior to and 2 hours after dosing from vehicle treated (Group 1A) animals (3 animals/sex/group), and at 1, 2, 4, 8, 12, and 24 hours after dosing from Groups 2A-4A animals (3 animals/sex/group). Plasma was analyzed by (b) (4) for CC-10004 and (b) (4)) concentrations. There were no samples collected after dose reduction of the main study animals in week 73 (18 months). The lower limit of detection was 1 ng/mL.

Increasing doses of CC-10004 resulted in less than dose-proportional increases in CC-10004 C_{max} and AUC_{0-24} for both males and females on both days 22 and 175. (b) (4) was not detected. At the high dose, C_{max} and AUC_{0-24} were consistently greater in females than males on both days (C_{max} day 22: 157% of males, day 175: 132%; AUC_{0-24} day 22: 158%, day 175: 141%). Also, for the high dose both C_{max} and AUC_{0-24} were reduced on day 175 compared to day 22 (C_{max}: males 69%, females 58%; AUC_{0-24}: males 74%, females 66%).

Table 26: Toxicokinetic Summary

Dose (mg/kg/kg)		100		300		1000	
	Day	M	F	M	F	M	F
C_{max} (ng/mL)	22 (wk 3)	2391	2199	4011	3609	5141	8084
	175 (wk 25)	2319	3822	3227	3318	3573	4722
AUC_{0-24} (ng-h/mL)	22 (wk 3)	26297	21028	44234	51658	71604	113694
	175 (wk 25)	32419	37655	45397	47305	52856	75049
		35037		46351		52856	75049
	average					63952	

Dosing Solution Analysis

Homogeneity
Duplicate samples (1 mL each) for homogeneity were collected from vehicle and CC-10004 formulations prepared for use during study weeks 0, 1, 14, 51, 74, 91, and 102. Prior to the initiation of the first dose, duplicate samples were collected from the top, middle, and bottom strata of the 10 and 100 mg/mL dosing formulations and stored frozen. From the batch preparations, an aliquot of each of the 10 and 100 mg/mL dosing formulations was prepared and stored refrigerated for 8 days. Samples collected from the middle stratum were used for determination of time zero concentration. Homogeneity of the dosing formulations was acceptable with %CV ranging from 0.2% to 5.3% for each dosing preparation.

Stability
Results from the middle stratum analyses following 8 days of refrigeration were compared to the time zero concentration analyses for determination of formulation stability and found to be within acceptable limits.

Concentration
Duplicate samples (1 mL each) for concentration determinations were collected on from vehicle and CC-10004 formulations prepared for use during study weeks 0, 1, 14, 51, 74, 91, and 102. The concentrations ranged from -7.9% to 8.6% of their targeted concentrations of 10, 20, 30, 50, and 100 mg/mL. Vehicle control samples were devoid of detectable CC-10004. Therefore, the concentration of the dosing solutions was acceptable.

RAT

Study title: CC-10004: A 104-Week Oral Carcinogenicity Study in Rats

Study no.:	CC-10004-TOX-007
Study report location:	Module 4.2.3.4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 20, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, Batch 54560-05, Purity 99.9% (b) (4) • (b) (4) in Batch 54560-05, used for dosing the animals • (b) (4) in Batch 53625-04, used for the bioanalytical assay
CAC concurrence:	Yes, Dose and Protocol Recommendation at the Meeting of Sept 26 2006 (refer to Appendix 14) Concurrence on Study Results and Conclusions at the Meeting of July 2, 2012.(refer to Appendix 15)

Key Study Findings

- CC-10004 was administered once daily by gavage to Crl:CD(SD) rats (n=70/sex/dose) at 0 (vehicle, 1.0% methocellulose), 2, 10 or 20 mg/kg/day in males and at 0 (vehicle, 1.0% methocellulose), 0.3, 1, or 3 mg/kg/day in females. In study week 66 (16.5 months), dosing of the 20 mg/kg/day males was stopped and the mid group dose of 10 was reduced to 6 mg/kg/day due to animal morbidity and deaths. All dose groups were terminated between study week 91 and 104.
- There was a dose-related decrease in survival for CC-10004 treated males compared to control males.
- There were no malignancies related to apremilast treatment in either male or female rats. In female rats, there was a significant trend (p=0.046) for a dose-related increase in the incidence of ovarian Sertoli cell tumors. However with the low incidences of only 1 at the mid dose and 2 at the high dose of 70 animal per dose group, the pairwise comparison with control incidences of 0 were not significant. There were no other dose-related malignancies.
- Non-neoplastic changes occurred in the adrenal cortex, bones, gastrointestinal tract, heart, liver, intra-abdominal vasculature, skeletal muscle, and

vagina/cervix. These findings were often present in the early mortality animals, prior to month 18 and prior to dose reductions. These findings were generally consistent with findings in previous rat toxicology studies.

- Satellite animals (18/sex/group) were dosed on a comparable regimen for approximately 48 weeks for clinical pathology and toxicokinetic evaluation. The clinical pathology findings of hematology and serum chemistry were consistent with an acute inflammatory response (higher white blood cell counts with increased lymphocytes, neutrophils, and monocytes and low serum albumin and high serum globulin concentrations), which could have arisen from CC-10004-induced gastrointestinal inflammation and lesions as the sponsor proposes.
- Dose-related increases in systemic exposure occurred in male and females; however the increase in males was less than dose proportional. Females had substantially greater AUC exposure than males for the same dosage (26-fold greater in females at 3 mg/kg/day) due to greater bioavailability in female rats (females 61-80%, males 2-12%; Report 1398/215-D1140). Based on the approximate human exposure of 7440 ng-h/mL for a MRHD of 30 mg BID,(refer to Clinical Study CC-10004-RA-002), there is an exposure margin of 0.08X for the high dose male dose group (20 mg/kg/day) and 1.1X for the high dose female (3 mg/kg/day) dose group.

  Note: The mean AUC values reported in this study for females, 7721 ng-h/mL, was reasonably approximate (110%) to the value reported in the 3 month dose-determining study (CC-10004-TOX-003) of 6984 ng-h/mL. However, the mean AUC for males, 608 ng-h/mL at day 179 (6 months) in this study was ~30% lower than expected from the dose-determining 3 month study (30 mg/kg/day dose resulted in 1281 ng-h/mL on day 88, and extrapolating to a 20 mg/kg/day dose resulted in ~860 ng-h/mL). Even if these values were comparable, the margin of exposure would still be less than 1 relative to the maximum proposed human dose. Higher doses could not be administered, as dosing was limited by non-carcinogenic toxicity.

Adequacy of Carcinogenicity Study

The study was adequate, although for males, the mid dose was reduced and the high dose was stopped at week 66 (16.5 months) due to drug-related mortalities. In retrospect, the 3-month dose determining study did not allow an adequate prediction of toxicity for this drug in the rat.

Appropriateness of Test Models

The 2-year lifetime treatment in rats is a standard and acceptable carcinogenicity study.

Evaluation of Tumor Findings

The sponsor's analysis concluded there was no drug-related carcinogenicity. The FDA analysis by Dr. Jackson found there was a significant trend (p=0.046) for a dose-related increase in the incidence of ovarian Sertoli cell tumors in females. This was based on

tumors present in 3 animals as indicated in the summary analysis below. However, the pairwise comparisons with control incidences of 0 were not significant due to the low incidences. Therefore, there were no definitive CP-10004-related malignancies in either male or female rats Refer to Appenidix 15 for ECAC conconcurence of these results at the meeting on July 2 2013.

Table 27: Analysis of Sertoli Cell Tumors in Females*

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 205437
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Sertoli cell tumors	P-value of test of trend or comparison	.0456		.4886	.2066
	Number of animals reported with tumor	0	0	1	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	5.2%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,7.5)	(0.06,12.3)	(0.63,17.7)
	Poly-3 adjusted number of animals at risk	45.6	47.3	43.6	38.3

* The analysis was conducted by Dr. Matthew Jackson, PhD, (CDER/OTS/OB/DBVI), refer to the Biometrics Review of Nov 15, 2013.

Methods

Doses:	M: 0, 3, 10/6, 20 F: 0, 0.3, 1, 3 See table below for a summary of adjustments to dosing
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral by gavage
Formulation/Vehicle:	1.0% carboxymethylcellulose (CMC)
Basis of dose selection:	Doses were based on the results of a 90-day oral toxicity study in rats (CC-10004-TOX-003). The males were dosed at 0, 30, 100, 300 and 1000 mg/kg/day and females at 0, 0.3, 3, 10, and 30 mg/kg/day. These doses produced death in males at all doses and in females at doses ≥10 mg/kg/day along with acute inflammation and lymphoid depletion in multiple tissues. A NOAEL was not identified and the maximum tolerated dose was <30 mg/kg/day for males and <3 mg/kg/day for females.
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	70/sex/dose
Age:	7 weeks old at the initiation of dosing
Animal housing:	Housed individually
Paradigm for dietary restriction:	*ad libitum*

Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	Toxicokinetic and Clinical Pathology assessment groups (Groups 1A to 4A, n=18/sex/dose) Hematology and serum chemistry parameters (up to 10 animals/sex/group) were evaluated from blood samples obtained on days 26 and 179 (weeks 4 and 26).
Deviation from study protocol:	Dose adjustments and animal necropsy times are described below. Other than these changes, there were no deviations that would be expected to affect the data interpretation and conclusions.

Study Dose and Necropsy Adjustments

	Initial dose	Reduced dose and day	Study day that dosing stopped	Study day of necropsy
Males	**0**	-	663 (wk 94)	703 (wk 100)
	3	-	639 (wk 91)	704(wk 100)
	10	**6** (at day 464, wk 66)	626 (wk 89)	687 (wk 98)
	20	-	464 (wk 66)	670 (wk 95)
Females	**0**	-	721 (wk 103)	728 (wk 104)
	0.3	-	721 (wk 103)	728 (wk 104)
	1	-	708 (wk 101)	728 (wk 104)
	3	-	659 (94)	728 (wk 104)

Table 28: Study Design

Group Number	Test Article	Dosage Level (mg/kg/day)		Dosage Concentration (mg/mL)		Dose Volume (mL/kg)	Number of Animals	
Toxicology Animals [a]		**Males**	**Females**	**Males**	**Females**		**Males**	**Females**
1	Vehicle	0	0	0	0	10	70	70
2	CC-10004	3 [b]	0.3 [c]	0.3 [b]	0.03 [c]	10	70	70
3	CC-10004	10/6 [d]	1 [c]	1/0.6 [d]	0.1 [c]	10	70	70
4	CC-10004	20/NLD [e]	3 [c]	2/NLD [e]	0.3 [c]	10	70	70
Satellite Animals [f]		**Males**	**Females**	**Males**	**Females**		**Males**	**Females**
1A	Vehicle	0	0	0	0	10	18	18
2A	CC-10004	3	0.3	0.3	0.03	10	18	18
3A	CC-10004	10	1	1	0.1	10	18	18
4A	CC-10004	20	3	2	0.3	10	18	18

[a] = Various dosing modifications were made due to mortality and to maintain survival.

[b] = At 3 mg/kg/day in males, dosing was discontinued in study week 91 with necropsy of the remaining animal in study week 100.

[c] = In females at 0.3, 1, and 3 mg/kg/day, dosing continued until study weeks 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups in study week 104.

[d] = In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.

[e] = In study week 66, dosage of males at 20 mg/kg/day was terminated and remaining males were maintained on study until necropsy during study week 95 without receiving the test article.

[f] = Toxicokinetic group animals were dosed according to the same initial regimen as the toxicology group animals. Blood samples for toxicokinetic evaluation were collected in accordance with the initial dosage levels on study days 26 and 179. Remaining toxicokinetic animals were euthanized at the scheduled necropsy during study weeks 47 and 48.

NLD = No longer dosed.

Observations and Results

Sentinel Animals

Sentinel animals (15/sex) from the same shipment of animals as used for the main study were housed in the same main study room but were not treated. They were observed for mortality and moribundity twice daily and detailed physical observations were conducted weekly. Body weights were recorded weekly through study week 14 and then biweekly. Sentinel animals that survived to the end of the study or were euthanized in extremis were euthanized by carbon dioxide inhalation. Blood and a full set of tissues were collected and stored for possible analysis.

There was no analysis of sentinel animals since there was no evidence of disease outbreak in the animal room.

Mortality

Animals were checked at least twice daily.

There was a significant dose-related increase in mortality for males, but not females compared to control groups. Dosing of males at 20 mg/kg/day was stopped in week 66 due to mortalities and reduced to 6 mg/kg/day for the mid dose males.

The causes of deaths were unidentified for the majority of animals. The 2 most commonly identified causes of death were pituitary adenoma of pars distalis and gastrointestinal inflammation/necrosis, however to due the high number of animals with pituitary adenomas in the control groups, only deaths associated with gastrointestinal lesions appear to be related to CC-10004 treatment.

Table 29: Survivors and Mortalities in Relationship to Dose Adjustments

	Males				Females			
Dose (mg/kg/day)	**0**	**3**	**10**	**20**	**0**	**0.3**	**1**	**3**
n, Day 1	70	70	70	70	70	70	70	70
n, wk 52	65	63	56	48	67	68	65	61
n, wk 66*	57 (81%)	52 (75%)	41 (59%)	30 (43%)	59 (84%)	64 (91%)	60 (86%)	54 (77%)
wk 66 dose adjustment (mg/kg)	-	-	**6**	**0**	-	-	-	-
n, wk 89 (% alive)	31 (45%)	23 (33%)	18 (26%)	20 (29%)	38 (55%)	39 (56%)	32 (46%)	30 (44%)
wk 89 dose adjustment (mg/kg)	-	-	**0**	-	-	-	-	-
n wk 91	27 (39%)	20 (29%)	17 (25%)	20 (29%)	32 (46%)	35 (51%)	31 (44%)	25 (36%)
wk 91 dose adjustment (mg/kg)	-	**0**	-	-	-	-	-	-
n, wk 94	24 (35%)	17 (25%)	16 (23%)	17 (24%)	27 (39%)	30 (44%)	28 (40%)	20 (29%)
wk 94dose adjustment (mg/kg)	**0**	-	-	-	-	-	-	**0**
n, wk 95	24 (35%)	17 (25%)	16 (23%)	**15 (21%)**	25 (36%)	27 (39%)	28 (40%)	19 (28%)
n, wk 98	19 (27%)	17 (25%)	**15 (22%)**		22 (32%)	26 (38%)	24 (34%)	18 (26%)
n, wk 100	**18 (26%)**	**16 (23%)**	-	-	22 (32%)	23 (33%)	21 (30%)	18 (26%)
wk 101 dose adjustment(mg/kg)	-	**-**	-	-			**0**	
n, wk 103							18 (26%)	17 (25%)
wk 103 dose adjustment(mg/kg)	-	-	-	-	**0**	**0**		

n wk 104	-	-	-	-	**21 (30%)**	**19 (28%)**	**18 (26%)**	**16 (23%)**

- Not applicable
* Dosing accidental deaths were removed from the total animals treated to determine percentages (Male doses, 0: n=1, 3: n=1, 10: n=1; Female doses, 0: n=1, 0.3: n=1, 3: n=1)
Bold back digits represent animal numbers and percentage at time of termination

Table 30: Common Causes of Unscheduled Deaths

	Males				Females			
Group (mg/kg/day):	**0**	**3 [a]**	**10/6 [b]**	**20 [c]**	**0**	**0.3 [d]**	**1 [d]**	**3 [d]**
Animals [e]	**52**	**54**	**55**	**55**	**49**	**51**	**52**	**54**
Undetermined (number)	14	24	18	14	9	15	10	14
(percentage of all early deaths)	26.9%	44.4%	32.7%	25.5%	18.4%	29.4%	19.2%	25.9%
Gastrointestinal necrosis and/or inflammation	0	7	22	21	0	0	4	8
(percentage of all early deaths)	0%	13.0%	40.0%	38.2%	0%	0%	7.7%	14.8%
Adenoma, pars distalis	12	5	1	1	20	23	29	21
(percentage of all early deaths)	23.1%	9.3%	1.8%	1.8%	40.8%	45.1%	55.8%	38.9%

[a] = At 3 mg/kg/day in males, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
[b] = In study week 66, dosage in males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
[c] = In study week 66, dosing of males at 20 mg/kg/day was terminated and the remaining males were maintained on study until necropsy in study week 95 without receiving the test article.
[d] = In females at 0.3, 1, and 3 mg/kg/day, dosing continued until study weeks 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups in study week 104.
[e] = Number of animals not surviving to scheduled necropsy from each group.

Table 31: Survival Plots for males (above) and females (below)

(b) (4)

(b) (4)

Clinical Signs

Observations were conducted at least twice daily, and detailed physical examinations, which included noting the presence of palpable masses (time of onset, location, size, appearance, and progression), were conducted weekly.

There was no effect of CC-10004 treatment on clinical observations or the incidence of palpable masses. For males that died or were euthanized *in extremis* during the first 18 months of the study, the incidence of swollen paws was increased and this corresponded to CC-10004-related hypertosis of the underlying bone. There was no increase in palpable masses with increasing dose. Rather, the number of masses decreased with increasing dose. There was no effect of CC-10004 on the time of onset of masses.

Table 32 : Palpable Masses (from sponsor's table 13 and 14)

	Males				Females			
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
n	70	70	70	70	70	70	70	70
Animals with masses	25	16	14	**12**	36	39	33	**21**
Animals with multiple masses	4	4	2	3	17	12	9	9
Mean number of days to first mass	527	530	548	535	535	526	536	558

Body Weights

Body weights were recorded weekly through week 14, and then monitored biweekly until study termination.

There was a trend of lower body weight in males with increasing dose of CC-10004 compared to the control group after the first year. There was no effect of CC-10004 on body weight in females.

Table 33: Body Weights (g) at Selected Time Points

Gender	**Males**				**Females**			
Dose (mg/kg/day)	**0**	**3**	**10**	**20**	**0**	**0,3**	**1**	**3**
n	70	70	70	70	70	70	70	70
Mean Body Weight (g)								
week 0	241	240	240	240	172	173	170	169
4	400	398	402	392	233	236	237	235
8	498	491	501	494	127	273	276	274
12	546	537	551	542	291	294	300	296
26	644	637	634	624	339	338	341	337
52	746	714	719	713	425	417	420	423
(n)	(65)	(65)	(56)	(49)	(68)	(68)	(65)	(61)
66	719	**740**	747[#]	**731***	471	460	471	459
(n)	(57)	**(54)**	(42)	**(30)**	(59)	(64)	(60)	(54)
72	790	**727**	**731**	735	484	464	462	470
(n)	(52)	**(48)**	**(38)**	(29)	(58)	(62)	(58)	(45)
94	770[c]	729[b]	744[a]	735	482	447	417	493[c]
(n)	(25)	(17)	(17)	(17)	(29)	(32)	(28)	(20)
98	783	727	737	-	487	429	461	493
(n)	(20)	(17)	(16)		(24)	(26)	(25)	(18)
100	791	**702**	-	-	464	407	472	484
	(18)	**(17)**			(22)	(24)	(22)	(18)
104	-	-	-	-	429	388	467[d]	482
(n)					(22)	(19)	(18)	(17)

* Dosing was stopped in this dose group in week 66
[#] Dosing was reduced from 10 to 6 mg/kg/day in week 66
[a] Dosing was stopped in week 89
[b] Dosing was stopped in week 91
[c] Dosing was stopped in week 94
[d] Dosing was stopped in week 101

Table 34: Body Weights of Males (above) and Females (below)

(b) (4)

(b) (4)

Feed Consumption

Food consumption was recorded weekly, through study week 14, then biweekly. Food intake was calculated as g/animal/day for the corresponding body weight intervals

There were no treatment-related effects on food consumption.

Hematology

Blood smears were obtained to aid in the diagnosis of hematopoietic disorders. Blood samples were collected from the vena cava of all animals euthanized *in extremis* and at the scheduled necropsy. Only smears from 3 males in the high dose group were examined.

For hematology analysis of satellite animals (Groups 1A-4A, up to 10 animals/sex/group) blood samples were obtain at study weeks 9, 21, and 47/48 from the retro-orbital sinus under isoflurane anesthesia. Parameters examined were as follows:

Hematology and Coagulation

Total leukocyte count (White Cells)
Erythrocyte count (Red Cells)
Hemoglobin
Hematocrit
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count (Platelet)
Reticulocyte count
  Percent (Reticulocyte)
  Absolute (Retic Absolute)

Differential leukocyte count -
  Percent and absolute
  -Neutrophil
  -Lymphocyte
  -Monocyte
  -Eosinophil
  -Basophil
  -Large unstained cell
Platelet estimate[a]
Red cell morphology (RBC Morphology)[a]

( ) - Designates tabular abbreviation.

[a] - Presented on individual tables if a manual differential was performed, and the manual data were accepted and reported instead of the automated differential data.

Effects of CC-10004 treatment were elevated white blood cell, lymphocyte, neutrophil, and monocyte counts in the high dose females compared to the control group. There were no samples obtained on prior to day 1 or on day 1 of dosing to determine potential time dependent effects in control animals. These observed effects in the high dose females were consistent with a slight inflammatory response, and corresponded with serum chemistry findings of an acute phase response. Although the sponsor indicated that measures of red blood cell mass (red blood cells, hemoglobin and hematocrit) were

slightly lower in the high dose female group and absolute reticulocytes slightly higher, the changes were small and not toxicologically significant.

In males, the elevated values at week 47 for mean white blood cell counts, neutrophils, lymphocytes, and monocytes were due to 2 animals (#3671 and #3633) with blood smears consistent with lymphocytic leukemia. These animals were also anemic with lower mean RBC and hematocrit values but without a regenerative increase in reticulocytes.

Table 35: Summary of Hematology Findings from Satellite Animals

Gender	Male				Female			
Dose (mg/kg/day)	**0**	**3**	**10**	**20**	**0**	**0.3**	**1**	**3**
n	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
WBC (10^3/µL)								
week 9	10.97	12.47	13.07	12.38	8.47	8.59	9.07	**11.97 (141%)**
week 21	10.80	11.17	13.29	10.55	6.31	6.96	7.50	**11.78 (187%)**
week 47	9.30	9.12	9.56	**32.16 (345%)**	5.64	5.02	5.85	7.30 (129%)
Neutrophils (%)								
week 9	13.1	10.5	11.4	15.6	12.2	9.1	12.8	12.1
week 21	17.1	15.7	14.1	15.2	12.2	10.3	8.4	18.8
week 47	21.8	22.8	19.6	**34.8 (160%)**	19.1	20.8	20.2	26.2 (137%)
Lymphocytes (%)								
week 9	81.7	83.8	83.7	79.1	83.0	85.9	813.8	83.4
week 21	77.2	79.5	81.4	78.7	82.8	85.1	87.3	77.1
week 47	70.9	70.5	74.6	**53.5 (75%)**	73.8	72.7	73.2	68.1 (92%)
Monocyte (%)								
week 9	2.4	2.8	2.3	2.7	2.1	1.9	2.2	1.8
week 21	2.7	2.6	2.4	3.0	2.1	2.1	2.0	1.9
week 47	4.4	3.8	3.1	**9.7 (220%)**	3.9	3.5	3.5	**2.9 (74%)**
RBC (10^6/µL)								
week 9	9.31	9.06	9.08	9.18	8.61	8.65	8.47	**8.10**
week 21	9.29	9.16	9.01	9.09	8.43	8.19	8.22	**7.92**
week 47	9.10	9.07	8.64	**8.43 (93%)**	8.20	8.16	8.10	7.99 (97%)
Hematocrit (%)								
week 9	46.8	44.9	46.4	46.5	44.2	44.2	43.4	**42.3 (96%)**
week 21	45.6	44.5	45.1	45.2	44.2	44.6	42.8	41.9
week 47	46.8	44.9	43.9	**42.8 (91%)**	44.2	43.5	43.3	43.1 (98%)

Hemoglobin (g/dL)								
week 9	17.1	16.6	16.9	17.0	16.8	16.5	**16.1 (96%)**	**15.9 (95%)**
week 21	16.5	16.3	16.2	16.3	16.2	15.6	**15.5 (96%)**	**15.2 (94%)**
week 47	16.7	16.2	15.6	15.3 (92%)	15.9	15.7	15.6	15.6 (98%)
Reticulocytes (10^3/µL)								
week 9	218	221	207	220	167	153	158	158
week 21	190	201	212	196	142	142	155	166
week 47	220	198	**179 (81%)**	216 (98%)	156	161	162	174 (111%)
Reticulocytes (%)								
week 9	2.2	2.6	2.3	2.4	2.0	1.8	1.9	2.0
week 21	2.0	2.2	2.4	2.2	1.7	1.7	1.9	2.1
week 47	2.4	2.2	2.1 (88%)	2.6 (108%)	1.9	2.0	2.0	2.2 (116%)
Bolded values, p<0.05 compared to controls								

Serum Chemistry

Blood samples were obtain at study weeks 9, 21, and 47/48 from the retro-orbital sinus of satellite animals (Groups 1A-4A, up to 10 animals/sex/group) under isoflurane anesthesia. Parameters examined were as follows:

Serum Chemistry

Albumin
Total protein
Globulin [by calculation]
Albumin/globulin ratio (A/G Ratio) [by calculation]
Total bilirubin (Total Bili)
Urea nitrogen
Creatinine
Alkaline phosphatase (AlkalinePhos'tse)
Alanine aminotransferase (Alanine Transfer)
Aspartate aminotransferase (AspartatTransfer)
Gamma glutamyltransferase (GlutamylTransfer)
Glucose
Total cholesterol (Cholesterol)
Calcium
Chloride
Phosphorus
Potassium
Sodium
Triglycerides (Triglyceride)

( ) - Designates tabular abbreviation.

In the high dose females, there were small reductions in total protein and albumin and an increase in globulin, resulting in an overall reduction in the A/G ratio. Except for total protein these changes occured by week 9 and remained until the end of the study with satellite animals at week 47. Except for total protein, similar changes occurred in the high dose males but only at week 47. The high dose males also had elevations in blood urea nitrogen and creatinine in week 47, due to male #3633 with urea nitrogen of 169 mg/dL and creatinine of 5.2 mg/dL that also had a blood smear indicative of lymphocytic

leukemia. The other male #3671 had values within the range of the other animals in this group.

Table 36: Summary of Serum Chemistry Findings from Satellite Animals

Gender	Male				Female			
Dose (mg/kg/day)	**0**	**3**	**10**	**20**	**0**	**0.3**	**1**	**3**
n	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Total Protein (g/dL)								
week 9	6.8	6.9	6.9	7.0	7.3	7.4	7.4	7.1
week 21	7.3	7.5	7.4	7.4	8.0	7.9	7.9	7.6
week 47	7.2	7.3	7.2	7.2 (100%)	8.4	8.4	**7.9 (94%)**	**7.7 (92%)**
Albumin (g/dL)								
week 9	4.2	4.4	4.3	4.4	4.9	4.9	4.9	**4.2 (86%)**
week 21	4.4	4.5	4.5	4.5	5.4	5.3	5.2	**4.3 (80%)**
week 47	4.2	4.1	4.1	**3.9 (93%)**	5.7	5.6	**5.2 (91%)**	**4.6 (81%)**
Globulin (g/dL)								
week 9	2.6	2.6	2.6	2.7	2.4	2.5	2.5	**2.9 (121%)**
week 21	3.0	3.0	2.9	3.0	2.6	2.6	2.6	**3.3 (127%)**
week 47	3.1	3.2	3.1	**3.4 (110%)**	2.8	2.8	2.7	**3.1 (111%)**
A/G ratio								
week 9	1.64	1.70	1.66	1.63	2.07	2.01	1.98	**1.48 (71%)**
week 21	1.49	1.51	1.54	1.52	2.12	2.04	2.01	**1.35 (64%)**
week 47	1.39	1.39	1.35	**1.19 (86%)**	2.08	2.05	1.91	**1.47 (71%)**
Urea Nitrogen (mg/dL)								
week 9	12.9	13.1	13.2	13.2	15.3	14.9	13.9	14.3
week 21	13.4	12.1	12.2	13.0	15.3	14.3	14.3	14.7
week 47	11.6	12.8	11.9	**27.6 (238%)**	14.8	15.5	13.1	14. 8 (100%)
Creatinine (mg/dL)								
week 9	0.2	0.3	0.2	0.2	0.3	0.3	0.3	0.3
week 21	0.2	0.3	0.2	0.2	0.3	0.3	0.3	0.3
week 47	0.3	0.3	0.2	**0.8 (267%)**	0.3	0.3	0.3	0.4 (133%)

Organ weights (Satellite Animals)

The following organs were weighed from the satellite group animals (Groups 1A-4A) at necrospy at week 47:

Adrenals	Prostate
Brain	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroids with parathyroids*
Ovaries with oviducts	Uterus
Pituitary gland	

CC-10004-related changes in organ weights occurred only in the high dose female group. There was an increase in ovarian/oviduct weight and a decrease in uterine weight. Both spleen and thymus weights were also increased. The large mean increase (>3-fold) in thymus weight in high dose females compared to the control group was due to one animal (#3999) with a thymus weight of 3.3577 g. There was also an indication from the gross necropsy table that one animal in this dose group had a large thymus lobulated mass (25 x 17 x 12 mm). Although no histopathology was conducted for the satellite animals, in the main study animals, 1 thyoma occurred in a low dose male. Therefore it is likely that the mass is probably a thyoma of incidental nature, not CC-10004 related. Removing this animal from the mean value calculations yielded a mean and relative absolute weight of only 116% and 105%, respectively, of control values. This small change is not toxicological significant for interpretation of the carcinogenicity findings. Generally, the satellite animals had similar findings at this week 47 timepoint as they did in earlier shorter toxicological studies.

Table 37: Summary of Organ Weight Findings of Females from Satellite Animals

Gender	**Female**			
Dose (mg/kg/day)	**0**	**0.3**	**1**	**3**
n	17	18	17	16
Spleen				
g	0.56	0.57	0.58	**0.67 (125%)**
% BW	0.150	0.151	0.160	0.165
Thymus				
g	0.0804	0.0894	0.0914	**0.2974 369%** **0.0934* (116%)**
% BW	0.021	0.024	0.026	**0.078 (371%)** **0.022* (105%)**
Ovary/oviduct				
g	0.1034	0.1264	0.1230	**0.1609 (156%)**
% BW	0.028	0.034	0.034	**0.041 (146%)**
%BrW	5.079	6.296	6.054	**8.026**

				(158%)
Uterus				
g	1.04	0.86	0.87	**0.76 (73%)**
% BW	0.278	0.232	0.246	**0.193 (69%)**
* recalculated values after removing the animal with a thymus mass of total weight 3.3577				

Gross Anatomic Pathology

There were gross anatomic pathology findings in all animals. Findings from animals that died prior to the scheduled termination and that corresponded to histopathological findings and appeared to be CC-10004 related are presented in the table below. Distention of the gastrointestinal tract occurred all along the GI tract. Gastrointestinal distension, thickening of the small intestine, and dark red areas and/or erosion of the stomach were most commonly noted in animals found dead or euthanized *in extremis* primarily within the first 18 months of the study. After dosing ended in the high dose group of males, as well as ending in the other groups, these changes were rarely observed.

The sponsor mentioned the finding of distended bile duct in CC-10004 treated males was a misinterpretation or misidentification of mesenteric vasculitis based on histopathology. While there is no way for the reviewer to verify this; these two particular findings would not alter the overall interpretation, although it was unclear if the gross observation of distended bile duct was actually present or not present.

Table 38: Toxicologically Relevant Gross Necropsy Observations (Unscheduled Deaths)

	Males				**Females**			
Dose (mg/kg/day)	**0**	**3**	**10**	**20**	**0**	**0.3**	**1**	**3**
n	**70**	**70**	**70**	**70**	**70**	**70**	**70**	**70**
week dosing stopped	94	91	89	66	103	103	101	94
week group terminated	100	100	98	95	104	104	104	104
Duodenum								
thickened	1	3	0	1	0	0	0	1
Ileum								
thickened	0	2	3	5	0	0	0	3
Jejunum								
thickened	0	2	1	1	0	0	0	2
Stomach								
red areas	10	7	18	8	3	4	6	8
erosion	2	3	10	6	0	0	0	0
Paws								
swollen	0	7	8	6	0	0	1	0

Histopathology

Peer Review: Yes, conducted by [redacted] (b) (4) and consisted of examination of tissues as follows:

[redacted]

In a preliminary analysis of the data file by Dr. Jackson, he noted (email of April 30 2013) that the autolysis rates for the jejunum were high, and 15% of male rats lacked examination of the Zymball gland. Due to the high incidence of animals found dead, it is not surprising that autolysis would be so prevalent. There were still substantial tissues of adequate quality examined to enable a reasonable conclusion as to the carcinogenic potential of CC-10004.

Neoplastic Findings

There were no malignancies related to apremilast treatment in either male or female rats (refer to Appendices 3, 4, and 5). In female rats, there was a significant trend (p=0.046) for a dose-related increase in the incidence of ovarian Sertoli cell tumors identified in the analysis by Dr. Jackson when analyzed as a composite endpoint detected in the ovary and the spleen. However with the low incidences of only 1 at the mid dose and 2 at the high dose of 70 animal per dose group, the pairwise comparison with control incidences of 0 were not significant. There were no other dose-related malignancies in either male or female rats. The results of Dr Jackson's analysis are presented below

Table 39: Incidence of Sertoli Cell Tumors in Female Rats

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 205437
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Sertoli cell tumors	P-value of test of trend or comparison	.0456		.4886	.2066
	Number of animals reported with tumor	0	0	1	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	5.2%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,7.5)	(0.06,12.3)	(0.63,17.7)
	Poly-3 adjusted number of animals at risk	45.6	47.3	43.6	38.3

The spleen finding was probably a metastasis from the ovary, but there was no primary tumor identified in the ovary of this animal. These tumors are uncommon (b) (4) Sertoli cell tumors are considered to be related to sex cord tumors. There was one incidence noted in female mice in the accompanying carcinogenicity study. A related tumor does occur in women. This tumor can be benign or malignant, and range from pure sertoli cellular structure to a mix of sertoli and leydig cell structure. They may secrete both estrogen and progesterone.

Non-Neoplastic Findings

Non-neoplastic changes occurred in the adrenal cortex, bones, gastrointestinal tract, heart, liver, intra-abdominal vasculature, skeletal muscle, and vagina/cervix. These findings were often present in the early mortality animals, prior to month 18 and dose reductions. The sponsor tabulated the lesion findings or the ileum, liver and femur (refer to the Tables below as representative for multiple lesion sites in the intestine, vasculature and bones, that had respectively, similar location specific lesions.

Adrenal cortex: Adrenal cortical necrosis characterized by focally extensive area(s) of coagulation necrosis increased in incidence and severity with increasing dose of CC-10004. It was only present in animals that died or were euthanized *in extremis*, primarily within the first 18 months on study.

Table 40: Adrenal Gland (Males) Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose (mg/kg/day)	**0**	**3[b]**	**10/ 6[c]**	**20[d]**	**0**	**3[b]**	**10/ 6[c]**	**20[d]**	**0**	**3[b]**	**10/ 6[c]**	**20[d]**
n	25	33	37	45	27	21	18	10	18	16	15	15
Adrenal Cortex[a]												
Necrosis	1	0	4	6	1	0	0	0	NA	NA	NA	NA
Minimal	0	0	1	3	1	0	0	0				
Mild	1	0	0	3	0	0	0	0				
Moderate	0	0	3	0	0	0	0	0				

	Males (all animals)			
Dose (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	70	70	70
Adrenal Cortex[a]				
Necrosis	2	0	4	6
Minimal	1	0	1	3
Mild	1	0	0	3
Moderate	0	0	3	0

[a] - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
[b] - At 3 mg/kg/day, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
[c] - In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
[d] - In study week 66, dosage of males at 20 mg/kg/day was terminated and the remaining males were maintained on study without receiving the test article until study week 95.
NA - Not applicable, findings not present
FD/EE - found dead/euthanized *in extremis*

Bone: CC-10004-related hyperostosis (periosteal new and mature bone formation occurred in the femur, sternum, and incidental or gross findings in the skull and bones of the paws and/or tail of both males and females. Hyperostosis was seen as pale eosinophilic bony trabeculae radiating perpendicularly from the periosteal surface of mature cortical bone. Most cases of periosteal new bone formation occurred in the animals that did not survive past 18 months on study. The sponsor attributed this finding to an inflammatory process either direct or indirectly affecting the bone, such as ulcerative pododermatitis affecting the bones of the paws or pharyngeal (hard palate) or ulceration affecting the bone associated with the rostral nasal sections. The only necropsy evidence of periosteal new bone formation was noted as swollen paws in a small number of males from the 3, 10/6, and 20 mg/kg/day dose groups that died or were euthanized *in extremis* within the first 18 months on study and did not have concurrent ulcerative pododermatitis. A related change in the bone, seen after the 18-month time on study, was thickening of the bone due to an excessive amount of mature bone on the periosteal surface (hyperostosis, mature bone); on occasion, bone marrow was also present. Periosteal mature bone hyperostosis was the only CP-10004-related change seen in a small number of scheduled necropsy 10/6 mg/kg/day group males

and 3 mg/kg/day group females, and which the sponsor suggests may represent remodeling/maturation of prior periosteal new bone formation.

Table 41: Femur (Males), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose (mg/kg/day):	**0**	**3[b]**	**10/ 6[c]**	**20[d]**	**0**	**3[b]**	**10/ 6[c]**	**20[d]**	**0**	**3[b]**	**10/ 6[c]**	**20[d]**
n	25	33	37	45	27	21	18	10	18	16	15	15
Femur												
Hyperostosis-periosteal new bone	0	6	19	22	0	8	8	0	1	0	0	1
Minimal	0	1	7	9	0	5	4	0	0	0	0	1
Mild	0	5	10	11	0	3	4	0	1	0	0	0
Moderate	0	0	2	2	0	0	0	0	0	0	0	0
Hyperostosis-periosteal mature bone	NA	NA	NA	NA	0	2	1	0	0	1	6	1
Minimal					0	1	1	0	0	1	6	1
Mild					0	1	0	0	0	0	0	0

	Males (all animals)			
Dose (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	70	70	70
Femur				
Hyperostosis-periosteal new bone	1	14	27	23
Minimal	0	6	11	10
Mild	1	8	14	11
Moderate	0	0	2	2
Hyperostosis-periosteal mature bone	0	3	7	1
Minimal	0	2	7	1
Mild	0	1	0	0

Table 42: Femur (Females), Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**0.3[b]**	**1[b]**	**3[b]**	**0**	**0.3[b]**	**1[b]**	**3[b]**	**0**	**0.3[b]**	**1[b]**	**3[b]**
n	19	18	28	30	30	33	24	24	21	19	18	16
Femur [a,c]												
Hyperostosis-periosteal new bone (minimal)	0	0	0	1	0	1	0	1	NA	NA	NA	NA
Hyperostosis-periosteal mature bone	NA	NA	NA	NA	0	0	2	5	1	2	1	4
Minimal					0	0	0	3	1	1	1	4
Mild					0	0	2	2	0	1	0	0

	Females (all animals)			
Dose Group (mg/kg/day):	**0**	**0.3[b]**	**1[b]**	**3[b]**
n	70	70	70	70
Femur [a,c]				
Hyperostosis-periosteal new bone (minimal)	0	1	0	2
Hyperostosis-periosteal mature bone	1	2	3	9
Minimal	1	1	1	7
Mild	0	1	2	2

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 0.3, 1, and 3 mg/kg/day, dosing continued until study week 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups at study week 104.
c - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
FD/EE - found dead/euthanized *in extremis*

Gastrointestinal tract: CP-10004-related changes were seen in the 3, 10/6, and 20 mg/kg/day group males, the 1 and 3 mg/kg/day group females, and primarily in those animals that did not survive past 18 months on study. Acute to subacute inflammation was the most consistent change seen in all gastrointestinal segments (stomach to rectum). In both sexes, the ileum tended to be the most commonly and severely affected of the gastrointestinal tissues. Additional findings in the ileum included distention (a gross observation) and goblet cell hyperplasia. Stomach ulceration and erosion occurred in the glandular and nonglandular regions. Extensive acute to subacute inflammation with or without necrosis (erosion or ulceration) of the intestines was considered a frequent cause of death.

Table 43: Gastrointestinal (Males), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	25	32	37	45	27	21	18	10	18	16	15	15
Stomach, nonglandular [a]												
Ulceration	1	3	11	7	4	2	6	0	NA	NA	NA	NA
Minimal	0	3	3	4	3	0	2	0				
Mild	1	0	5	3	1	2	0	0				
Moderate	0	0	3	0	0	0	3	0				
Severe	0	0	0	0	0	0	1	0				
n	25	32	37	45	27	21	18	10	18	16	15	15
Stomach, glandular [a]												
Inflammation, acute	0	3	12	14	0	2	7	0	NA	NA	NA	NA
Minimal	0	2	8	12	0	2	6	0				

Mild	0	1	4	2	0	0	1	0				
n	24	33	35	43	24	18	18	7	18	16	15	15
Ileum [a, e]												
Hyperplasia, goblet cell	0	2	6	6	0	4	3	0	1	0	0	0
Minimal	0	2	2	2	0	3	0	0	1	0	0	0
Mild	0	0	4	3	0	1	3	0	0	0	0	0
Moderate	0	0	0	1	0	0	0	0	0	0	0	0
Inflammation, acute	0	6	22	29	0	4	8	0	NA	NA	NA	NA
Minimal	0	4	9	11	0	1	4	0				
Mild	0	1	6	11	0	1	3	0				
Moderate	0	1	7	5	0	2	1	0				
Severe	0	0	0	2	0	0	0	0				

	Males (all animals)			
Dose Group (mg/kg/day)	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	69	70	70
Stomach, nonglandular [a]				
Ulceration	5	5	17	7
Minimal	3	3	5	4
Mild	2	2	5	3
Moderate	0	0	6	0
Severe	0	0	1	0
n	70	69	70	70
Stomach, glandular [a]				
Inflammation, acute	0	5	19	14
Minimal	0	4	14	12
Mild	0	1	5	2
n	66	67	68	65
Ileum [a, e]				
Hyperplasia, goblet cell	1	6	9	6
Minimal	1	5	2	2
Mild	0	1	7	3
Moderate	0	0	0	1
Inflammation, acute	0	10	30	29
Minimal	0	5	13	11
Mild	0	2	9	11
Moderate	0	3	8	5
Severe	0	0	0	2

Table 44: Gastrointestinal (Females), Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]
n	19	18	28	30	30	33	24	24	21	19	18	16
Stomach, nonglandular [a]												
Ulceration	1	3	3	4	0	0	1	3	2	0	0	0
Minimal	0	3	2	2	0	0	0	2	1	0	0	0
Mild	0	0	1	2	0	0	1	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	1	0	0	0
Severe	1	0	0	0	0	0	0	0	0	0	0	0
n	19	18	28	30	30	33	24	24	21	19	18	16
Stomach, glandular [a]												
Inflammation, acute;	0	0	2	3	1	0	1	2	1	0	0	0
Minimal	0	0	2	3	1	0	1	2	1	0	0	0
Erosion	0	0	2	7	2	2	2	6	0	1	0	0
Minimal	0	0	2	6	1	2	1	5	0	1	0	0
Mild	0	0	0	0	1	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	1	0	0	0	0	0
n	15	16	24	26	28	30	23	24	21	19	18	16
Ileum [a, c]												
Hyperplasia, goblet cell	0	0	1	2	0	0	0	3	NA	NA	NA	NA
Minimal	0	0	0	2	0	0	0	2				
Mild	0	0	1	0	0	0	0	1				
Inflammation, acute	0	0	3	6	0	0	1	2	NA	NA	NA	NA
Minimal	0	0	0	5	0	0	1	2				
Mild	0	0	2	1	0	0	0	0				
Moderate	0	0	1	0	0	0	0	0				

	Females (all animals)			
Dose Group (mg/kg/day):	0	0.3[b]	1[b]	3
n	70	70	70	70
Stomach, nonglandular [a]				
Ulceration	3	3	4	7
Minimal	1	3	2	4
Mild	0	0	2	3
Moderate	1	0	0	0
Severe	1	0	0	0
n	70	70	70	70
Stomach, glandular [a]				
Inflammation, acute;	2	0	3	5
Minimal	2	0	3	5

Erosion	2	3	4	13
Minimal	1	3	3	11
Mild	1	0	0	1
Moderate	0	0	1	1
n	64	65	65	66
Ileum [a, c]				
Hyperplasia, goblet cell	0	0	1	5
Minimal	0	0	0	4
Mild	0	0	1	1
Inflammation, acute	0	0	4	8
Minimal	0	0	1	7
Mild	0	0	2	1
Moderate	0	0	1	0

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 0.3, 1, and 3 mg/kg/day, dosing continued until study week 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups at study week 104.
c - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
FD/EE - found dead/euthanized *in extremis*

Heart: Myocardial coagulative necrosis often with associated fibroplasia was present in males of the mid and high dose that died within the first 18 months of the study. In severe incidences, these findings were considered to be the cause of death for these animals. There were no CC-10004 related pathological effects in the heart of females.

Table 45: Heart (Males), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	25	33	37	45	27	21	18	10	18	16	15	15
Heart [a]												
Fibroplasia	0	0	1	4	0	0	0	1	NA	NA	NA	NA
Minimal	0	0	0	1	0	0	0	0				
Mild	0	0	1	2	0	0	0	0				
Moderate	0	0	0	1	0	0	0	1				
Necrosis	0	0	3	7	0	0	2	0	NA	NA	NA	NA
Minimal	0	0	1	3	0	0	1	0				
Mild	0	0	2	4	0	0	0	0				
Moderate	0	0	0	0	0	0	1	0				

	Males (all animals)			
Dose Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	70	70	70
Heart [a]				
Fibroplasia	0	0	1	5
Minimal	0	0	0	1
Mild	0	0	1	2
Moderate	0	0	0	2
Necrosis	0	0	5	7
Minimal	0	0	2	3
Mild	0	0	2	4
Moderate	0	0	1	0

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 3 mg/kg/day, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
c - In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
d - In study week 66, dosage of males at 20 mg/kg/day was terminated and the remaining males were maintained on study without receiving the test article until study week 95.
e - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
NA - Not applicable, findings not present.
FD/EE - found dead/euthanized *in extremis*

Blood Vessels (Abdominal): Vasculitis occurred in hepatic, pancreatic, and mesenteric vessels at doses ≥1 mg/kg/day in both sexes. Vasculitis was characterized by a perivascular proliferation of loose connective tissue admixed with variable numbers of inflammatory cells. Mesenteric vasculitis occurred at doses ≥3 mg/kg/day in both sexes. The sponsor pointed out that although the mesentery was not a protocol-required tissue, it was examined as part of the toxicity associated with the bile duct dilatation. The mesentery vasculitis was morphologically similar to that of pancreatic and hepatic vasculitis and similar to spontaneously developing polyarteritis.

Table 46: Blood Vessels, Abdominal (Males), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	25	33	37	45	27	21	18	10	18	16	15	15
Liver [a, e]												
Vasculitis	0	2	6	5	1	5	4	1	NA	NA	NA	NA
Minimal	0	2	5	2	0	1	3	0				
Mild	0	0	1	3	0	1	1	0				
Moderate	0	0	0	0	0	1	0	0				
Severe	0	0	0	0	1	2	0	1				

	Males (all animals)			
Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	70	70	70
Liver [a, e]				
Vasculitis	1	7	10	6
Minimal	0	3	8	2
Mild	0	1	2	3
Moderate	0	1	0	0
Severe	1	2	0	1

Table 47: Blood Vessels, Abdominal (Female), Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**0.3[b]**	**1[b]**	**3[b]**	**0**	**0.3[b]**	**1[b]**	**3[b]**	**0**	**0.3[b]**	**1[b]**	**3[b]**
n	19	18	28	30	30	33	24	24	21	19	18	16
Liver [a, c]												
Vasculitis; minimal	0	0	1	0	0	0	0	2	NA	NA	NA	NA

	Females (all animals)			
Dose Group (mg/kg/day):	**0**	**0.3[b]**	**1[b]**	**3[b]**
n	70	70	70	70
Liver [a, c]				
Vasculitis; minimal	0	0	1	2

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 0.3, 1, and 3 mg/kg/day, dosing continued until study week 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups at study week 104.
c - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
NA - Not applicable, findings not present
FD/EE - found dead/euthanized *in extremis*

Lymphoid Tissues: In the mesenteric lymph node in males there was a dose-dependent increase in lymphoid hyperplasia in animals that died or were euthanized prior to 18 months of the study. The sponsor considered this to be secondary to the Peyer's patches inflammation along the gastrointestinal tract which is a reasonable explanation. The absence of related hyperplasia in the mandibular lymph node also supports this explanation. Acute inflammation of the Peyer's patches was often associated with acute inflammation of the ileum. In the thymus acute inflammation was either within the thymus and/or in the surrounding mediastinal soft tissue. Dose-dependent cellular depletion occurred in the thymus, spleen, lymph nodes (mandibular and mesenteric), and Peyer's patches. Since cellular depletion was a common finding in animals that died or were euthanized prior to 18 months of the study, the sponsor claimed that the response was a secondary response due to stress and morbidity. While a secondary indirect effect of CC-10004 is a possibility, similar lymphoid depletion occurred in the 3-month repeated dose rat study (Report CC-10004-TOX-003) used to

determine doses for this carcinogenicity study. Given the multiple pathological findings, the stress of chronic disease as a cause of lymphoid tissue findings is possible, but did not always coincide with expected adrenal cortical hypertrophy.

Table 48: Lymphoid Node (Males), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	25	33	37	44	27	21	17	10	18	16	15	15
Lymph node, mesenteric [a]												
Hyperplasia, lymphoid	0	3	3	10	1	2	2	0	NA	NA	NA	NA
Minimal	0	3	1	8	1	1	2	0				
Mild	0	0	2	2	0	1	0	0				

	Males (all animals)			
Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	70	70	69	69
Lymph node, mesenteric [a]				
Hyperplasia, lymphoid	1	5	5	10
Minimal	1	4	3	8
Mild	0	1	2	2

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 3 mg/kg/day, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
c - In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
d - In study week 66, dosage of males at 20 mg/kg/day was terminated and the remaining males were maintained on study without receiving the test article until study week 95.
e - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
NA - Not applicable, findings not present
FD/EE - found dead/euthanized *in extremis*

Table 49: Peyer's Patches (Males) Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**
n	21	33	35	41	26	19	17	8	18	15	14	15
Inflammation, acute	0	4	17	19	0	3	7	0	NA	NA	NA	NA
Minimal	0	3	8	11	0	1	5	0				
Mild	0	1	8	8	0	2	1	0				
Moderate	0	0	1	0	0	0	1	0				

	Males (all animals)			
Dose Group (mg/kg/day):	0	3[b]	10/6[c]	20[d]
n	65	67	66	64
Inflammation, acute	0	7	24	19
Minimal	0	4	13	11
Mild	0	3	9	8
Moderate	0	0	2	0

Table 50: Peyer's Patches (Female), Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]
n	18	16	23	23	30	31	22	21	20	18	18	16
Inflammation, acute	0	0	2	4	0	0	0	2	NA	NA	NA	NA
Minimal	0	0	1	4	0	0	0	2				
Mild	0	0	1	0	0	0	0	0				

	Females (all animals)			
Dose Group (mg/kg/day):	0	0.3[b]	1[b]	3[b]
n	68	65	63	60
Inflammation, acute	0	0	2	6
Minimal	0	0	1	6
Mild	0	0	1	0

[a] - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
[b] - At 0.3, 1, and 3 mg/kg/day, dosing continued until study week 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups at study week 104.
[c] - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
NA - Not applicable, findings not present.
FD/EE - found dead/euthanized *in extremis*

Table 51: Thymus (Male), Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day):	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]
n	23	28	35	44	25	21	16	9	17	16	14	15
Inflammation, acute	0	1	5	9	NA	NA	NA	NA	NA	NA	NA	NA
Minimal	0	1	2	5								
Mild	0	0	2	4								
Moderate	0	0	1	0								

	Males (all animals)			
Dose Group (mg/kg/day):	0	3[b]	10/6[c]	20[d]
n	65	65	65	68
Inflammation, acute	0	1	5	9
Minimal	0	1	2	5

Mild	0	0	2	4
Moderate	0	0	1	0

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 3 mg/kg/day, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
c - In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
d - In study week 66, dosage of males at 20 mg/kg/day was terminated and the remaining males were maintained on study without receiving the test article until study week 95.
NA - Not applicable, findings not present.
FD/EE - found dead/euthanized *in extremis*

Skeletal muscle: There was a dose-related increased incidence and severity of skeletal muscle degeneration and mineralization in males. Muscle degeneration likely contributed to moribundity and the decision to euthanize the animals that died or were euthanized in extremis prior to 18 months of the study. Although the sponsor indicated it is a common age-related incidental finding, the incidence in CC-10004-treated males was greater than vehicle treated controls. The increase in mineralization was not associated with evidence of renal disease in the CC-10004 treated animals, in contrast to the 3 of 4 control group animals with both skeletal muscle mineralization and renal disease (n=2 with chronic progressive nephropathy, n=1 with a kidney tumor). At the scheduled necropsy, the incidence of degeneration was similar between controls and CC-10004 treated animals, without findings of mineralization. This degeneration was likely an increase in the normal age-related muscle changes also noted in the control males.

Table 52: Skeletal Muscle (Male), Non-Neoplastic Findings

	FD/EE ≤ 18 mos.				FD/EE > 18 mos.				Scheduled Necropsy			
Group (mg/kg/day):	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6[c]**	**20[d]**	**0**	**3[b]**	**10/6**	**20[d]**
n	25	33	37	45	27	21	18	10	18	16	15	15
Skeletal muscle[a]												
Degeneration	3	11	21	23	9	7	7	1	8	4	1	3
Minimal	3	9	15	16	7	4	4	0	8	2	1	3
Mild	0	2	5	6	1	1	3	1	0	2	0	0
Moderate	0	0	1	0	1	2	0	0	0	0	0	0
Severe	0	0	0	1	0	0	0	0	0	0	0	0
Mineralization	1	4	12	9	3	1	2	0	NA	NA	NA	NA
Minimal	0	3	8	3	3	0	1	0				
Mild	1	1	2	3	0	0	1	0				
Moderate	0	0	2	3	0	1	0	0				

	Males (all animals)			
Group (mg/kg/day):	0	3 [b]	10/ 6 [c]	20 [d]
n	70	70	70	70
Skeletal muscle [a]				
Degeneration	20	22	29	27
Minimal	18	15	20	19
Mild	1	5	8	7
Moderate	1	2	1	0
Severe	0	0	0	1
Mineralization	4	5	14	9
Minimal	3	3	9	3
Mild	1	1	3	3
Moderate	0	1	2	3

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 3 mg/kg/day, dosing was discontinued in study week 91 with necropsy of the remaining animals in study week 100.
c - In study week 66, dosage of males at 10 mg/kg/day was decreased to 6 mg/kg/day. Treatment was discontinued in study week 89 and the remaining animals were sent to necropsy in study week 98.
d - In study week 66, dosage of males at 20 mg/kg/day was terminated and the remaining males were maintained on study without receiving the test article until study week 95.
NA - Not applicable, findings not present.
FD/EE - found dead/euthanized *in extremis*

Vagina: Dose-related increased incidences of mucification occured in the vagina and to a lesser extent in the cervix. Mucification was characterized by the presence of mucus-containing epithelial cells (stratum mucification). The cause of this finding is probably sex hormone related, but it is unclear whether this is an adrenal or ovarian source since in aging female rats pituitary hormone secretion is disrupted and interpretation is confounded by the common occurrence of pituitary tumors.

Table 53: Vagina, Non-Neoplastic Findings

	FD/EE ≤ 18 mo				FD/EE > 18 mos.				Scheduled Necropsy			
Dose Group (mg/kg/day)	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]	0	0.3[b]	1[b]	3[b]
n	19	18	27	30	30	33	24	24	21	19	18	16
Vagina [a]												
Mucification	1	3	5	8	6	10	10	12	9	7	14	10
Minimal	0	3	3	4	4	8	1	7	3	6	10	6
Mild	0	0	2	2	1	2	5	3	6	0	3	3
Moderate	1	0	0	2	1	0	3	1	0	1	1	1
Severe	0	0	0	0	0	0	1	0	0	0	0	0

	Females (all animals)			
Dose Group (mg/kg/day):	**0**	**0.3[b]**	**1[b]**	**3[b]**
n	70	70	69	70
Vagina [a]				
Mucification	16	20	29	30
Minimal	7	17	14	17
Mild	7	2	10	9
Moderate	2	1	4	4
Severe	0	0	1	0

a - Number of tissues (or tissue pairs, if 1 or both were evaluated) examined from each group.
b - At 0.3, 1, and 3 mg/kg/day, dosing continued until study week 103, 101, and 94, respectively, followed by necropsy of the remaining animals in all groups at study week 104.
c - Due to the multiple sites with identical lesions, only the data for the ileum, liver, and femur are tabulated as representatives of the intestinal, vascular, and bony changes, respectively.
NA - Not applicable, findings not present.
FD/EE - found dead/euthanized *in extremis*

Clitoral Gland: There was a dose-related increased incidence in clitoral gland dilatation and inflammation. In males however, there was no dose-related effect for the preputial gland.

Table 54: Clitoral Gland, Non-Neoplastic Findings

Dose (mg/kg/day)	0	0.3	1	3
Clitoral Gland				
n	40	67	67	70
dilatation	37	42	50	58
n	70	67	67	70
inflammation	11	9	15	28

Toxicokinetics

Blood samples from the retro-orbital sinus were collected on days 26 and 179 (weeks 4 and 25) prior to and 2 hours after dosing from vehicle treated (Group 1A) animals (3 animals/sex/group), and at 1, 2, 4, 8, 12, and 24 hours after dosing from Groups 2A-4A animals (3 animals/sex/group). Plasma was analyzed by (b) (4) for CC-10004 and (b) (4) concentrations. There were no samples collected after dose reduction of the main study animals in week 73 (18 months). The lower limit of detection was 1 ng/mL.

Increasing doses of CC-10004 resulted in approximately proportional increases in CC-10004 C_{max} and AUC_{0-24} in females on both days 26 and 179, but less than dose proportional in males at both timepoints. (b) (4) was not detected. As expected, females had substantially greater C_{max} and AUC_{0-24} values than males, one of the reason for the differential dosages for males and females in the study. The C_{max} for the female high dose, 3 mg/kg/day, was 17.8 higher on day 26 than the 3 mg/kg/day (low dose) in males, and this difference was 7.4 higher on day 179. For AUC_{0-24} at this dose, the mean females value was 51.7- and 26.7-fold higher than males on study days 26

and 179, respectively. There was an approximate 2-fold increase in exposure between days 26 and 179 for the low and mid doses in males. There was no differences in exposure between days for females.

Table T1: Summary Of Toxicokinetic Evaluation of CC-10004

	Males			Females		
mg/kg/day	3	10	20	0.3	1	3
Study Day 26						
C_{max} (ng/mL)	38.4	43.3	89.1	87.6	282	684
AUC_{24h} (ng•hr/mL) [a]	106	192	434	389	1491	5485
Study Day 179						
C_{max} (ng/mL)	115	145	115	80.4	242	851
AUC_{24h} (ng•hr/mL) [a]	289	537	608	529	1814	7721

[a] = t ranged from 8 to 24 hours

Dosing Solution Analysis

Homogeneity

Duplicate samples (1 mL each) for homogeneity were collected from vehicle and CC-10004 formulations prepared for use during study weeks 0, 1, 14, 51, 74, 91, and 102, respectively. Prior to the initiation of the first dose, duplicate samples were collected from the top, middle, and bottom strata of the 0.03 and 2.0 mg/mL dosing formulations and stored frozen. From the batch preparations, an aliquot of each dosing formulations was prepared and stored refrigerated for 8 days. Samples collected from the middle stratum were used for determination of time zero concentration. Homogeneity of the dosing formulations was acceptable with %CV within ±15%.

Stability

Results from the middle stratum of 0.03 and 2.0 mg/mL solutions following 8 days of refrigeration (2°C to 8°C) were compared to the time zero concentration analyses for determination of formulation stability and found to be within acceptable limits (5.5% to 10% of nominal concentration).

Concentration

Duplicate samples (1 mL each) for concentration determinations were collected from vehicle and CC-10004 formulations prepared for use during study weeks 0, 1, 3, 12, 15-18, 51, and 68 (with the exception of the Group 4 (high dose)males). Inconsistent assay results were noted during the initial formulation analysis. Although the source of this inconsistency could not be definitively determined, it was thought to be due to analytical variance at lower concentrations, technical errors during dose formulation preparation, and sampling difficulties when obtaining a small aliquot by syringe. Collection of a larger sample volume resulted in more consistent values and resolved the issue.

No CC-10004 was detected in control formulations. The CC-10004 dose formulations were within ±15% (most ±5%) of the target concentrations for 0, 0.03, 0.3, 0.1, 0.6, 1, and 2 mg/mL solutions prepared during weeks 0, 3, 12, 15, 51, 68, 91, and 102. There were a few instances in week 98 in which variability was greater than 15% between the formulation and targeted concentration, but this was unlikely to affect the study results. The CC-10004 concentrations prepared for dosing were acceptable.

9 Reproductive and Developmental Toxicology

Reproductive and Developmental Toxicology studies were were previously reviewed under (b) (4) and are provided in the Appendices (Appendix 2, review of September 7, 2005; Appendix 9, review of July 21, 2009; Appendix 10, review of August 26, 2010, Appendix 11, review of November 24 2010;and Appendix 12, review of April 4 2012).

9.1 Fertility and Early Embryonic Development

Study title: Oral (Gavage) Fertility and General Reproduction Toxicity Study of CC-10004 in Male Mice

Study no.:	**CC-10004-TOX-011**
Study report location:	Mod. 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 1, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-1004, Batch 54560-05, Purity 99.9%; (b) (4)

Study # CC-10004-TOX-011 was previously reviewed Aug 26 2010, for (b) (4) (refer to Appendix 10) by Dr. Carmen Booker.

In this study, male Crl:CD1(ICR) mice (25 mice per dose group) were administered CC-10004 by oral gavage once daily at doses of 0 (vehicle,1% w/v carboxymethylcellulose), 1, 10, 25 or 50 mg/kg/day starting 70 days before cohabitation and continuing through the day of termination at the end of the 3 week mating phase (95-98 days).

An Addendum to the original review of this study is provided here.to discuss Amendment 1 to the study report, signed June 3, 2009 (initiated Jan 16 2008 and completed May 15 2009), which was a histopathological analysis of male reproductive tissues by (b) (4)
This amendment revised the histopathology tables from “necrosis of individual spermatids/residual bodies” in the testes, to cellular debris/residual bodies.” It was not clear as to what was reviewed for this analysis, the text states

"Microscopic examinaition was made of the testes, epididymis, prostate and seminal vesicles, but only testes and epididymides of CC-10004 treated mice."

Additionally, Amendment 2 to the study report, signed Sept 14 2009, corrected the level of (b) (4) impurity in the administered drug.

Histopathology

Histopathology revealed an increase in cellular debris and residual bodies and exfoliated spermatogenic cells, ranging between minimal to mild severity at the high dose, 50 mg/kg/day, however there was no detrimental effect on fertility. Previous identification of cellular debris and residual bodies were minimal or mild in severity, with greater severity in the high dose (Report CC-10004-TOX-001). The finding was also present in some control animals. The expert working group concluded the findings were a normal physiological process, and not caused by CC-10004. From the reviewer's perspective, based on the previously submitted mouse general toxicology and fertility studies to this NDA (Reports 1398/289, 1398 297, 1398/333, 1398 373, CC-10004-TOX-002, CC-10004-TOX-001), there was a consistent increase in these findings at the high doses, regardless of the magnitude of the high dose, and there appears to be, in this reviewer's experience, an increase in incidence in control animals relative to other mouse studies submitted from different applicants. However, despite these findings, there was no detrimental effect on fertility.

Histology Summary

Table 1
Incidence and Degree of Severity of Histomorphologic Observations

Dose Group:	I	II	III	IV	V
Sex:	M	M	M	M	M
Number of Animals/Group:	25	25	25	25	25
TESTES:					
NO. EXAMINED	25	24	25	25	25
NO. NORMAL	18	18	18	17	12
-degeneration, seminiferous tubules, multifocal, unilateral					
minimal	0	0	1	0	0
moderate	0	0	0	1	0
Total Incidence, All Grades	0	0	1	1	0
-degeneration, seminiferous tubules, multifocal, bilateral					
minimal	0	0	0	0	1
Total Incidence, All Grades	0	0	0	0	1
-cellular debris/residual bodies					
minimal	7	6	5	6	10
mild	0	0	1	1	2
Total Incidence, All Grades	7	6	6	7	12
EPIDIDYMIDES:					
NO. EXAMINED	25	25	25	25	25
NO. NORMAL	17	21	21	21	14
-exfoliated spermatogenic cells					
minimal	8	4	4	3	10
mild	0	0	0	1	1
Total Incidence, All Grades	8	4	4	4	11
-hypospermia	0	0	0	1	0
PROSTATE:					
NO. EXAMINED	24	0	0	0	24
NO. NORMAL	22	0	0	0	23
-inflammation, chronic, multifocal					
minimal	2	0	0	0	1
Total Incidence, All Grades	2	0	0	0	1
SEMINAL VESICLES:					
NO. EXAMINED	24	0	0	0	24
NO. NORMAL	24	0	0	0	24

Study title: Combined Oral (Gavage) Fertility and Developmental Toxicity Study of CC-10004 in Female Mice

Study no.:	**CC-10004-TOX-012**
Study report location:	Mod 4.2.3.5.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 24, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-1004, Batch 54560-05, Purity 99.9%; (b) (4)

Study CC-10004-TOX-012 was previously reviewed Aug 26, 2010 for (b) (4) (refer to Appendix 10) by Dr. Carmen Booker.

In this study, female Crl:CD1(ICR) mice (25 mice per dose group) were administered CC-10004 by oral gavage once daily at doses of 0 (vehicle,1% w/v carboxymethylcellulose), 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through DG 15.

An Addendum to the original review of this study is provided here to present data for the findings of reduced maternal body weight gain which occurred later during gestation, after there was an increase in weight gain during the initial dosing in CC-10004-treated group, as well as to present select data in tabular form. The presented data include maternal body weight and weight gain, estrous and mating parameters, embryofetal effects, and skeletal variations in tabular formats.

Additionally, Amendment 2 to the study report, signed Sept 14 2009, corrected the level of (b) (4) impurity in the administered drug.

Body Weight

Body weights gain was increased in all the C-10004 treatment group during the initial dosing period prior to cohabitation and mating, as noted in the original review. Additionally, body weight gain was less than control weight gain during the second week of gestation, and was attributed to embryofetal loss in the 40 and 80 mg/kg/day groups. This correlated with increased litter resorption in these groups.

Maternal Body Weights (selected days)

Dose (mg/kg/day)	**0 (vehicle)**	**10**	**20**	**40**	**80**
Precohabitation Phase (Dosing)					
Body Weight					
N	25	25	25	25	25

Day 1	27.0	26.8	27.1	27.0	26.7
Day 8	27.0	26.3	27.8	27.8	27.9
Day 15	27.3	28.1	28.6	28.5	28.3
Body Weight Gain					
Day 1-8	0.0	-0.5	**0.7**	**0.8**	**1.2**
Day 8-15	0.4	1.8	0.8	0.7	0.4
Day 1-15	0.3	**1.3**	**1.5**	**1.5**	**1.6**
Gestation					
Body Weight					
Day 0	27.5	28.2	28.7	28.9	28.9
Day 6	29.6	30.4	**31.0**	**31.1**	**31.0**
Day 16	47.3	49.6	50.7	45.6	46.2
Day 18	54.5	56.6	57.7	51.1	51.3
Body Weight Gain					
Days 0-6	2.1	2.2	2.3	2.2	2.1
Days 0-16	19.8	21.4	22.0	16.7	**17.3**
Days 16-18	7.2	7.0	7.0	**5.5**	**5.1**
Days 0-18	27.0	28.4	28.9	22.2	**22.4**
Bold values, significantly different from vehicle control, p<0.05					

Estrous and Mating Parameters

Dose (mg/kg/day)	**0 (vehicle)**	**10**	**20**	**40**	**80**
Estrous Cycles					
N	25	25	25	25	25
Predosing (14 days)	2.6	3.0	2.9	2.6	2.8
N with ≥6 consecutive days of diestrus	1	0	0	0	1
Precohabition (14 days)	2.8	2.6	2.8	**2.2**	**2.3**
N with ≥6 consecutive days of diestrus	1	0	3	0	**5**
Mating					
N cohabitating	**25**	**24**	**25**	**25**	**25**
Means Days in Cohabitation	1.9	1.9	3.4	2.8	4.3
N, Mated	25 100%	24 100%	25 100%	25 100%	25 100%
Fertility Index (N pregnancies / N mated)	100% 25/25	75% 18/24	92% 23/25	88% 22/25	88% 22/25
Bold values, significantly different from vehicle control, p<0.05					

Summary of Embryofetal Effects

Dose (mg/kg/day)	0 (vehicle)	10	20	40	80
Pregnant	**25**	**18**	**23**	**22**	**22**
Implantations	12.6	13.2	14.7	14.0	14.6
Litter Size	11.4	11.9	12.0	9.3	**8.9**
Live Fetuses/Litter	11.4	11.9	12.0	10.2	9.8
Dead Fetuses, N N/Litter	1 0.0	0 0.0	1 0.0	2 0.1	0 0.0
Early Resorptions, N, N/Litter	28 1.1	20 1.1	55 2.6	**81** **3.8**	**134** **6.1**
Late, Resorptions, N, N/Litter	1 0.0	2 0.1	1 0.0	1 0.0	0 0.0
Mice with all conceptuses dead or resorbed	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	2 (9.1)
% Dead or Resorbed Conceptuses/Litter	10.4	9.8	19.0	**26.6**	**31.8**
Bold values, significantly different from vehicle control, p<0.05					

Skeletal Variations

Dose (mg/kg/day)	0 (vehicle)	10	20	40	80
Ossificiation Sites					
Skull: Supraoccipital Litter incidence, N (%) Fetal incidence, N (%)	 1 (4.2) 1 (0.7)	 0 (0.0) 0 (0.0)	 1 (4.8) 1 (0.7)	 **2 (11.1)** **2 (2.0)**	 **4 (20.0)** **4 (3.9)**
Tarsals Mean Ossification sites/Limb	0.81	**0.44**	**0.38**	**0.34**	**0.14**
values in bold indicate significantly different from controls, p<0.05.					

Study title: Histopathology Expert Report

Study no.:	**CC-10004-histoexpertreport**
Study report location:	**Mod 4.2.3.5.1**
Conducting laboratory and location:	(b) (4)
Date of study initiation:	**not indicated, Report signed June 9, 2009**

Key Study Findings

Refer to Appendix 10 for the July 21, 2009 review of this study by Dr. Barbara Hill. An Addendum to the original review of this study is provided here to present additional commentary to the applicant's conclusions.

- A peer review was conducted by a pathologist to evaluate tissue slides and organ weight data of the mouse testis and epididymis findings in Reports CC-10004-TOX-001 and CC-10004-011. For comparison purposes tissues were also examined from previously conducted mouse general toxicology studies that included the 3-month study Report CC-10004-TOX-002 and the 6-month study Report CC-10004-TOX-004.
- The review was conducted by (b) (4) at (b) (4) Whether the peer review was "independent" as stated by the applicant is questionable since the two fertility studies were conducted by (b) (4) although at a different location.
- The conclusion of the peer reviewer was that the microscopic finding originally recorded in the testis (necrosis, individual spermatid/residual bodies) was cellular debris from residual bodies and there were no microscopic findings attributed to the administration of CC-10004 in the testis and epididymis of animals examined and no effects on sperm parameters.
- During the peer review process, the incidence of the microscopic finding in the epididymides was revised and found to be comparable between males in the 50 mg/kg/day group compared to control animals. The microscopic finding originally recorded in the testis (necrosis, individual spermatid/residual bodies) was regarded to be cellular debris from residual bodies. The Histopathology Expert Report states that although the incidence of the prominent cellular debris/residual bodies was slightly higher in male mice given 50 mg/kg/day compared to controls, this change graded minimal to mild in severity was interpreted to be a normal physiological process. The report cited a widely used reference (Russell, 1990), that indicated the debris of normal spermatogenesis is known to stain deeply in virtually all sections and may be confused with degenerating cells.
- Also, the histopathological slides for the testes and epididymides from control and 1000 mg/kg/day animals from the 90 day and 6 month mouse toxicity studies (CC-10004-TOX-002 and CC-10004-TOX-004, respectively) were evaluated. The peer reviewer concurred with the conclusions in the final reports of these studies concerning CC-10004 related microscopic findings in the testes and epididymides.
- While the NDA reviewer accepts the findings of the applicant and the peer reviewer, that there were no differences between histological findings of control and CC-10004 treated animals, the interpretation that the findings were not CC-10004-related cannot be determined due to the high incidence of adverse findings in the control animals. In the majority of toxicological studies, there are no adverse findings in control animal testis and epididymis. The peer reviewer also cited a study (Creasy, 2001) that indicated the ease in which testicular

tissue may be damaged resulting in the findings noted above during processing the tissue. However, this was misinterpreted as evidence of a common control finding by the peer reviewer. Furthermore, tissues at the mid and low doses in the long term toxicology studies used for comparison were not evaluated which could have helped determine if the findings were artifact or drug-related.

- Despite the above concerns, functional tests of fertility in the mouse, indicated no deficits in fertility, and there is no need for additional histopathological assessments.

9.2 Embryonic Fetal Development

MOUSE

Study title: CC-10004: Oral (Gavage) Study of Embryo-Foetal Development in the Mouse

Study no.:	1398/309
Study report location:	Mod 4.2.3.5.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 19, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, batch FP0032, purity 97.57

Key Study Findings

Study 1398/309 was previously reviewed Sept 7 2005 for (b) (4) (refer to Appendix 2) by Dr. Paul Brown. In this study, CC-10004 was administered orally by gavage to pregnant CD-1 mice from GD 6 through 15 at doses of 0 (vehicle), 250 500 or 750 mg/kg/day.

An Addendum to the original review of this study is provided here to present selected data of the effects of CC-10004 on dams and their fetuses in a tabular format.

Summary of Effects on Dams in Mice (selected parameters)

Dose (mg/kgday)	**0 (Vehicle)**	**250**	**500**	**750**
N	48	24	24	24
N Pregnant (% of control)	44 (91.7%)	21 (87.5%)	21 (87.5%)	22 (91.7%)
Mortalities	0	0	0	1
Body Weight Change				
GD 6-15 (% of control)	52.2	**48.2 (92%)**	**44.6 (85%)**	**39.6 (76%)**

GD 15-18	23.6	21.3	23.1	20.8
GD 4-18	102.6	92.9	88.9	83.1
Food Consumption				
GD 6-14, g/animal/day (% of control)	9.2	**8.0** **(87%)**	**6.8** **(74%)**	**7.0** **(76%)**
Uterine Weight				
Gravid uterus, g (% change)	21.8 g	**17.6** **(81**	**16.9** **(77%)**	**17.1** **(78%)**
% body wt change (corrected for uterine weight)	34.6	36.2	36.2	35.0
Embryofetal Effects				
N of Females with Total Litter Loss (% of pregnant)	4 (9%)	3 (14%)	2 (9.5%)	**6** (27%)
N with live fetuses on GD 18 (% of pregnant)	36 (82%)	17 (81%)	18 (86%)	**15** **(68%)**
Mean N Corpora Lutea	13.4	14.3	15.4	13.1
Mean N Implantation sites	12.4	12.3	12.7	12.9
Mean % Preimplantation Loss N dams affected	7.2 19	14.0 13	16.9 14	11.5 11
Mean % Postimplantation Loss N dams affected	18.9 29	**31.7** **19**	**26.1** **20**	**41.4** **19**
Mean N Early Intrauterine Deaths	1.3	3.1	2.5	4.5
Mean N. Late Intrauterine Deaths	0.3	0.5	0.6	0.5
Mean N Fetuses/Female	10.8	8.8	9.5	7.9

Summary of Effects on Fetuses in Mice

Dose (mg/kgday)	**0** **(Vehicle)**	**250**	**500**	**750**
N	**48**	**24**	**24**	**24**
Pregnant	44 (91.7%)	21 (87.5%)	21 (87.5%)	22 (92%)
N Litters Evaluated (% of pregnant)	36 (81.8%)	17 (81%)	18 (85.7%)	**15** **(68%)**
N Live Fetuses	433	175	190	165
Mean N of Dead Fetuses (mean/litter) N dams affected	0.0 1	0.1 1	0.1 2	0.1 1
Number of male fetuses	214	93	106	88

Number of female fetuses	219	82	84	77
Mean % male fetuses	49.3	52.0	55.5	53.7
Mean litter weight (g)	17.27	**13.84 (80%)**	**13.26 (77%)**	**12.87 (74%)**
Mean placental weight (g)	0.11	0.11	**0.10**	**0.10**
Mean fetal weight (g)	1.45	**1.37 (94%)**	**1.28 (88%)**	**1.22 (84%)**
Mean fetal weight (g) -males only	1.47	**1.40**	**1.31**	**1.23**
Mean fetal weight (g) -females only	1.42	**1.35**	**1.24**	**1.21**

Summary of External, Visceral, and Skeletal Defects

Dose (mg/kgday)	**0 (Vehicle)**	**250**	**500**	**750**
EXTERNAL/VISCERAL DEFECTS				
N fetuses examined	433	175	190	165
N litters examined	36	17	18	15
N malformations	5	4	5	2
Mean % of fetuses	1.4	2.2	2.3	1.1
Number of litters affected (% of pregnant)	5 (13.8%)	4 (23.5%)	5 (27.8%)	2 (13.3%)
N with variations	69	23	48	36
Mean % of fetuses	17.0	12.9	24.8	21.2
N litters affected (% of litters examined)	32 (88.9%)	11 (64.7%)	17 (94.4%)	14 (93.3%)
SKELETAL DEFECTS				
N of fetuses examined	291	117	128	109
N of litters examined	36	17	18	15
N with malformations	3	2	4	2
Mean % of fetuses examined	0.9	1.5	2.5	1.5
N litters affected (% of litters examined)	3 (8.3%)	2 (11.8%)	4 (22.2%)	2 (13.3%)
N with variations	218	97	123	108
Mean % of fetuses examined	75.7	84.9	94.6	97.8
N litters affected (% of litters examined)	36 (100%)	17 (100%)	18 (100%)	15 (100%)

Total number of fetuses with malformations	5	4	5	3
% of fetuses examined	1.2	2.3	2.6	1.8
N of litters affected (% of litters examined)	5 (13.9%)	**4** **(23.5%)**	**5** **(27.8%)**	**3** **(20.0%)**

Summary of Fetal Skeletal Effects

Dose (mg/kg/day)	**0 (Vehicle)**	**250**	**500**	**750**
Litters Evaluated	**36**	**17**	**18**	**15**
Number of Litters with Skeletal Malformations	3	2	4	2
Skull – Frontal, ossification incomplete	1	9	22	28
Skull – Hyoid arch, ossification incomplete	2	3	3	5*
Skull – Frontal, ossification incomplete	1	**9**	**22**	**28**
Skull – Parietal, ossification incomplete	12	15	**23**	**17**
Skull – Supraoccipital, ossification incomplete	14	**57**	**89**	**100**
Sternebra – Additional ossification site between 5/6	-	2	**9**	**6**
Sternebra – Ossification centers not fused	4	**9**	**18**	**29**
Sternebra – Ossification centers incompletely fused	1	3	**5**	**10**
Sternebra – Ossification incomplete	1	1	**6**	**23**
Sternebra – Unossified	-	-	-	**9**
Vertebral, lumbar centrum – Ossification incomplete	-	**4**	**3**	**4**
Vertebral, thoracic centrum – Ossification incomplete	3	5	**9**	3
Vertebral, thoracic centrum – Unossified	-	-	3	**10**
- = No noteworthy findings Values in bold type indicate significant difference from controls, p< 0.05				

RABBIT

Embryofetal studies in rabbits were previously reviewed for [redacted] (b) (4) September 7 2005 (Appendix 2) for the November 24, 2010 review of this study by Dr. Paul Brown. No adverse effects were observed but this was associated with the lack of adequate systemic exposure with the oral dosing route of administration. Further studies indicated that adequate systemic exposure of CC-10004 could not be obtained due to poor bioavailability even at doses up to 1000 mg/kg/day (Reports 1398/290, 1398/291, and 1398/292). An intravenous infusion dose-range finding study (Report CC-10004-TOX-009) resulted in excessive toxicity and mortality. Therefore, the rabbit was not an appropriate species for CC-10004 study. The toxicities leading to maternal deaths following intravenous administration were not defined, as there were no clinical pathology or histopathology assessments. However, the sponsor acknowledged that in retrospect, the vehicle formulation was not suitable for a developmental study in rabbits due to the presence of ethanol, a know teratogen and neurotoxicant. In addition, the level of compounds comprising the vehicle were not supported for the IV route of administration.

Report 1398/292 mentioned that possible causes of poor bioavailability (e.g., absorption, metabolism) or instability in frozen samples stored prior to analysis were being investigated. Report 1398/261 found that the metabolism of CC-10004 by rabbit microsomes under in vitro conditions occurred faster than the other species examined (rabbit>>monkey>mouse=male rat>human>dog>female rat), but it is doubtful this would explain why samples were not detectable at the first sampling timepoint.

MONKEY

Based on the inability to successfully study CC-10004 toxicity in embryofetal developmental studies in rabbits, the sponsor conducted the second species embryofetal development study in the cynomolgus monkey.

Study title: Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey

Study no.:	CC-10004-TOX-013
Study report location:	Mod 4.2.3.5.2
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	December 10, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, Batch 59692-07, Purity 99.6%

Study # CC-10004-TOX-013 was previously reviewed under [redacted] (b) (4) (refer to Appendix 11 for the November 24, 2010 review of this study by Dr. Carmen Booker). The addenum presented here presents information not previously included that supports placental transfer of CC-10004.

In this study, pregnant cynomolgus monkeys were orally administered CC-10004 at doses of 20, 50, 200 or 1000 mg/kg/day, once daily, from GD 20 to GD 50. Fetuses were examined after Cesarean section on GD 100.

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Placental passage of CC-10004

- On the day of cesarean section, CC-10004 was administered to examine maternal-fetal transfer. A single maternal blood sample and a sample from the umbilical cord was obtained at 5 hours after maternal dosing.
- Fetal blood concentrations were approximately 40% of the maternal concentration. The time of sampling was expected to be approximately at the T_{max} based on GD 20 and 50 analysis.

Summary of Maternal:Fetal Toxicokinetic Concentrations

Dose (mg/kg/day, from GD 20-50)	**0**	**20**	**50**	**200**	**1000**
N	**17**	**14**	**9 or 10**	**8**	**2 or 3**
Maternal Concentration (ng/mL)	BLOQ	650± 853	748± 307	421± 139	429± 185
Fetal Concentration (ng/mL)	BLOQ	176± 161	253± 113	165± 83	130± NC
Fetal:Maternal Ratio	NA	0.3± 0.1	0.4± 0.1	0.4± 0.1	0.4± NC
BLOQ: below the limit of quantitation (<1.00 ng/mL). NA: Not Applicable NC Not Calculated					

9.3 Prenatal and Postnatal Development

Study title: Oral (Gavage) Developmental and Perinatal/Postnatal Reproduction Toxicity Study of CC-10004 in Mice, Including Maternal Function and Postnatal Behavioral/Functional Evaluation

Study no.:	CC-10004-TOX-1139
Study report location:	Module 4.2.3.5.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 11, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, Batch 82633-09, Purity 99.4% (b) (4)

Key Study Findings

- CC-10004 was administered orally (via gavage) to pregnant female Crl:CD1(ICR) mice (25/group) at doses of 0 (1% w/v aqueous carboxymethylcellulose), 10, 80, or 300 mg/kg/day from day 6 of gestation (DG 6) through day 20 of lactation (DL 20). In mice that did not deliver a litter, dosing ended on DG 22.

Maternal (F_0) Generation

- There were mortalities in the high dose group associated with difficulty in delivering at 300 mg/kg/day (1 death, evidence indicating it occurred during delivery), and overt clinical observations including those associated with difficulty in delivering at 80 and 300 mg/kg/day (pale ears, hunched posture, mild dehydration, dyspnea, hyperpnea, and in 1 high dose animal the occurrence of clonic convulsion).
- The high dose group had reduced maternal body weight and weight gain compared to the control group. Reductions in maternal body weights on DLs 4 and 14 (5% to 10% below control) and reductions in body weight gain on DGs 12 to 15 and 15 to 18 (11% to 17% below control) and DLs 1 to 4 and 7 to 14 (59% to 55% below control) at 300 mg/kg/day.
- There were no effects of apremilast on the duration of pregnancy, number of pregnant mice at the end of the gestation period and the number of mice that delivered a litter.
- Maternal NOAEL was 10 mg/kg/day, due to early abortions, premature delivery and associated dystocia.

F_1 Generation

- Increased postnatal pup mortality on DLs 1 through 7 included increased stillbirths, missing and presumed cannibalized pups, pups found dead or sacrificed due to adverse signs, and correlated with decreases in pup viability index (85% for the mid dose and 57% for the high dose compared to 98.6% for the control group) and live litter size at DL 21 (10.2 for the mid dose and 8.4 for the high dose, compared to 13.4 for the control group). This was based on 3 dams at 80 mg/kg/day and 9 dams at 300 mg/kg/day that had lost all pups by DL 5.
- Surviving pup mean body weights per litter through DL 7 at 80 and 300 mg/kg/day were reduced compared to controls (87.5% and 75% of mean control weights, respectively), however by day 21 (weaning) and thereafter, there were no differences from control group body weights. Pups that died had a dose-related increase incidence in the absence of milk in their stomachs.
- There were no effects of F_0 treatment with apremilast on the F_1 generation for clinical or necropsy observations after weaning; body, testes or epididymis weights; sexual maturation; passive avoidance; motor activity; mating; fertility or F2 embryofetal parameters.
- The NOAEL for the F_1 generation was 10 mg/kg/day due to early postnatal mortality.

Methods	
Doses:	0, 10, 80 and 300 mg/kg/day
Frequency of dosing:	Once daily from GD 6 through day 20 of LD 20, or LD 22 if mice did not deliver a litter
Dose volume:	10 mL/kg
Route of administration:	Oral, by gavage
Formulation/Vehicle:	1% w/v aqueous carboxymethylcellulose
Species/Strain:	Mouse, Crl:CD1(ICR)
Number/Sex/Group:	25/dose group for F_0 and F_1 generationse
Satellite groups:	There were no satellite groups.
Study design:	Refer to tables below

F_0 Generation Mating and Dosing

Within dose groups, one male and one female mouse were cohabitated for a maximum of 5 days. Female mice with a copulatory plug observed *in situ* were considered to be at GD 0 and assigned to individual housing.

Dosage Group	Number of Mice	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	F0 Generation Mouse Numbers
I	25	0 (Vehicle)	0	10	2301 - 2325
II	25	10	1	10	2326 - 2350
III	25	80	8	10	2351 - 2375
IV	25	300	30	10	2376 - 2400

[a] The test article was considered 100% active/pure for the purpose of dosage calculations.

F_0 Generation Mice	**Dates**
Arrival	12 Apr 2011
Cohabitation Period	20 Apr 2011 PM - 25 Apr 2011 AM
Day 0 of Gestation	21 Apr 2011 - 25 Apr 2011
***Dosage Period* (DG 6 through DL 20) or DG 22** (for mice that did not deliver a litter)	27 Apr 2011 - 02 Jun 2011
Delivery Period (DL 1)	09 May 2011 - 16 May 2011
DG 23 Sacrifice (for mice that did not deliver a litter)	14 May 2011
DL 21 Sacrifice (for dams and litters not selected for continued evaluation)	29 May 2011 - 03 Jun 2011

F_0 Observations

- Mortality observations were made twice daily.
- Clinical observations, as well as observations for abortions, premature deliveries, and deaths were made 1-2 hours after dosing
- Body weights were recorded daily during the dosing period.
- Observations were recorded for adverse clinical signs during parturition,

duration of gestation (DG 0 to the day the first pup was observed), litter sizes (all pups delivered) and pup viability at birth. • Maternal behavior was evaluated on DLs 1, 4, 7, 14, 18, and 21. Abnormal maternal behaviors were also recorded when observed at other times. • Dams with no surviving pups were sacrificed after the last pup was found dead or missing, presumed cannibalized. A gross necropsy of the thoracic, abdominal, and pelvic viscera was performed and implantation sites were recorded. Mice that died or were sacrificed before scheduled termination were examined for the cause of death or condition. • Gross lesions were retained for histopathology and a random set of normal comparative tissues were also retained.	
Deviation from study protocol:	Procedural deviations occurred but were general minor in nature and had no overall impact on the study interpretation and conclusions.

Observations and Results

F_0 DAMS

F_0 Survival

One dam in the 300 mg/kg/day group (#2395) was found dead on gestation day 19 after delivering 2 pups (preterm delivery). Necropsy of this animal revealed an additional 2 fetuses and 9 early resorptions and one late resorption. Clinical observations before death included red peri-vaginal substance, hyperpnea, and a clonic convulsion (5 seconds in duration). Body weight gain during gestation was within the range of other mice and tissues appeared normal at necropsy. This death was considered to be related to apremilast treatment.

Three dams in the vehicle control group were found dead (#2304 on day 15, #2305 on day 17, and #2324 on day 13), and one dam in each of the 10 and 80 mg/kg/day dosage groups were sacrificed due to adverse clinical observations mid-lactation (10 mg/kg/day: #2341 on day 16, and 80 mg/kg/day: # 2362 on day 16). These deaths were attributed to lactational ileus due to necropsy findings and clinical observations. At necropsy, the stomachs or intestines were distended with gas and/or brown granular material. Associated clinical observations included abdominal distention, dyspnea, bradypnea, hyperpnea, tachypnea, dehydration, lost righting reflex, decreased motor activity, ungroomed coat, lacrimation, and cold to touch. The occurrence of lactational ileus was not considered to be related to apremilast treatment by the reviewer. Additionally, one dam in the vehicle control group was sacrificed following an intubation error.

Table 55: Observations in Mice that Were Found Dead or Sacrificed Due to Adverse Clinical Observations, (from Sponsor's Table 6)

Mouse Number	Dosagea	Day of Death	Mode of Death	Noteworthy Clinical History	Gross Necropsy Findings	Cause of Death
2318	0	DL 9	SAC	Decreased motor activity, impaired righting reflex, head tilt, bradypnea and barrel-rolling, ~ 35 to 45 min postdose.	Trachea perforation	Intubation error
2304	0	DL 15	FD	None	Intestines distended with gas	Lactational ileus
2305	0	DL 17	FD	Mild to moderate dehydration, abdominal distention, tachypnea, hyperpnea, ungroomed coat, decreased motor activity,	Intestines distended with gas	Lactational ileus

				chromodacryorrhea.		
2324	0	DL 13	FD	None	Intestines distended with gas	Lactational ileus
2341b	10	DL 16	SAC	Hyperreactivity to touch, swollen and/or splayed hindlimb, limited use and muscle atrophy of hindlimb, irregular gait, loss of righting reflex, abdominal distention, dyspnea, bradypnea. Body weight loss DL 15 to 16: 14%.	Stomach distended with gas; Intestines distended with brown granular material.	Lactational ileus
2362c	80	DL 16	SAC	Lacrimation, ptosis, moderate dehydration, abdominal distention, bradypnea, decreased motor activity, low carriage, cold to touch. Body weight loss DL 15 to 16: 12%.	Intestines distended with brown granular material.	Lactational ileus

DL = Day of Lactation, SAC = Sacrificed; FD = Found Dead
a mg/kg/day
b Litter consisting of 14 pups was retained.
c Litter consisting of 11 pups was retained.

F_0 Clinical signs

Except for signs of lactational ileus described above, the only adverse clinical signs occurred in 2 dams with difficulty delivering, (#2362 and #2395 in the 80 and 300 mg/kg/day dose groups, respectively). These observations included pale ears, hunched posture, mild dehydration, dyspnea, clonic convulsion, and hyperpnea.

F_0 Body weight

During the F_0 gestation period, although mice gained weight, the body weight gain was slightly reduced for female mice in the 300 mg/kg/day group, but there was no dose-dependent trend in body weight gain and no overall difference between groups over the entire gestation period.

During the last week of lactation and dosing, there was a slight increase in body weight (106-112%) in all CC-10004 treatment groups.

Table 56: F_0 Body Weights during Gestation

Dose (mg/kg/day)	**0**	**10**	**80**	**300**
N	**25**	**25**	**25**	**25**
N, pregnant	**22**	**21**	**22**	**23**
Gestation				
Day				
0	27.8	27.7	27.8	27.8
6 (dosing day 1)	31.0	31.0	30.9	30.7
7	31.8	31.8	31.5	30.9
8	32.4	32.6	32.4	32.1
9	33.6	33.6	33.5	33.3
10	35.2	35.3	35.3	34.9
11	37.4	37.5	37.7	37.1
12	40.0	39.9	40.3	39.6
13	42.6	42.1	42.8	42.2
14	45.5	44.9	46.2	44.4
15	49.4	48.7	49.4	47.4
16	53.3	52.7	53.3	50.9
17	57.4	56.4	56.7	54.0
18	60.7	58.9	61.4	57.9 **(95%)**
Weight gain				
days 0-6	3.2	3.3	3.1	3.0
days 6-18	29.9 n=17	28.2 n=15	30.4 n=18	27.2 (91%) n=18
days 0-18	32.9 n=17	31.4 n=15	33.6 n=18	30.1 (91%) n=18
Lactation				
delivered a litter, n	**22**	**20**	**22**	**22**
day				
1	36.5	36.5	37.0 (101%)	36.8 (101%)
4	39.9	40.8	39.5 (99%)	**38.1 (95%)**
7	42.5	43.0	41.4 (97%)	**40.8 (96%)**
14	47.6	47.6	45.2 (95%)	**43.0 (90%)**

21	43.1	**45.7 (106%)**	**48.1 (112%)**	**46.8 (108%)**
Weight change				
days 1-4	3.4	4.3	2.3 n=20	**1.4** n=13
days 4-7	2.6	2.2	1.7 n=19	2.7 n=13
days 7-14	5.1 n=20	4.6	3.8 n=19	**2.3** n=13
days 14- 21	-4.9 n=18	**-1.7** n=19	**3.0** n=18	**3.8** n=13
days 1-21	6.3 n=18	**9.2** n=19	**10.9** n=18	**10.1** n=13
• Excludes values for dams that were found dead, sacrificed due to adverse clinical observations or no surviving pups. • **Bold values**, significantly different than controls, p<0.5 or greater				

F_0 Feed consumption

Food consumption was not monitored.

F_0 Parturition

The pregnancy rate was similar between the control group (88%) and all CC-10004 treated groups (84% to 92%). Except for 1 dam in the low dose and 1 dam in the high dose groups, all pregnant dams delivered a litter with no differences in group mean gestation length.

Natural delivery and litter observations were unaffected by treatment at 10 mg/kg/day. One mouse (#2326) in the 10 mg/kg/day dosage group did not deliver, but was found to be pregnant with two early resorptions in utero at sacrifice on DG 23; this event was not regarded as treatment-related. Mouse #2395 in the 300 mg/kg/day dosage group died during delivery on DG 19, as described in the F_0 survival section, above.

There was no effect of CC-10004 treatment on the numbers of dams delivering litters, the duration of gestation, number of pregnant mice at the end of gestation, averages for implantation sites per delivered litter, the gestation index (number of dams with one or more liveborn pups/number of pregnant mice) and percent male pups per number of pups sexed per litter.

Table 57: Maternal (F_0) Effects of CC-10004 Administeration

Dose (mg/kg/day)	**0**	**10**	**80**	**300**
N	**25**	**25**	**25**	**25**
N, pregnant	22 (88%)	21 (84%)	22 (88%)	23 (92%)
Delivered a litter, N	22 (100%)	20 (95.2%)	22 (100%)	22 (95.6%)
Dams with stillborn pups, N, (%)	0 (0.0%)	2 (10.0%)	**6 (27.3%)**	**8 (38.1%)**
Dams with no liveborn pups, N, (%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.8%)
Gestation Index, %, N/N (N with live offspring/N of pregnant mice)	100.0% 22/ 22	95.2% 20/ 21	95.4% 21/ 22	95.2% 20/ 21c
Dams with all pups dying, day 1-4 postpartum, N, (%)	0 (0.0%)	0 (0.0%)	1# (4.5%)	7# (31.8%)**
Dams with all pups dying days 5-21 postpartum, N, (%)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)

3 dams in the 80 mg/kg/day dosage group and 9 dams in the 300 mg/kg/day groups had no surviving pups on DLs 1, 2 or 5.

Bold values indicate significantly different from controls, $p<0.05$

F_0 Necropsy observation

There were no CC-10004 gross findings, and therefore the sponsor indicated there was no histopathology conducted on the retained tissues.

F_0 Toxicokinetics

Blood samples for toxicokinetic analysis were not collected.

Dosing Solution Analysis

Homogeniety: The CC-10004 dosing formulations were homogeneous with a percent relative standard deviation (%RSD) for the first analysis of the first preparation ranging from 1.2% to 5.7%. Re-suspension homogeneity of the first preparation dosing formulations was also evaluated following 7 days of refrigerated storage, with %RSD for group ranging from 3.0 to 4.5%.

Concentration Analysis: The CC-10004 dosing formulations were formulated within -10.4 to -1.2% of targeted concentrations of 1, 8, and 30 mg/mL. There was no detectable CC-10004 in the analyzed vehicle administered to the control group.

F_1 GENERATION

Table 58: Evaluations of the F_1 Generation

Methods

Doses:	None, F_1 from maternally dosed animals
Number/Sex/Group:	25/dose group Litters were not culled during the lactation period. At weaning on postpartum day 21, F_1 mice were randomly selected to dose groups (25/sex) for continued evaluation incorporating at least 1 male pup and 1 female pup/litter, when possible.
Satellite groups:	None
Study design:	Refer to tables below

F_1 Generation Mice	**Dates**
Passive Avoidance (Session 1)	01 Jun 2011 - 05 Jun 2011
Passive Avoidance (Session 2)	08 Jun 2011 - 12 Jun 2011
Motor Activity (Postpartum Day 22 and 61)	30 May 2011 - 04 Jun 2011
Motor Activity (Postpartum Day 61 ± 2)	07 Jul 2011 - 15 Jul 2011
Fertility Assessment	
Cohabitation Period	17 Aug 2011 PM - 31 Aug 2011 AM
DG 0	18 Aug 2011 - 30 Aug 2011
Male Mice Sacrificed	12 Sep 2011
DG 13 Caesarean-Sectioning	31 Aug 2011 - 13 Sep 2011

Litters of mice that died or were sacrificed before scheduled termination were necropsied, with the exception of the litters of dams 2341 and 2362 in the 10 and 80 mg/kg/day dosage groups, respectively. These pups were retained and monitored beyond postpartum day 21 at the request of the Study Director.

F_1 General Methods and Assessments

- Day 1 of lactation (postpartum) was defined as the day of birth.
- Individual pup body weights were recorded on DLs 1, 4, 7, 14, 18 and 21, then weekly after weaning.
- Each litter was evaluated for viability at least twice daily and pups in each litter were counted once daily.
- Clinical observations were recorded once daily during the preweaning period.
- Female mice were evaluated for the age of vaginal patency, beginning on day 21 postpartum.
- Male mice were evaluated for the age of preputial separation, beginning on

day 27 postpartum.

- Passive avoidance test for learning, short-term retention, and long-term retention was assessed from day 23 ± 1 day postpartum with 1 male and 1 female from each litter, where possible
- Motor activity was evaluated on days 22 and 61 (± 2 days) postpartum. One male and 1 female (when possible) from each litter were examined throughout the two testing periods.
- At approximately 90 days of age, the F_1 generation mice within each dosage group were assigned to cohabitation, 1 male mouse per female mouse, with the exclusion of sibling matings. The cohabitation period occurred for a maximum of 14 days, followed by removal and individual housing of females with copulatory plugs.
- All male mice were necropsied after completion of the cohabitation period, and testes and epididymides were weighed.
- On DG 13, female mice were necropsied. Female mice without a confirmed mating date were sacrificed on an estimated DG 13 and the uteri of apparently nonpregnant mice were examined to confirm the absence of implantation sites.
- The number and distribution of corpora lutea were recorded. The uterus of each mouse was examined for pregnancy, number and distribution of implantation sites, and viable and nonviable embryos.

F_1 Survival:

There was a significant increase in the number of stillborn pups from dams of the mid and high dose groups. This also contributed to a reduction in the number of liveborn pups (total and average pup numbers) in the mid and high dose groups, and the resultant reduced live litter size in the high dose group.

F_1 pup survival and weight were reduced in dams in the 80 and 300 mg/kg/day groups. During the first week postpartum (DL 1, 2, and 4 to 7), the numbers of pups found dead, sacrificed due to adverse signs or missing and presumed cannibalized were increased in the mid and high dose groups. As noted earlier, dead pups in the 80 and 300 mg/kg dose groups lacked the presence of milk in their stomachs. The viability index (N live pups on day 4 postpartum/N live born pups on day 1 postpartum) was reduced in the mid and high dose groups compared to the vehicle control. Also the lactation index (N live pups on day 21, weaning, postpartum/ N live pups on day 4 postpartum) was reduced in the mid and high dose groups.

Table 59: Summary of F_1 Litter Characteristics and F_1 Pup Survival

Dose (mg/kg/day)	**0**	**10**	**80**	**300**
N	**25**	**25**	**25**	**25**
N, pregnant	22	21	22	23

	(88%)	(84%)	(88%)	(92%)
Delivered a litter, N	22 (100%)	20 (95.2%)	22 (100%)	22 (95.6%)
Mean delivered litter size	13.5	13.6	12.2	11.2*
Mean number of liveborn pups	13.5	13.4	**11.2****	**10.0****
Mean number of stillborn pups	0	0.2	**1.0***	**1.0****
Pups with unknown vital status	0	1	2	6
% pups found dead, sacrificed early, or missing/cannibalized				
Day 1	0.7	0	11.9	**34.7****
Days 2-4	0.7	1.1	3.4	**13.1****
Days 5-7	0	0.4	**2.0****	**1.8****
Viability Index	98.6	98.9	85.1	**56.8****
Lactation Index	100	98.5	**97****	**96.5****
Live litter size (DL 21)	13.4	13.0	**10.2****	**8.4****

F_1 Clinical signs:

There were no abnormal findings in F_1 offspring related to CC-10004 treatment of F_0 dams

F_1 Body weight:
Pup body weights were significantly reduced during the first week of lactation in pups from dams of the 80 and 300 mg/kg/day dose groups. By day 21 and thereafter, there were no meaningful differences in body weights between groups. By three months of age weight gain in the high dose animals was significantly greater than controls, although only 1 to 2 grams. This may indicate a prolonged effect or possible permanent change in weight regulating behavior long after dosing of CC-10004 ended. However, since only 2 litters were followed beyond 21 days of age, further studies would be need to verify this.

Table 60: F_1 Body Weight (pup weight/litter, g)

Dose Group (mg/kg/day) (F_1 mice were not dosed)	**0**	**10**	**80**	**300**
Day1	1.6	1.6	**1.5***	**1.4****
Day 4	2.6	2.4	**2.3***	**1.9****
Day 7	4.0	3.8 (95%)	**3.5**** **(87.5%)**	**3.0**** **(75.0%)**
Day 21	10.4	10.0	10.2	9.6

F_1 Physical development:

There was no effect of CC-10004 treatment on the occurrence and timing of sexual maturation, preputial separation, or vaginal patency. There were no effects of CC-10004 on F_1 testes or epididymides weights or the ratios of these weights to the terminal body weight determined after the mating phase of the study.

F_1 Neurological assessment

Passive Avoidance
There was no effect of CC-10004 on performance in a passive avoidance paradigm (learning, short-term retention, long-term retention, or response inhibition)

Motor Activity
There was no effect of CC-10004 on motor activity (average number of movements or the time spent in movement).

F_1 Reproduction and Fertility

Mating and Fertility
There was no effect of CC-10004 on mating and fertility parameters evaluated in the F1 generation male and female mice (number of days in cohabitation, number of mice that mated, the fertility index, number of pregnancies per number of mice that mated, the number of mice with confirmed mating dates during the first and second weeks of cohabitation, and the number of pregnancies per number of mice in cohabitation).

F_2 GENERATION

F_2 Survival
There was no effect of F_0 CC-10004 treatment on F_2 fetal survival.

F_2 Body weight:
There was no effect of F_0 CC-10004 treatment on F_2 generation fetal weights.

F_2 External evaluation:
There was no effect of F_0 CC-10004 treatment on F_2 generation fetal litter parameters obtained at Ceasarian section (F_1 corpora lutea, F_2 implantations, F_2 preimplantation loss, viable and nonviable F_2 embryos, and F_2 postimplantation loss).

F_2 Male/Female ratio:
There was no effect of F_0 CC-10004 treatment on F_2 generation sex ratio.

F_2 Other Findings:
No F_1 dam had a litter consisting of only nonviable embryos. Caesarean-sectioning observations were based on 19 (76.0%), 20 (83.3%), 22 (88.0%), and 23 (92.0%) pregnant mice with one or more live fetuses in Groups I through IV, respectively.

10 Special Toxicology Studies

Study title: An Acute Dermal Irritation Study in Rabbits of CC-10004 in Ethanol:Propylene Glycol

Study no.:	CC-10004-TOX-500
Study report location:	Module 4.2.3.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 20, 2005
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	CC-10004, Batch 52690-04, Purity 99.4%

Key Study Findings

- CC-1004 is a not a dermal irritant.

Methods

Three female rabbits [New Zealand White Hra:(NZW)SPF; approximately 8 months of age; 3.92 to 4.19 kg] were each treated with CC-10004 applied dermally The dose was 0.3 mg/mL in 0.5 mL applied first to a 1 $inch^2$ (~6 cm^2) area of gauze patch which was then placed against the dorsal trunk and held by tape for 4 hours. Verification of the dose concentration indicated they were properly prepared and homogeneous, demonstrating concentrations that ranged from 102.9% to 104.4%. After exposure the patch was removed and excess CC-10004 was washed away. The site was scored using the Draize scale for erythema/eschar and edema within 30 to 60 min and at 24 and 48 hours later (the standard assessment at 72 hour was not conducted).

Results

There was no effect on survival or body weight. There was no dermal irritation in any of the three rabbits.

Study title: A Skin Sensitization Study (Buehler Method) in Guinea Pigs of CC-10004 in Ethanol:Propylene Glycol

Study no.:	CC-10004-TOX-501
Study report location:	Module 4.2.3.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 20, 2005
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	CC-10004 Batch 52690-04, Purity 99.4%

Key Study Findings

- CC-10004 in ethanol:propylene glycol is a weak sensitizer when applied dermally to guinea pigs at a concentration of 3 mg/mL.

Methods and Results

Dose range finding study: In an initial dose range-finding study, Crl:HA (Albino Hartley) guinea pigs (n=2/sex, 10-11 weeks of age, males 617-896 g, females 499-741 g) were treated simultaneously with four doses of CC-10004 (0, 0.05, 0.5, and 3.0 mg/mL) applied at 0.4 mL to four different dermal sites along the dorsal truck scapular area using a closed topical patch. The vehicle was ethanol:propylene glycol (40:60 % v/v). The positive control was 50% hexylcinnamic aldehyde. Verification of the dose concentration indicated they were homogeneous but the low concentration was 25%-31% greater than expected, the mid concentration 20.3 to 25.6% lower than expected and the high dose 0.4% to 2.7% of expected. The site was scored using the Draize scale for erythema/eschar and edema. The reactions elicited were compared for incidence, severity, and duration control groups and CC-10004-treated and a severity index (SI) and a sensitization index (SII) were calculated.

Dermal Score Calculations
$SI^{a} = \frac{\text{Sum of the Grades at Interval}}{\text{Total Number of Animals}}$ $SII^{b} = \frac{\text{Number of Animals Showing a Positive Response at 24 and 48 hours}}{\text{Total Number of Animals}} \times 100$
[a]Determined separately for 24 and 48 hour intervals.   [b]Animals that show a positive response at both intervals will be counted as one incidence.

There were no signs of irritation at any dose in the range-finding study at either the 24 or 48 hour timepoints. The high dose of 3.0 mg/mL was therefore used in the sensitization study. Since the high dose was selected for later study, there is no concern that the lower doses were inappropriately prepared.

Sensitization Study: In the skin sensitization study, guinea pigs were treated as indicated in the table below with 3.0 mg/mL CC10004 or control solutions applied by a topical patch. The dose was administered to the same site once a week for 3 weeks. The challenge application was made to the shaved left or right posterior flank. The duration of topical exposure was 6 hours, and then the site was washed to remove residual compound.

Group Assignment - Induction and Challenge Phase				
Group	Dose Level (Induction)	Dose Level (Challenge)	Number of Animals	
			Male	Female
Control (Group 2)	EtOH:PG (40:60 % v/v)	100% test article	5	5
Positive Control (Group 3)	100% HCA	50% HCA	5	5
Test Article (Group 4)	100% test article	100% test article	10	10
HCA-Hexylcinnamic Aldehyde				

There was no irritation in the CC-10004-treated animals in the challenge phase of the sensitization study, resulting in a 0% Sensitization Incidence Index. However, there were 3 control group animals that had equivocal signs of irritation (erythema score of 0.5), 1 at the 24 hour score and 2 at the 48 hour score. In the positive control group, 2 animals (10%) were observed with erythema scores of 1 and 12 animals (60%) with erythema scores of 0.5. Due to the equivocal challenge scores in the controls, the CC-10004 and positive control groups were rechallenged.

Table 61: Summary of Dermal Irritation Scores combined males and females

Group	Number of Animals	Sum of 24 Hour Scores	Sum of 48 Hour Scores	Number of Animals with Scores of ?? 1 at either 24 and/or 48 hours[a]	Severity Index (SI)		Sensitization Incidence Index (SII)
					24 Hour Score	48 Hour Score	
Control	10	0.5	1	0	0.1	0.1	.00%
Positive Control	10	3.5	3.5	1	0.4	0.4	10%
Test Article	20	0	0	0	0.0	0.0	.00%

A set of animals was rechallenged along with naive control animals as presented in the following table since the results from the first challenge were equivocal.

Group Assignment - Rechallenge Phase			
Group Number	Dose Level (mg/mL)	Number of Animals	
		Male	Female
Control (Group 5)[a]	100% test article	5	5
Positive Control (Group 3)	50% HCA	5	5
Test Article (Group 4)	100% test article	10	10
[a]Separate set of naïve animals. HCA-Hexylcinnamic Aldehyde			

The rechallenge results indicated the control group had no signs of irritation, and the positive control group had 14 animals with erythema scores of 1 or greater, corresponding to a strong sensitizer. Only one CC-10004 treated animal had positive

signs of irritation which occurred at the 48 hour timepoint and resulted in a 5% Sensitization Incidence Index, corresponding to a weak sensitizer.

Table 62: Summary of Dermal Irritation Scores (Rechallenge), combined males and females

Group	Number of Animals	Sum of 24 Hour Scores	Sum of 48 Hour Scores	Number of Animals with Scores of ≥ 1 at either 24 and/or 48 hours[a]	Severity Index (SI)		Sensitization Incidence Index (SII)
					24 Hour Score	48 Hour Score	
Control	10	0	0	0	0.0	0.0	.00%
Positive Control	10	8.5	8.5	7	0.9	0.9	70%
Test Article	20	1.5	3	1	0.1	0.2	5.0%

Study title: Neutral Red Uptake Phototoxicity Assay of CC-10004 in Balb/c 3T3 Mouse Fibroblasts

Study no.: CC-10004-TOX-1170
Study report location: Module 4.2.3.7.7
Conducting laboratory and location: (b) (4)
Date of study initiation: Nov 20, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: CC-10004, Batch 82633-09, Purity 99.4%

Key Study Findings

CC-10004, at doses up to 101.8 mg/L, was not phototoxic in the neutral red phototoxicity assay, but there are a few points that question the validity of the study.

1) The incubation times with CC-10004 and chlorpromazine are not provided.
2) The UVR exposure time is not provided.
3) Since cellular UVB exposure intensity is substantially lower with plate covers over the cells, it's unclear if chlorpromazine is a proper control for the lower wavelength radiation and if potential toxicity due to UVB exposure was adequately assessed.

Methods

The study consisted of a dose range-finding assay followed by two definitive assays.Mouse cryopreserved permanent Balb/c 3T3 fibroblasts (clone A31) were incubated in 96 weel plates with doses of CC-10004, from 1.8 mg/L to 101.8 mg/L, which was the highest achievable target concentration in the vehicle. The vehicle consisted of 1% dimethylsulfoxide in Dulbecco's phosphate buffered saline with Ca^{2+} and Mg^{2+}. Negative controls were blank wells and vehicle treated fibroblasts. The positive control was chlorpromazine (0.1 to 120 mg/L). Additional control plates were also placed in the UVR field and had opaque covers. Analysis of the dosing solution indicated that the concentration of CC-10004 were 88.2% to 96% of targeted concentrations.

Table 63: Concentrations of CC1004 and Chlorpromazine Tested

Test Material	Range-Finding Assay Concentrations in 1% DMSO/DPBS (mg/L)							
Chlorpromazine	0.1	0.2	1.0	2.0	10.0	20.0	40.0	120.0
CC-10004	0.032	0.102	0.322	1.018	3.22	10.18	32.22	101.8
Test Material	**Definitive Assays 1 and 2 Concentrations in 1% DMSO/DPBS (mg/L)**							
Chlorpromazine	0.1	0.2	1.0	2.0	10.0	20.0	40.0	120.0
CC-10004	1.80	3.20	5.70	10.14	18.05	32.13	57.19	101.8

The ultraviolet radiation (UVR) source was a Xenon arc solar simulator, equipped with a Schott WG 320 filter. It was noted that a non-validated software version OL 756 v.2.21. for the OL 756 spectroradiometer was used for measurement of the spectral emission of the Atlas xenon arc lamp. Also, the spectral emission of the xenon radiation was not measured for these specific assay runs, the historical UVR dose intensities (through the lid of the cell culture plate) were 5 J/cm^2 for UVA and 17-25 mJ/cm^2 for UVB. It's unclear if the historical values were also derived from studies with non-validated software. The applicant stated that the spectral distribution of the lamp conforms to spectra measured by previous instruments and published data for this lamp and filter configuration and that comparison of the spectral emission data from the unvalidated software and the validated software demonstrated concordance between the two spectra.

The optical density (OD) of the vehicle controls and the blank wells for each plate was determined. The percent survival of the 3T3 cells exposed to UVR was calculated by comparing the OD_{540} of cells exposed to UVR with the OD_{540} of cells not exposed to UVR.

$$\%\ \text{of Control} = \frac{\text{corrected mean } OD_{540} \text{ of Test Article}}{\text{corrected mean of } OD_{540} \text{Vehicle Control}} X\,100$$

The IC_{50}(-UVR) and IC_{50}(+UVR) could not be calculated since there was no cytotoxicity with CC-10004 treatment and UVR exposure, and therefore PIF = *1 was used to characterize this result:

$$PIF = *1 = \frac{\text{Concentration}_{max}(\text{-UVR})}{\text{Concentration}_{max}(+\text{UVR})}$$

The Mean Phototoxic Effect (MPE) was also calculated.

Table 64: Criteria for determination of a valid test (OECD guideline)

Mean Photo Effect (MPE)	Photoirritancy Factor (PIF)	Phototoxic Potential
<0.1	<2	Non-phototoxic
>0.1 and <0.15	>2 and <5	Probably phototoxic
>0.15	>5	Phototoxic

Results

In the range-finding assay, the percent UVR exposure survival was 91% and the OD_{540} was 0.616. In the definitive assays 1 and 2, the percent survival was 92% and 92% and the OD_{540} was 0.565 and 0.557, respectively. CPZ cytotoxicity IC_{50} range from 7.0 to 90 mg/L) and the phototoxicity IC_{50} ranged from 0.1 to 2.0 mg/L, with a photoirritancy factor (PIF) less than 6. These values are within the OECD recommended criteria for positive and negative controls and concluding a negative effect for CC-10004.

There was no cytotoxicity of cells exposed to CC-10004 with or without UVR exposure, and CC-10004 was not phototoxic under the conditions of this assay.

Table 65: Summary of Results of Range-Finding and Definitive Assays

Results, Range-Finding Assay					
Test Material	IC_{50} (mg/L) (-UVR cytotoxicity)	IC_{50} (mg/L) (+UVR phototoxicity)	Photoirritancy Factor (PIF)	Mean Photo Effect (MPE)	Phototoxic Potential
Chlorpromazine	26.47	1.002	26.427	0.376	Phototoxic
CC-10004	–	–	*1	0.006	Non-Phototoxic
Definitive Assays					
Chlorpromazine	31.29	1.134	27.595	0.445	Phototoxic
CC-10004 (Assay 1)	–	–	*1	-0.020	Non-Phototoxic
CC-10004 (Assay 2)	–	–	*1	-0.005	Non-Phototoxic

IC_{50}: Inhibitory Concentration.
+UVR: with exposure to 5 J/cm^{2}UVA (315-400 nm) and from 17 to 25 mJ/cm^2 of UVB (290-315 nm)
- UVR: without UVR exposure
–: IC_{50} was not achieved
*1: Both IC_{50}(-UVR) and IC_{50}(+UVR) could not be calculated (the test article does not show cytotoxicity without or with UVR exposure), this indicates a lack of phototoxic potential. In this case, a formal PIF = *1 is used to characterize the result:

11 Integrated Summary and Safety Evaluation

Pharmacology

CC-10004 (apremilast) is a new moleculat entity that inhibits phosphodiesterase 4 (PDE4) enymes. From published studies, it is known the inhibition of PDE4 results in increased levels of intracellular cAMP, initiation of an intracellular signaling pathway that involves the activation of protein kinase A, and activation of cAMP responsive element binding protein (CREB/ATF-1) family of transcription factors, as well as downregulation of nuclear factor kappaB (NF-κB) transcriptional activity. Published studies by the applicant's scientists (Shafer et al., 2010) using PDE4 isolated from U937 human monocytic cells (predominately PDE4b and PDE4D activity) and 1 μM cAMP, found that CC-10004 had an IC_{50} of 74 nM, binds competivitly with the cAMP-PDE4 complex with an estimated K_i of 68 nM, and that dilution will reverse the inhibition. Inhibition of PDE4 results in increased levels of intracellular cAMP, initiating an intracellular signaling pathwasy that involves the activation of protein kinase A, and activation of cAMP responsive element binding protein (CREB/ATF-1) family of transcription factors, as well as downregulation of nuclear factor kappaB (NF-κB) transcriptional activity. The functional result is alteration of both inflammatory and anti-inflammatory mediators. The applicant demonstrated that CC-10004 alters many of mediators in numerous in vitro and in vivo conditions, including various animal models of arthritis. Some of the mediators assessed by the applicant were inducible nitric oxide synthase, tumor necrosis factor-alpha (TNF-α), and interleukins (IL-17, IL-23, and IL-10).

Primary Pharmacology
The primary pharmacodynamic properties of CC-10004 were evaluated in assays examining effects on other phosphodiesterases, receptors, enzymes, and kinases. CC-10004 had a IC_{50} of 74 nM for PDE4 isolated from U937 monocytic cells (b) (4) CC-10004 was approximately 279- to 40,000-fold more selective for PDE4 inhibition than for other PDE subtypes, but was non-selective for subtypes A1A, B1, B2, C1, and D2 within the PDE4 group. In screening assays, CC-10004 lacked activity with 255 kinases, 68 cell surface receptors, and 17 enzymes. Metabolites M7 (CC-10055) and M17 (CC-16401) had PDE4 inhibitory activity and inhibited TNF-α production, but comprise low levels (1% in human) of plasma concentration of CC-10004.

Arthritis Models
CC-10004 inhibited TNF-α production in human synoviocytes obtained from rheumatoid arthritis (RA) patients. At oral doses of 5 and 25 mg/kg, CC-10004 reduced the clinical and histological severity in a collagen-induced arthritis model in mice, and inhibited hind paw swelling in the collagen monoclonal antibody/lipopolysaccaride-induced arthritis model similar to that of oral 1 mg/kg dexamethsaone or intraperitoneal 5 mg/kg etanercept.

Secondary Pharmacology

CC-10004 is derived from a core thalidomide moiety with modification of the side chains. In many of the pharmacology studies, the applicant included thalidomide or approved thalidomide-related compounds to demonstrate that CC-10004 has a different profile of phamacodynamic activity. They demonstrated that CC-10004 did not bind to cereblon, an E3 ubiquitin ligase substrate coreceptor identified as the primary teratogenic target of thalidomide. CC-10004 metabolites were not tested, but since they lack the cereblon-binding aminoglutarimide moiety of thalidomide, also absent in CC-10004, they are also not expected to bind with cereblon.

A prominent clinical sign in monkeys and humans is emesis, especially during the initial oral dosing days. The sponsor attempted to rationalize that this was not a CNS effect due to the finding of low (<0.5) brain-plasma ratios in rats and ferrets, as well as the protective effects of P-glycoprotein. However, the chemosensitive center in the medulla lies outside the blood brain barrier, so additional studies are needed before dismissing a CNS-initiating site.

Safety Pharmacology
Following single oral doses of CC-10004 to rats, there were findings of initial concern in studies of neurobehavioral and cardiovascular function, but not respiratory function or gastroinstestinal transport. There was one animal that died in the high dose the day after neurological testing. CC-10004 produced symapthetic activation responses. In the hERG assay, the IC_{50} of 184 μM for I_{Kr} would be greater than 100-times the human C_{max} at 30 mg BID dose. The lack of QT prolongation was confirmed in a follow-up study in anesthetized dogs, but there was increase left ventricular pressure with increasing doses. Further studies were conducted in monkeys as part of the general toxicology assessments. There were also negative for QT prolongation, but there was insufficient information provided to assess the validity of these studies and minimal data listings were provided. A tQT evaluation in humans was negative for inducing QT prolongation (refer to the Medical Officer's Review)

ADME/Pharmacokinetics

Absorption and Distribution:
The main studies for characterizing the absorption, distribution, metabolism, and elimination of CC-10004 were conducted with radiolabeled [^{14}C]-CC-10004, administered both orally by gavage and intravenously. Oral bioavailability of CC-10004 was approximately 27% in the mouse, but not accurately determined for the monkey due to low concentrations with the intravenous dosing aspect of the study. However, based on a comparison of total radioactivity in blood in ADME studies, it was estimated to be approximately 80%. Studies in rats found oral bioavailability to be sex dependent (65% in females, but only 12 % in males). This is one reason rats were not used in most toxicology studies. There was <1% oral bioavailability in the rabbit. Thus, monkeys were used in the embryofetal developmental study instead of the rabbit. In mice, the volume of distribution was 2 to 3-fold that of body water volume indicating it distributed well to extravascular tissue spaces. Systemic clearance of CC-10004 was also species dependent. In mice, it was very low (<1/6 liver blood flow), but high in male rats and

female rabbits (>50% liver blood flow). In monkeys, the apparent clearance after oral administration was moderate. The terminal half-life of CC-10004 ranged from 1 to 3 h, usually considered of short duration.

CC-10004 had a low brain-plasma concentration ratio in rats and ferrets (Reports (b) (4) which may occur because CC-10004 is a substrate for P-glycoprotein and it has no inhibitory effect on P-glycoprotein. CC-10004 also has no effect on the activity of breast cancer resistant protein (BCRP), multidrug resisitance proteins (MRP1, MRP2, or MRP4), organic anion transporting polypeptides (OATP1B1 and OATP1B3), organic anion transporters (OAT1 and OAT3), or organic cation transporter (OCT2). In vivo studies demonstrated that [^{14}C]-CC-10004 was moderately protein bound to plasma proteins (~70-80%), and is extensively distributed in tissues with no specific tissue having an unusual extended residency for radioactivity.

Distribution into Milk and into Fetus
CC-10004 distributed to milk in mice and across the placenta into the fetal compartment in mice and monkeys. Following a single injection of 10 mg/kg, CC-10004 was found in milk from mice collected during day 13 of lactation at approximately 1.5-times that of simultaneously collected blood samples (Report CC-10004-DMPK-034). In an embryofetal developmental study in mice (Report CC-10004-TOX-012), blood was collected from both fetuses and dams at necropsy. The mean fetal-to-maternal plasma (pooled fetal blood) concentration ratios ranged from 0.3 to 1.07. In the monkey embryofetal developmental study (Report CC-10004-TOX013), prior to necropsy on gestation day 100, CC-10004 was administered orally at mg/kg and was detected in fetal monkey blood at concentrations approximately 40% of the maternal concentration. Blood collection was based on the approximate time of maternal T_{max}, from maternal toxicokinetic analysis on GD 20 and GD 50.

(b) (4)
In the toxicology studies in mice and monkeys, plasma CC-10004 did not exhibit accumulation with once daily dosing for up to 6 months in mice and 12 months in monkeys. There were no sex differences in toxicokinetic parameters. In the long term toxicological studies in which (b) (4) assays were validated, there was no detectable conversion of CC-10004 (b) (4) (mouse: Reports CC-10004-TOX-002 and CC-10004-TOX-004; monkey: Report CC-10004-TOX-005), which was demonstrated to lack the ability to cause severe toxicity that was induced with CC-10004 at the same dose (Report CC-10004-TOX-004). (b) (4) was administered daily at 50 mg/kg for 1 month. All animals in the CC-10004 (S-enantiomer) group were terminated after the day 2 dose due to substantial weight loss and poor condition. Only 1 animal in the (b) (4)) group was terminated early, on day 10 due to poor condition. Adverse effects other than poor body condition and grooming included swollen abdomens, beginning about day 10-11 in the (b) (4) group. The conclusion was that (b) (4) was substantially less adverse then CC-10004. (b) (4)
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Metabolism:
In vitro studies with [^{14}C]-CC-10004 with liver microsomes or hepatocytes and in vivo studies indicated extensive metabolism, although there were some species differences. Compared with findings with human microsomes and hepatocytes, all metabolites from human tissues were found in the toxicology species; there were no unique human metabolites. There was also no difference in metabolism of [^{14}C]-CC-10004 between adult and juvenile tissues in male mice or humans. Metabolism in rabbit and sex difference in metabolism in the rat corresponded with the difficulty in attaining systemic exposure in the rabbit and the vastly different dose-exposure profiles between male and female rats, respectively. The main metabolic pathway in all species including human is oxidation through O-demethylation, forming M3, and subsequent glucuronidation, forming M12 the major metabolite. Non-cytochrome P450 hydrolysis also produced detectable in vivo metabolites M1/M2. CYP3A4 was the major isozyme metabolizing CC-10004 to M3, CYP3A4 and CYP2A6 contributed to the formation of M5. Other isozymes that were demonstrated to influence metabolite formation includes CYP1A2, CYP2A6, CYP2C9 and CYP2C19. In vitro studies found that CC-10004 did not inhibit or induce CYP isozymes

Excretion:
In animals, studies with oral or intravenous [^{14}C]- CC-10004 dosing found the primary route of excretion was hepatobiliary. Following an intravenously administered dose, 56% to 71% was excreted in feces. Urinary excretion was minor, comprising 8% to 18% of an intravenous dose. The excreted form consisted primarily of metabolites.

General Toxicology
The pivotal studies consisted of daily oral dosing by gavage in GLP toxicology studies in CD-1 mice and cynomolgus monkeys. Of note, there were no recovery groups in these studies, and therefore at the request of DDDP, a recovery study was conducted in mice. Studies in rats were conducted to enable the selection of doses for the 2-year carcinogenicity assay. In initial studies in rats, a substantial sex difference was noted in rats that was not apparent in mice, so mice were used for the majority of the repeated dose studies including the 6 month study.

Mouse
Multiple repeated dose studies were conducted to arrive at a NOAEL. The initial study (Report 1398/277), administered doses of 500, 1000, and 2000 mg/kg/day for 14-days. All doses produced gastrointestinal adverse effects (distension, thickening, irregular surface and raised foci in the stomach) along with reduced food consumption and body wieght loss. Clinical pathology findings included an increased neutrophils with lymphocytopenia, and increase total protein and globulin and a reduced albumin reduction in AST and ALT.

Doses were lowered in the following 28-day study (Report 1398/289) to 250, 600, and 1500 mg/kg/day. Mortalities occurred in the 600 and 1500 dose groups. The major histopathological findings were a dose related arteritis occuring at multiple sites including the heart (at the root of the aorta and at the base of the heart), thymus, liver,

stomach, and the hemopoietic system. Perivascular inflammatory cell infiltration occurred in the lung. Synovitis was present in the stifle. Other findings included centrilobular hepatocyte hypertrophy and hyperkeratosis in the forestomach. In a second 28-day study (Report 1398/297), doses were further reduced to 5, 25, 75 and 150 mg/kg/day. Arteritis was noted at all dose levels, although only at 150 mg/kg/day in females. A third 28-day study (Report 1398/333) was conducted with doses of 1, 2, and 4 mg/kg/day. The NOAEL was finally attained at 4 mg/kg/day (AUC_{0-24} = 3900 ng-h/mL). The AUC exposure was 62% of the AUC of the 5 mg/kg/day dose in the previous study, a steep fall in exposure for 1 mg/kg/day drop in dose to attain the NOAEL.

In the 13-week study (Report 1398/373) the doses were 2, 4, 8 and 16 mg/kg/day. Arteritis was present at 16 mg/kg/day in a few animals, at the root of the aorta and in 1 female also the thymus. The NOAEL was 8 mg/kg/day (AUC_{0-24} = 9298 ng-h/mL).

In a second 13-week study (Report CC-10004-TOX-002), doses were 100, 300 and 1000 mg/kg/day. There were no mortalites, but histopathology indicated inflammatory lesions associated with organs in the thoracic cavity (heart, aortic root, and lung) at dose of 300 and 1000 mg/kg/day, as was also found in the shorter studies. The NOAEL was 100 mg/kg/day (AUC_{0-24} = 24898 ng-h/mL). However, it is doubtful this was a true NOAEL, since many tissues were not evaluated. A vascular lesion such as arteritis, does not necessarily appear at the same locations or within the same organs. In the mouse, the occurrence of CC-10004 related arteritis was usually within the thoracic cavity organs, particularly the aortic root-heart interface, and less often at other locations, but in the monkey, arteritis was infrequent and usually at different locations across studies. The infrequent occurrence (due to the way it is categorized by location) and few animals studied indicates that it could be difficult to distinquish from an incidental finding.

In the 6-month study in mice (Report CC-10004-TOX-004), CC-10004 was administered at doses of 10, 100 and 1000 mg/kg/day. Mortalities occurred at the 100 and 1000 mg/kg/day doses and histopathology findings were similar to those in previous studies. but more extensive in this longer study, and included arteritis of the aortic root and other cardiac arteries and myocardium, and inflammation and vascular lesions in abdominal organs. The NOAEL was 10 mg/kg/day (AUC_{0-24} = 5728 ng-h/mL).

A final study was conducted to address the concerns of DDDP for lack of recovery data for adverse lesions, since none of the previous studies had included recovery groups. In this study (Report CC-10004-TOX-008) female mice were administered either 300 or 1000 mg/kg/day for up to 90 days and with necropsy at various recovery times, 31 or 76 days of recovery. All histopathological changes due to CC-10004 treatment were recoverable within 90 days. These included effects in the thymus (inlammation, lymphoid depletion, and lymphoid hyperplasia), liver (hypertrophy), mesenteric lymph node (inflammation and lymphoid hyperplasia), and arteritis of the aortic root. In some cases there were only 1 or 2 incidences of lesions, and therefore, the absence of these in the recovery group had a high probability of being a false positive for recovery, ie. the lesion may not have ever been present in the recovery animals.

Rat
A 90-day rat study was conducted to determine doses for a 2-year carcinogenicity bioassay. The studied doses were 0, 0.3, 3, 10 and 30 mg/kg/day in females and 0, 30, 100, 300 and 1000 mg/kg/day in males. CC-10004 caused acute inflammation and lymphoid depletion in multiple tissues in all dose groups which manifested clinically by prostration and a neutrophilic leukocytosis, increased acute phase proteins (haptoglobin), and decreased albumin. Lethality was noted in all male dose groups and the mid-high and high dose females. Histpathology indicated the occurrence of lymphoid depletion and/or subacute inflammation of the thymus, small intestines and/or mesentery in all CC-10004 dose groups. No NOAEL was identified, but a MTD for 13 weeks of dosing was determined to be 30 mg/kg/day in males and 3 mg/kg/day in females. Even these doses were too high for the long carcinogenicity study as the selected lower doses used in the carcinogencity study had to be reduced even further during the study (refer to the Carcinogenicity studies in Section 8 of the review).

Monkey
Studies in monkeys included dose-finding studies and a 14 day repeated dose study (Report 1398/283) with a minimal number of animals per group (2-3) at what was suspected to be the maximum tolerated dose of 750 mg/kg/day. The applicant determined that the monkey would not tolerated a long-term study at this dose. Emesis was observed at ≥300 mg/kg and was often observed as a finding in all monkey studies. There was a 9-14% body weight loss over the 14 days of repeated dosing. The histopathology findings were few, including atrophy of the thymus, sternal marrow hemopoiesis, and lesions of the tail that may have contributed to pyemic foic in the heart and lung, lymphadenitis and arteritis in the epididymis. Due to the few animals, these may have been incidental findings. The only consistent finding with the mouse studies was the case of arteritis, although arteritis was more common in the thoracic region (heart - aortic junction) in the mouse.

In another 14-day dose-finding study for an embryofetal development study (Report CC-10004-TOX-010), female monkeys of at least 4 years of age, the oldest ones studied with histopathology evaluations, were dosed once or twice daily with total daily doses of 100, 200, 500 or 1000 mg/kg/day. With few animals again, there was no effect on body weight, but the high dose group appeared thin. Emesis was common during the first week. The major finding of concern was myocardium degeneration/necrosis with acute to subactue inflammation and hemorrhage in 1 female at 200 mg/kg/day and 2 females at 1000 mg/kg/day. These tissues were submitted for peer review evaluation. The original findings were confirmed and there was also no signs of vasculitis. Additonal sections stained for granulocytes, determined the two high dose animals had a eosinophilic tissue infiltrate, while the 200 mg/kg/day animal had an infiltrate consisting of lymphocytes and neutrophils. This was used to conclude that the findings for the 200 mg/kg/day animal were more typical of common background lesions while the high dose animals had a hypersensitivity myocarditis, which was likely CC-10004 related. Although the NOAEL was limited to the 500 mg/kg/day dose, if this lesion was actually a hypersensitivity reactions, then it may not necessarily occur in humans, since immune responses in animals are usually not predictive for occurrence in humans. Based on

results of this study, doses selected for the monkey embryo-fetal study were 20, 50, 200, and 1000 mg/kg/day, and doses ≥50 resulted in fetal abortions (see Report CC-10004-TOX-013 in Section 9 of this review).

A 28-day study (Report 1398/296) followed the initial dose range finding study with doses of 50, 180 or 650 mg/kg/day. The hematology profile at termination consisted of a dose-dependent increase in white blood cells due to an increase in neutrophils and a reduction in lymphocytes. There were no clinical pathology effects or changes in organ weights. The major finding of concern was vasculitis occuring in 1 male at 180 mg/kg/day in connective tissue of the sciatic nerve, and in 2 females at 650 mg/kg/day, one with vasculitis also in connective tissue of the sciatic nerve and another in connective tissue adjacent the kidney. The NOAEL was 50 mg/kg/day (AUC_{0-24} = 12372 ng-h/mL).

In a 13-week study (Report 1398/368), monkeys were administered doses of 25, 85, or 300 mg/kg/day. There were no findings of vasculities, and no adverse pathology. The only effects other than excessive salivation in all dose groups, was occassional emeis or retching in the high dose group. The NOAEL was 300 mg/kg/day (AUC_{0-24} = 27915 ng-h/mL).

A 12-month study (Report CC-10004-TOX-005) was conducted with doses of 60, 180 and 600 mg/kg/day. Although there were now 5/sex/dose group, the animals were only 2 years of age at the start, thus the study was conducted using juvenile animals. As such, there was no assessment of toxicity by histopathology of mature sexual organs in the monkey general toxicology studies. As seen in the 13 week study, there was an increase in total white blood cells due to an increase in neutrophils and a reduction in lymphocytes. Fibrinogen was also elevated in the later part of the study. There were no adverse pathological findings. The NOAEL was 600 mg/kg/day (AUC_{0-24} = 34774 ng-h/mL).

In the monkey, the uncommon situation occurred in which a longer period of treatment resulted in a gradual increase in the NOAEL level. It appears the short duration studies had a greater incidence of adverse effects, although relatively few animals were studied. The major adverse finding in these studies were emesis and vasculitis. The incidences of vasculitis were few in the monkey and at locations different from the mouse. It is possible that the monkey is able to resolve vasculitic events over time such that they are not apparent in the longer term studies.

All of the pivotal toxicological studies in monkeys were conducted with mostly juvenile monkeys. Therefore, there was not an adequate histopathologiocal assessment of mature sexual organs health in the monkey general toxicology studies. Although this was addressed in the mouse general toxicology and fertility studies, with an absence of CC-10004-related toxicity,the monkey would have been a more appropriate species for analysis due to the relatively high incidences of adverse findings in control mice.

Genetic Toxicology

CC-10004 was negative in a standard series of genetic toxicology assays that included the bacterial reverse mutation assay, in vitro chromosomal aberration assay using human peripheral blood lymphocytes pooled from 3 individuals, and the in vivo mouse micronucleus assay. An early assessment (b) (4) a process impurity that initially (b) (4) compared to a specification of (b) (4), was negative in the bacterial reverse mutation assay when (b) (4) was added to CC-10004 at (b) (4) of the CC-10004 parent. Although not an appropriate genetic toxicology assessment of (b) (4) it does reduce the concern for mutagenicity and this impurity is now controlled at (b) (4). Furthermore, (b) (4) is also a metabolite of CC-10004 identified as (b) (4) The levels of this metabolite were greater in animal toxicology studies than that detected in human volunteers or patients, assuring characterization of potential toxicological effects. The lack of CC-10004 malignancies in mice and rat carcinogenicity studies also supports the safety of (b) (4) although the toxicokinetics of this metabolite was not measured in those studies.

Carcinogenicity

Mouse Carcinogenicity Study:

Crl:CD-1 (ICR) Mice (n=70/sex/dose) were dosed once daily by gavage with CC-10004 at doses of 0 (vehicle:1.0% sodium carboxymethylcellulose in deionized water), 100, 300, and 1000 mg/kg/day. Due to morbidity and deaths in the latter part of the study, dosing of the high dose males was terminated and dosing of the high dose females was reduced to 500 mg/kg/day during week 73 (month 18). The dose of the 300 mg/kg/day group was also lowered to 200 mg/kg/day at this time and maintained through weeks 98 and 96 in males and females, respectively. Dosing was then stopped and the remaining animals were maintained until the scheduled necropsy (study weeks 103 and 102 in males and females, respectively).

There were no definitive CC-10004-related malignancies in either male or female rats. For combined osteomas and osteosarcomas in females, there was a statistically significant trend of increasing incidence with dose ($p = 0.0128$). However these tumors were only present in the high dose group and pairwise comparison with the control group was not significant due to the low incidences in the control and high dose groups (0 and 3, respectively; $p= 0.0918$).

Rat Carcinogenicity Study

CC-10004 was administered once daily by gavage to Crl:CD(SD) rats (n=70/sex/dose) at 0 (vehicle, 1.0% methocellulose), 2, 10 or 20 mg/kg/day in males and at 0 (vehicle, 1.0% methocellulose), 0.3, 1, or 3 mg/kg/day in females. In study week 66 (16.5 months), dosing of the 20 mg/kg/day males was stopped and the mid group dose of 10 mg/kg/day was reduced to 6 mg/kg/day due to animal morbidity and deaths. All dose groups were terminated between study week 91 and 104.

There were no malignancies related to CC-10004 treatment in either male or female rats. In female rats, there was a significant trend ($p=0.046$) for a dose-related increase in the incidence of ovarian Sertoli cell tumors. However with the low incidences of only 1

at the mid dose and 2 at the high dose of 70 animals per dose group, the pairwise comparison with control incidences of 0 were not significant.

Reproductive and Developmental Toxicology
Fertility and pre- and post-natal developmental studies were conducted in the mouse. Embryofetal developmental studies were conducted in mice and monkeys.

Fertility

Fertility studies consisted of an initial study in which CC-10004-treated males and CC-10004-treated females were mated within the same dose group. Adverse findings from the resultant pregnancies were followed up with separate studies in which CC-10004-treated males were mated with untreated females and CC-10004-females were treated with unmated males.

In the initial study, (Report CC-10004-TOX-001) CC-10004 was administered to male and female mice orally by gavage, once daily at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated from 28 days before cohabitation until the end of the 3 week mating phase. Females were treated from 15 days prior to cohabitation through gestation day 7 (GD 7). In males, body weight increased with CC-10004 treatment. Testes weight increased, but seminal vesicle and prostate weight decreased at the mid and high doses. There was no effect on sperm numbers or motility. Mating time was increased with a reduction in the number of matings in a dose-dependently manner. The fertility index was reduced. There was an increase in postimplantation losses in all CC-10004 groups compared to the control. No NOAEL was determined for either males or females. In males androgenic effects resulting from testes growth appear to be attenuated. In females estrous cyclicty might have been disturbed as well as hormones involved in the maintenence of pregnancy. Since the safety of apremilast on male or female fertility could not be concluded, another study was conducted.

In the follow-up fertility studies (Reports CC-10004-TOX-011 and CC-10004-TOX-012), mice were administered doses of CC-10004 orally by gavage. The males were dosed at 0 (vehicle), 1, 10, 25, or 50 mg/kg/day of CC-10004 and females received 0 (vehicle), 10, 20, 40, or 80 mg/kg/day of CC-10004. Note that these doses were substantially less than the lowest dose (100 mg/kg/day) of the initial fertility study. In these studies males were mated with untreated females and females were mated with untreated males. In both males and females either body weight or weight gain increased during the dosing phase, 70 days for males, and from 2 weeks before mating through gestation day 15 for females. In males, testes weight also increased, but there was no effect of CC-10004 on sperm motility or sperm counts. There were no detrimental or dose related effects in embryofetal evaluations of the treated males mated with untreated females. The NOAEL for fertility in males was the high dose of 50 mg/kg/day corresponding to an $AUC_{0\text{-}24}$ of 21040 ng-h/mL.

For treated females, estrous cyclicity was prolonged due to an increase in diestrus period. This resulted in a longer time until mating occurred. However, all females did

mate and there was no difference in pregnancy rates between dose groups. The NOAEL for female mating which probably reflects an unidentified CC-10004 effect on the brain-pituitary-ovarian axis was 10 mg/kg/day corresponding to a premating AUC_{0-24} of 7407 ng-h/mL. There was no effect on numbers of corpora lutea and implantations, however early resorptions were increased for doses ≥20 mg/kg/day. There was no effect on the sex ratios. Fetal body weights were reduced at 40 and 80 mg/kg/day doses. There were no increased incidence of malformation, and only a few cases where variations increased. These were associated with a reduction in ossification sites that occur during late gestation and is susceptible to maternal nutritional stress, which was evident in this study by reduced maternal weight gains and reduced fetal weights at the higher doses. Toxicokinetic comparison of simultaneous fetal and maternal blood collection at necrospy, indicated that fetal concentrations of CC-10004 were detectable, but highly variable in magnitude at the collection time 24 hours after the last dose was administered. Due to preimplantation losses and reductions in fetal body weights, the NOAEL for embryofetal development was also the low dose of 10 mg/kg/day corresponding to an AUC_{0-24} of 9450 ng-h/mL.

Embryofetal Development

In the mouse, CC-10004 was administered orally by gavage to pregnant CD-1 mice from GD 6 through 15 at doses of 0 (vehicle), 250 500 or 750 mg/kg/day (Report 1398/309). Maternal effects included reduced weight gain and food consumption (both up to a 24% reduction compared to control). The reduction in weight gain was attributed to the CC-10004 related reduction in uterine weight, since when body weight was corrected for uterine weight changes, there was no difference in maternal weight between groups. While this may lead to question if the highest dose administered was sufficient for a valid study, one needs to remember that the general toxicology studies resulted in a weight gain in the initial weeks of repeated dose studies. Therefore, in the embryofetal study, the absence of normal maternal weight gain could be an indicator of CC-10004 toxicity. There were no effects on pregnancy rates, corpora lutea numbers, implantation sites, and preimplantation losses. The percentage of pregnancies that had total litter losses was greater in the high dose group (27% compared to 9% for controls). This resulted in a reduction in the number of pregnancies with live fetuses on GD 18 in the high dose group (68%, compared to 82% for the control group). The reduction in litters and litter size of CC-10004 treated dams was due to postimplantation losses which were greater in all CC-10004 dose groups than the control (litters: from 26.1% to 41.4% compared to 18.9% for the control group; litter size: high dose 7.9 compared to 10.8 for the control group). Toxicokinetic data was not collected for this study. Fetal weight (total and mean fetal weight) was also significantly reduced in a dose dependent manner (up to 74% and 84%, respectively, compared to control). Both male and female mean fetal weights were reduced. There was no effect on the sex ratio.

The total number of fetuses with malformations (expressed as a percentage of fetuses examined) and the percentage of the litters with malformations was greater for CC-10004 treatment groups. However, when separated into external/visceral and skeletal groupings, there was no dose-related effect. For external and visceral effects, the low

and mid dose were greater than the control numbers expressed as mean % of fetuses and % of litters affected. For skeletal malformations there was an increase in these values relative to control, but the greatest effect was in the mid dose.

There was a dose-related increased incidence in skeletal variations that consisted of incomplete ossification sites, but this could be a secondary effect associated with reduced fetal weight, reflecting retarded growth, and a consequence of maternal toxicity. There was no effect of CC-10004 on external/visceral variations.

The rabbit was not an appropriate species for CC-10004 study. Preliminary studies (Reports 1398/290, 1398/291, and 1398/292) indicated that adequate systemic exposure of CC-10004 could not be obtained due to poor bioavailability. Therefore, an intravenous infusion initial dose-range finding study (Report CC-10004-TOX-009) was conducted but animals quickly became moribund and had to be euthanized. The vehicle also contributed to the toxicity profile. The sponsor then switched to an alternative species, the cynomolgus monkey.

Pregnant cynomolgus monkeys were orally administered CC-10004 at doses of 20, 50, 200 or 1000 mg/kg/day, once daily, from GD 20 to GD 50. Fetuses were examined after Cesarean section on GD 100 (Report CC-10004-TOX-013). The 20 mg/kg dose group was added to the study after dose-related increased incidences of abortions were noted in the initial dose groups. There was a dose-related increase in the incidence of fetal losses, (37.5%, 50%, and 81% for the 50, 200 and 1000 mg/kg doses, respectively). Losses in the 20 mg/kg/day group (12.5%) were similar to controls (15%). Losses were more common during week 3 and 4 of CC-10004 dosing, with only 1 abortion in the 50 mg/kg dose (day 62) and 1 abortion in the 200 mg/kg dose (day 90) occurring after the dosing period.

There was an initial mean weight loss during the first week of dosing in the 200 and 1000 mg/kg dose groups compared to the control group, and a reduction in gestational body weight gain in the high dose group compared to the control group. Placenta weight and fetal weight tended to be reduced in the 1000 mg/kg dose group compared to the control group, again limited by the few fetuses surviving to day 100. There were no treatment-related changes in fetal body weights, fetal body measurements, or placental weights, or fetal organ weights. However, organ weight analysis was not calculated in terms of % body weight, so this analysis was incomplete. CC-10004 was also administered at the time of necropsy so that fetal blood levels could be quantified. CC-10004 was detected in fetal blood with concentrations approximately 40% of the maternal concentration at the approximate time of T_{max}, which was based on maternal toxicokinetic analysis on GD 20 and GD 50.

As mentioned in the review of Dr Booker (see Appendix 9), the teratogenic effects of CC-10004 in the monkey were not adequately evaluated due to the high incidence of dose-related fetal abortions, coupled with the absence of examination of these fetuses. Of the 3 fetuses examined in the high dose group, there was only one skeletal malformation, scoliosis, due to vertebra abnormalities (fetus #14695 of the high dose

group). Numerous skeletal variations were observed in all dose groups, including the control animals, particularly with regards to ossification sites and misaligned tail vertebrae. However, the findings were not dose related and were noted as common background findings for the conducting laboratory. Although a definitive conclusion regarding overall teratogenic potential of CC-10004 was not possible, compared to control incidences and given the lack of appropriate numbers of fetuses examined, the increased incidence of skeletal variations was considered an effect of CC-10004.

Pre and Post-Natal Development

In the pre- and post-natal development study (Report CC-10004-TOX-1139) CC-10004 was administered orally (via gavage) to pregnant female Crl:CD1(ICR) mice (25/group) at doses of 0 (1% w/v aqueous carboxymethylcellulose), 10, 80, or 300 mg/kg/day from day 6 of gestation (GD 6) through day 20 of lactation (LD 20). There were mortalities in the high dose group associated with difficulty in delivering at 300 mg/kg/day (1 death, evidence indicating it occurred during delivery), and overt clinical observations including those associated with difficulty in delivering at 80 and 300 mg/kg/day (pale ears, hunched posture, mild dehydration, dyspnea, hyperpnea, and in 1 high dose animal the occurrence of clonic convulsion). The high dose group had reduced maternal body weight and weight gain compared to the control group. Reductions in maternal body weights on LDs 4 and 14 (5% to 10% below control) and reductions in body weight gain on GDs 12 to 15 and 15 to 18 (11% to 17% below control) and LDs 1 to 4 and 7 to 14 (59% to 55% below control) at 300 mg/kg/day. There were no effects of apremilast on the duration of pregnancy, number of pregnant mice at the end of the gestation period and the number of mice that delivered a litter. The maternal NOAEL was 10 mg/kg/day, due to early abortions, premature delivery and associated dystocia.

The F_1 generation had an increased postnatal pup mortality on LDs 1 through 7 including increased stillbirths, missing and presumed cannibalized pups, pups found dead or sacrificed due to adverse signs, with correlating decreases in pup viability index (85% for the mid dose, 57% for the high dose compared to 98.6% for the control group) and live litter size at LD 21 (10.2 for the mid dose, 8.4 for the high dose, compared to 13.4 for the control group). This was based on 3 dams at 80 mg/kg/day and 9 dams at 300 mg/kg/day that had lost all pups by LD 5. Surviving pup mean body weights per litter through LD 7 at 80 and 300 mg/kg/day were reduced compared to controls (87.5% and 75% of mean control weights, respectively), however by day 21 (weaning) and thereafter, there were no differences from control group body weights. Pups that died had a dose-related increase incidence in the absence of milk in their stomachs. There were no effects of F_0 treatment with apremilast on the F_1 generation for clinical or necropsy observations after weaning; body, testes or epididymis weights; sexual maturation; passive avoidance; motor activity; mating; fertility or F2 embryofetal parameters. The NOAEL for the F_1 generation was 10 mg/kg/day due to early postnatal mortality.

Apremilast in Milk

In a single dose study (Report CC-10004-DMPK-034, refer to Section 5 Pharmacokinetics), lactating mice (approximately day 13 of lactation), were administered one dose of 10 mg/kg apremilast and blood and milk samples were obtained simultaneously at 1, 6 and 24 hours after apremilast administration. Apremilast was detected in the milk of lactating mice at levels at levels approximately 1.5-times that of simultaneously collected blood plasma samples at 1 and 6 hours, and not detectable in either milk or plasma at 24 hours.

Recommendations

The nonclinical safety program for apremilast is complete. There are adequate nonclinical safety margins (approximately 1 for mouse and 5 for monkey on an AUC basis) for the proposed MRHD of 30 mg BID apremilast at the NOAELs of the chronic toxicology studies. From a PharmTox perspective, the application is recommended for approval. There is no need for further nonclinical studies.

Exposure margins relevant to application approval and product labeling are provided in the table below.

Table 66: Nonclinical Toxicologically Relevant Exposure Margins

		Adverse Effect	NOAEL (mg/kg/day)	AUC (ng-h/mL)	Exposure Margin+
General Toxicology					
Mouse 6-month study Report CC-10004-TOX-004		Mortality, Vascular Inflammation	**10**	**5728**	**0.77X**
Cyn. Monkey 1 year study Report CC-10004-TOX-005		None	**600**	**34772**	**4.7X**
Carcinogenicity					
Mouse Report CC-10004-TOX-006		None	1000	63952	**8.6X**
Rat Report CC-10004-TOX-007	**male**	None	20	608	**0.08X**
	female	None	3	7721	**1.1X**
Fertility					
Mouse	**male** Report CC-10004-TOX-011	None	50	21040	**2.8X**
	female Report CC-10004-TOX-012	Estrous cyclicity and Mating	10	7407[a]	**1.0X**
		Postimplantation Loss	10	9450[b]	**1.3X**
Embryofetal Development					
Mouse Report CC-10004-TOX-012		Postimplantation Loss	10	9450[b]	**1,3XX**
Cyn. Monkey Report CC-10004-TOX-013		Postimplantation Loss (Abortion)	20	10100	**1.4X**
			50,	15400	**2.1X**
Pre-Postnatal Development*					
Mouse Report CC-10004-TOX-1139	**labor**	Premature Delivery, Dystocia	10	4902*	**0.66X**
	postnatal development	Early Postnatal Mortality	10	4902*	**0.66x**
		Postnatal Development	80	29215*	**3.9X**

+ Exposure margins were based on comparisons between the area under the concentration-time curve (AUC) for a 24 hour period in toxicology studies and the human population PK value of 7440 ng-h/mL for the MRHD of 30 mg BID. The human value was derived from data that included clinical study CC-1004-RA-002 with an AUC_{0-24} of ~7200 ng-h/mL and CC-1004-PSOR-005-PK with an AUC_{0-24} of ~8900 ng-h/mL

* TK was not determined in this study; values from the fertility study, Report CC-10004-TOX-012, were used to determin exposure margins.

[a] AUC at day 14 of premating

[b] AUC at day 15 of gestation

Labeling Review

The applicant's label was submitted in SD-6 June 24, 2013. A consult with the Maternal Health Team for recommended wording in Pregnancy Section 8 was requested on Oct 30, 2013 and suggestions changes from the consult are incorporated into this review based on the draft response (email from Dr. Carrie Ceresa on Nov 14, 2013). Labeling negotiations with the applicant will occur after the finalization of this review. The maximum recommended human dose (MRHD) is 30 mg twice daily. Due to the extensive changes from the appicant's proposed label The label changes below were rewritten as separate paragraphs rather than the ususal format of incorporating the new wording into original paragraphs.

8 USE IN SPECIFIC POPULATIONS

The Pregnancy section was completely rewritten from the applicant's proposed labeling. This new version is a hybrid of the current CFR labeling and the expected to-be-established (in 2014) new pregnancy labeling rule. The rule change is anticipated to present a more complete and more readily interpretable assessment for the prescriber of drug risks during pregnancy, labor, and nursing. The changes that were incorporated in this label included a risk summary, clinical considerations and animal data. The risk summary is based on the animal data, since women of child bearing potential and men were required to use effective contraceptive methods in the phase 3 trials, precuding the availability of human data to inform labeling. Although the embryofetal study in monkeys was inconclusive for teratogenicity at high doses due to early fetal losses, there was sufficient number of animals at lower doses to determine exposure margins and characterize human risk. (b) (4) Clinically-related information was provided by the consult from Carrie M. Ceresa, Pharm D, MPH, of the Maternal Health Team (email of the draft consult on Nov 14 2013).

8.1 Pregnancy

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

Pregnancy Category C

Risk Summary

Adequate and well-controlled studies with TRADE NAME have not been conducted in pregnant women. In animal embryofetal studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximal recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. Although no teratogenic effects were observed in monkeys at doses corresponding to 2.1-times the MRHD, the study was insufficient to thoroughly evaluate the teratogenic risk due to abortion/embryofetal loss at higher doses. In mice, there were no ampreilast-induced malformations up to exposures (b) (4) -times the MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for TRADE NAME. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. TRADE NAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Labor or delivery

The effects of TRADENAME on labor and delivery in pregnant women are unknown. In mice, premature delivery and dystocia were noted at doses corresponding to (b) (4) times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data
Monkey embryofetal development: In an embryofetal developmental study, cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during weeks 3 to 4 of dosing during the first trimester, at doses approximately 2.1 times the MRHD and greater (on an AUC basis at doses ≥ 50 mg/kg/day). No abortifacent effects were observed at a dose approximately 1.4 times the MRHD (on an AUC basis at a dose of 20

mg/kg/day). Although there was no evidence for a teratogenic effect at 20 mg/kg/day, there were insufficient numbers of fetal monkeys to adequately address teratogenic risk at doses approximately 4.5 times the MRHD and greater (on an AUC basis at doses ≥50 mg/kg/day).

Mouse embryofetal development: In an embryofetal study, apremilast was administered at dosages of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation day 6 through 15). In a combined fertility and embryofetal development study, apremilast was administered at dosages of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of (b) (4) times the MRHD (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately (b) (4) -times the MRHD (10 mg/kg/day).

Mouse pre- and postnatal development: In a pre- and post-natal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from day 6 of gestation through day 20 of lactation, with weaning at day 21. Premature delivery, dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to (b) (4) -times the MRHD (on an AUC basis at doses ≥80 mg/kg/day). No adverse effects occurred at a dose (b) (4) -times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to approximately (b) (4) -times the MRHD (up to 300 mg/kg/day).

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

The following label changes include the recommendations by the Maternal Health Team as well as CFR language. Studies in lactating mice provided data that CC-10004 (apremilast) was detectable in mouse milk after oral administration to dams.

It is not known whether TRADENAME or its metabolites are present in human milk; however, apremilast was detected in milk of lactating mice. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal

condition. Caution should be exercised when TRADENAME is administered to a nursing woman.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

There is substantial information provided by the applicant that CC-10004 (apremilast) is a PDE4 inhibitor. Although cAMP levels were not measured in the applicant's studies, there is substantial evidence in the published literature to indicate that in the presence of PDE4 inhibitor, intracellular cAMP levels increase. The applicant also conducted numerous studies in vitro and in vivo demonstrating in that CC-10004 inhibits the level of inflammatory and non-inflammatory cytokines. However, per 21CFR 201.57(c)(13), this section of the label must contain information relating to the human clinical pharmacology and actions of the drug in humans, therefore, (b) (4)

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, affecting numerous cellular functions in PDE4 responsive cells. The specific mechanism(s) by which TRADE NAME exerts its therapeutic action in psoriatic arthritis patients is not well defined

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Sponsor's proposed label

(b) (4)

(b) (4)

Reviewer's Recommendation

The label for the carcinogenesis information was expanded slighly and included exposure margins based on the mouse and rat 2-year bioassay studies.

> Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors were observed in mice at oral doses up to (b) (4)-times the MRHD on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD in males and females, respectively (3 mg/kg/day in females and 20 mg/kg/day in males).

Sponsor's proposed label

(b) (4)

Reviewer's Recommendation

Suggested edits to mutagenesis language were considered minor in nature and were made to ensure conformity with current mutagenesis labeling practices.

> Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

Sponsor's proposed label

(b) (4)

(b) (4)

Reviewer's Recommendation

The fertility section was modified to more clearly state the findings.and exposure margins.

> *Impairment of Fertility:* In a fertility study of male mice, apremilast at oral dosages up to approximately 3-times the MRHD based AUC (up to 50 mg/kg/day) produced no effects on male fertility.
>
> In a fertility study of female mice, apremilast was administered at oral dosages of 10, 20, 40, and 80 mg/kg/day. At dosages (b) (4)-times the MRHD (20 mg/kg/day), estrous cycles were prolonged and time to mating was increased. There was no effect of apremilast at approximately (b) (4) times the MRHD (10 mg/kg/day).

12 Appendix/Attachments

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Appendix 1: Sponsor's References

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/s/

LAWRENCE S LESHIN
11/20/2013

MARCIE L WOOD
11/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205437
Supporting document/s:	SD-1, SD-6 (labeling)
Applicant's letter date:	March 20 2013, July 31 2013
CDER stamp date:	March 21 2013, July 31 2013
Product:	Otezla (apremilast)
Indication:	Psoriatic Arthritis
Applicant:	Celgene Corp
Review Division:	DPARP
Reviewer:	L. Steven Leshin, D.V.M., Ph.D.
Supervisor/Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Michelle Jordan Garner

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205437 are owned by Celgene Corp. for which Celgene Corp. has obtained a written right of reference. Any information or data necessary for approval of NDA 205437 that Celgene Corp.does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205437.

1 Executive Summary

1.1 Introduction

This document is an Addendum to the Pharmacology-Toxicology review of NDA 205437 submitted Nov 20, 2013. Appendices 2 - 15 are contained with this document.

12 Appendix/Attachments

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: [redacted]
Review number: 1
Sequence number/date/type of submission: 000 / 28 July 2004 / original
006 / 1 November 2004 / IT
011 / 14 April 2005 / new protocol

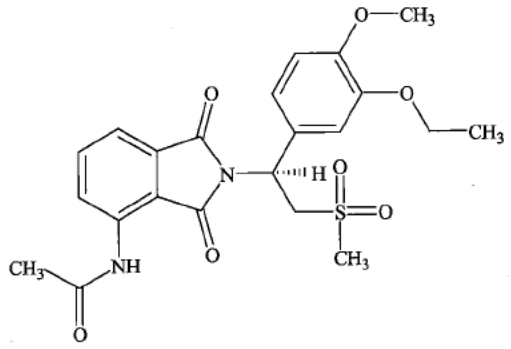
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Celgene Corporation
Manufacturer for drug substance: [redacted]

Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: September 7, 2005

Drug:

Trade name: NA
Generic name: NA
Code name: CC-10004
Chemical name: [redacted]

CAS registry number: NA
Molecular formula/molecular weight: 460.5 / $C_{22}H_{24}N_2O_7S$
Structure:



Relevant INDs/NDAs/DMFs: None

Drug class: phosphodiesterase type IV (PDE4) inhibitor

Intended clinical population: psoriasis patients

Clinical formulation: white capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Route of administration: oral

Proposed clinical protocol: **Open-label, single-arm pilot study to evaluate the pharmacodynamics, pharmacokinetics, safety and preliminary efficacy of CC-10004 in subjects with moderate to severe plaque psoriasis.** Protocol No. CC-10004-PSOR-001. CC-1004 will be administered at a dose of 2 x 10 mg BID (20 mg/dose, 40 mg/day) for 29 days to approximately 21 male or female subjects between the ages of 10 and 65. Drug will be taken in the morning under fasted conditions and in the evening >1 hour after the evening meal. Women of childbearing potential must have negative pregnancy test at screening and every 4 weeks and they must use adequate contraception while on study medication. Males must agree to use barrier contraception while on the study and 4 weeks after taking the last dose. Safety assessment includes physical exam and vital signs, adverse event reporting, clinical laboratory evaluations (urinalysis, chemistry, hematology at screening and days 1, 3, 8, 15, 22 and 29), 12-lead ECG (screening day 1, 8 and 29), CD3+, CD4+ and CD8+ lymphocytes (days 1 , 15 and 29), chest x-ray (at screening) and purified protein derivative testing (at screening). Efficacy assessments will include PASI and static physician global assessment. Skin biopsies will be obtained on days 1, 15 and 29 and will be assessed immuno-histochemically and by rtPCR for various pharmacodynamic endpoints. Blood samples will also be assessed for pharmacodynamic endpoints on days 1, 15 and 29. Steady state blood levels will be assessed on day 29 at 0, 0.5, 1, 2, 3, 4, 8 and 24 hours post-dose. In some subjects, 12 and 16 hours samples will also be collected. Dose selection was based on phase 1 studies and nonclinical results that suggest that this dose will produce pharmacodynamic effects.

(Note: The time during which women of child bearing potential should continue to use contraception after stopping drug is not specified.)

After discussions with the Division, the above protocol was modified to a dose of 20 mg/day and it will be conducted only in patients with severe psoriasis with BSA involvement of at least 15%. In addition, the study assessments were amended to include tests for HIV and hepatitis at baseline and prior to starting the study medication, ECGs at each study visit, and laboratory testing for ESR, fibrinogen, and C-reactive protein for all subjects at each visit. The protocol was clarified so that the physician will be available at any time to physically assess any signs and symptoms of subjects that may be indicative of an early manifestation of drug-induced vasculitis. In addition, follow-up visits at 2 and 4 weeks after the last dose of study drug were added.

(b) (4)

Previous clinical experience:

One study with CC-10004 and three with the racemic mixture (CC-7085) have been conducted. The study with CC-10004 was a phase 1, double-blind, placebo-controlled ascending dose, safety and pharmacokinetic study in healthy subjects conducted in the UK (Study 1398/317 [CC-10004-PK-001]). Forty subjects were enrolled. Doses of 10, 20 and 40 mg/day as once daily and 80 and 100 mg/day as twice daily doses were administered orally. Each subject received a single oral dose followed by multiple oral doses over a period of 5 days. Blood was collected from all dose groups and urine from the 10 mg/day group. The sponsor reports that CC-10004 was well tolerated in this study. Adverse events appeared to increase with dose. Gastrointestinal adverse events appeared most frequently at the 40, 80 and 100 mg/day doses and included nausea, abdominal distension, abdominal pain and diarrhea. Headache and dizziness also appeared to be more frequent at the higher doses. The sponsor states that there were no clinically significant findings in vital signs, 12-lead ECGs, clinical laboratory parameters or physical examinations. The pharmacokinetics of CC-10004 showed Tmax of 1-3 hours. Plasma CC-1004 levels decreased in a biphasic manner with an elimination half-life of approximately 5-7 hours. No accumulation was observed at 10 to 40 mg/day while slight accumulation was observed at 80 and 100 mg/day. The AUC and Cmax appeared to increase in a less than dose proportional manner. At 40 mg/day the $AUC_{0-\infty}$ was 3379 ng·h/mL at day 1 and AUC_{0-24} was 3289 ng·h/mL at day 7.

Introduction and drug history:

The sponsor intends to develop this drug for the treatment of psoriasis. No pre-IND meeting was held with the sponsor. The sponsor already completed one study with CC-10004 (see above). (b) (4)

(b) (4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Pharmacology:

1. Anti-inflammatory activities of the novel PDE4 inhibitor CC-10004 against human leukocytes in vitro. Study Number: 5042/107
2. Effect of the PDE4 inhibitors CC-10004, CC-10082 (cilomast), CC-11050 and CC-14064 (roflumilast), and the IMiD CC-5013 on IL-6 production by human, rat, mouse and monkey whole blood stimulated with LPS in vitro. Study Number 5265-117

Safety pharmacology:

1. CC-10004: Effects in general activity and behaviour in the mouse following oral administration Study Number: 1398/443
2. Effects of CC-10004 on cloned hERG channels expressed in mammalian cells. Study Number: 03126.DFN
3. CC-10004: Cardiovascular and respiratory effects in the anaesthetized dog following intravenous administration Study Number: 1398/264-D6146

Pharmacokinetics/toxicokinetics:

1. (^{14}C)-CC-10004: A pilot study of plasma pharmacokinetics following oral administration to the rabbit. Study Number: 1398/387-D1145.
2. Determination of the oral pharmacokinetics and bioavailability of racemic [redacted] and its enantiomers in the male and female rat. Study Number: 1398/215-D1140.
3. Investigation into the pharmacokinetics, excretion and metabolism of [^{14}C]-CC-10004 in the male and female rat following single and repeated oral administrations. Study Number: 1398/259-D1145.
4. (^{14}C)-CC-10004: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the mouse. Study number: 1398/376-D1145.
5. (^{14}C)-CC-10004: A study of absorption, excretion and metabolism following oral and intravenous administration to the cynomolgus monkey. Study number: 1398/399-D1145.
6. Metabolic stability of [redacted] CC-10004 [redacted] and racemic [redacted] in microsomes isolated from male and female rat, monkey and human and human cDNA expressed isozymes and identification of major metabolites in plasma from orally dosed rats. Study number: 1398/186-D1145.
7. Metabolism of [^{14}C]-CC-10004 [redacted] in microsomes isolated from mouse, rat, rabbit, dog, monkey and man. Study No. 1398/261.
8. Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of [^{14}C]-CC-10004 in human liver microsomes. Study No. 1398/393.
9. Effects of CC-10004 on selected cytochrome P450 activities in human liver microsomes: prediction of drug interactions. Study No. 1398/227.
10. Stability of [redacted] and [redacted] in plasma isolated from human *in vitro* and *in vivo*. Study No. 1398/229
11. CC-10004: *In vitro* binding to plasma proteins in rat, mouse, dog, rabbit, monkey and human, [redacted] *in vitro* binding to plasma proteins in rat. Study No. 1398/293.

Toxicology:

1. Single dose intravenous toxicity study in the mouse. Study Number: 1398/279-D6154
2. Single dose oral toxicity study in the mouse. Study Number: 1398/278-D6154
3. Single dose intravenous toxicity study in the rat. Study Number: 1398/277-D6154
4. Single dose oral toxicity study in the rat. Study Number: 1398/276-D6154
5. CC-10004 and (b) (4) Oral (gavage administration) comparative toxicity study in the female rat. Study No. 1398/213
6. CC-10004: 14 day oral (gavage) administration range-finding toxicity study in the mouse. Study No. 1398/262.
7. CC-10004: Maximum tolerated dose (MTD) followed by a 14 day fixed dose oral (gavage) administration toxicity study in monkey Study No. 1398/283
8. CC-10004: 28 day oral (gavage) administration toxicity study in the mouse Study no.: 1398/289
9. CC-10004: 4 week oral (gavage) administration toxicity study in the mouse Study no.: 1398/297
10. CC-10004: 4 week oral (gavage) administration toxicity study in the mouse Study no.: 1398/333
11. CC-10004: 13 week oral (gavage) administration toxicity study in the mouse Study no.: 1398/373
12. CC-10004 28 day oral (gavage administration) toxicity study in the monkey Study no.: 1398/296
13. CC-10004: 13 week oral (gavage) administration toxicity study in the monkey Study no.: 1398/368

Genetic toxicology

1. CC-10004: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*. Study no.: 1398/282
2. CC-10004: Induction of micronuclei in the bone marrow of treated mice Study no.: 1398/281
3. CC-10004: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes. Study no.: 1398/280

Reproductive and developmental toxicology:

1. CC-10004: Oral (gavage) range-finding study of embryo-fetal development in the mouse Study no.:1398/308
2. CC-10004: Oral (gavage) study of embryo-fetal development in the mouse Study no.: 1398/309-D6154
3. CC-10004: oral (gavage) preliminary study in the non-pregnant rabbit Study no.: 1398/290
4. CC-10004: Oral (gavage) range-finding study of embryo-fetal development in the rabbit Study no.: 1398/291
5. CC-10004: Oral (gavage) study of embryo-fetal development in the rabbit Study no.: 1398/292

Special toxicology:

1. Evaluation of biomarkers for predicting toxicity of CC-10004 in rat Study no.: AP1012R

Studies not reviewed within this submission:

The following studies where not reviewed because they were not considered relevant to the indication in the current IND.

Effect of CC-10004 on LPS-induced lung neutrophilia in the rat. Study Number: [redacted]576R, [redacted]500R and [redacted]1025R

Therapeutic index of SelCIDs in ferret lung neutrophilia and emesis model. Study Number: 121401

Effect of CC-10004 in a murine ovalbumin-induced asthma model. Study Number: [redacted]998R and [redacted]1036R

Mouse type II collagen arthritis model. Study Number: [redacted]01-027

Evaluation of anti-arthritic activity in the mAb/LPS-induced experimental murine arthritogenic model. Study Number: CLG/002/EM

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

CC-10004 is a selective PDE4 inhibitor. It inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. The NOAEL for general behavioral effects after a single oral dose in male mice was 500 mg/kg. Higher doses produced relatively minor, possibly autonomic, effects. CC-10004 inhibited the hERG only partially and only at very high concentrations. CC-10004 induced a dose related increase in dP/dt_{max} and heart rate in dogs. Corrected QT interval was not affected. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in the dog.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

The sponsor submitted a report (5042/107) that assessed in the in vitro activity of CC-10004 in a number of anti-inflammatory pharmacodynamic assays. CC-10004 inhibited PDE4 purified from a human monocytic cell line with an IC_{50} of 33.8 ng/mL (73.5 nM). (b) (4) (b) (4) CC-10004 was much less active at inhibiting PDE 1, 2, 3, 5, 6, 7 and 11. PDE 1, 2, 3, 5, 6, 7 and 11 were inhibited less than 50% at 10 μM. One form of PDE4 isolated from rat brain has been correlated with emetic potential of PDE inhibitors. CC-10004 binds to this form of PDE4 (referred to as HARBS for High Affinity Rolipram Binding Site) with an IC_{50} of 10.6 ng/mL (23 nM). This is a lower affinity than the prototypical PDE4 inhibitor Rolipram which has an IC_{50} for this form of PDE4 of 5 nm. This study report also showed that CC-10004 inhibited the LPS mediated release of TNF-α and IL-12 from PBMC with IC_{50} values of 35 ng/mL (77 nM) and 64 ng/mL 9140 nM), respectively. In the same system CC-10004 increased IL-10 release with and EC_{50} of 1100 ng/mL (2300 nM). TNF-α release from PBMC induced by IL-1ß or from whole blood induced by LPS was also reduced by CC-10004. Staphylococcal enterotoxin B induced IL-2 and IFN-γ production from PBMC was inhibited by CC-10004 with IC_{50} values of 134 ng/mL (291 nM) and 21 ng/mL (46 nM). (b) (4) (b) (4) IL-5 production from stimulated $CD4^+$ T cells was inhibited by CC-10004 with an IC_{50} of 405 ng/mL (890 nM). Prostaglandin E_2 induced elevation of cAMP in PBMC is enhanced by CC-10004, which is an effect observed with other PDE4 inhibitors. CC-10004 was shown to inhibit N-formyl-methione-leucine-phenylalanine-induced leukotriene B4 production, CD18/CD11b expression and endothelial cell adhesion by neutrophils. CC-10004 inhibited IL-1ß stimulated NO production human endothelial cells by 87% at 4.6 μg/mL.

In another report submitted by the sponsor (5265-117), CC-10004 was shown to cause a dose dependent elevation of IL-6 production from LPS-stimulated whole blood from the mouse and rat but not from monkey or human in vitro. This was similar to the PDE4 inhibitors, cilomast and roflumilast.

Drug activity related to proposed indication:

The sponsor believes that the ability of CC-10004 to interrupt TNF-α release from leukocytes will provide some antipsoriatic activity since TNF-α may be involved in the etiology of psoriasis.

2.6.2.3 Secondary pharmacodynamics

As noted above, CC-10004 was much less active at inhibiting PDE 1, 2, 3, 5, 6, 7 and 11.

2.6.2.4 Safety pharmacology

Neurological effects:

1. Study title: CC-10004: Effects in general activity and behaviour in the mouse following oral administration

Study no.: 1398/443
Volume #4, and page #:(submission not consecutively numbered)
Conducting laboratory and location: [redacted]

Date of study initiation: 4 December 2003
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, Batch 61590-03, 101.3% Purity

Methods:

Male Crl:CD-1(ICR)BR mice (6/group) were treated by oral gavage with a single dose of CC-10004 in 1% carboxymethylcellulose at 0, 500, 1000 and 2000 mg/kg. Animals were 5-6 weeks of age. Animals were examined for general behavior based on the Irwin screen. This includes cage observations, locomotion, alterness, startle response, righting reflex, grip strength, pain response, pupil response, lacrimation, salivation, grooming, gait and other observations. These observations were made 30, 60, 90, 180 and 300 minutes after dosing. The animals were also kept for 7 days and general observations were made.

Results:

Mice treated with CC-10004 at 500 mg/kg showed no differences in behavior compared to vehicle treated control animals. At 1000 mg/kg lacrimation (slight) was observed at 60, 90 and 180 minutes after dosing in some animals and slight ptosis (eye closure) was observed in one animal at 180 minutes. At 2000 mg/kg lacrimation (slight to moderate) was observed at 60, 90, 180 and 300 minutes after dosing in some animals and slight to moderate ptosis (eye closure) was observed in multiple animals at 60, 90, 180 and 300 minutes. Several animals in the 2000 mg/kg group showed slight apathy (slightly sluggish movement) at 60 minutes and one animal showed slight apathy at 60, 90, 180 and 300 minutes. In addition, the 2000 mg/kg animal that showed apathy at 60, 90, 180 and 300 minutes was found dead on day 2 of the study.

Individual study findings:
The NOAEL for general behavioral effects after a single oral dose in male mice was 500 mg/kg. Higher doses produced relatively minor, possibly autonomic, effects. Justification for using males only was not provided. (*The males in the acute dose studies (see below) appeared to be more sensitive and exhibited eye closure and so this may be why only males were used in this study.*)

Cardiovascular effects:
2. Study title: Effects of CC-10004 on cloned hERG channels expressed in mammalian cells

Study no.: 03126.DFN
Volume #4 and page #:(submission not consecutively numbered)
Conducting laboratory and location: [redacted] (b) (4)
Date of study initiation: 15 December 2003
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch number 61590-03, 98.09% pure by HPLC

Methods
Human embryonic kidney cells (HEK293) were stably transfected with hERG cDNA. hERG current was measured with patch clamped cells held at -80mV and using a +20 mV pulse for 1 second every 5 second. The effect of CC-10004 at target doses of 10, 30, 100 and 300 μM was assessed (actual measured dose were 16.8, 49.7, 87.5 and 249.7 μM). Terfenadine (60 nM) was used as a positive control.

Results:
CC-10004 inhibited the hERG channel current with an IC_{50} of 184.2 μM. The mean maximum inhibition produced by CC-10004 was 59.0% and occurred at the high dose of 249.7 μM. Terfenadine produced a mean inhibition of 87.1% at 60 nM.

(*Note: In SN 006 the sponsor submitted some preliminary data from another hERG assay in which CC-10004 was found to inhibit hERG current by 51% at an estimated concentration of 1μM. This is greater inhibition than reported above. The sponsor believes that the results of study 03126.DFN are more reliable since it was conducted with multiple doses and was a GLP compliant study. This reviewer agrees that the data from study 03126.DFN are probably more reliable and the safety assessment should be based on that study and the other cardiovascular data reviewed here and collected in the human studies.)*

3. Study title: CC-10004: Cardiovascular and respiratory effects in the anaesthetized dog following intravenous administration

Study no.: 1398/264-D6146
Volume #4 and page #:(submission not consecutively numbered)

Conducting laboratory and location: [redacted]

Date of study initiation: 20 November 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch number FP0032, 97.57% pure by HPLC

Methods

Doses: Vehicle group and 0.5, 1, 5 mg/kg dose escalation group
Species/strain: dog/beagle
Number/sex/group or time point (main study): 2 animals/sex/group
Route, formulation, volume, and infusion rate: intravenous, 8% DMSO in intralipid, 0.125, 0.25 and 1.25 mL/kg, 200 mL/hour
Unique study design or methodology (if any):
Animals were anesthetized with propofol and intubated with a cuffed endotracheal tube. Animal temperature was monitored with a rectal probe. A pulse oximeter was used to monitor blood oxygen. A blood pressure transducer in a femoral artery was used to monitor blood pressure. While a flow probe was placed in the contralateral femoral artery to measure systemic resistance. Another catheter was placed in a femoral vein for blood sampling. A catheter tip transducer was placed in the left carotid artery and advanced to the left ventricle to measure left ventricle pressure.
Observations: After allowing the preparation to stabilize for 30 minutes, baseline readings were taken. Vehicle or test article was injected intravenously in the jugular vein. After at least 30 minutes vehicle or test article was administered in ascending doses. One female was subject to a gross necropsy since this animal vomited dark brown fluid. Blood was taken for pharmacokinetics before test article administration and 2, 10, 15 and 30 minutes after dose 1 and 2. Additional samples were taken at 60, 90 and 120 minutes after dose 3. Respiratory variables were monitored by pneumotachograph.

Results:
There was a dose related increase in dP/dt_{max} and heart rate.
dP/dt_{max} increased after 0.5 mg/kg from 4293 mmHg/s to 4673 mmHg/s, 2 minutes after dosing. After 1 mg/kg dP/dt_{max} increased to 5555 mmHg/s, 2 minutes after dosing and after the 5 mg/kg dose dP/dt_{max} increased to 6504 mmHg/s, 2 minutes after dosing and peaked at 7450 at 45 minutes after dosing. Group mean heart rate at baseline was 82 bpm. This went up to 92, 105 and 149 bpm after 0.5, 1 and 1.5 mg/kg, respectively.

PR and QT intervals were increased although this was a reflection of the increased heart rate since the corrected QT was not increased.

Peak inspiratory flow and peak expiratory flow were both increased with increasing dose. Mean peak inspiratory flow rate was 248 mL/s at baseline and went up to maximum mean values of 314, 382, and 429 mL/s after doses of 0.5, 1 and 1.5 mg/kg, respectively. These maximum values occurred from 10 to 90 minutes after dosing.

The mean C_{max} after 0.5 mg/kg was 947.5 ng/mL and occurred at 2 minutes. The mean C_{max} after 1 mg/kg was 1538.5 ng/mL and occurred at 2 minutes. The mean C_{max} after 1.5 mg/kg was 5224.5 ng/mL and occurred at 2 minutes.

Pulmonary effects:
See above cardiovascular study.

Renal effects:
Not assessed.

Gastrointestinal effects:
Not assessed.

Abuse liability:
Not assessed.

2.6.2.5 Pharmacodynamic drug interactions
Not assessed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table 1 Summary of Enzymatic, Cellular, and Animal Model Data

(b) (4)	CC-10004	(b) (4)
PDE Inhibition		
PDE4 IC_{50} (from U937 cells) (nM)	73.5	
PDE1 (% inhibition at 10μM)	23%	
PDE2 (% inhibition at 10μM)	6%	
PDE3 (% inhibition at 10μM)	20%	
PDE5 (% inhibition at 10μM)	3%	
PDE6 (% inhibition at 10μM)	-6%	
PDE7 IC_{50} (nM)	20500	
PDE Specificity Ratios from above data *(fold)*		
PDE4/PDE1	>500	
PDE4/PDE2	>10000	
PDE4/PDE3	>1200	
PDE4/PDE5	>30000	
PDE4/PDE6	>40000	
PDE7 IC_{50}/PDE4 IC_{50}	279	
HARBS Binding IC_{50}	23	
Human PBMC assays *(all values in nM)*		
LPS-induced TNF-α IC_{50}	77	
LPS-induced IL-12 IC_{50}	140	
LPS-induced IL-10 EC_{50} (3.5-fold increase)	2300	

IL-1β-induced TNF-α IC_{50}	[redacted]	83	[redacted]
SEB-induced IL-2 IC_{50}		291	
SEB-induced IFN-γ IC_{50}		46	
PGE_2-induced cAMP EC_{50}		1510	
Human Neutrophil Assays *(all values in nM)*			
PGE_2-induced cAMP EC_{50}		4570	
fMLF-induced LTB4 IC_{50}		2.48	
Zymosan-induced IL-8 IC_{50}		94	
fMLF-induced CD18 expression IC_{50}		390	
fMLF-induced CD11b expression IC_{50}		74	
fMLF-induced adhesion to HUVEC IC_{50}		150	
Other Cellular Assays			
IL-1β-induced HUVEC NO at 10μM (% inhib.)		87%	
CD4+ T cell IL-5 IC_{50} (nM)		890	
Human Whole Blood LPS-induced TNF-α IC_{50} (nM)		294	
Human Whole Blood LPS-induced IL-6 at 10 μM		No effect	
Monkey Whole Blood LPS-induced IL-6 at 10 μM		Inhibited 50%	
Rat Whole Blood LPS-induced IL-6 at 10 μM		Elevated 2-fold	
Mouse Whole Blood LPS-induced IL-6 at 10 μM		Elevated 4-fold	
***In Vivo* Models**			
Mouse LPS-induced serum TNF-α inhibition (ED_{50}, mg/kg, p.o.)		0.05	
Rat lung neutrophilia and total white blood cell infiltration inhibition (ED_{50}, mg/kg, p.o.)		0.25	
Rat lung neutrophilia and total white blood cell infiltration inhibition (ED_{50}, mg/kg, i.t.)		0.003	
Rat neutrophilic leukocytosis (at mg/kg p.o.)		Present at 10 and 6	
Ferret lung neutrophilia (ED_{50}, mg/kg, p.o.)		0.8	
Ferret threshold emetic dose (mg/kg, p.o.)		10	
Mouse ovalbumin-induced asthma AHR inhibition (ED_{50}, mg/kg, p.o.)		<1	
Mouse collagen-induced arthritis (% inhibition at mg/kg, p.o.)		49% at 1 32% at 10	
Mouse collagen antibody-induced arthritis (% inhibition at mg/kg, p.o.)		80% at 5 80% at 25	

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Oral bioavailability was very variable in rats (2 to 12% in males and 61 to 80% in females). Female rats experience higher AUC and C_{max} values than males. In the mouse, oral bioavailability was 24 to 27%. Male and female monkey exhibited similar exposure after oral administration and the bioavailability was approximately 78%. After oral

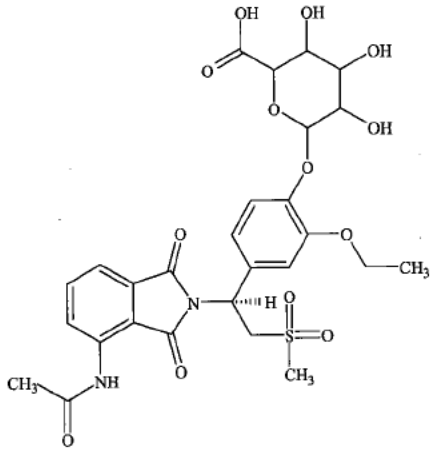
administration of radiolabeled CC-10004 to mice, the highest levels of radioactivity were detected in the gastrointestinal tract, kidney, liver and pancreas. The CNS tissues appeared to have lower levels than most other tissues. The major metabolite after in vitro microsome studies was M3 which is the O-desmethyl metabolite. This was observed in all species and sexes except the female rat. The human was most similar quantitatively and qualitatively to the dog and male rat. The greatest metabolism occurred with CYP3A4 and CYP2A6. The principal route of excretion appears to be the feces in both rodent and monkeys with approximately 70% of the drug excreted by this route. There appears to be little interconversion [redacted] in plasma. CC-10004 is relatively highly bound to plasma proteins (96.9, 96.5, 93.9, 99.7, 98.5 and 99.5% in rat, mouse, rabbit, dog, monkey and human, respectively.)

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

1. (^{14}C)-CC-10004: A pilot study of plasma pharmacokinetics following oral administration to the rabbit. Study No. 1398/387-D1145. This was a GLP study conducted at [redacted] The study was initiated on May 23, 2003. The study report state that this study was conducted to confirm exposure following oral dosing in the rabbit since the plasma levels of CC-10004 were below the limit of quantification in the rabbit embryofetal study. Four New Zealand White female rabbits were dosed by gavage with CC-10004 at 1000 mg/kg in 1% carboxymethyl cellulose. For the first two animals a dose volume of 10 mL/kg was used and for the second two a dose volume of 5 mL/kg was used. The radioactive dose was 400 µCi or about 100 µCi/kg. One of the first animals dosed with the 10 mL/kg volume died within 2 minutes of dosing. Upon necropsy, white material was found in the lungs and the cause of death was concluded to probably be reflux and inhalation of test article. The second animal treated with 10 mL/kg showed no adverse signs but was found dead 8 hours after dosing. No caused of death was determined. One animal treated with the 5 mL/kg volume was euthanized at around 3 hours after dosing for humane reasons. No cause of the animal's ill health was determined. The second animal treated with the 5 mL/kg volume was euthanized at around 8 hours after dosing for humane reasons. This animal was not subject to post-mortem examination. The cause of toxicity in this study was not apparent since similar doses in other studies were not as toxic. Mean pharmacokinetic parameters collected from this study are as follows: C_{max}=11,380 ng eq./g; T_{max}=1.2 h; $t_{1/2elim}$=5.1 h; $AUC_{0\text{-}inf}$=100,900 ng·h/g. Although detailed metabolic profiling was not possible the major metabolite appears to be O-desmethyl glucuronide of CC-10004 (see structure below).



O-desmethyl CC-10004 glucuronide

2. Determination of the oral pharmacokinetics and bioavailability of racemic [(b) (4)] in the male and female rat. Study No. 1398/215-D1140. This was a GLP study conducted at [(b) (4)] The study was initiated on 17 October 2000. [(b) (4)] which is the [(b) (4)] and the [(b) (4)] were administered to Sprague-Dawley rats by the oral and intravenous routes. For oral administration the test articles were suspended in 1% aqueous carboxy methyl cellulose and for the intravenous administration the test articles were dispersed in PEG 400 and Intralipid 20. Each test article was administered intravenously at 5 mg/kg and orally at 10 mg/kg in females and 50 mg/kg in males. Blood was collected after intravenous administration at 5, 10, 20 and 30 minutes, 1, 1.5, 2, 4, 8 and 12 hours. Blood was collected after oral administration at 10 and 30 minutes, 1, 2, 4, 6, 8, 10 and 12 hours. Plasma levels of [(b) (4)] were assessed by solid phase extraction followed by LC-MS/MS with a lower limit of quantification of 5 ng/mL. The assay was not enantio-selective and so only characterized total levels of [(b) (4)] C_{max} and AUC values after oral administration were significantly higher in females than males even though the oral dose in females was one-fifth the dose in males. The oral bioavailability in was 2 to 12% in males and 61 to 80% in females. T_{max} occurred at between 2 to 6 hours in both males and females after oral administration. $T_{1/2}$ was from between 0.6 to 6.2 hours. Mean C_{max} and AUC values are shown in the following table.

Parameter	**Male**		**Female**	
	5 mg/kg IV	50 mg/kg Oral	5 mg/kg IV	10 mg/kg Oral
[(b) (4)]				
C_{max} (ng/mL)	499.5	46.5	890.7	810.0
$AUC_{(0\text{-inf})}$ (ng·h/mL)	1265.2	420.2	5488.1	7209.8
CC-10004				
C_{max} (ng/mL)	3173.5	455.8	6602.8	1118.1
$AUC_{(0\text{-inf})}$ (ng·h/mL)	1923.8	2217.7	11407.0	14249.2
[(b) (4)]				

C_{max} (ng/mL)	[redacted]
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	

3. Investigation into the pharmacokinetics, excretion and metabolism of [^{14}C]-CC-10004 in the male and female rat following single and repeated oral administrations. Study No. 1398/259-D1145. This was a GLP study conducted at [redacted] in [redacted] The study was initiated on 11 October 2001. Sprague-Dawley rats were administered a single oral dose of radiolabeled CC-10004 diluted with either cold CC-10004 (10 mg/kg) or the [redacted] (20 mg/kg), or animals were dosed with cold CC-10004 or [redacted] for 6 or 5 days followed by one radiolabelled dose on day 6 or 7. Blood was collected at 10 and 30 minutes, 1, 2, 4, 6, 8, 10, 12 and 24 hours. Urine and feces were collected over the entire period. Total radioactivity was assessed in the various biological matrices by liquid scintillation counting and parent and metabolites were assessed by LC-MS/MS. T_{max} for total radioactivity was variable and occurred between 2 to 10 hours. Females experienced significantly higher C_{max} and AUC values than males. The following tables are taken from the report and summarize the pharmacokinetic parameters.

Total radioactivity

Parameter (units)	Dose Group			
	A (single dose, CC-10004)		B (repeat dose, CC-10004)	
	M	F	M	F
C_{max} (ng eq./g)	383.3	2018.8	476.0	3084.1
T_{max} (h)	4	8	6	10
$t_{½\ elim}$ (h)[1]	17.8	4.7	10.1	NC
AUC_{all} (h.ng eq./g)	4534.1	25812.4	5055.4	50524.9
$AUC_{(0\text{-}\infty)}$ (h.ng eq./g)[1]	6649.5	27166.7	6407.3	NC

Parameter (units)	Dose Group			
	CR (single dose, racemate)		D (repeat dose, racemate)	
	M	F	M	F
C_{max} (ng eq./g)	925.3	2430.2	490.6	2461.2
T_{max} (h)	2	6	6	2
$t_{½\ elim}$ (h)[1]	16.9	8.8	42.2	44.7
AUC_{all} (h.ng eq./g)	10331.5	39101.7	7093.7	42468.7
$AUC_{(0-\infty)}$ (h.ng eq./g)[1]	15059.5	48620.4	20978.7	128138.3

Parent compound

Parameter (units)	Dose Group			
	A (single dose, CC-10004)		B (repeat dose, CC-10004)	
	M	F	M	F
C_{max} (ng/mL)	82.9	654.4	32.7	1594.2
T_{max} (h)	1	6	1	2
$t_{½\ elim}$ (h)[1]	2.4	2.0	1.6	NC
AUC_{all} (h.ng/mL)	183.5	7531.8	80.3	24023.6
$AUC_{(0-\infty)}$ (h.ng/mL)[1]	235.1	7550.5	92.6	NC

Parameter (units)	Dose Group			
	CR (single dose, racemate)		D (repeat dose, racemate)	
	M	F	M	F
C_{max} (ng/mL)	30.6	828.4	33.6	2203.8
T_{max} (h)	1	1	1	4
$t_{½\ elim}$ (h)[1]	74.9	5.8	NC	7.7
AUC_{all} (h.ng/mL)	107.3	11414.6	106.2	24019.8
$AUC_{(0-\infty)}$ (h.ng/mL)[1]	1252.1	12560.4	NC	28218.6

NC: not calculated
[1]: $t_{½\ elim}$ estimated from limited data; therefore this parameter and $AUC_{(0-\infty)}$ should be interpreted with caution

4. (^{14}C)-CC-10004: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the mouse. Study number: 1398/376-D1145. This was a GLP-compliant, quality-assured report in which radiolabeled CC-10004 was administered intravenously (10 mg/kg) or orally (500 mg/kg) to male and female CD-1 mice. Blood was collected for pharmacokinetic analysis over 48 hours and feces and urine were collected over 168 hours. Whole body radiography was also conducted in albino CD-1 mice at intervals up to 168 hours and in pigmented B6C3F1 mice at intervals up to 35 days. Pharmacokinetic parameters were similar in males and females. Mean plasma pharmacokinetic parameters for both sexes combined for CC-10004 and total radioactivity are shown in the following table.

Parameter	Intravenous		Oral	
	CC-10004	Total radioactivity	CC-10004	Total radioactivity
$C_{(t)}$ or C_{max} (µg/mL)	7.395	9.073	14.79	29.88
t_{max} (h)	-	-	2.5	3.4
$t_{1/2}$ (h)	2.0	25.0	18.7	18.4
AUC_{0-t} (µg·h/mL)	16.6	47.8	201.7	484.7
AUC_{0-inf} (µg·h/mL)	17.2	49.0	234.6	562.1
V_d (kg/kg)	1.7	7.5	-	-
Cl_{total} (g/min/kg)	9.8	3.7	-	-

The bioavailability after oral administration was approximately 24 to 27%.

5. (^{14}C)-CC-10004: A study of absorption, excretion and metabolism following oral and intravenous administration to the cynomolgus monkey. Study number: 1398/399-D1145. This was a GLP-compliant, quality-assured report in which radiolabeled CC-10004 was administered intravenously (1 mg/kg) or orally (10 mg/kg) to male and female cynomolgus monkey. Blood was collected for pharmacokinetic analysis over 48 hours and feces and urine were collected over 168 hours. After intravenous administration the levels of CC-10004 were below the limit of quantification within 30 minutes therefore pharmacokinetic parameters were not calculated for the parent drug but only for total radioactivity. The blood to plasma concentration ratio throughout the sampling times was 0.6 indicating that drug did not penetrated well into blood cells. Mean pharmacokinetic parameters for total plasma radioactivity after intravenous administration are shown in the following table.

Parameter	Male	Female
$C_{(t)}$ (ng/g)	1671±86.57	1689±90.32
$t_{1/2}$ (h)	19.2±3.5	29.2±1.6
AUC_{0-t} (ng·h/g)	4195.5±384.7	4068.1±415.0
AUC_{0-inf} (ng·h/g)	4716.7±378.1	5063.1±370.9
V_z (kg/kg)	6.4±1.4	9.0±1.2
Cl_{total} (kg/h/kg)	0.23±0.02	0.21±0.02

Mean pharmacokinetic parameters for CC-10004 in plasma and total plasma radioactivity after oral administration are shown in the following table.

Parameter	CC-10004		Total radioactivity	
	Male	Female	Male	Female
C_{max} (ng/g)	2003.0±505.1	2291.5±163.5	3061±439.8	3862±433.2
$t_{1/2}$ (h)	2.0±0.05	1.7±0.6	20.9±1.2	21.7±2.4
AUC_{0-t} (ng·h/g)	7508.7±1119.6	8059.5±1650.9	27541.1±6477.9	29538.9±1405.6
AUC_{0-inf} (ng·h/g)	7812.2±1185.8	8322.2±1795.7	31951.6±7.62.3	34445.6±1048.4

The oral bioavailability was approximately 78%.

2.6.4.4 Distribution

Quantitative whole body radiography was conducted in mice in the study described above (1398/376-D1145). After oral administration the highest levels of radioactivity were detected in the gastrointestinal tract, kidney, liver and pancreas. The CNS tissues appeared to have lower levels than most other tissues. Levels diminished in all tissues with time. Skin levels were similar to other tissues and decreased with time. By 72 hours only the liver had quantifiable levels of radioactivity and by 168 hours no radioactivity was detected in any tissue in albino mice. Radioactivity in the uveal tract of pigmented mice was approximately 3 times greater than in albino mice. In albino mice this level was below the limit of quantification by day 3 and in the pigmented mice it was below the limit of quantification by day 7. Other tissues in the pigmented mice also had quantifiable

levels of radioactivity on day 3 while only the liver had quantifiable levels on day 3 in the albino mice.

2.6.4.5 Metabolism

The following figure was taken from the report and summarizes the metabolites identified by LC-MS in the rat study described above (1398/259-D1145). The metabolites labeled RP, RF and RU were found in plasma, feces and urine respectively. Other unidentified components were also found and the principle radioactive peak was not identified. Aside from this unidentified compound the most common metabolites in plasma and urine were 10, 11 and 12. Metabolites 15 and 18 were the most common in feces. The parent compound (20) was mostly not detected in plasma of males but was routinely detected in females.

Principal metabolites of (b) (4) identified in the rat

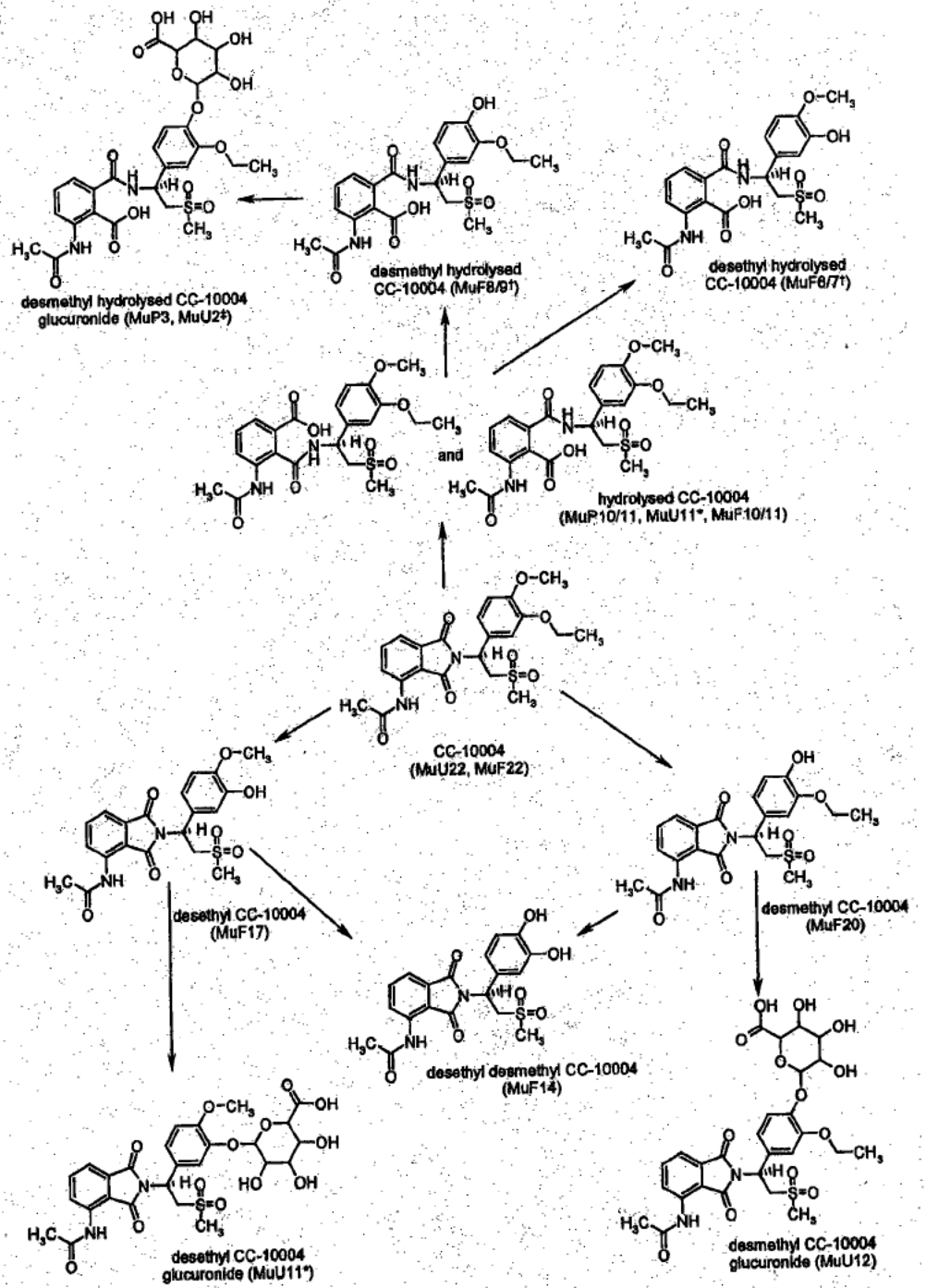
(b) (4)

(b) (4)

The following figure is taken from the report of the mouse study described above (1398/376-D1145). It shows the primary identified metabolites. CC-10004 was extensively metabolized in the mouse. The metabolites identified in the urine and feces

represented 44-65% of the administered radioactivity after intravenous dosing and 56-61% of the dose after oral dosing.

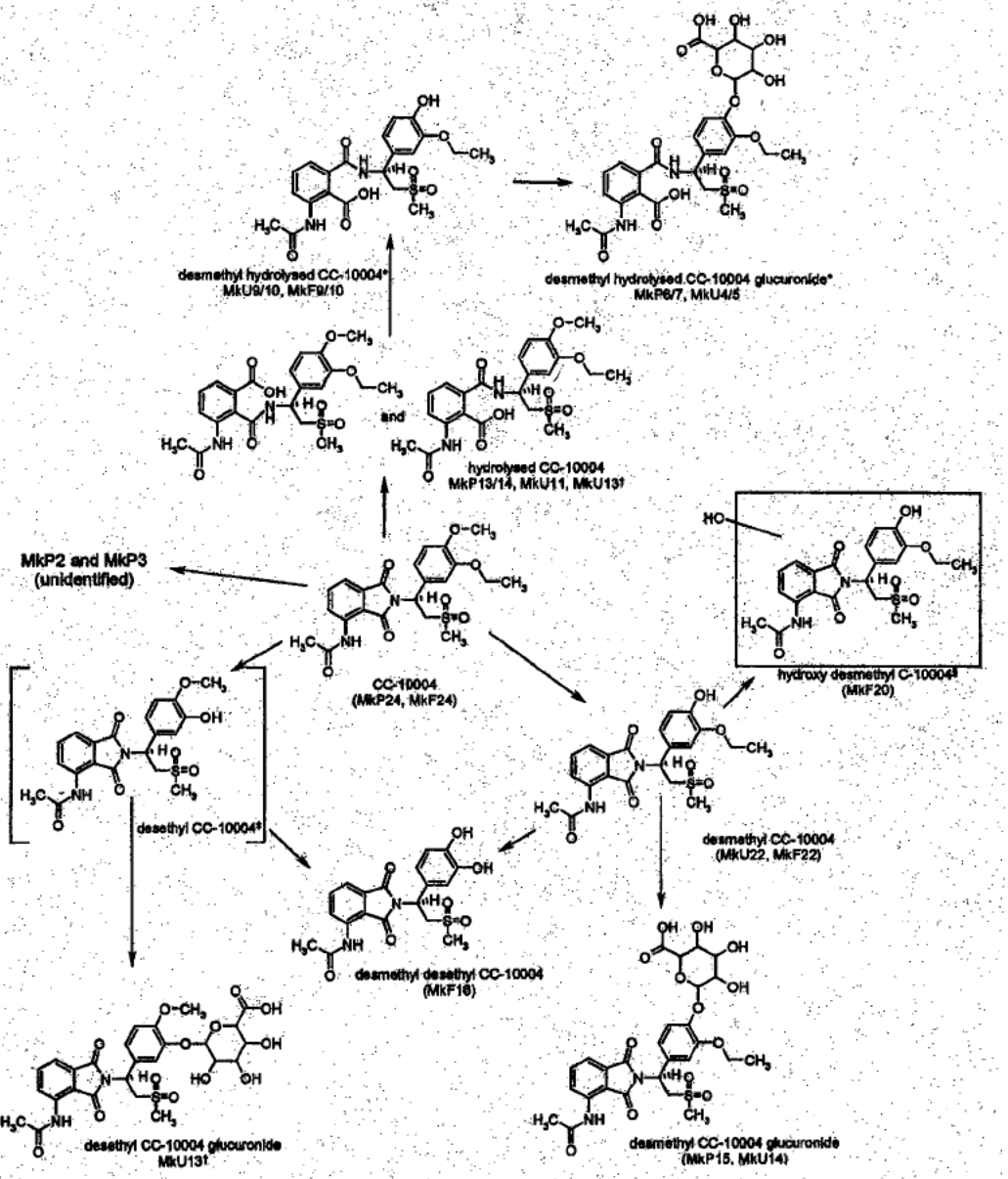
Proposed major metabolic pathways of CC-10004 in the mouse



*: radioactive peak MuU11 contained at least two test substance-related components
†: both hydrolysis products undergo dealkylation; for clarity, only one isomer shown
‡: its was not possible to determine which of the two hydrolysis products MuP3 or MuU2 were derived from

The following figure is taken from the report of the monkey study described above (1398/399-D1145). CC-10004 was extensively metabolized in the monkey. Only low levels of unchanged CC-10004 were present in feces even after oral administration. The principal routes of metabolism appear to be hydrolysis of the imide bond, demethylation and conjugation with glucuronic acid. The most abundant metabolites found in the feces are labeled in the figure as MkF9, MkF10 MkF21 and MkF22. The most abundant metabolite in the urine was MkU14. MkP6, MkP13 and MkP14 appear to be the most consistently observed metabolites in plasma although other metabolites were occasionally higher.

Principal metabolites of CC-10004 in the cynomolgus monkey



*: both hydrolysis products undergo further biotransformation; for clarity, only one isomer is shown
†: the principal component under peak MkU13 was identified as desethyl CC-10004 glucuronide. However, this peak also contained relatively weak ions indicating the presence of hydrolysed CC-10004.
‡: not identified in this study.
§: the position of hydroxylation could not be determined from the data generated.

6. Metabolic stability of (b) (4) CC-10004 (b) (4) and racemic (b) (4) in microsomes isolated from male and female rat, monkey and human and human cDNA expressed isozymes and identification of major metabolites in plasma from orally dosed rats. Study number: 1398/186-D1145. There was a relatively high degree of loss of the parent compound even in control incubations in this study (30%).

There appeared to be only a small amount of in vitro metabolism. Only trace amounts of N-deactylated, O-desmethyl and O-desethyl metabolites were detected in the microsomal incubation samples. No evidence of selective metabolism by human cDNA expressed CYP isozymes was noted (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). Given the limitations of the studies, there was no evidence for selective metabolism of the enantiomers.

7. Metabolism of [^{14}C]-CC-10004 and [redacted] in microsomes isolated from mouse, rat, rabbit, dog, monkey and man. (Study No. 1398/261). A number of components were found in the *in vitro* incubations although some of these were degradants instead of metabolites since they were also observed in the control incubations. The major metabolite was M3 which is the O-desmethyl metabolite. This was observed in all species and sexes except the female rat. Another metabolite (M5 tentatively the O-desethyl metabolite) was found in mouse and monkey incubations. Several other minor metabolites were apparent. The human was most similar quantitatively and qualitatively to the dog and male rat.

8. Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of [^{14}C]-CC-10004 in human liver microsomes. (Study No. 1398/393). Metabolism in following human microsomes and cDNA expressed isozymes was assessed: CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The greatest metabolism occurred with CYP3A4 and CYP2A6. Lesser amounts of metabolism occurred with CYP1A2, CYP2C8, CYP2C19 and CYP2E1.

2.6.4.6 Excretion

In the rat study described above (1398/259-D1145), the principle route of excretion for CC-10004 [redacted] was the feces over the 24 hour observation period; however, significant radioactivity was also observed in the urine. Total recovery in this study varied from 25 to 88% and the residual radioactivity in the carcass was not assessed.

In the mouse study described above (1398/376-D1145), the principle route of excretion was the feces. Approximately 70% of the excreted radioactivity was recovered within the first 24 hours after intravenous administration and within 48 hours after oral administration.

In the monkey study described above (1398/399-D1145), the principle route of excretion was the feces (70% of the dose). About 80% of the dose was excreted by 168 hours after intravenous dosing and about 95% was excreted by 168 hours after oral administration.

2.6.4.7 Pharmacokinetic drug interactions

9. Effects of CC-10004 on selected cytochrome P450 activities in human liver microsomes: prediction of drug interactions. (Study No. 1398/227). The ability of CC-10004 to inhibit that metabolism of select P450 substrates was investigated in human liver microsomes. CC-10004 did not inhibit marker enzyme activity for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

2.6.4.8 Other Pharmacokinetic Studies

(b) (4)

11. CC-10004: *In vitro* binding to plasma proteins in rat, mouse, dog, rabbit, monkey and human, (b) (4) *in vitro* binding to plasma proteins in rat. (Study No. 1398/293). Corrected plasma protein binding of [^{14}C]-CC-10004 were 96.9, 96.5, 93.9, 99.7, 98.5 and 99.5% in rat, mouse, rabbit, dog, monkey and human, respectively. Corrected plasma protein binding of (b) (4) was 100% in the rat since no free drug could be detected.

2.6.4.9 Discussion and Conclusions

Oral bioavailability of CC-10004 is variable. The primary route of excretion is in the feces. Half life appears to be around a day in mouse and monkey and possibly shorter in rats. CC-10004 appears to have relatively low potential to inhibit CYP450 mediated metabolism. CC-10004 is relatively highly protein bound although the binding does vary somewhat between doses.

2.6.4.10 Tables and figures to include comparative TK summary

See summaries above.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Arteritis was one of the primary toxicity findings in repeat dose studies. In 4 week studies in mice arteritis was seen at doses as low as 5 mg/kg. The NOEL was 4 mg/kg for both males and females. The arteritis occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. Neutrophil and globulin levels were also increased. Other findings included centrilobular liver hypertrophy, effects on the stomach and lymphoid tissue effects.

Four week dosing with CC-10004 in monkeys resulted in increased neutrophil levels at all doses of 50, 180 and 650 mg/kg. One high dose male had a body weight loss of 10%.

Slight increases in liver weight were also observed in all drug treated groups. Several occurrences of vasculitis were noted in the 180 and 650 mg/kg groups although these were infrequent and did not follow a dose response. A NOEL was not identified, although the 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse.

In monkeys treated for 13 weeks, the effects that appeared to be drug related included salivation at all doses (25, 85 and 300 mg/kg or 300, 1020 and 3600 mg/m^2) and vomiting at the high dose. In addition, there was an increase in hepatocyte vacuolation that was not dose related. No vasculitis was described. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug treated animals. A NOEL was not established. The report considered 300 mg/kg a NOAEL.

Genetic toxicology:
CC-10004 did not induce mutations in the in the *Salmonella typhimurium* reverse mutation assay. CC-10004 did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. CC-10004 did not induce micronuclei in the bone marrow of mice after two daily oral gavage administrations of up to 2000 mg/kg.

Carcinogenicity:
No carcinogenicity studies have been conducted with CC-10004 at this time.

Reproductive toxicology:
Oral doses of 250, 500 and 750 mg/kg (2250 mg/m^2) were not teratogenic in the mouse. Although these doses did cause decreased fetal weight and delayed ossification.
Oral doses of 250, 500 and 1000 mg/kg (12,000 mg/m^2) were not teratogenic in the rabbit.

Special toxicology:
A special study of CC-10004 was conducted in rats to assess possible biomarkers of inflammation and vasculitis. The animals were treated by oral gavage with 0 (vehicle), 6 or 10 mg/kg using a dose volume of 5 mL/kg for 7 consecutive days. Some animals were maintained for an additional 11 day recovery period and sacrificed on day 18 while other animals were sacrificed on days 3, 6, 8 and 14. CC-10004 caused an acute inflammatory reaction in female rats. This was characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment. Peritoneal fluid increased (ascites) and analysis of this fluid also showed markers of inflammation. Decreased leptin and increased lipase levels suggested that adipocytes may be affected.

2.6.6.2 Single-dose toxicity

1. Study title: Single dose intravenous toxicity study in the mouse.
Study Number: 1398/279-D6154
Volume #9, and page # 1 (submission not consecutively numbered)

Conducting laboratory and location: [redacted]

Date of study initiation: 10 October 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch number FP0032, 97.57% pure by HPLC

Methods: Drug was dispersed in 8% v/v DMSO in Intralipid 20. Dose volume was 20 mL/kg. In a preliminary experiment one male and one female Crl:CD-1 (ICR)BR mouse per dose was injected via the tail vein with 50, 75, 100 150 or 200 mg/kg. In the main study five male and five females were injected with a single dose of 120 mg/kg. Clinical signs were observed frequently on day 1, twice daily on days 2, 3 and 4 and once daily until the end of the study. Mice were weighed on day -1, 1, 4, 8, and 15 of the main study. Mice were killed on day 8 for the preliminary study and day 15 for the main study. Gross necropsies were performed.

Results:

Preliminary study:

The male dosed with 150 mg/kg and both animals dosed with 200 mg/kg died within 30 minutes of dosing. Clinical signs before death included gasping, unkempt appearance and proneness. Clinical signs among the lower dose groups included tachypnoea, lethargy and palpebral closure for 24 to 48 hours. No effect on body weight was observed and no gross abnormalities were observed at necropsy.

Main Study:

One male died during drug administration. All surviving mice developed tachypnoea immediately after dosing that persisted for at least 4 hours, but that resolved by day 2. Males also exhibited palpebral closure 3 to 4 hours after dosing. No effect on weight gain was apparent although there is no control data for comparison. No macroscopic abnormalities were observed.
(*Note: The individual animal data in the report does not identify the sex of the individual animals.*)

Individual study conclusion:

The minimum lethal dose of CC-10004 in mice after single intravenous administration appears to be approximately 120 mg/kg.

2. Study title: Single dose oral toxicity study in the mouse.
Study Number: 1398/278-D6154
Volume #9, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]

Date of study initiation: 10 October 2001
GLP compliance: Yes
QA report: Yes

Drug, lot #, and % purity: CC-10004, batch number FP0032, 97.57% pure by HPLC

Methods: Drug was dispersed in 1% aqueous carboxymethylcellulose. Dose volume was 10 mL/kg. In a preliminary experiment one male and one female Crl:CD-1 (ICR)BR mouse were treated by gavage with 2000 mg/kg. In the main study five male and five females were treated by gavage with 2000 mg/kg. Clinical signs were observed frequently on day 1, twice daily on days 2, 3 and 4 and once daily until the end of the study. Mice were weighed on day -1, 1, 4, 8, and 15 of the main study. Mice were killed on day 8 for the preliminary study and day 15 for the main study. Gross necropsies were performed.

Results:

Preliminary study:

Neither mouse dosed with 2000 mg/kg died. Clinical signs included tachypnoea within two hours of dosing but this resolved by 4 hours and the male had palpebral closure on day 1. No effect on body weight was observed and no gross abnormalities were observed at necropsy.

Main Study:

There were no deaths. Two males exhibited palpebral closure on day 1 or 2. No effect on weight gain was apparent although there is no control data for comparison. No macroscopic abnormalities were observed.

Individual study conclusion:

The minimum lethal dose of CC-10004 in mice after single oral administration appears to be greater than 2000 mg/kg.

3. Study title: Single dose intravenous toxicity study in the rat.
Study Number: 1398/277-D6154
Volume #9, and page # (submission not consecutively numbered)
Conducting laboratory and location: [redacted]

Date of study initiation: 10 October 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch number FP0032, 97.57% pure by HPLC

Methods: Drug was dispersed in 8% v/v DMSO in Intralipid 20. Dose volume was 20 mL/kg. In a preliminary experiment one male and one female Crl: WI(Glx/BRL/Han)BR rat per dose was injected via the tail vein with 50, 75 or 100 mg/kg. A further group of two male and two female rats were dose with 60 mg/kg. In the main study five male and five females were injected with a single dose of 60 mg/kg. Clinical signs were observed frequently on day 1, twice daily on days 2, 3 and 4 and once daily until the end of the study. Mice were weighed on day -1, 1, 4, 8, and 15 of the main study. Mice were killed

on day 8 for the preliminary study and day 15 for the main study. Gross necropsies were performed.

Results:

Preliminary study:

The females dosed with 75 and 150 mg/kg died within 24 hours. Clinical signs at 75 and 150 mg/kg included tachypnoea, lethargy, hematuria, salivation, palpebral closure pilo-erection, and rales with isolated cases of tremors or stained snout. Prior to death the females showed anogenital soiling, hunched posture and labored breathing. Animals in the 50 and 60 mg/kg dose groups also showed some of these signs. The females that died and surviving females showed weight loss. Upon necropsy the female at 1000 mg/kg that died had gelatinous mandibular lymph nodes, slight gastric distension and the stomach contained a clear fluid.

Main Study:

There were no deaths. All animals developed tachypnoea immediately after dosing and other signs developed later such as lethargy, lacrimation, pilo-erection, stained snout and unkempt appearance. Some animals also exhibited palpebral closure and anogenital soiling. Females exhibited transient decreases in body weight although there is no control data for comparison. No macroscopic abnormalities were observed when animals were sacrificed on day 15.
(*Note: The individual animal data in the report does not identify the sex of the individual animals.*)

Individual study conclusion:

The minimum lethal dose of CC-10004 in rats after single intravenous administration appears to be between 60 and 75 mg/kg.

4. Study title: Single dose oral toxicity study in the rat.
Study Number: 1398/276-D6154
Volume #9, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]
Date of study initiation: 10 October 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch number FP0032, 97.57% pure by HPLC

Methods: Drug was dispersed in 1% aqueous carboxymethylcellulose. Dose volume was 10 mL/kg. In a preliminary experiment one or two male and female Crl:WI(Glx/BRL/Han)BR rats were treated by gavage with 1000, 1500 or 2000 mg/kg. In addition, groups of 2 or 3 females were also dosed at 200, 400 or 700 mg/kg. In the main study five male rats were treated by gavage with 2000 mg/kg and five female rats were treated by gavage with 300 mg/kg. Clinical signs were observed frequently on day 1, twice daily on days 2, 3 and 4 and once daily until the end of the study. Mice were

weighed on day -1, 1, 4, 8, and 15 of the main study. Mice were killed on day 8 for the preliminary study and day 15 for the main study. Gross necropsies were performed.

Results:

Preliminary study:

The one male dosed at 2000 mg/kg exhibited palpebral closure, staining of snout, pilo-erection, anogenital soiling, an unkempt and wasted appearance. This mouse was not sacrificed at 8 days, but was held until day 15. The animal lost weight until day 8 and the clinical signs resolved by day 12. No gross abnormalities were observed at necropsy in the males. All of the females at 700, 1000, 1500 and 2000 mg/g died on day 3 or 4. Extensive clinical signs of ill-health were observed. Gross necropsies revealed no abnormalities for rats treated at 700 mg/kg but at higher doses dark foci, red areas and distension in the stomach and jejunum were common and isolated changes to the thymus, lungs, spleen and adrenals were noted. At 400 mg/kg, one of three females died on day 4. Both females treated with 200 mg/kg survived. Weight loss was apparent at day 4 at 200 and 400 mg/kg. Staining of the snout, anogenital soiling and unkempt appearance was observed at 200 and 400 mg/kg. No gross abnormalities were observed in the surviving females at 400 mg/kg or either female at 200 mg/kg but red inflated lungs were observed in the one that died at 400 mg/kg.

Main Study:

One of five males died at 2000 mg/kg. Vasodilation was noted on day 1 in all males. Diarrhea was observed in all males on day 5 and 6. Other general signs of ill health were noted in the male that died and in one other male. Tachypnoea was noted shortly after drug administration in the females given 300 mg/kg. This persisted for 7 days. Other commons signs of ill health observed in females through the study included discolored feces, lethargy, pilo-erection, hunched posture, unkempt appearance, stained snout, anogenital soiling and a wasted appearance. Weight loss was observed it he two males rats that showed clinical signs and all females lost weight during the first 8 days after dosing. No macroscopic abnormalities were observed.

Individual study conclusion:

A sex difference was apparent in this study. The minimum lethal dose of CC-10004 in male mice appears to be 2000 mg/kg or greater while it may be 300 mg/kg in females.

2.6.6.3 Repeat-dose toxicity

5. Study title: CC-10004 [redacted] Oral (gavage administration) comparative toxicity study in the female rat. (Study No. 1398/213) Female rats (Crl:CD(SD)IGSBR; 15/group) were given vehicle or 50 mg/kg/day CC-10004 or 50 mg/kg/day [redacted] for 14 days. At the end of 14 days the rats dose with [redacted] were dosed for an additional 16 days due to absence of toxicity. All animals given CC-10004 were terminated after two doses due to poor condition characterized by weight loss, poor food consumption, thinness, hunched posture, staining of head and urogenital areas. Swollen abdomen was

observed on day 10 in animals receiving [redacted] One of these animals was sacrificed due to poor condition, but, in the remaining animals, the swelling resolved by day 17. There were no remarkable macroscopic findings. A dose of 50 mg/kg/day of CC-10004 was not well tolerated in female rats; whereas, a dose of 50 mg/kg/day [redacted] was relatively well tolerated in female rats for 30 days. (*This study is not reviewed in greater detail because of its limited scope and utility.*)

6. Study title: **CC-10004: 14 day oral (gavage) administration range-finding toxicity study in the mouse.** (Study No. 1398/262). Doses of 0, 500, 1000, 2000 mg/kg/day were given by gavage to CD-1 mice for 14 days. There were no mortalities or clinical observations related to treatment. Group mean body weight was lower for males in drug treated groups. Neutrophil counts were elevated in drug treated animals. Total protein levels were increased most notably at 1000 and 2000 mg/kg/day. Some gross distension, thickening, irregular surface and raised foci were noted in stomachs of drug treated animals. No histopathology was performed. (*This study is not reviewed in greater detail because of its limited scope and utility.*)

7. Study title: CC-10004: Maximum tolerated dose (MTD) followed by a 14 day fixed dose oral (gavage) administration toxicity study in monkey (Study No. 1398/283). Doses of 100, 300, 650 and 1000 mg/kg were administered sequentially to the same male and female cynomolgus monkeys (2 per sex) for four days for each dose. The sequence of dosing was 100, 300, 1000 then 650 mg/kg. There was a 3 day break between the 1000 and 650 mg/kg dose. Then naïve male and female monkeys (2/sex) were administered 750 mg/kg/day for 14 days. Vomiting was noted at dose of 300 mg/kg and above. At the end of the dose escalation phase the monkeys had slight reductions in body weight, reduced red cell parameters and increased neutrophils. Organ weights were unaffected and there were no macroscopic findings for this phase. In the 14 day phase, vomiting and reduced food consumption were noted. Body weight was reduced 9 to 14% after the 14 days of dosing. Red cell parameters were reduced and neutrophils and plasma globulins were increased. Organ weights were unaffected. Thymic atrophy was noted grossly and microscopically. The 750 mg/kg dose was considered the MTD for 14 days of treatment although it was also considered not suitable for longer term studies. (*This study is not reviewed in greater detail because of its limited scope and utility.*)

8. Study title: **CC-10004: 28 day oral (gavage) administration toxicity study in the mouse**

Key study findings: CC-10004 induced arteritis in the mouse at doses of 250, 600 and 1500 mg/kg. This occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. The arteritis was described as acute inflammatory cell infiltrate in all layers of the vessel wall, perivascular edema and hemorrhage, disruption of the elastic lamina, occasional minor areas of necrosis and areas of fibrosis. Neutrophil and globulin levels were also increased. Other findings included centrilobular liver hypertrophy, effects on the stomach and lymphoid tissue effects.

Study no.: 1398/289

Volume #11, and page #1 of volume
Conducting laboratory and location: [redacted]
Date of study initiation: December 18, 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61548-01, purity stated as 97.5%

Methods

Doses: 0, 250, 600, 1500 mg/kg/day
(The report notes that the dose of 1500 mg/kg could be delivered with a dose concentration of 75 mg/mL while a higher dose concentration of 100 mg/mL was too viscous to pass through the dosing catheter.)

Species/strain: mouse/CD-1

Number/sex/group or time point (main study): 12/sex/group

Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 20 mL/kg

Satellite groups used for toxicokinetics or recovery: 18 animals /sex/dose except only 3/sex in control

Age: 6-8 weeks

Weight: males 27.0 to 40.3 g, females 18.4 to 30.9 g

Results:

Mortality: One male at 1500 mg/kg was found dead during week 2 and this was determined to be due to a gavage error. One female in the 1500 mg/kg groups was found dead during week 5 and one female in this group was sacrificed early due to morbidity during week 4. The cause of death was considered to be arteritis particularly of organs of the thoracic cavity. One female in the 600 mg/kg dose groups was found dead during week 2. No cause of death was determined for this animal.

Clinical signs: The female in the 1500 mg/kg group that was sacrificed on week 4 was noted as sluggish and cold with rapid respiration. Swollen abdomen was noted in two females at 1500 mg/kg and one female at 600 mg/kg. One female in the 1500 mg/kg group was noted as hunched at week 5 and one female in the 600 mg/kg group was noted as hunched and thin in weeks 4 and 5.

Body weights: Body weight gain in 1500 mg/kg males was lower than control males although the difference was not statistically significant (control weight gain=3.5 g versus 1500 mg/kg weight gain=2.7 g). Other groups gained weight similarly to control.

Food consumption: Group mean food consumption in females was 38.3, 35.7, 36.5 and 32.8 g/animal/week in control, 250, 600 and 1500 mg/kg groups, respectively The difference between control and 1500 mg/kg was statistically significant. Food consumption in males was similar in all groups.

Ophthalmoscopy: The only reported finding after pre-treatment and week 4 ophthalmoscopic examinations was hyper-reflectivity of the fundus in one control female at week 4.

EKG: Not assessed.

Hematology: Increased neutrophil count and decreased lymphocyte counts were noted in drug treated groups with these findings reaching significance in the 1500 mg/kg group. These findings are summarized in the following table.

Group	Neutrophils		Lymphocytes	
	1000/cmm	%WBC	1000/cmm	%WBC
Males				
0	0.8	13	4.0	76
250	1.9	30	3.9	64
600	2.4	35	3.1	58
1500	2.3	38*	2.3	55
Females				
0	0.6	13	3.6	81
250	1.3	25	3.5	68
600	1.0	27	2.3	65
1500	4.5*	48*	2.9	44*

*Statistically significantly different from control

Clinical chemistry: Total protein levels increased with drug treatment. This appeared to be due to increased levels of globulin which was reflected in globulin levels and decreased albumin/globulin ratios.
These findings are summarized in the following table.

Group	Total protein	Albumin	Globulin	A/G ratio
	g/L	g/L	g/L	
Males				
0	51	34	17	2.0
250	54	31	23	1.4*
600	57*	32	25*	1.3*
1500	58*	32	26*	1.3*
Females				
0	49	36	14	2.6
250	56*	32	23*	1.5*
600	55*	30*	24*	1.3*
1500	57*	32*	26*	1.3*

*Statistically significantly different from control

Total bilirubin was statistically significantly decreased in drug treated animals compared to control.

Urinalysis: Not assessed.

Gross pathology: Large livers were noted in one male in the 600 mg/kg group and one in the 1500 mg/kg group. Large livers were noted in one female in each of the control, 250 and 600 mg/kg groups and three females in the 1500 mg/kg group. Large spleens were noted in 1, 2 and 4 females in the 250, 600 and 1500 mg/kg groups, respectively. Stomach findings such as distension, paleness, raised foci and thickening were noted in drug treated animals and not control animals and the frequency of these findings appeared to increase with dose. Distension in other parts of the gastrointestinal tract was also noted in occasionally in other drug treated animals. A large mandibular lymph node was noted in two females in the 600 mg/kg group and two females in the 1500 mg/kg group. Gall bladder distension was noted in one male and two females in the 600 mg/kg group and one female in the 1500 mg/k group.

Organ weights: Liver weight was increased in drug treated animals compared to controls. Although the group mean liver weight was only statistically different from controls in the 1500 mg/kg males where the liver weight was increased approximately 11%. Spleen weights were also elevated approximately 19 to 65% in drug treated animals compared to controls and this was statistically significant in males in the 250 mg/kg group and in males and females in the 1500 mg/kg group. Testes/epididymides weight was slightly but statistically higher in the males treated with 600 and 1500 mg/kg and brain weight was slightly but statistically lower in females treated with 1500 mg/kg.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)
Note: The complete list of tissues was only examined in the control and high dose animals and in all decedents. Femur and marrow, liver, spleen, mesenteric lymph nodes, stomach, mandibular lymph nodes, heart, lung and thymus were examined in all groups after the results of the initial assessment.

The following table is taken from the report and shows selected microscopic findings.

Group incidence of selected microscopic findings – all animals

Tissue and finding	Level (mg/kg/day)	Males 1M 0	2M 250	3M 600	4M 1500	Females 1F 0	2F 250	3F 600	4F 1500
Heart	No. examined:	12	12	12	12	12	12	12	12
arteritis	Incidence	0	2	5	3	0	2	3	8
Lung	No. examined:	12	12	12	12	12	12	12	12
arteritis	Incidence	0	4	4	6	0	1	6	6
Thymus	No. examined:	12	11	12	12	12	12	12	12
arteritis	Incidence	0	0	3	4	0	0	0	3
Liver	No. examined:	12	12	12	12	12	12	12	12
centrilobular hypertrophy	Incidence	0	4	5	7	0	2	5	8
Stomach	No. examined:	12	12	12	12	12	12	12	12
hyperkeratosis	Incidence	0	6	8	10	0	6	10	10
forestomach gastritis	Incidence	0	0	0	1	0	0	0	2
Joint	No. examined:	12	12	12	12	12	12	12	12
synovitis	Incidence	0	1	0	2	0	0	0	3
Spleen	No. examined:	12	12	12	12	12	12	12	12
haemopoiesis	Grade -	2	0	1	2	1	2	0	0
	1	3	1	0	0	6	3	0	1
	2	5	6	5	2	3	3	4	2
	3	2	4	6	8	2	3	8	7
	4	0	1	0	0	0	1	0	2

Key: "-" = finding not present, 1 = minimal, 2 = slight, 3 = moderate, 4 = moderately severe,

Arteritis was also noted occasionally in a variety of other organs in drug treated animals such as the femur, sciatic nerve, pancreas, lymph nodes, stomach, ileum, cecum, kidney, urinary bladder, uterus and thyroid. The arteritis was described as acute inflammatory cell infiltrate in all layers of the vessel wall, perivascular edema and hemorrhage, disruption of the elastic lamina, occasional minor areas of necrosis and areas of fibrosis.

The centrilobular hypertrophy in the liver, the hyperkeratosis and gastritis of the stomach and the hemopoiesis in the spleen are consistent with the gross findings noted above. An increased incidence of inflammatory cell foci, peribronchitis/bronchitis, pleuritis and pneumonitis was also observed in the lungs of drug treated animals. Lymph nodes and thymuses of drug treated animals also exhibited increased incidences of lymphoid hyperplasia, lymphocytolysis and medullary hyperplasia.

Toxicokinetics: Tmax in males and females was 2 to 4 hours at day 1 and 4 to 8 hours at day 28. C_{max} values were generally similar at day 1 and day 28 for all dose groups. AUC_{0-24} values were 10-20% higher in males and 10-40% higher in females at day 28 compared to day 1. AUC_{0-24} and C_{max} increased with dose although this increase was less than dose proportional. $T_{1/2}$ was between 2 and 10 hours. The following AUC_{0-24} values were obtained at day 28.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
250	101172.5	117864.7

600	162964.5	194261.8
1500	205842.4	279734.0

9. Study title: CC-10004: 4 week oral (gavage) administration toxicity study in the mouse

Key study findings: CC-10004 induced arteritis in the mouse. Some arteritis was observed at all doses (5, 25, 75, 150 mg/kg). Hyperkeratosis of the stomach was also noted at doses of 75 and 150 mg/kg. Lymphocytes were decreased at 25, 75 and 150 mg/kg. A NOEL was not established for males in this study.

Study no.: 1398/297
Volume #12, and page #1 of volume
Conducting laboratory and location: [redacted]
Date of study initiation: May 21, 2002
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61590-03, purity stated as 101.3%

Methods

Doses: 0, 5, 25, 75, 150 mg/kg/day
Species/strain: mouse/CD-1
Number/sex/group or time point (main study): 12/sex/group
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 20 mL/kg
Satellite groups used for toxicokinetics: 18 animals /sex/dose except only 3/sex in control
Age: 5½ weeks
Weight: males 23.6 to 31.8 g, females 20.1 to 26.4 g

Results:
Mortality: One male animal in the 75 mg/kg group was removed from the study on day 9 because of skin lesions and swelling on the back.
Clinical signs: No treatment related signs were noted during daily observations.
Body weights: Body weight was determined weekly and no affect of drug treatment noted.
Food consumption: Food consumption was determined weekly and no affect of drug treatment noted.
Ophthalmoscopy: No drug-related findings in control or high dose groups at week 4.
EKG: Not assessed.
Hematology: At week 4, lymphocytes were decreased 26 to 36% in males in groups receiving 25, 75 and 150 mg/kg and 29 to 39% in females in groups receiving 75 and 150 mg/kg.

Clinical chemistry: At week 4, albumin levels were reduced 9% and globulin levels increased 25% in females receiving 150 mg/kg. The A/G ratio was reduced 32%.
Organ weights: Organs weighed included kidneys, spleen, liver, heart, brain and testes/epididymides. Kidneys weights in females in the 150 mg/kg group were reduced approximately 12% compared to control.
Gross pathology: Most of the macroscopic findings were infrequent and not clearly related to the drug treatment. One female at 150 mg/kg had a thickened stomach.
Histopathology: Microscopic examination was conducted on gross lesions from all animals and the following tissues from all animals: heart, thymus, lung, bone marrow, mesenteric lymph node, mandibular lymph node and stomach. A complete set of tissues was examined from the control and high dose animals and the one animal sacrificed early.

The male animal from the 75 mg/kg group that was sacrificed on day 9 had moderately severe dermatitis/folliculitis in the skin and arteritis in the heart. The arteritis was described as consisting of acute inflammatory cell infiltrate in all layers of the vessel wall, disruption of the internal elastic lamina and minor necrosis and fibrosis.

Hyperkeratosis of the stomach was noted in 2 males and 1 female in the 75 mg/kg group and 3 males and 3 females in the 150 mg/kg group.

Arteritis was noted in several animals in different tissues.

The following table is taken from the report and it summarizes the arteritis and hyperkeratosis findings.

Group incidence of selected microscopic findings – all animals

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	5	25	75	150	0	5	25	75	150
Heart	No. examined:	12	12	12	12	12	12	12	12	12	12
arteritis	Incidence -	0	1	1	2	0	0	0	0	0	3
Lung	No. examined:	12	12	12	12	12	12	12	12	12	12
arteritis	Incidence -	0	0	0	2	1	0	0	0	0	0
Thymus	No. examined:	12	12	12	12	12	12	12	12	12	12
arteritis	Incidence -	0	0	1	0	0	0	0	0	0	0
Kidney	No. examined:	12	12	12	12	12	12	12	12	12	12
arteritis	Incidence -	0	0	0	0	1	0	0	0	0	0
Stomach	No. examined:	12	12	12	12	12	12	12	12	12	12
hyperkeratosis	Incidence -	0	0	0	2	3	0	0	0	1	3

Toxicokinetics: Tmax in males and females was 1 to 2 hours at day 2 and 1 to 8 hours at day 28. C_{max} values were generally similar at day 2 and day 28 for all dose groups. AUC_{0-24} values varied somewhat between days 2 and 28 although no clear pattern of accumulation was evident. AUC_{0-24} and C_{max} increased with dose although this increase was less than dose proportional. $T_{1/2}$ was between 4 and 30 hours. The following AUC_{0-24} values were obtained at day 28.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
5	6327.1	6254.2
25	16206.5	17108.9
75	54157.6	41374.4
150	65576.1	66846.3

10. Study title: **CC-10004: 4 week oral (gavage) administration toxicity study in the mouse**

Key study findings: Essentially no toxicity was observed in this study in mice with oral doses of CC-10004 of 1, 2, and 4 mg/kg. The NOEL was 4 mg/kg for both males and females.

Study no.: 1398/333
Volume #13**, and page** #1 of volume
Conducting laboratory and location: [redacted]
Date of study initiation: October 22, 2002
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61590-03, purity stated as 101.4%

Methods

Doses: 0, 1, 2, 4 mg/kg/day
Species/strain: mouse/CD-1
Number/sex/group or time point (main study): 12/sex/group
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 20 mL/kg
Satellite groups used for toxicokinetics: 18 animals /sex/dose except only 3/sex in control
Age: 8 weeks
Weight: males 29.3 to 41.8 g, females 22.5 to 30.8 g

Results:

Mortality: One male in the 4 mg/kg group died of gavage error.
Clinical signs: No treatment related signs were noted during daily observations.
Body weights: Body weight was determined weekly and no affect of drug treatment noted.
Food consumption: Food consumption was determined weekly and no affect of drug treatment noted.
Ophthalmoscopy: No drug-related findings in control or high dose groups at week 4.
EKG: Not assessed.
Hematology: No drug related changes were noted.
Clinical chemistry: No drug related changes of significance were noted.

Organ weights: Organs weighed included kidneys, spleen, liver, heart, brain and testes/epididymides. No drug related changes were noted.
Gross pathology: Most of the macroscopic findings were infrequent and not related to the drug treatment.
Histopathology: Microscopic examination was conducted on gross lesions from all animals and the following tissues from all animals: heart, thymus, lung and stomach. A complete set of tissues was examined from the control and high dose animals and the one animal that died early.
Most of the microscopic findings were infrequent and not related to drug treatment.

Toxicokinetics: Tmax in males and females was 1 to 2 hours at day 1 and 1 hour at day 28. C_{max} and AUC_{0-24} values were somewhat lower at day 28 than day 1. AUC_{0-24} and C_{max} increased with dose although this increase was greater than dose proportional at day 1 and approximately dose proportional on day 28. The following AUC_{0-24} values were obtained at day 28.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
1	841.8	881.8
2	2176.1	1375.5
4	3809.7	3991.9

11. Study title: CC-10004: 13 week oral (gavage) administration toxicity study in the mouse

Key study findings: Arteritis in the root of the aorta and the thymus was observed at 16 mg/kg (48 mg/m^2). No arteritis or other toxicities were observed at 8 mg/kg or lower. The NOAEL of CC-10004 appears to be 8 mg/kg (24 mg/m^2, AUC_{0-24} = 8987.5-9607.8 ng·h/mL) in mice after oral administration for 13 weeks.

Study no.: 1398/373
Volume #14, and page #1 of volume
Conducting laboratory and location: [redacted]
Date of study initiation: April 9, 2003
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61590-03, purity stated as 101.4%

Methods

Doses: 0, 2, 4, 8, 16 mg/kg
Species/strain: mouse / Crl:CD-1(ICR)BR
Number/sex/group or time point (main study): 12
Route, formulation, volume, and infusion rate: gavage, stock solution was 0.8 mg/mL in 1% carboxymethylcellulose, dose volume was 20 mL/kg

Satellite groups used for toxicokinetics: 18 animals/sex/dose except 3/sex/dose for control

Age: 6-7 weeks

Weight: males 20.6 to 34.9 g, females 20.9 to 28.2 g

Results:

Mortality: No drug related deaths occurred.

Clinical signs: There were no drug-related clinical signs.

Body weights: Group mean body weights were not significantly affected in drug treated groups compared to control. The group mean body weight gain was statistically lower in males treated with 8 mg/kg during the first 4 weeks of the study. However, it is not clear that this is a drug related effect since a decrease was not observed at 16 mg/kg and no decrease was observed in females (in fact, a significant increase in body weight gain was observed in females at 8 mg/kg).

Food consumption: Food consumption was not significantly affected in drug treated groups compared to control.

Ophthalmoscopy: No ophthalmic findings were noted in control or high dose animals during week 12.

EKG: Not assessed.

Hematology: There were only a few statistically significant changes in hematology parameters determined at week 13 but these do not appear to be drug related since the effects were small and sporadic.

Clinical chemistry: There were only a few statistically significant changes in clinical chemistry parameters determined at week 13 but these do not appear to be drug related since the effects were small and sporadic.

Urinalysis: Not assessed.

Gross pathology: The macroscopic findings appeared to be incidental and not related to drug treatment.

Organ weights: There did not appear to be any differences in the group mean organ weights for kidneys, livers, hearts, brains, spleens or testes/epididymides.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)
Note: The complete list of tissues was only examined in the control and high dose animals and in all decedents. Heart, lung and thymus were examined in all groups after the results of the initial assessment.

Arteritis at the root of the aorta was observed in the heart of one male and two females in the 16 mg/kg group. This was described as being characterized by minor, predominately mononuclear inflammatory cell infiltration, sometimes with cartilaginous metaplasia and intimal proliferation. In one of these females there was also perivascular inflammatory cell infiltration in the lung described as mononuclear cells infiltrating the blood vessel wall. In another female, without heart arteritis, minimal arteritis was noted in the thymus. No arteritis was noted in the heart, lung and thymus of the 2, 4 and 8 mg/kg groups although there appeared to be slightly greater incidence of inflammatory cell foci in the lungs of animals at 8 and 16 mg/kg.

Toxicokinetics: Tmax in males and females was 1 to 2 hours at both day 1 and week 13. AUC_{0-24} and C_{max} values were generally similar at day 1 and week 13 for all dose groups, indicating no accumulation. AUC_{0-24} increased approximately in a dose proportional manner while C_{max} increased in a less than proportional manner. $T_{1/2}$ was between 2 and 10 hours. The following AUC_{0-24} values were obtained at week 13.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
2	2143.2	2417.5
4	4068.5	4763.9
8	9607.8	8987.5
16	15959.8	14895.1

12. Study title: CC-10004 28 day oral (gavage administration) toxicity study in the monkey

Key study findings: Four week dosing with CC-10004 in monkeys resulted in increased neutrophil levels at all doses of 50, 180 and 650 mg/kg. One high dose male had a body weight loss of 10%. Slight increases in liver weight were also observed in all drug treated groups. Several occurrences of vasculitis were noted in the 180 and 650 mg/kg groups although these were infrequent and did not follow a dose response. A NOEL was not identified, although the 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse.

Study no.: 1398/296
Volume #15 **and page** #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]
Date of study initiation: May 1, 2002
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61590-03, purity stated as 101.4%

Methods

Doses: 0, 50, 180 and 650 mg/kg

Species/strain: cynomolgus monkey
Number/sex/group or time point (main study): 3/sex/dose
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 4 mL/kg
Satellite groups used for toxicokinetics or recovery: none, toxicokinetic sampling was performed on main study animals on day 1 and 28 predose and at 0.5, 1, 2, 4, 8, 12 and 24 hours after dosing.
Age: 60 to 99 weeks
Weight: 1.80 to 2.25 kg

Results:
Note: No statistical evaluation was conducted on the endpoints in the report.
Mortality: None.

Clinical signs: Vomiting was observed at 180 and 650 mg/kg. Salivation was observed in the drug treated groups immediately after dosing.

Body weights: Body weight was measured twice weekly. In general body weights were similar in the different groups through out the study, although one male in the 650 mg/kg group lost approximately 10% of its weight.

Food consumption: The methods section states that food consumption was monitored visually and any adverse effects noted. The report notes that no effect was noted although no further detailed results of these observations were provided in the report.

Ophthalmoscopy: The report states that no ophthalmologic findings were noted at pretreatment or during week 4.

EKG: EKGs were obtained pretreatment and in week 4. Only the heart rate, QT and QT_c data are presented and there does not appear to be an effect on these parameters.

Hematology: The neutrophil counts in the drug treated groups were higher than control at 4 weeks. The increase was 2, 2.3 and 4 fold for males and 1.6, 2.2 and 3.7 fold for females in the 50, 180 and 650 mg/kg groups, respectively.

Clinical chemistry: No effect at week 4.

Urinalysis: No effect at week 4.

Gross pathology: There were only a few gross pathology findings and these appear to be sporadic and not clearly related to drug treatment.

Organ weights: There appeared to be a slight increase in liver weights in all treated groups although in all cases this was no more than 25% greater than controls. There did not appear to be any differences in the group mean organ weights for adrenals, brain,

kidneys, hearts, spleens, pituitary, thyroids/parathyroids, prostate, ovaries, uterus or testes/epididymides.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
Tissues listed in histopathology table from all animals in all groups were examined.

There was an increase in intermediate erythroblasts at all doses in males. It is not clear if this is related to treatment since overall the erythropoietic cell count was similar in all groups, including control.

Most of the microscopic findings appeared to be infrequent and occurred with similar incidence in control and drug treated animals.

Vasculitis was noted in the connective tissue surrounding the sciatic nerve in one high dose female and one intermediate dose male. This was described as vascular wall degeneration/necrosis with formation of small thrombi, perivascular edema and minor inflammatory cell infiltration. There was also one occurrence of vasculitis in the small blood vessels within the connective tissue adjacent to the kidney in one high dose female.

Toxicokinetics: Tmax in males and females was 2 to 8 hours at day 1 and 1 to 8 hours on day 28. C_{max} values at 50 mg/kg were similar at day 1 and 28 in both sexes. C_{max} values at 180 and 650 mg/kg were greater at day 28 than at day 1 for both males and females. AUC_{0-24} values were generally similar at day 1 and 28 at 50 mg/kg for both sexes but AUC_{0-24} values at 180 and 650 mg/kg were higher at day 28 than at day 1 in both sexes. This may indicate the possibility of accumulation especially at the higher doses. Neither AUC_{0-24} or C_{max} increased in a dose proportional manner. Both were less than dose proportional. $T_{1/2}$ was very variable. At the 50 mg/kg dose the $T_{1/2}$ ranged from 3.5 to 193.4 hours. The following AUC_{0-24} values were obtained at day 28.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
50	15079.0	9665.6
180	52892.7	34772.4
650	78988.8	58271.1

13. Study title: CC-10004 13 week oral (gavage) administration toxicity study in the monkey

Key study findings: Effects that appeared to be drug related included salivation at all doses (25, 85 and 300 mg/kg or 300, 1020 and 3600 mg/m^2) and vomiting at the high dose. In addition, there was an increase in hepatocyte vacuolation that was not dose related. No vasculitis was described. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug treated animals. A NOEL was not established. The report considered 300 mg/kg a NOAEL.

Study no.: 1398/368
Volume #16 **and page #**(submission not consecutively numbered)
Conducting laboratory and location: [redacted]
Date of study initiation: April 9, 2003
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004, batch No. 61590-03, purity stated as 101.4%

Methods

Doses: 0, 25, 85 and 300 mg/kg
Species/strain: cynomolgus monkey
Number/sex/group or time point (main study): 3/sex/dose
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 4 mL/kg
Satellite groups used for toxicokinetics or recovery: none, toxicokinetic sampling was performed on main study animals on day 1 and during week 13 at 0.5, 1, 2, 4, 8, 12 and 24 hours after dosing.
Age: 80 to 108 weeks
Weight: males 2.05 to 2.51 kg, females 2.08 to 2.75 kg
Unique study design or methodology (if any):

Results:
Note: No statistical evaluation was conducted on the endpoints in the report.
Mortality: None.

Clinical signs: Salivation was observed in the drug treated groups immediately after dosing. In the 300 mg/kg group retching, white froth and vomiting was also observed. Other clinical signs noted in drug treated animals but not control included thinning fur and soft feces. These did not appear to follow a dose response, however, so it is not clear that they are related to drug treatment.

Body weights: Although animals in the 85 and 300 mg/kg groups had lower body weights through out the study, this appears to be associated with a lower starting body weight for these animals. The body weight gain was similar for all groups.

Food consumption: The methods section states that food consumption was monitored daily and any adverse effects noted. No information on the results of these observations is provided in the report.

Ophthalmoscopy: No ophthalmoscopic findings were noted at pretreatment or during week 12.

EKG: EKGs were obtained pretreatment and in week 12. The report states that there were no treatment related effects on EKG waveform. Only the heart rate data are presented and there does not appear to be an effect on heart rate.

Hematology: The neutrophil counts in the drug treated groups were sometimes higher than control at 9 and 13 weeks. However, these effects did not follow a dose response so it is not clear that they were drug-related.

Clinical chemistry: No effect at week 13.

Urinalysis: No effect at week 12.

Gross pathology: There were only a few gross pathology findings and these appear to be sporadic and not clearly related to drug treatment.

Organ weights: There did not appear to be any differences in the group mean organ weights for adrenals, brain, kidneys, livers, hearts, spleens, pituitary, thyroids/parathyroids, prostate, ovaries, uterus or testes/epididymides.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
Tissues listed in histopathology table from all animals in all groups were examined.

There appeared to be a slightly greater incidence and severity of hepatocyte vacuolation in drug treated animals although a clear dose response was not evident. The finding was described as being clear vacuoles with indistinct borders in the cytoplasm of hepatocytes, especially in the centrilobular region. The report states that this is suggestive of glycogen vacuolation which is a common background finding.

Inflammatory cell foci were noted in a number of tissues. In the liver, the drug treated groups appeared to have higher incidence of inflammatory cell foci. In addition, most drug treated groups and in particular the 300 mg/kg group had a greater overall incidence of inflammatory cell foci if this finding is summed across all tissues.

Toxicokinetics: Tmax in males and females was 2 to 8 hours at day 1 and 1 to 4 hours during week 13. C_{max} values at 25 mg/kg were similar at day 1 and at week 13 in both sexes. C_{max} values at 85 mg/kg were similar at day 1 and week 13 for males but C_{max} values at 85 mg/kg were greater at week 13 than at day 1 for females. C_{max} values at 300 mg/kg were higher at week 13 than at day 1 in both males and females. AUC_{0-24} values were generally similar at day 1 and week 13 at 25 and 85 mg/kg for both sexes but AUC_{24} values at 300 mg/kg were higher at week 13 than at day 1 in both sexes. This may indicate the possibility of accumulation especially at the higher doses. Neither AUC_{0-24} or C_{max} increased in a dose proportional manner. Both were less than dose proportional. $T_{1/2}$ was very variable. At the 25 mg/kg dose the $T_{1/2}$ ranged from 3.4 to 12.0 hours. The following AUC_{0-24} values were obtained at week 13.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
25	13254.2	12460.9
85	12592.2	20293.1

300	32523.2	23306.7

Histopathology inventory

Study	1398/373 13 week	1398/368 13 week	1398/297 4 week	1398/289 28 day	1398/296 28 day
Species	Mouse	Monkey	Mouse	Mouse	Monkey
Adrenals	X	X*	X	X	X*
Aorta	X	X	X		X
Bone Marrow smear	X		X	X	X
Bone (femur)	X	X	X	X	X
Brain	X*	X*	X*	X*	X*
Cecum	X	X	X	X	X
Cervix					
Colon	X	X	X	X	X
Duodenum	X	X	X	X	X
Epididymis	X*	X*	X	X*	X*
Esophagus	X	X	X	X	X
Eye	X	X	X	X	X
Fallopian tube					
Gall bladder	X	X	X	X	X
Gross lesions	X	X	X	X	X
Harderian gland	X				
Heart	X*	X*	X*	X*	X*
Ileum	X	X	X	X	X
Injection site					
Jejunum	X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*
Lachrymal gland					
Larynx	X		X		
Liver	X*	X*	X*	X*	X*
Lungs	X	X	X	X	X
Lymph nodes, cervical					
Lymph nodes mandibular	X	X	X	X	X
Lymph nodes, mesenteric	X	X	X	X	X
Mammary Gland	X	X	X	X	X
Nasal cavity					
Optic nerves	X	X	X	X	X
Ovaries	X	X*	X	X	X*
Pancreas	X	X	X	X	X
Parathyroid	X	X*	X	X	X*
Peripheral nerve					
Pharynx					
Pituitary	X	X*	X	X	X*
Prostate	X	X*	X	X	X*
Rectum					
Salivary gland	X	X	X	X	X
Sciatic nerve	X	X	X	X	X

Seminal vesicles	X	X	X		X
Skeletal muscle	X	X	X		X
Skin	X	X	X	X	X
Spinal cord	X	X	X	X	X
Spleen	X*	X*	X*	X*	X*
Sternum	X	X	X	X	X
Stomach	X	X	X	X	X
Testes	X*	X*	X*	X*	X*
Thymus	X	X	X	X	X
Thyroid	X	X*	X	X	X*
Tongue	X	X	X		X
Trachea	X	X	X	X	X
Urinary bladder	X	X	X	X	X
Uterus	X	X*	X	X	X*
Vagina	X	X	X		X
Zymbal gland					

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

1. Study title: **CC-10004; Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium***

Key findings: CC-10004 did not induce mutations in the in the *Salmonella typhimurium* reverse mutation assay.

Study no.: 1398/282

Volume #16**, and page** #(submission not consecutively numbered)
Conducting laboratory and location: [redacted] (b) (4)
[redacted] (b) (4)

Date of study initiation: October 30, 2001
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: CC-10004, batch No. FP0032, purity not provided

Methods

Strains/species/cell line: *Salmonella typhimurium* / strains TA98, TA100, TA1535, TA1537 and TA102

Doses used in definitive study: 156.25, 312.5, 625, 1250, 2500, 5000 µg/plate

Basis of dose selection: dose range finder study with doses of 1.6, 8, 40, 200, 1000 and 5000 µg/plate, in which toxicity to background lawn was assessed and revertant colonies counted.

Negative controls: DMSO

Positive controls: With S9: benzo[a]pyrene for TA98 and 2 aminoanthracene for the rest of the strains

Without S9: 2-nitorfluorene for TA98, sodium azide for TA100 and TA1535, 9-aminoacridine for TA1537, glutaraldehyde for TA102

Incubation and sampling times: In the rangefinder study, the bacteria were mixed with test article with and without S9 and molten agar. These plates were then incubated for 3 days before counting. In the definitive experiments the test article, bacteria and S9 mix were preincubated for one hour at 37°C before mixing with agar and plating and then counting after 3 days. Each incubation condition was conducted in triplicate.

Results

Study validity: The study was valid since the mean negative control counts were within normal ranges, the positive controls induced clear increases in revertants and no more than 5% of the plates were lost through contamination or other reasons.

Study outcome: At 5000 µg/plate there was some precipitation present in most cases and in some cases the background lawn showed some thinning at this dose. CC-10004 did not induce a significant dose related increase in revertants in any strain tested either in the absence or presence of metabolic activation.

2. Study title: CC-10004: Induction of micronuclei in the bone marrow of treated mice

Key findings: CC-10004 did not induce micronuclei in the bone marrow of mice after two daily oral gavage administrations of up to 2000 mg/kg.

Study no.: 1398/281

Volume #16, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]

Date of study initiation: November 5, 2001
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: CC-10004, batch No. FP0032, purity not provided

Methods
Strains/species/cell line: mouse/CD-1

Doses used in definitive study: 500, 1000 and 2000 mg/kg

Basis of dose selection: range finder of 2000 mg/kg in 3 males and 3 females

Negative controls: 1% carboxymethyl cellulose

Positive controls: 2 mg/mL cyclophosphamide

Dosing and sampling times: Six male animals per dose were dosed by oral gavage once daily for two consecutive days except the positive control was given once. Animals were sacrificed 24 hours after the last dose. Bone marrow was collected from the femur. Smears were prepared and stained with Giemsa. The ratio of polychromatic to normochromatic erythrocytes (PCE/NCE) was determined in a minimum of 1000 cells per animals. Micronuclei were determined in a minimum of 2000 polychromatic erythrocytes per animal.

Results
Study validity: The study was considered valid since the incidence of micronucleated PCE in the vehicle control group fell within the historical control range, at least five animals per group were available for analysis and the positive control induced a statistically significant increase in the frequency of micronucleated PCE. The high dose used appears to be acceptable as it is the limit dose. It may have been preferable to include a 48 hour sampling time in addition to the 24 hour sampling time.

Study outcome: There appears to have been a slight decrease in body weight in the animals treated with 2000 mg/kg but no other signs of toxicity were noted in the drug treated animals. The PCE/NCE ratio was similar in drug treated and control animals. The group mean frequency of micronucleated PCE was not higher in the drug treated animals than in the vehicle treated animals.

3. Study title: CC-10004: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes.

Key findings: CC-10004 did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation.

Study no.: 1398/280

Volume #16, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]

Date of study initiation: November 5, 2001
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: CC-10004, batch No. FP0032, purity not provided

Methods

Strains/species/cell line: human/cultured whole blood

Doses used in definitive study: 15.76 to 700 µg/mL

Basis of dose selection: maximum solubility

Negative controls: DMSO

Positive controls: 4-nitroquinoline 1-oxide in absence of S9 and cyclophosphamide in presence of S9.

Incubation and sampling times: In experiment 1 duplicate cultures of the cells were incubated in the presence and absence of S9 mix for 3 hours, washed and then incubated for an additional 17 hours before harvesting. In experiment 2, duplicate cultures were incubated in the presence of S9 mix for 3 hours washed and then incubated for an additional 17 hours before harvesting while cultures in the absence of S9 mix were incubated with the test article for 20 hours continuously. Approximately 2 hours before harvest, colchicine was added (1 µg/mL) to arrest cells in metaphase. Cells were fixed, spread on a slide and stained with Giemsa. Mitotic index was determined and doses for chromosome analysis selected such that the highest dose analyzed should give at least 50% mitotic index inhibition. A total of 100 metaphase cells from each replicate was read for aberrations.

Results

Study validity: The study was considered valid since there was acceptable heterogeneity between replicates, the proportion of cells with structural aberrations in negative controls cultures was within the historical range, at least 160 cells were analyzable at each dose level and the positive control induced a significant increase in structural aberrations.

Study outcome: In experiment 1 precipitate was observed at 448 µg/mL and above. The mitotic inhibition was 37% at this dose and this was the highest dose used for chromosome analysis in this experiment. In experiment 2, 448 µg/mL was again the highest dose used for chromosome analysis in the 3+17 hour incubation with S9 and exhibited an inhibition of the mitotic index of 46%. In experiment 2, the highest dose used for chromosome analysis in the 20 hour incubation without S9 was 700 µg/mL and this dose inhibited the mitotic index by 45%. No increase in structural chromosome aberrations were observed at any of the doses analyzed.

The following table summarizes the results.

Treatment	Dose (µg/mL)	MI inhibition (%)[1]	CA[2]
Experiment 1			
3+17 hours, -S9	0	0	0.5
	60.13	6	1.5
	183.5	41	0.5
	448.0	37	0.5
3+17 hours, +S9	0	0	0

	60.13	2	1
	183.5	31	1
	448.0	46	0.5
Experiment 2			
20 hours, -S9	0	0	1.5
	358.4	24	1.5
	560.0	26	5.5
	700.0	46	3
3+17 hours, +S9	0	0	1
	60.13	17	0.5
	183.5	31	0
	448.0	46	2.5

[1]Percent inhibition of mitotic index
[2]Structural chromosomal aberrations excluding gaps/100 cells

2.6.6.5 Carcinogenicity

No carcinogenicity information has been provided at this time.

2.6.6.6 Reproductive and developmental toxicology

Embryofetal development

1. Study title: CC-10004: Oral (gavage) range-finding study of embryo-fetal development in the mouse (Study no.:1398/308). CC-10004 was administered to pregnant female CD-1 mice (7/dose) at doses of 250, 500 and 750 mg/kg during gestation days 6 to 15. At 500 and 750 mg/kg there was a slight, dose-related decrease in body weight gain, food intake and gravid uterus weight. Pregnancy rate and implantation rate were not affected. Mean fetal weight was reduced in the 750 mg/kg group. No external fetal defects were noted that were related to treatment. These doses were considered suitable for the definitive embryofetal study in mice. (*This study is not reviewed in greater detail since this was a dose-ranging study and the definitive study is reviewed below.*)

2. Study title: CC-10004: Oral (gavage) study of embryo-fetal development in the mouse

Key study findings: Administration of CC-10004 to pregnant CD-1 mice at doses up to 750 mg/kg did not produce any teratogenic effects. Fetal growth was significantly reduced in a dose dependent manner as indicated by decreased fetal weight and delayed ossification. The high dose (750 mg/kg) in this study may not have been as high as desirable since this dose did not induce clear maternal toxicity. Decreased food consumption and decreased weight gain was observed in drug treated animals although the decreased weight gain appeared to be due to the decreased uterine weights. The sponsor appears to argue that 750 mg/kg is the highest feasible dose since this required a

dose concentration of 75 mg/mL and a higher concentration of 100 mg/mL was too viscous to pass through the dosing catheter.

Study no.: 1398/309-D6154
Volume #17, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]
Date of study initiation: September 19, 2002
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: CC-10004, batch FP0032, purity 97.57

Methods

Doses: 0, 250, 500 and 750 mg/kg/day
Species/strain: mouse/CD-1
Number/sex/group: 24 female/group except 48 in control
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 10 mL/kg
Satellite groups used for toxicokinetics: none
Study design: daily administration from days 6 to 15 of gestation, sacrifice on day 18 of gestation
Parameters and endpoints evaluated: clinical signs, mortality, body weight, food intake, gross necropsy, uterus examinations, fetal examinations

Results

Mortality (dams): One female in the 750 mg/kg dose group was killed on day 11 of gestation following clinical signs of pallor, sluggish behavior, labored breathing, red discharge from the urogenital area, semi-closed eyes and sore/lesion on the neck. Necropsy of this animal showed distended gall bladder and stomach and raised foci in the mucosal surface of the stomach.

Clinical signs (dams): Other than those mentioned above, none of the clinical observations appeared to be related to drug treatment since they occurred with similar frequency in control.

Body weight (dams): There was a dose related decrease in body weight gain during treatment. This decreased body weight gain appears to be entirely due to decreased gravid uterine weight in the treated animals. There is no difference in body weight gain between the different groups when the body weights are corrected for uterine weight differences.

Food consumption (dams): There was a dose related decreased food consumption in females during the drug treatment period.

Toxicokinetics: Not assessed.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): Pregnancy rate was unaffected by drug treatment. Total embryo loss was observed in 4, 3, 2, and 6 females in the 0, 250, 500 and 750 mg/kg/day groups, respectively. There was no difference between control and treated in the number of corpora lutea per female, number of implantations per female or the preimplantation loss. Post implantation loss was 18.9, 31.7, 26.1 and 41.4% in the 0, 250, 500 and 750 mg/kg/day groups, respectively. This was statistically significant at the 250 and 500 mg/kg/day doses. This appears to be due primarily to increases in early intrauterine deaths and to a lesser extent on late intrauterine deaths. In spite of this, the group mean litter size was similar.

Offspring (malformations, variations, etc.):
Group mean litter weights were 17.27, 13.84, 13.26 and 12.87 g in the 0, 250, 500 and 750 mg/kg/day groups, respectively. The mean individual fetal weights were also decreased in a dose dependent manner for both males and females.

The following malformations were noted (incidence):
Control: cleft palate (2), absent eyelid (1), exencephaly (1), open eyelid (1), displaced ovary (1)

250 mg/kg: cleft palate (1), absent kidney (1), lengthened innominate artery (1), fused lung lobes and fused sternbrae (1)

500 mg/kg: cleft palate (2), pseudohermaphrodite (1), exencephaly (2), retinal folding (1), thickened cervical arches (1)

750 mg/kg: fused cervical arches (1), exencephaly (1), absent gall bladder (1)

There were several defects of incomplete ossification (parietal, supraoccipital, sternbrae, vertebral) with statistically increased incidence in drug treated animals.

3. Study title: CC-10004: oral (gavage) preliminary study in the non-pregnant rabbit (Study no.: 1398/290). Female New Zealand White rabbits (3/dose) were given CC-10004 by gavage for 13 consecutive days at doses of 250, 500 and 1000 mg/kg. There were no deaths or clinical signs of toxicity. Body weight and food intake was unaffected. No drug-related gross necropsy findings were noted.

4. Study title: CC-10004: Oral (gavage) range-finding study of embryo-fetal development in the rabbit (Study no.: 1398/291) CC-10004 was administered to pregnant female New Zealand White rabbits (7/dose) at doses of 0, 250, 500 and 1000 mg/kg during gestation days 7 to 19. Body weight and food consumption were unaffected by drug treatment. Pregnancy rate and implantation rate were not affected. Mean fetal weight was unaffected. No external fetal defects were noted that were related to treatment. These doses were considered suitable for the definitive embryofetal study in

rabbits. It is not clear why a higher dose was not considered appropriate since essentially no toxicity was noted. (*This study is not reviewed in greater detail since this was a dose-ranging study and the definitive study is reviewed below.*)

5. Study title: CC-10004: Oral (gavage) study of embryo-fetal development in the rabbit

Key study findings: Administration of CC-10004 to pregnant New Zealand white rabbits at doses up to 1000 mg/kg did not produce any teratogenic effects. A slight dose related decrease in maternal body weight gain and food consumption was observed. Fetal weight and growth did not appear to be affected. The report considered the high dose of 1000 mg/kg to be the limit dose and, therefore, adequate. Note that CC-10004 was not detected in plasma samples. This study may not be adequate if exposure was too low since little maternal toxicity was noted.

Study no.: 1398/292
Volume #18, and page #(submission not consecutively numbered)
Conducting laboratory and location: [redacted]
Date of study initiation: June 26, 2002
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: CC-10004, batch 61590-03, purity 101.4

Methods

Doses: 0, 250, 500 and 1000 mg/kg/day
Species/strain: rabbit/New Zealand white
Number/sex/group: 24 female/group
Route, formulation, volume, and infusion rate: gavage, 1% carboxymethyl cellulose, 5 mL/kg
Satellite groups used for toxicokinetics: blood taken from main group animals (4 animals per group per time point) on day 7 and 19 of gestation at 0, 1, 2, 4, 8 and 24 hours after drug administration
Study design: daily administration from days 7 to 19 of gestation, sacrifice on day 29 of gestation
Parameters and endpoints evaluated: clinical signs, mortality, body weight, food intake, gross necropsy, histopathology of select maternal tissues in control and high dose groups (cervix, uterus, pituitary, thymus, vagina, ovaries, pancreas, liver, heart, lungs, stomach, kidney, spleen and gross lesions), uterus examinations, fetal examinations

Results

Mortality (dams): One female in the control was killed on day 12 of gestation following inappetance since the start of the study. One female in the 1000 mg/kg dose group aborted on day 27 of gestation and was killed. Necropsy of this animal revealed a pale and mottled liver.

Clinical signs (dams): Only occasional clinical signs were noted and these do not appear to be drug-related.

Body weight (dams): The percent body weight increase during the dosing period was 13.5, 9.9, 11.6 and 11.2% for the control, 250, 500 and 1000 mg/kg groups, respectively. The percent body weight increase during days 4 to 29 of gestation was 15.8, 13.7, 13.8 and 12.4% for the control, 250, 500 and 1000 mg/kg groups, respectively. This decrease in body weight gain does not appear to be due to differences in uterus weights since uterus weights were essentially the same in all groups.

Food consumption (dams): Food consumption was decreased in a dose related fashion during the drug dosing period. Food consumption remained decreased in drug treated groups after dosing had stopped, although a dose response was no longer apparent.

Toxicokinetics: CC-10004 was not quantifiable in any of the plasma samples. The reason for this is not clear. The report notes that the samples were stored at -70°C for 8 months prior to analysis.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): There was no drug-related affect on the number of corpora lutea, pre-implantation losses, post-implantation losses or litter size. There were no gross necropsy findings or histopathology findings (control and high dose only) that were clearly related to drug treatment.

Offspring (malformations, variations, etc.): Group mean litter weights were similar in control and drug treated groups. Mean fetal weights for males were similar in all groups. Mean fetal weights for females were 40.8, 37.4, 39.6 and 37.0 g for the control, 250, 500 and 1000 mg/kg groups, respectively. The mean fetal weights for the females in the 250 and 1000 mg/kg group were statistically lower than control. These differences were not considered significant since there was not a dose response and since the range of control mean female fetal weights for the most recent 6 studies from this laboratory was 37.0 to 39.8 g.

There were no dose related increases in fetal malformations and the malformations observed in the drug treated groups do not appear to be significantly different from concurrent or historical control in incidence or type.

2.6.6.7 Local tolerance

None

2.6.6.8 Special toxicology studies

1. Study title: Evaluation of biomarkers for predicting toxicity of CC-10004 in rat

Key study findings: CC-10004 caused an acute inflammatory reaction in female rats. This was characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment. Peritoneal fluid increased (ascites) and analysis of this fluid also showed markers of inflammation. Decreased leptin and increased lipase levels suggested that adipocytes may be affected.

Study no.: AP1012R
Volume #3, and page #:(submission not consecutively numbered)
Conducting laboratory and location: Celgene, San Diego
Date of study initiation: 12/2/03
GLP compliance: No
QA reports: No
Drug, lot #, and % purity: CC-10004, Lot No. 5115-105-B, 99.3% pure
Formulation/vehicle: suspension (2 mg/mL) in aqueous 0.5% carboxymethyl-cellulose/0.25% Tween-80

Methods:
Female rats (Crl:CD(SD)IGS) were dosed by oral gavage with 0 (vehicle), 6 or 10 mg/kg using a dose volume of 5 mL/kg for 7 consecutive days. Some animals were maintained for an additional 11 day recovery period and sacrificed on day 18 while other animals were sacrificed on days 3, 6, 8 and 14. The animals treated with 6 mg/kg were all sacrificed at day 8. Body weight, clinical signs and behavior were recorded daily. Blood was collected on days 2, 3, 4, 6, 7, 8, 11, 14 and 18. Blood was analyzed for clinical chemistry, hematology and a biochemical marker panel. (*Note: The antigen panel was optimized for mouse.*) Blood was also collected at sacrifice and, in addition to the parameters just listed, analyzed for serum lipase, troponin T and I, fibrinogen, IL-6, TNF-α, G-CSF and myeloperoxidase (MPO). At sacrifice, the peritoneal cavity was lavaged with 2 mL saline. These peritoneal samples were assayed for cell differentials, TNF-α, Il-6 and the biochemical marker panel. The following organs were weighed: brain, adrenals, kidney, liver, lung, spleen, heart and thymus. The heart, small intestine, mesentery and thymus were examined histologically.

Results:
Clinical signs: Diarrhea was noted in the animals treated with 6 and 10 mg/kg on days 6, 7 and 8. Around this same time some of the animals at the 10 mg/kg dose had hypoactivity, staining around the nose, and rear limb weakness. One animal in the 10 mg/kg died on day 9.

Body weight: Body weight was significantly decreased in the 10 mg/kg dose during days 6-8 but recovered after stopping dosing.

Clinical chemistry: Albumin was decreased in the 10 mg/kg group during days 2 through 11. The levels recovered at days 14 and 18. Serum lipase was elevated in the 10 mg/kg group compared to control at days 3, 6 and 8 and in the 6 mg/kg group at day 8. This peaked at day 6 and was approximately 8 times control levels in the 10 mg/kg group.

Hematology:
Treatment with CC-10004 produced an increase in total white blood cells and this was largely due to a large increase in neutrophils. There were also increases in platelets and monocytes. These cell numbers returned toward baseline values during recovery but had not completely returned to normal at day 18.

Organ weights: Thymus weights were decreased by CC-10004 treatment.

Gross pathology: By days 6 and 8 animals treated with 6 or 10 mg/kg had small to large amounts of fluid in the peritoneal cavity. By day 14 mild to moderate peritonitis was observed in 2/4 animals and enlarged sections of the ileum and jejunum were noted in 4/4 animals and 2/4 animals, respectively.

Histology:
10 mg/kg
Day 3: minimal acute neutrophilic inflammation of the mesentery and tunica muscularis of the small intestine
Day 6: moderate to severe neutrophilic inflammation of the mesentery and small intestine, peritonitis, thymus atrophy, thymus and lymph node inflammation
Day 8: severe inflammation of the mesentery and small intestine, severe thymus atrophy, thymus inflammation
Day 14: minimal to moderate chronic inflammation of the mesentery and tunica muscularis of the small intestine, thymus atrophy, moderate villous atrophy of small intestine
Day 18: mononuclear inflammation of mesentery, perivascular mesentery fibrosis, thymus fibrosis, moderate villous atrophy of small intestine

Some inflammation was reported in the mesenteric arteries in areas of surrounding inflammation on day 8 but this was reported to resolve by day 18. Arterial lesions were not reported in the thymus or intestine.

Plasma biomarkers:
TNF-α was elevated on days 8 and 14 in the animals treated with CC-10004. IL-6 appeared to be elevated in CC-10004 treated animals at day 18 (day 11 of recovery). Fibrinogen was elevated on days 3 and 6 but returned to baseline on day 8. Myeloperoxidase appeared to be relatively unaffected and G-CSF appeared to be elevated in some animals treated with CC-10004 at day 6.

CRP, fibrinogen, MCSF, and VEGF were increased in CC-10004 treated animals during the treatment period but returned to control values during the recovery period. MCP-3 (mast cell protease 3) increased on day four and remained elevated until day 18. Leptin, MDC (macrophage derived chemokine) and von Willebrand factor decreased during treatment.

Peritoneal lavage analysis:

The percent neutrophil in the lavage fluid from the peritoneal cavity increased during drug treatment and returned to normal during the recovery period. Protein concentration increased during treatment in the lavage fluid. Other changes in biochemical markers were also measured in the lavage fluid although these assays are not validated for this biological fluid. Some changes were noted such as increased fibrinogen and haptoglobin levels and decreased von Willebrand factor and leptin levels.

2.6.6.9 Discussion and Conclusions

Genotoxicity:

Negative in ICH battery of three assays.

Reproductive toxicity:

Not teratogenic in mouse (750 mg/kg or 2250mg/m^2). Not teratogenic in rabbit (1000 mg/kg or 12,000 mg/m^2)

Safety Pharmacology:

CC-10004 appears to be a very low potency inhibitor of the hERG channel with an IC_{50} of 184.2 μM. The mean maximum inhibition produced by CC-10004 was 59.0% and occurred at the high dose of 249.7 μM. By comparison the positive control, terfenadine, produced a mean inhibition of 87.1% at 60 nM. Intravenous administration in the dog produced increased dP/dt_{max} and increased HR, but the mean arterial BP and QT_c were not affected (effects seen at 0.5 mg/kg i.v with C_{max}=947.5 ng/mL, human C_{max} with 40 mg/kg=530 ng/mL).

The nonclinical studies suggest that CC-10004 does not have a high risk for producing QT prolongation.

General toxicity:

Study No.	Study design	Dose (mg/kg)	Finding	NOAEL
1398/289	28 day mouse	250, 600, 1500	Arteritis, inflammation at all doses	No NOAEL. AUC @ 250 mg/kg =101172.5 ng·h/mL
1398/297	28 day mouse	5, 25, 75, 150	Arteritis, inflammation at all doses (1 Male at 5 mg/kg)	No NOAEL. AUC @ 5 mg/kg =6327.1 ng·h/mL
1398/333	28 day mouse	1, 2, 4	No significant toxicity	NOAEL=4 mg/kg or 12 mg/m^2, AUC @ 4 mg/kg =3809.7 ng·h/mL
1398/373	13 week mouse	2, 4, 8, 16	Arteritis at16 mg/kg (48 mg/m^2).	NOAEL=8 mg/kg or 24 mg/m^2, AUC @ 8 mg/kg = 8987.5ng·h/mL
1398/296	28 day monkey	50, 180, 650	Possible vasculitis at 180 and 650 mg/kg. Increased neutrophils at all doses.	No NOAEL. AUC @ 50 mg/kg =9665.6 ng·h/mL
1398/296	13 week monkey	25, 85, 300	No vasculitis. Some increases in neutrophils.	NOAEL for vasculitis=300 mg/kg. AUC at 300

				mg/kg=23306.7 ng·h/mL

CC-10004 appears to produce a systemic inflammatory reaction with associated vasculitis. This appears to be more readily seen in rodents than in monkeys.

In the mouse, thickening of the stomach was observed grossly and this correlated with hyperkeratosis. This was noted by the sponsor as having been reported with another PDE4 inhibitor (rolipram).

In a human phase 1 study at 40 mg/day the AUC_{0-24} was 3289 ng·h/mL at day 7.
Therefore:
The NOAEL dose in the mouse 28 day study is about **1x** the human dose of 40 mg/day.
The NOAEL dose in the monkey 28 day study is about **3-7x** the human dose of 40 mg/day.

2.6.6.10 Tables and Figures

None. See above for summary toxicity table.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None provided by sponsor. See above for summary toxicity table.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:
In discussions with the review team, concern was raised about the vasculitis observed in the animal studies. Possible additional parameters that might help in assessing vasculitis are CBC with neutrophils, albumin, lipase, C-reactive protein, fibrinogen, sed rate. Vasculitis has been observed with other PDE4 inhibitors and similar monitoring has been used in those cases.

This and other issues were discussed with the sponsor on August 25, 2004. It was felt that reducing the dose to 20 mg/day would provide a better safety margin for the study. In addition, it was felt that the study should be conducted only in patients with severe psoriasis with BSA of at least 15%. The sponsor agreed to make these changes. In addition, the study assessments will be amended to include tests for HIV and hepatitis at baseline and prior to starting the study medication, ECGs at each study visit, and laboratory testing for ESR, fibrinogen, and C-reactive protein for all subjects at each visit. The protocols will also clarify that the physician will be available at any time to physically assess any signs and symptoms of subjects that may be indicative of an early manifestation of drug-induced vasculitis. In addition, follow-up visits at 2 and 4 weeks after the last dose of study drug will be added.

With the reduction in dose and the addition of the monitoring mentioned above, the proposed protocol was considered reasonably safe to initiate.

External comments (to sponsor):
These comments apply to future nonclinical studies:

1. All clinical studies should be supported with nonclinical toxicity studies in two species (rodent and nonrodent) as per ICH M3. Psoriasis is a chronic indication and so drugs used to treat psoriasis should be supported by chronic toxicity studies (6 month rodent, 9-12 month nonrodents). It is recommended that more than 3 animals per sex per dose be used in the nonrodent studies. Carcinogenicity studies in two species would also be required for an NDA.

2. Because of the concern about vasculitis with CC-10004, it is recommended that the rodent chronic toxicity study be conducted before expanded phase 2 studies and the reversibility of vasculitis be assessed.

3. Essentially no toxicity was noted in the rabbit embryofetal toxicity studies (range finding and definitive). In addition, no drug was detected in the plasma of these animals. These studies may not be an adequate assessment of embryofetal toxicity if no exposure to drug can be documented. It is recommended that either a new rabbit embryofetal study be conducted with higher maternally toxic doses and adequate toxicokinetics or, if the rabbit is not an appropriate species, then an embryofetal study should be conducted in another species.

4. Other reproductive and developmental toxicity studies should be conducted as outlined in ICH M3 and related ICH guidances.

APPENDIX/ATTACHMENTS:
None

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

/s/

Paul Brown
9/7/2005 06:12:39 PM
PHARMACOLOGIST

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: [redacted]
Review number: 2
Sequence number/date/type of submission: 018 / 7 November 2005 / IT
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Celgene Corporation
Manufacturer for drug substance: [redacted]

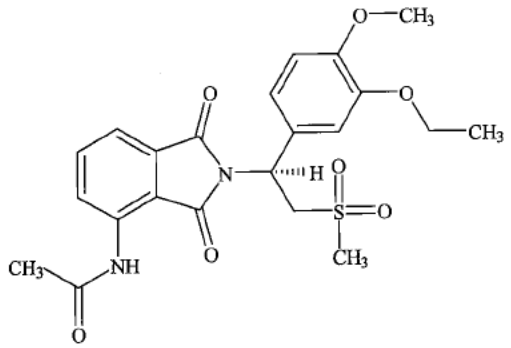
Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: December 2, 2005

Drug:

Trade name: NA
Generic name: NA
Code name: CC-10004
Chemical name: [redacted]

Note: The racemic mixture is code named [redacted] *and* [redacted]

CAS registry number: NA
Molecular formula/molecular weight: 460.5 / $C_{22}H_{24}N_2O_7S$
Structure:



Relevant INDs/NDAs/DMFs: None

Drug class: phosphodiesterase type IV (PDE4) inhibitor

Intended clinical population: psoriasis patients

Clinical formulation: white capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose [redacted]	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Route of administration: oral

Proposed clinical protocol: The original submission proposed a study entitled: **Open-label, single-arm pilot study to evaluate the pharmacodynamics, pharmacokinetics, safety and preliminary efficacy of CC-10004 in subjects with moderate to severe plaque psoriasis.** Protocol No. CC-10004-PSOR-001.
289 ng·h/mL at day 7.

Introduction and drug history:
The sponsor intends to develop this drug for the treatment of psoriasis. This submission contains three pharmacology study reports.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
Pharmacology:
1. The effect of thalidomide and IMiDs including lenalidomide (CC-5013), CC-11006, and CC10015, and the PDE4 inhibitors CC-10004 and CC-11050 on thromboxane B_2 and prostacyclin production in endothelial cell/platelet co-cultures Study No. 5299-148

2. Effect of IMiDs, PDE4 inhibitors, and tubulin inhibitors on COX-2 expression and PGE_2 production by human PBMC. Study No. 5197-130

3. Effect of CC-10004 +/- 16.16-diemthyl PGE_2 and CC-4047 on cell adhesion molecules in TNF-α stimulated human umbilical vein endothelial cells (HUVEC) Study No. 5226-086-5265-012

Studies <u>not</u> reviewed within this submission: none

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

CC-10004 is a selective PDE4 inhibitor. It inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. The NOAEL for general behavioral effects after a single oral dose in male mice was 500 mg/kg. Higher doses produced relatively minor, possibly autonomic, effects. CC-10004 inhibited the hERG only partially and only at very high concentrations. CC-10004 induced a dose related increase in dP/dt_{max} and heart rate in dogs. Corrected QT interval was not affected. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in the dog.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:
See brief summary above.

Drug activity related to proposed indication:

The sponsor believes that the ability of CC-10004 to interrupt TNF-α release from leukocytes will provide some antipsoriatic activity since TNF-α may be involved in the etiology of psoriasis.

2.6.2.3 Secondary pharmacodynamics

1. The effect of thalidomide and IMiDs including lenalidomide (CC-5013), CC-11006, and CC10015, and the PDE4 inhibitors CC-10004 and CC-11050 on thromboxane B_2 and prostacyclin production in endothelial cell/platelet co-cultures Study No. 5299-148

Thalidomide and IMiDs have been shown to inhibit COX-2 but not COX-1 expression in monocytes and macrophages. This study examined the potential inhibitory effects of thalidomide, various IMiDs including lenalidomide (CC-5013), CC-11006, and CC-10015, and the PDE4 inhibitors CC-10004 and CC-11050 on prostacyclin and thromboxane production in a human endothelial cell/platelet co-culture system. Aspirin, used as a non-selective COX inhibitor, blocked prostacyclin and thromboxane similarly. The selective COX-2 inhibitor, NS-398, preferentially blocked prostacyclin as expected. However, celecoxib inhibited thromboxane and prostacyclin with comparable potencies but 3x less the IC_{50} of aspirin. Thalidomide, IMiDs including lenalidomide (CC-5013), CC-11006, and CC-10015, and the PDE4 inhibitors CC-10004 and CC-11050 had no effect on either prostacyclin or thromboxane production. Moreover, the combination of lenalidomide/dexamethasone had no effect on either prostacyclin or thromboxane B_2 production, indicating that lenalidomide does not behave as a COX inhibitor in these cell types.

2. Effect of IMiDs, PDE4 inhibitors, and tubulin inhibitors on COX-2 expression and PGE_2 production by human PBMC. Study No. 5197-130

The sponsor examined the effect of several compounds on COX-2 protein expression and PGE_2 production by LPS- or PHA-stimulated PBMC using western blot analysis and

ELISA. While the IMiD CC-4047 was found to consistently inhibit COX-2 expression (64% inhibition at 10 μM), inhibition of PGE_2 production was less pronounced (PGE_2 IC_{50}=50 μM in LPS-stimulated PBMC). Thalidomide, CC-5013, and CC-15093 had no effect on PGE_2 production by LPS- or PHA-stimulated PBMC, while CC-11006 had a slight inhibitory effect on PGE_2 production under both stimulation conditions (10-15% maximal inhibition). The TNF-selective IMiDs CC-12031 and CC-12062 inhibited COX-2 expression by 31% and 59% respectively at 10 μM, while the IL-2-selective IMiD CC-15085 did not inhibit COX-2 expression. The PDE4 inhibitor CC-10004 elevated COX-2 expression by 50% at 10 μM. All PDE4i's consistently elevated both COX-2 expression and PGE_2 production, raising PGE_2 levels to 150% or 200% of baseline at concentrations in the 5 nM – 2 μM range. IMiDs designed to also have PDE4 inhibitory activity (CC-15486 and CC-15551) had no net effect on COX-2 expression, indicating that it is possible to counteract the IMiD-induced inhibition of COX-2 expression with PDE4 inhibitory activity. The tubulin inhibitors had no consistent effect on COX-2 expression, yet tended to promote PGE_2 production at low concentrations and inhibit at high concentrations.

3. Effect of CC-10004 +/- 16.16-diemthyl PGE_2 and CC-4047 on cell adhesion molecules in TNF-α stimulated human umbilical vein endothelial cells (HUVEC) Study No. 5226-086-5265-012

Several adhesion markers expressed on human umbilical vein endothelial cells (HUVEC) were examined in the TNF-a stimulated and unstimulated conditions in conjunction with the IMiD CC-4047 (10μM) or the PDE4 inhibitor CC-10004 (10μM). In the unstimulated condition, CD51/61 cell surface expression was unaffected by either CC-4047 or CC-10004. PGE2 (10μM) treatment resulted in a 20% reduction in CD51/61 cell surface expression. Cell surface expression of ICAM-1 displayed a modest 10-20% increase resulting from both CC-10004 and CC-4047 treatments. The addition of PGE2 with CC-10004 enhanced the cell surface expression of ICAM-1 to approximately 25-30%, although the observed increase was not additive. E-Selectin cell surface expression levels were low, possibly due to insufficient sensitivity at the level of detection. Nevertheless, CC-10004 and CC-4047 seem to inhibit E-Selectin cell surface expression and PGE2 blocked the CC-10004 induced inhibition, restoring E-Selectin expression to baseline levels. P- Selectin expression was also inhibited by CC-10004 and CC-4047 by approximately 55 and 35%, respectively. PGE2 reduced the level of inhibition caused by CC-10004 from approximately 55% to 27% when used in combination, however the remaining expression level was similar to that of PGE2 alone. In the TNF-α (1ng/ml) stimulated condition, CC-4047 (10 μM) inhibited the TNF-α-induced increase of E-Selectin expression by approximately 20%. The inhibition of E-Selectin expression by CC-4047 as measured by cell surface ELISA was statistically significant. The combination of CC-10004 and PGE2 inhibited TNF-α-induced expression of E-Selectin by approximately 25% and VCAM-1 expression by more than 50% (both statistically significant) but did so in a less than additive manner compared to PGE2 alone using the flow cytometric method. PGE2 alone resulted in a 50% reduction in the TNF-α-induced E-Selectin expression as measured by flow cytometry. Using the cell surface ELISA method, the combination of CC- 10004 and PGE2 inhibited TNF-α-induced E-Selectin expression in a statistically significant manner. Both CC-10004 and CC-4047 increased

the TNF-α-induced P-Selectin expression to 40% and < 2-fold above baseline, respectively. Combining CC-10004 and PGE2 increased TNF-a-induced P-Selectin expression to levels comparable to PGE2 alone. No significant effects on TNF-α-induced expression of adhesion molecules CD56/61 ($\alpha_v\beta_3$ integrin), ICAM-1, ICAM-2, P-Selectin, HLA class I, HLA-class II, VE-cadherin, and CD44 were observed with either CC-4047 and CC-10004. Notably, both CC-4047 and CC-10004 tended to increase P-Selectin expression in a variable manner.

2.6.2.4 Safety pharmacology

No new studies were included in this submission. See original review.

2.6.2.5 Pharmacodynamic drug interactions

Not assessed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table 1 Summary of Enzymatic, Cellular, and Animal Model Data

(b) (4)	CC-10004	(b) (4)
PDE Inhibition		
PDE4 IC_{50} (from U937 cells) (nM)	73.5	
PDE1 (% inhibition at 10μM)	23%	
PDE2 (% inhibition at 10μM)	6%	
PDE3 (% inhibition at 10μM)	20%	
PDE5 (% inhibition at 10μM)	3%	
PDE6 (% inhibition at 10μM)	-6%	
PDE7 IC_{50} (nM)	20500	
PDE Specificity Ratios from above data *(fold)*		
PDE4/PDE1	>500	
PDE4/PDE2	>10000	
PDE4/PDE3	>1200	
PDE4/PDE5	>30000	
PDE4/PDE6	>40000	
PDE7 IC_{50}/PDE4 IC_{50}	279	
HARBS Binding IC_{50}	23	
Human PBMC assays *(all values in nM)*		
LPS-induced TNF-α IC_{50}	77	
LPS-induced IL-12 IC_{50}	140	
LPS-induced IL-10 EC_{50} (3.5-fold increase)	2300	

	(b) (4)	(b) (4)
IL-1β-induced TNF-α IC_{50}		83
SEB-induced IL-2 IC_{50}		291
SEB-induced IFN-γ IC_{50}		46
PGE_2-induced cAMP EC_{50}		1510
Human Neutrophil Assays *(all values in nM)*		
PGE_2-induced cAMP EC_{50}		4570
fMLF-induced LTB4 IC_{50}		2.48
Zymosan-induced IL-8 IC_{50}		94
fMLF-induced CD18 expression IC_{50}		390
fMLF-induced CD11b expression IC_{50}		74
fMLF-induced adhesion to HUVEC IC_{50}		150
Other Cellular Assays		
IL-1β-induced HUVEC NO at 10μM (% inhib.)		87%
CD4+ T cell IL-5 IC_{50} (nM)		890
Human Whole Blood LPS-induced TNF-α IC_{50} (nM)		294
Human Whole Blood LPS-induced IL-6 at 10 μM		No effect
Monkey Whole Blood LPS-induced IL-6 at 10 μM		Inhibited 50%
Rat Whole Blood LPS-induced IL-6 at 10 μM		Elevated 2-fold
Mouse Whole Blood LPS-induced IL-6 at 10 μM		Elevated 4-fold
***In Vivo* Models**		
Mouse LPS-induced serum TNF-α inhibition (ED_{50}, mg/kg, p.o.)		0.05
Rat lung neutrophilia and total white blood cell infiltration inhibitio (ED_{50}, mg/kg, p.o.)		0.25
Rat lung neutrophilia and total white blood cell infiltration inhibitio (ED_{50}, mg/kg, i.t.)		0.003
Rat neutrophilic leukocytosis (at mg/kg p.o.)		Present at 10 and 6
Ferret lung neutrophilia (ED_{50}, mg/kg, p.o.)		0.8
Ferret threshold emetic dose (mg/kg, p.o.)		10
Mouse ovalbumin-induced asthma AHR inhibition (ED_{50}, mg/kg, p.o.)		<1
Mouse collagen-induced arthritis (% inhibition at mg/kg, p.o.)		49% at 1 32% at 10
Mouse collagen antibody-induced arthritis (% inhibition at mg/kg, p.o.)		80% at 5 80% at 25

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Oral bioavailability was very variable in rats (2 to 12% in males and 61 to 80% in females). Female rats experience higher AUC and C_{max} values than males. In the mouse, oral bioavailability was 24 to 27%. Male and female monkey exhibited similar exposure after oral administration and the bioavailability was approximately 78%. After oral

administration of radiolabeled CC-10004 to mice, the highest levels of radioactivity were detected in the gastrointestinal tract, kidney, liver and pancreas. The CNS tissues appeared to have lower levels than most other tissues. The major metabolite after in vitro microsome studies was M3 which is the O-desmethyl metabolite. This was observed in all species and sexes except the female rat. The human was most similar quantitatively and qualitatively to the dog and male rat. The greatest metabolism occurred with CYP3A4 and CYP2A6. The principal route of excretion appears to be the feces in both rodent and monkeys with approximately 70% of the drug excreted by this route. There appears to be little interconversion between the *R* and *S* enantiomers in plasma. CC-10004 is relatively highly bound to plasma proteins (96.9, 96.5, 93.9, 99.7, 98.5 and 99.5% in rat, mouse, rabbit, dog, monkey and human, respectively.)

2.6.4.2 Methods of Analysis
See brief summary above.

2.6.4.3 Absorption
See brief summary above.

2.6.4.4 Distribution
See brief summary above.

2.6.4.5 Metabolism
See brief summary above.

2.6.4.6 Excretion
See brief summary above.

2.6.4.7 Pharmacokinetic drug interactions
See brief summary above.

2.6.4.8 Other Pharmacokinetic Studies
See brief summary above.

2.6.4.9 Discussion and Conclusions

Oral bioavailability of CC-10004 is variable. The primary route of excretion is in the feces. Half life appears to be around a day in mouse and monkey and possibly shorter in rats. CC-10004 appears to have relatively low potential to inhibit CYP450 mediated metabolism. CC-10004 is relatively highly protein bound although the binding does vary somewhat between doses.

2.6.4.10 Tables and figures to include comparative TK summary

See summaries above.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
Arteritis was one of the primary toxicity findings in repeat dose studies. In 4 week studies in mice arteritis was seen at doses as low as 5 mg/kg. The NOEL was 4 mg/kg for both males and females. The arteritis occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. Neutrophil and globulin levels were also increased. Other findings included centrilobular liver hypertrophy, effects on the stomach and lymphoid tissue effects.

Four week dosing with CC-10004 in monkeys resulted in increased neutrophil levels at all doses of 50, 180 and 650 mg/kg. One high dose male had a body weight loss of 10%. Slight increases in liver weight were also observed in all drug treated groups. Several occurrences of vasculitis were noted in the 180 and 650 mg/kg groups although these were infrequent and did not follow a dose response. A NOEL was not identified, although the 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse.

In monkeys treated for 13 weeks, the effects that appeared to be drug related included salivation at all doses (25, 85 and 300 mg/kg or 300, 1020 and 3600 mg/m^2) and vomiting at the high dose. In addition, there was an increase in hepatocyte vacuolation that was not dose related. No vasculitis was described. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug treated animals. A NOEL was not established. The report considered 300 mg/kg a NOAEL.

Genetic toxicology:
CC-10004 did not induce mutations in the in the *Salmonella typhimurium* reverse mutation assay. CC-10004 did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. CC-10004 did not induce micronuclei in the bone marrow of mice after two daily oral gavage administrations of up to 2000 mg/kg.

Carcinogenicity:
No carcinogenicity studies have been conducted with CC-10004 at this time.

Reproductive toxicology:
Oral doses of 250, 500 and 750 mg/kg (2250 mg/m^2) were not teratogenic in the mouse. Although these doses did cause decreased fetal weight and delayed ossification.
Oral doses of 250, 500 and 1000 mg/kg (12,000 mg/m^2) were not teratogenic in the rabbit.

Special toxicology:
A special study of CC-10004 was conducted in rats to assess possible biomarkers of inflammation and vasculitis. The animals were treated by oral gavage with 0 (vehicle), 6 or 10 mg/kg using a dose volume of 5 mL/kg for 7 consecutive days. Some animals were maintained for an additional 11 day recovery period and sacrificed on day 18 while other animals were sacrificed on days 3, 6, 8 and 14. CC-10004 caused an acute inflammatory reaction in female rats. This was characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment. Peritoneal fluid increased (ascites) and analysis of this fluid also showed markers of inflammation. Decreased leptin and increased lipase levels suggested that adipocytes may be affected.

2.6.6.2 Single-dose toxicity
See summary above.

2.6.6.3 Repeat-dose toxicity
See summary above.

2.6.6.4 Genetic toxicology
See summary above.

2.6.6.5 Carcinogenicity
No carcinogenicity information has been provided at this time.

2.6.6.6 Reproductive and developmental toxicology
See summary above.

2.6.6.7 Local tolerance
None

2.6.6.8 Special toxicology studies
See summary above.

2.6.6.9 Discussion and Conclusions
No new toxicology information was included in the current submission. See original review.

2.6.6.10 Tables and Figures
None.

2.6.7 TOXICOLOGY TABULATED SUMMARY
None provided by sponsor. See above for summary.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:
The current submission included three pharmacology studies. These showed that CC-10004 had no effect on thromboxane and prostacyclin production in an in vitro human endothelial cell/platelet culture. CC-10004 elevated COX-2 expression by 50% at a concentration of 10 μM in human PBMC. CC-10004 also increased PGE_2 production in these cells. CC-10004 had small and variable effects on expression of several cell surface adhesion molecules.

These studies are part of the sponsor's ongoing investigations into the pharmacology of CC-10004 and other compounds. They have no impact on the safety assessment of CC-10004 at this time.

External comments (to sponsor): None

APPENDIX/ATTACHMENTS:

None

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

/s/

Paul Brown
12/2/2005 02:37:35 PM
PHARMACOLOGIST

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date:	8/10/06
Serial No.:	029
Submission type:	IT; Submission of nonclinical study reports
Drug:	CC-10004 (S-enantiomer)
Drug class:	Phosphodiesterase type IV (PDE4) inhibitor
Indication:	Psoriasis
Route:	Oral
Sponsor:	Celgene Corporation, Summit, NJ

Review date: October 30, 2006

Clinical formulation: White capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose [redacted]	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has proposed to develop CC-10004 [redacted] for the treatment of psoriasis. The original IND was submitted on July 29, 2004. Concern was raised about the vasculitis observed in the animal studies conducted to support the initial proposed clinical study contained in the original IND submission. Additional safety parameters to monitor for possible vasculitis were incorporated into the clinical study protocol. In addition, the initial dose was reduced to 20 mg/day and only patients with severe psoriasis were to be enrolled in the initial clinical study. The sponsor agreed to incorporate the changes into the initial clinical study and it was determined that the revised initial clinical study protocol was reasonably safe to initiate.

The current submission contains three nonclinical study reports which are reviewed in the following section.

Review of submitted nonclinical study reports:

Nonclinical Study #1 – In vitro evaluation of CC-10004 as an inducer of cytochrome P450 expression in cultured human hepatocytes (Study No. CC-10004-DMPK-012; Initiation date: 9-3-05; non-GLP; (b) (4)

Three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with 0 (vehicle; 0.1% DMSO), 1, 10 or 100 μM CC-10004, or one of three known human CYP inducers (100 μM omprazole, 750 μM phenobarbital or 10 μM rifampin). After the last treatment, cells were harvested for microsomal preparation for analysis of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 related metabolism.

Treatment of cultured human hepatocytes with the prototypical inducers caused the anticipated increases in CYP activity. Treatment of cultured human hepatocytes with 10 and 100 μM CC-10004 caused a concentration dependent decrease in CYP1A2 and CYP2C9 activity (10 μM: ↓35%; 100 μM: ↓45-73%). Treatment of cultured human hepatocytes had little to no effect on CYP2B6 or CYP2C19 activity. Treatment of cultured human hepatocytes with 100 μM CC-10004 caused a 3.7-fold increase in CYP3A4 activity, which was about half as effective as rifampin at inducing CYP3A4 activity. Treatment of cultured human hepatocytes with up to 100 μM CC-10004 did not cause any detectable cytotoxicity measured by LDH release.

Nonclinical Study #2 – PDE4 and TNF-α inhibitory activity of CC-10004 metabolites M1, M2, M3 (racemate), M5 (racemate) and M7 (Study No. 5275-179; Date: 9-7-05; non-GLP; (b) (4) (b) (4)

The metabolic products of CC-10004 (CC-15091 {M1/M2}, CC-15604 {M3 racemate}, CC-10047 {M5 racemate} and CC-10055 {M7}) were analyzed for PDE4 (purified from a human monocytic cell line) and TNF-α (measured from human peripheral blood mononuclear cells) inhibitory activity. The PDE4 and TNF-α inhibitory activity of the CC-10004 metabolites were compared to inhibitory activity of the parent CC-10004 compound in this study.

CC-15091, CC-15604 and CC-10047 were relatively ineffective at blocking PDE4 activity with IC_{50} values of 120, 17 and 44 μM, respectively, compared to CC-10004 (IC_{50} = 0.074 μM). CC-10055 (M7) demonstrated a potent inhibition of PDE4 activity with an IC_{50} = 0.16 μM), which is ~2X less potent than the parent CC-10004.

CC-15091, CC-15604 and CC-10047 were relatively ineffective at blocking TNF-α activity with IC_{50} values of 77, 16 and 4.9 μM, respectively, compared to CC-10004 (IC_{50} = 0.077 μM).). CC-10055 (M7) demonstrated a potent inhibition of TNF-α activity with an IC_{50} = 0.13 μM), which is ~2X less potent than the parent CC-10004.

Nonclinical Study #3 – CC-11050 and CC-10004 in treatment of psoriasisform (Study No. TECH1102006; Date: 1-10-00; non-GLP; (b) (4)

Two PDE4 inhibitors, CC-11050 and CC-10004, were evaluated and compared to cyclosporine in a human NK cell driven model of psoriasis that utilized human skin xenotransplanted onto beige-severe combined immunodeficiency (SCID) mice. Results showed that all three test articles, CC-11050, CC-10004 and cyclosporine (each at 5 mg/kg/day, administered orally as bid doses) caused statistically significant reductions (≥ 50%) in both epidermal thickness and keratinocyte proliferation index as compared to the vehicle treated group (0.5% carboxymethylcellulose/0.25% Tween 80). In addition, all three test articles caused reductions in the psoriasisform histological features and immunohistochemical expression of the inflammatory markers TNF-α, HLA-DR and ICAM-1. These results suggest that CC-10004 may be effective for the treatment of psoriasis.

Conclusions:

Treatment of cultured human hepatocytes with CC-10004 had little to no effect on CYP2B6 and CP2C19 activity, caused a concentration dependent decrease in CYP1A2 and CYP2C9 activity (10 μM: ↓35%; 100 μM: ↓45-73%), and caused a 3.7 fold increase in CYP3A4 activity at 100 μM. The study report states that the 3.7 fold increase in CYP3A4 activity at 100 μM CC-10004 is unlikely to be clinically relevant because 100 μM is over 100 fold higher than the C_{max} noted in humans.

The CC-15091 (M1/M2), CC-15604 (M3 racemate), CC-10047 (M5 racemate) metabolites are comparatively inactive CC-10004 metabolites for inhibition of PDE4 and TNF-α activity. The CC-10055 (M7) metabolite was an effective inhibitor of PDE4 and TNF-α activity suggesting that the CC-10005 metabolite is an active CC-10004 metabolite. The study report states that the pharmacokinetic profile of CC-10055 revealed a lower systemic exposure, after oral exposure, relative to CC-10004. In addition, the C_{max} and AUC values for CC-10055 were 50% and 15% of the values for CC-10004, respectively, which apparently indicated that the CC-10055 metabolite may be unsuitable for clinical development.

The PDE4 inhibitors, CC-11050 and CC-10004, exhibited beneficial effects in a psoriasis mouse model which included statistically significant reductions (≥ 50%) in both epidermal thickness and keratinocyte proliferation index compared to the vehicle control group and reductions in the psoriasisform histological features and immunohistochemical expression of the inflammatory markers TNF-α, HLA-DR and ICAM-1. The results of this study indicate that CC-10004 may be effective for the treatment of psoriasis.

Recommendations:

No regulatory action is indicated for this submission from a Pharmacology/Toxicology perspective, at this time.

cc:
DDDP/DIV DIR/WALKER
DDDP/ PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/CARR
DDDP/PM/OWENS

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

/s/

Barbara Hill
11/2/2006 08:36:46 AM
PHARMACOLOGIST

Paul Brown
11/2/2006 11:35:29 AM
PHARMACOLOGIST

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date:	10/23/06
Serial No.:	032
Submission type:	IT; Nonclinical study report
Drug:	CC-10004 (S-enantiomer)
Drug class:	Phosphodiesterase type IV (PDE4) inhibitor
Indication:	Psoriasis
Route:	Oral
Sponsor:	Celgene Corporation, Summit, NJ

Review date: June 6, 2007

Clinical formulation: White capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has proposed to develop CC-10004 [redacted] for the treatment of psoriasis. The original IND was submitted on July 29, 2004. Concern was raised about the vasculitis observed in the animal studies conducted to support the initial proposed clinical study contained in the original IND submission. Additional safety parameters to monitor for possible vasculitis were incorporated into the clinical study protocol. In addition, the initial dose was reduced to 20 mg/day and only patients with severe psoriasis were to be enrolled in the initial clinical study. The sponsor agreed to incorporate the changes into the initial clinical study and it was determined that the revised initial clinical study protocol was reasonably safe to initiate.

The current submission contains one nonclinical study report which is reviewed in the following section.

Review of submitted nonclinical study report:

Fertility and early embryonic development

Study title: CC-10004: Oral (gavage) fertility and general reproduction toxicity study in mice

Key study findings:

Increased body weight gain was noted in high dose males over the treatment period compared to control animals. No treatment related effects on body weight gain were noted in low and mid dose males. Body weight gains were increased in low, mid and high dose females for the entire precohabitation period. Body weight gain was decreased in high dose females from gestation days 0 – 13.

Increased heart weights were noted in high dose males. Increased testis weight was noted in low, mid and high dose males. Decreased seminal vesicle weight was noted in mid and high dose males and decreased prostate weight was noted in high dose males.

Although no treatment related effects on sperm parameters were noted in this study, prolonged time to mating and decreased numbers of matings led to a decrease in fertility index in low, mid and high dose groups. Of the mice that did mate successfully, post-implantation loss was increased in low, mid and high dose groups. A NOAEL for effects on male and female fertility could not be established in this study. The male and female fertility NOAEL is less than 100 mg/kg/day CC-10004.

Study no.:	AIB00071
Sponsor study no.:	CC-10004-TOX-001
Volume #, and page #:	Volume 1, page 1
Conducting laboratory:	[redacted] (b) (4)
Date of study initiation:	7-12-05
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, and % purity:	CC-10004, Lot# 53625-04, 98.1%
Vehicle:	1% carboxymethylcellulose

Methods

Doses: 0, 100, 300 and 1000 mg/kg/day

(Doses selected for the oral mouse fertility study were based on results of two 28-day oral mouse toxicology studies. Oral doses of 250, 600 and 1500 mg/kg/day were administered in the first study. Toxicities noted in this study included inflammation associated with arteritis, irritation in the stomach, liver toxicity and toxic effects on the hemolymphoreticular system. The high dose used in this study resulted in mortality. Oral doses of 5, 25, 75 and 150 mg/kg/day were administered in the second study. The only toxicity noted was arteritis in low, mid-low and mid-high dose males and high dose animals. The NOAEL for arteritis was 75 mg/kg/day in females and could not be established in males.)

Species/strain:	CD-1 mice; 72 days; males: 27.8-37.5 g; females: 24.3-33.2 g
Number/sex/group:	25/sex/dose
Route, formulation, volume, and infusion rate:	Oral, vehicle, 20 ml/kg
Satellite groups used for toxicokinetics:	N/A
Study design:	

Oral (gavage) doses were administered daily starting at 4 weeks prior to mating and during mating for males, and 14 days prior to mating and through gestation day 7 for females. Females were mated on a one to one basis with the correspondingly treated 4 week dosed males. Females showing a sperm positive vaginal smear were separated from the males and remained isolated until sacrifice on gestation day 13. Males were sacrificed after the mating period.

Parameters and endpoints evaluated:

Toxicity parameters evaluated in this study included mortality (daily), clinical signs (daily) and body weight (daily). Females were evaluated for estrous cyclicity 14 days prior to mating and until evidence of copulation was noted. Males were sacrificed for necropsy evaluation after completion of the mating period. A complete necropsy was performed in males and heart, epididymids, prostate, seminal vesicles and testes organ weights were obtained. An analysis (concentration, motility, morphology) of the sperm was performed using the right testis and epididymis. The left testis and epididymis, prostate, and seminal vesicle were preserved for possible histopathological evaluation. Females were sacrificed for necropsy evaluation on gestation day 13. Organ weights for heart, uterus and ovaries were obtained for all females. The following parameters were measured during the gross necropsy in females: the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. Ovaries, uterus and vagina were preserved for possible histopathological evaluation. The following fertility indices were evaluated in this study: Copulatory interval, male and female fertility index, male and female mating index, male and female fecundity index and estrous cyclicity (mean cycle time and # cycles/period).

Results

Mortality: No treatment related effects on mortality were noted in this study. Two high dose males and one mid dose male were found dead and one mid dose male was sacrificed moribund. These deaths were attributed to intubation errors.

Clinical signs: No treatment related effects on clinical signs were noted in this study.

Body weight: Body weight gain was increased in high dose males (↑68%) over the treatment period compared to control animals. No treatment related effects on body weight gain were noted in low and mid dose males. Body weight gains were increased in low, mid and high dose females for the entire precohabitation period (days 1 – 15; ↑171 – 186%). Body weight

gain was decreased in high dose females from gestation days 0 – 13 (↓18.1%).

Toxicokinetics: N/A

Necropsy: No treatment related effects on macroscopic parameters were noted in this study. Absolute and relative heart weights were increased (13% and 9%, respectively) in high dose males. No treatment related effects on heart weight were noted in low and mid dose animals and high dose females. The absolute and relative weights of the testes were increased (8 – 22%) in low, mid and high dose males. The absolute and relative weights of the seminal vesicles with or without fluid was decreased (9 – 21%) in mid and high dose males. The absolute and relative weights of the prostate were decreased (13 – 15%) in high dose males.

Fertility parameters:

No treatment related effect on estrous cyclicity was noted in this study. The average number of days in cohabitation was significantly increased in the mid and high dose groups (↑2.1X and ↑2.3X, respectively) compared to control animals. The percentage of mice that mated was significantly decreased in high dose animals (↓16.7%) compared to control animals. The fertility index (number of pregnancies per number of mice that mated) and the numbers of pregnancies per mouse were significantly decreased in the low, mid and high dose groups compared to control animals. Values for these parameters are provided in the table below.

Dose (mg/kg)	Days in cohabitation (mean ± SD)	Mice that mated [N (%)]	Fertility Index [N/N (%)]	Pregnancies per mouse [N/N (%)]
0	2.3 ± 1.3	25 (100)	25/25 (100)	25/25 (100)
100	3.5 ± 2.4	25 (100)	19/25 (76.0)	19/25 (76.0)
300	4.9 ± 3.4	22 (91.7)	19/22 (86.4)	19/24 (79.2)
1000	5.4 ± 4.6	20 (83.3)	16/19 (84.2)	16/23 (69.5)

Post implantation loss, the average numbers of non viable embryos and the percentage of mice with nonviable embryos were significantly increased in the low, mid and high dose groups compared to control animals. The average number of viable embryos was significantly reduced in the high dose group compared to control animals. One mouse in the high dose group had a gravid uterus containing all nonviable embryos. Values for these parameters are provided in the table below.

Dose (mg/kg)	Post-implantation loss (mean ± SD)	Viable embryos (mean ± SD)	Nonviable embryos (mean ± SD)	Mice with nonviable embryos [N (%)]
0	4.0 ± 7.6	11.6 ± 2.6	0.4 ± 0.6	8 (32.0)
100	18.2 ± 20.0	12.7 ± 3.7	3.0 ± 3.9	13 (68.4)
300	23.8 ± 18.2	10.0 ± 2.7	3.2 ± 2.4	17 (85.0)
1000	55.1 ± 27.7	6.2 ± 4.0	7.7 ± 4.5	17 (94.4)

The mean number of corpora lutea, uterine implantations, and pre-implantation loss for the low, mid and high dose groups were comparable to the control group.

No treatment related effects on sperm evaluations (quantity and percent motile sperm, number of nonmotile sperm, total sperm count and density) were noted in this study.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Oral embryofetal development studies have been conducted in mice and rabbits with CC-10004 (micronized). Oral (gavage) doses of 0 (vehicle), 250, 500 and 750 mg/kg/day CC-10004 were administered to pregnant female CD-1 mice from gestational days 6 - 15. The vehicle used in this study was 1% carboxymethylcellulose. Toxicokinetic analysis was not incorporated into this study. Administration of CC-10004 to pregnant CD-1 mice at doses up to 750 mg/kg (2250 mg/m^2) did not produce any teratogenic effects. Fetal growth was significantly reduced in a dose dependent manner as indicated by decreased fetal weight and delayed ossification. The high dose (750 mg/kg) in this study may not have been as high as desirable since this dose did not induce clear maternal toxicity. Decreased food consumption and decreased weight gain was observed in drug treated animals although the decreased weight gain appeared to be due to the decreased uterine weights. The sponsor appears to argue that 750 mg/kg is the highest feasible dose since this required a dose concentration of 75 mg/ml and a higher concentration of 100 mg/ml was too viscous to pass through the dosing catheter.

Oral (gavage) doses of 0 (vehicle), 250, 500 and 1000 mg/kg/day CC-10004 were administered to pregnant female New Zealand white rabbits from gestational days 7 - 19. The vehicle used in this study was 1% carboxymethylcellulose. Toxicokinetic analysis was incorporated into this study. However, CC-10004 was not quantifiable in any of the plasma samples. The reason for this is not clear. It may be possible that since the metabolism of CC-10004 appears to be very rapid in rabbits, that very little if any systemic exposure to CC-10004 occurred in this rabbit embryofetal development study. The study report noted that the samples were stored at -70°C for 8 months prior to analysis. Administration of CC-10004 to pregnant New Zealand white rabbits at doses up to 1000 mg/kg (12,000 mg/m^2) did not produce any teratogenic effects. A slight dose related decrease in maternal body weight gain and food consumption was observed. Fetal weight and growth did not appear to be affected. The report considered the high dose of 1000 mg/kg to be the limit dose and, therefore, adequate. Note that CC-10004 was <u>not</u> detected in plasma samples in this study. Therefore, this study may not be adequate if exposure was too low since little maternal toxicity was noted.

The following comments were relayed to the sponsor via fax on September 8, 2005 concerning nonclinical reproductive toxicology studies for CC-10004.

"Essentially no toxicity was noted in the rabbit embryofetal toxicity studies (range finding and definitive). In addition, no drug was detected in the plasma of these animals. These studies may not be an adequate assessment of embryofetal toxicity if no exposure to drug can be documented. It is recommended that either a new rabbit embryofetal study be conducted with higher maternally toxic doses and adequate toxicokinetics or, if the rabbit is not an appropriate species, then an embryofetal study should be conducted in another species."

"Other reproductive and developmental toxicity studies should be conducted as outlined in ICH M3 and related ICH guidances."

The sponsor has not responded to the notification that the rabbit embryofetal development study conducted with CC-10004 is not adequate. It is not known if the sponsor plans to repeat the rabbit embryofetal development study with higher maternally toxic doses or not.

The current submission contained a final study report for an oral mouse fertility study conducted with CC-10004. The results of the study indicate that CC-10004 does adversely affect fertility and that the male and female fertility NOAEL is less than 100 mg/kg/day. It is not necessary that the sponsor repeat this study to identify a NOAEL for rat male and female fertility. It will be adequate to incorporate the results of this study into a potential label for CC-10004 that will indicate that CC-10004 has an adverse effect on fertility.

It is interesting to note that the high dose tested in the oral mouse fertility study was 1000 mg/kg/day CC-10004. Therefore, it appears that use of 1000 mg/kg/day in the oral mouse embryofetal development study would be possible. Use of the 1000 mg/kg/day in the oral mouse embryofetal development study may elicit a greater extent of maternal toxicity than the high dose of 750 mg/kg/day that was used in this study. However, it is unclear how much additional useful information would be obtained from having the sponsor repeat the oral mouse embryofetal development study with a high dose of 1000 mg/kg/day CC-10004. It is this reviewer's opinion that repeat of the oral rabbit embryofetal development study with higher maternally toxic doses or use of another nonrodent species for conduct of the second embryofetal development study will provide more useful information to address the teratogenic potential of CC-10004. Therefore, conduct of a second oral mouse embryofetal development study with a high dose of 1000 mg/kg/day CC-10004 is not recommended at this time.

No regulatory action is indicated for this submission from a Pharmacology/Toxicology perspective, at this time.

External comments (to sponsor): None

cc:
DDDP/DIV DIR/WALKER
DDDP/ PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/CARR
DDDP/PM/OWENS

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/s/

Barbara Hill
6/19/2007 01:18:07 PM
PHARMACOLOGIST

Paul Brown
6/19/2007 02:03:34 PM
PHARMACOLOGIST

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date:	9/17/07
Serial No.:	055
Submission type:	IT; Submission of nonclinical final study reports
Drug:	CC-10004 (S-enantiomer)
Drug class:	Phosphodiesterase type IV (PDE4) inhibitor
Indication:	Psoriasis
Route:	Oral
Sponsor:	Celgene Corporation, Summit, NJ

Review date: September 20, 2007

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has proposed to develop CC-10004 [redacted] for the treatment of psoriasis. The original IND was submitted on July 29, 2004. Two draft nonclinical study reports were submitted in Serial #030 (date: 8-18-06) for 90 day oral rat and mouse toxicity studies. These studies served as dose range finding studies for the oral rat and mouse carcinogenicity study protocols included in Serial #030. The current submission contains two final nonclinical study reports for the 90 day oral rat and mouse toxicity studies.

Summary of submitted information:

The titles of the two final nonclinical study reports included in this submission are provided below.

1) CC-10004: A 90-day oral toxicity study in mice (Study No. CC-10004-TOX-002)
2) CC-10004: A 90-day oral toxicity study in rats (Study No. CC-10004-TOX-003)

No differences were noted between the draft and final study reports for these two nonclinical studies. The final study reports were submitted after the recommended 120 day time period after submission of the draft study reports. However, since no differences were noted between the draft and final study reports, there is no cause for concern.

Recommendations:

No regulatory action is indicated for this submission.

cc:
DDDP/DIV DIR/WALKER
DDDP/ PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/CARR
DDDP/PM/OWENS

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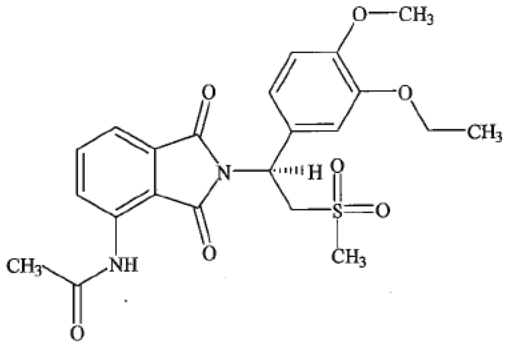
/s/

Barbara Hill
9/24/2007 02:03:50 PM
PHARMACOLOGIST

Paul Brown
9/25/2007 10:59:37 AM
PHARMACOLOGIST

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date: 11-7-07
Serial No.: 66
Submission type: Guidance meeting briefing document
Drug: CC-10004 (S-enantiomer)
Molecular formula: $C_{22}H_{24}N_2O_7S$
Molecular weight: 460.5
Structure:



Drug class: Phosphodiesterase type IV (PDE4) inhibitor
Indication: Psoriasis
Route: Oral
Sponsor: Celgene Corporation, Summit, NJ

Review date: November 19, 2007

Clinical formulation: White capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose [redacted]	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has

proposed to develop CC-10004 (b) (4) for the treatment of psoriasis. The original IND was submitted on July 29, 2004. Concern was raised about the vasculitis observed in the animal studies conducted to support the initial proposed clinical study contained in the original IND submission. Additional safety parameters to monitor for possible vasculitis were incorporated into the clinical study protocol. In addition, the initial dose was reduced to 20 mg/day and only patients with severe psoriasis were to be enrolled in the initial clinical study. The sponsor agreed to incorporate the changes into the initial clinical study and it was determined that the revised initial clinical study protocol was reasonably safe to initiate.

This submission contains a guidance briefing document for a meeting scheduled for December 10, 2007. The current submission contains summary information for two chronic systemic repeat dose toxicology studies in mice (6 months) and monkeys (12 months) conducted to support increasing the duration of therapy in the ongoing clinical study from 3 months to 12 months. The current submission also contains summary information for in vitro plasma protein binding for CC-10004 and a study conducted in mice to investigate the time course for development and recovery of inflammatory findings.

Previous clinical experience:

A total of eight clinical studies have been conducted with CC-10004, to date. Five Phase 1 clinical studies have been conducted in healthy volunteers. Three phase 2 clinical studies (one in subjects with moderate to severe psoriasis, one in subjects with severe plaque-type psoriasis and one in subjects with mild asthma) have been conducted with CC-10004. The design of each of these studies is summarized in the following table (copied from the briefing package).

Table 8: Summary of Clinical Studies With CC-10004

Study 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	Submitted to IND Serial Number (Submission Date)
Studies in Healthy Volunteers – Phase 1 Studies						
CC-10004-PK-001[b] 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 x 10 mg CC-10004 QD (10 mg) 2 x 10 mg CC-10004 QD (20 mg) 4 x 10 mg CC-10004 QD (40 mg) 4 x 10 mg CC-10004 BID (80 mg) 1 x 50 mg CC-10004 BID (100 mg)	10 6 6 6 6 6	0/40	000 (28 Jul 2004)
CC-10004-PK-007[b] 1 site (UK)	Single-center, double-blind, randomized, placebo-controlled, ascending multiple dose Healthy male subjects	14 days Completed	Placebo 40 mg CC-10004 QD (40 mg) 60 mg CC-10004 QD (60 mg) 80 mg CC-10004 QD (80 mg) 40 mg CC-10004 BID (80 mg) 40 mg CC-10004 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	054 (04 Sep 2007)
CC-10004-BA-001[b] 1 site (UK)	Single-center, open-label, randomized, 4-way crossover, relative bioavailability, food effect Healthy male subjects	4 x Single dose Completed	2 x 10 mg CC-10004 (20 mg) (micronized drug substance) fasted state 2 x 10 mg CC-10004 (20 mg) (micronized drug substance) fed state 2 x 10 mg CC-10004 (20 mg) (milled drug substance) fasted state 2 x 10 mg CC-10004 (20 mg) (milled drug substance) fed state	12	0/12	023 (21 Mar 2006)
CC-10004-PK-002[b] 1 site (US)	Single-center, open-label, single-dose ADME Healthy male subjects	Single dose Completed	20 mg (^{14}C)-CC-10004 as a suspension (100 µCi/20 mg)	6	0/6	027 (10 Jul 2006)
CC-10004-PK-005[b] 1 site (UK)	Single-center, open-label, ketoconazole effects on CC-10004 metabolism Healthy male subjects	2 x Single dose Completed	2 x 10 mg CC-10004 (20 mg)	18	0/18	025 (08 May 2006)

Table 8: Summary of Clinical Studies With CC-10004 (Continued)

Study 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	Submitted to IND Serial Number (Submission Date)
Studies in Subjects – Phase 2 Studies						
CC-10004-PSOR-003 34 sites[c] (Canada, Germany, Czech Republic)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison Male and female subjects with moderate-to-severe plaque-type psoriasis	12 weeks Completed	1 x 20 mg CC-10004 QD (20 mg) 1 x 20 mg CC-10004 BID (40 mg) Placebo	87 85 87	47/212	Not submitted – report preparation ongoing.
CC-10004-PSOR-001[b] 3 sites (US)	Multicenter, open-label, single-arm, pilot study Male and female subjects with severe plaque-type psoriasis	29 days Completed	2 x 10 mg CC-10004 QD (20 mg)	19	2/17	031 (07 Sep 2006)
CC-10004-ASTH-001[b] 4 sites (UK, Germany, South Africa)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, exercise challenge Male subjects with mild exercise- induced asthma	29 days Completed	2 x 10 mg CC-10004 QD (20 mg) 2 x 10 mg CC-10004 BID (40 mg) Placebo	26 23 24	5/68	023 (21 Mar 2006)

ADME = absorption, distribution, metabolism, excretion; BID = twice daily; IND = investigational new drug application; No. = number; QD = once daily; UK = United Kingdom; US = United States.
[a]Subjects who received at least 1 dose of study medication.
[b]Results of the study are presented in the attached investigator's brochure.
[c]Of the 34 sites, 28 sites randomized subjects, 2 sites screened but did not randomize any subjects, and 4 sites did not screen or randomize any subjects.

Summary information provided in the briefing document indicates that 351 subjects were exposed to CC-10004 daily doses ranging from 10 to 100 mg. In the European phase 2 clinical

study conducted in subjects with moderate to severe plaque-type psoriasis (European study), 87 subjects received 20 mg CC-10004 once daily and 85 subjects received 20 mg CC-10004 twice daily for 12 weeks. In the US phase 2 clinical study in subjects with severe plaque-type psoriasis (conducted under this IND), 19 subjects received 20 mg CC-10004 once daily for 29 days. In the European clinical study conducted in subjects with mild exercise-induced asthma, 26 subjects received 20 mg CC-10004 once daily and 23 subjects received CC-10004 twice daily for 29 days.

Summary information provided in the briefing package indicates that the most frequent reported adverse events were nausea (32 subjects; 71%) and headache (27 subjects, 60%). The sponsor states that the majority of the reported adverse events were rated as mild in severity and resolved after withdrawal of the treatment. The sponsor states that there was no evidence that systemic inflammatory/vasculitic changes developed following exposure to CC-10004. The sponsor states that there were no treatment related effects on white blood cell counts, neutrophil counts, albumin values, C-reactive protein values, fibrinogen values, erythrocyte sedimentation rate changes, antinuclear antibodies or antineutrophil cytoplasmic antibodies.

The sponsor states that even though there has been no evidence of a drug induced inflammatory or vasculitic syndrome in subjects exposed to CC-10004 to date, they intend to continue with careful medical monitoring in clinical studies. The monitoring program will incorporate the measurements of laboratory parameters that can be associated with systemic inflammation/vasculitis such as giant cell arteritis, polyarteritis or Wegener's vasculitis (elevated white blood cell count, neutrophil count, C-reactive protein values, fibrinogen values, erythrocyte sedimentation rate changes, antinuclear antibodies or antineutrophil cytoplasmic antibodies) along with careful clinical questioning and examination for physical signs and symptoms of drug-induced inflammation/vasculitis by the study investigators.

The sponsor states that the results of the Phase 2 European psoriasis clinical study (doses up to 20 mg CC-10004 were administered twice daily for 12 weeks) started to indicate an efficacious trend (PASI-75 of 24%). The onset of action occurred between 6 and 7 weeks after the start of treatment and the PASI response curves were on an upward slope at the end of the 3-month dosing period. The sponsor states that the results of the 12 week study conducted in moderate to severe psoriasis patients suggest that this profile may be further enhanced by study designs that continue to explore the dose range (up to 60 mg total daily dose) and study duration (up to 12 months).

The plasma pharmacokinetic parameters of CC-10004 following single dose administration or 14 days of administration are provided in the following table (copied from the briefing document).

Table 15: Plasma Pharmacokinetic Parameters of CC-10004 Following Multiple Oral Doses (Study CC-10004-PK-007)

	Dose of CC-10004								
	40 mg QD		60 mg QD		80 mg QD		40 mg BID[a]		40 mg QD with dose titration
Parameters[b]	Day 1 N = 9[c]	Day 14 N = 9	Day 1 N = 9[c]	Day 14 N = 9	Day 1 N = 9	Day 14 N = 9	Day 1 N = 9	Day 14 N = 9	Day 14 N = 8
C_{max} (ng/mL)	418 (31.7)	561 (29.5)	505 (25.6)	539 (37.1)	645 (40.4)	776 (28.9)	363 (27.0)	646 (25.0)	507 (28.2)
C_{trough} (ng/mL)	24.4 (72.9)	42.4 (63.1)	58.3 (123)	42.9 (70.7)	58.7 (85.7)	57.7 (68.8)	166 (53.3)	160 (54.3)	26.2 (151)
t_{max}[d] (h)	2.5 (1.5-4.0)	2.0 (1.5-4.0)	3.0 (2.0-4.0)	3.0 (3.0-3.0)	4.0 (1.5-8.0)	3.0 (3.0-4.0)	3.0 (2.0-6.0)	2.5 (1.0-3.0)	3.0 (2.0-4.0)
$AUC_{(0-\tau)}$ (ng•h/mL)	2836 (41.1)	4241 (43.6)	4111 (34.6)	4347 (39.5)	5841 (37.3)	6014 (37.3)	2347[e] (24.0)	3828[e] (33.6)	3697 (56.2)
$t_{1/2}$ (h)	6.80 (24.3)	7.14 (24.8)	8.03 (26.5)	8.14 (28.9)	6.76 (30.8)	8.98 (43.4)	NC	6.12 (27.5)	8.68 (36.7)
CL/F (L/h)	13.5 (34.6)	9.43 (43.6)	13.5 (44.3)	13.8 (39.5)	12.2 (40.9)	13.3 (37.3)	NC	11.6 (30.0)	10.8 (56.2)
Vz/F (L)	133 (44.5)	97.2 (39.4)	157 (43.1)	162 (46.2)	119 (33.5)	172 (65.7)	NC	102.5 (26.0)	136 (80.1)

AUC(0-τ) = area under the plasma concentration versus time curve over one dosing interval; BID = twice daily; CL/F = apparent total plasma clearance; Cmax = maximal plasma concentration; Ctrough = plasma concentration at the end of the dosing interval (12 hours for 40 mg BID and 24 hours for other doses); N = total number of subjects; NC = not calculated; QD = once daily; tmax = time to maximum concentration; t1/2 = apparent plasma terminal elimination half-life; Vz/F = apparent volume of distribution during the terminal phase.

aFor the 40 mg BID group, Cmax, tmax, and AUC(0-τ) were obtained post-AM dose, and the other parameters were obtained post-PM dose.

bFor all parameters except tmax, the geometric mean followed by the geometric coefficient of variation (in parentheses) is presented.

cN = 7 for t1/2 and CL/F.

dMedian (minimum – maximum).

eFor 40 mg BID, τ = 12 hours post-AM dose.

The mean apparent elimination half-life of CC-10004 was between 6 and 9 hours across all dose levels and was similar between days 1 and 14. The total plasma clearance on day 1 was comparable to that on day 14. The systemic exposure (AUC) appeared to increase in a dose proportional manner across the QD dose range from 40 – 80 mg on day 1. No apparent dose accumulation was noted in this study. The urinary excretion of CC-10004 was very low (<4%).

Proposed clinical studies:

On December 12, 2006 (Serial no. 042), the sponsor submitted protocol CC-10004-PSOR-004, "A phase 2, open-label multicenter study to evaluate the safety, pharmacodynamics, pharmacokinetics and efficacy of CC-10004 in subjects with recalcitrant plaque type psoriasis". Twenty subjects with recalcitrant psoriasis were to be enrolled in this study and treated with 20 mg bid CC-10004 for 3 months. I informed the Clinical reviewer (Dr. Brenda Carr) that there was adequate nonclinical toxicology data to support the proposed dosing regimen, provided that adequate safety monitoring to measure vasculitis formation were included in the study (which it was determined that there was adequate safety monitoring). An amended protocol that incorporated the Division's medical reviewer's comments was submitted on April 25, 2007 (Serial no. 47). The medical reviewer determined that the revised clinical study protocol was adequate. Pharmacokinetic assessment on days 1, 8, 15, 29, 43, 57, 71 and 85 were incorporated into this study. Dose reduction to 20 mg qd is allowed for subjects that cannot tolerated 20 mg bid. A bi-weekly assessment of safety parameters (standard laboratory parameters and vasculitis parameters) is incorporated into the study.

The sponsor would like to obtain agreement from the Agency to change the ongoing study in severe recalcitrant psoriasis patients (Study# CC-10004-PSOR-004) to include an increase in the treatment duration from 3 months to 6 months and an increase in dose from 20 mg bid to 30 mg bid in patients who have not responded (achieved a PASI-75) at 3 months. The sponsor has included summary data from a 6 month mouse toxicology study and a 12 month monkey toxicology study to support this increase in dose and duration. These studies are reviewed later in this document.

The sponsor also proposes to conduct a dose-ranging study (CC-10004-PSOR-005) in moderate to severe psoriasis plaque-type psoriasis patients with doses of 0 mg bid (placebo), 10 mg bid, 20 mg bid and 30 mg bid CC-1004 for a duration of 6 months with the possibility of extending treatment for up to 12 months (CC-10004-PSOR-005E). Approximately 328 subjects will be enrolled in this study for a randomization of 1:1:1:1 across the four dose groups. Pharmacokinetic assessment on days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155 and 169 are incorporated into this study. The same safety parameters incorporated into CC-10004-PSOR-004 are incorporated into this study.

Review of submitted nonclinical toxicology study information:

Information for four new nonclinical studies, listed below, was included in the briefing package. Only summary information was provided for study 1. The information provided for studies 2 – 4 included summary information, unaudited draft CTD summary tables, draft histopathology report, individual animal macroscopic and microscopic parameter line listings and histopathology incidence table. A full final study report was not provided for any of the new nonclinical studies included in this submission.

1) Plasma protein binding of CC-10004 (Study no. CC-100004-DMPK-026)
2) CC-10004: A 6-month oral toxicity study in mice (Study no. CC-10004-TOX-004)
3) CC-10004: 12-month oral toxicity study in cynomolgus monkeys (Study no. CC-10004-TOX-005)
4) CC-10004: Oral toxicity study in mice to investigate the time course for development and recovery of inflammatory lesions in multiple tissues (Study no. CC-10004-TOX-008)

Study 1

This study was conducted to evaluate the plasma protein binding of CC-10004 in mouse, rat, rabbit, monkey and human plasma. The overall mean CC-10004 percent bound was 88.6% in mouse plasma, 90.6% in rat plasma, 80.9% in rabbit plasma, 84.3% in monkey plasma and 68.3% in human plasma at the tested concentration range of 0.25 to 2.5 µg/ml. The extent of plasma protein binding was concentration independent over the concentration range tested in this study. The results indicate that significantly less plasma protein binding of CC-10004 occurs in humans compared to mice, rats, rabbits or monkeys.

Study 2

Study title: CC-10004: A 6-month oral toxicity study in mice

Key findings:

Treatment related effects on mortality were noted in mid and high dose animals. Increased body weight was noted in low, mid and high dose females with a corresponding increase in food consumption noted in mid and high dose females.

Treatment related effects on hematologic parameters (decreased total white blood cell count, decreased percent large unstained cells, decreased percent lymphocytes and increased percent neutrophils) were noted in week 12 in mid and high dose males. Treatment related effects on serum chemistry parameters were noted in week 12 and/or 26 in low, mid and high dose animals. Increased total protein and globulin was noted in high dose males in week 12/26, decreased albumin was noted in high dose females in week 12, decreased A/G in high dose females in week 12/26, decreased chloride in high dose females in week 26, increased protein low dose animals (week 12 only) and mid dose animals (week 26 only) and increased haptoglobin levels in mid and high dose animals in week 12 and/or 26.

Treatment related effects on organ weights were noted in mid and high dose animals. Increased liver weights were noted in mid and high dose animals, increased heart weight was noted in high dose females only, increased testes weights was noted in mid and high dose males and decreased brain weights were noted in mid and high dose females.

Microscopic lesions in the heart were noted in a few mid and high dose animals. These lesions involved inflammation of the aortic root or around other cardiac arteries and in the myocardium. Cartilaginous metaplasia of the aortic root, along with vascular mineralization was also noted. A loss of vascular integrity (i.e., vascular inflammation, hematoma formation and other lesions) was noted in animals found dead or euthanized in extremis. Centrilobular hepatocellular hypertrophy of the liver was noted in two-thirds of high dose mice. Additional lesions of vascular inflammation, hematoma in the mesentery adjacent to the pancreas were noted in one high dose female. Fibroplasia and inflammation in the gallbladder was noted in another high dose female. Vascular and perivascular inflammation of the liver and fibrosis around the bile ducts were noted in one mid dose male.

If the slight increase in body weight in low dose females and transient increase in total protein noted in low dose males are considered relatively minor, then the NOAEL is identified as 10 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 5614 and 5842 ng·hr/ml for CC-10004 in males and females respectively, on day 177) in mice after 6 months of daily oral administration.

Study no.:	CC-10004-TOX-004
Volume #, and page #:	Volume 3, tab 7.2.3
Conducting laboratory:	(b) (4)
Date of study initiation:	7/14/06
GLP compliance:	Yes (based on summary information)

QA reports: No
Drug, lot #, and % purity: CC-10004, Batch# 54560-05
Vehicle: 1% carboxymethycellulose

Methods

Oral (gavage) doses of 0 (vehicle), 10, 100 and 1000 mg/kg/day CC-10004 were administered to CD-1 mice (15/sex/group) for 6 months. Satellite TK animals (6/sex in control and 38/sex/dose in test article treated groups) were dosed orally (gavage) with CC-10004 for determination of toxicokinetics of CC-10004 (S-isomer), [redacted] (b) (4) and two metabolites CC-16805 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl C-10004 glucuronide). Toxicologic parameters evaluated in this study included: mortality, clinical signs, body weight, food consumption, clinical pathology (which included special chemistry for haptoglobin), ophthalmic examination, organ weights, macroscopic evaluation and microscopic examination of tissues (full array in control and high dose animals; heart, thymus, lung and gross lesions in low and mid dose animals). Blood samples were obtained on days 22 and 177 for toxicokinetic analysis of parent (days 22 and 177) and metabolites (day 177).

Results:

Treatment related mortality was noted in mid dose males (1/15), mid dose TK females (1/20) and high dose animals (2/15 males; 1/15 females) and high dose TK animals (3/20 males; 1/20 females). One high dose male that was found dead on day 103 was observed with a liver infarction with severe chronic active inflammation on the surrounding liver parenchyma, adhesions to body wall and fibrosis. One high dose male that was euthanized in extremis on day 128 was observed with a large hematoma with vascular and perivascular inflammation and pigment deposition in the dorsal abdominal wall. A high dose TK female that was found dead on day 168 was observed with a large hematoma in the mammary gland along with inflammation extending into the adjacent muscle and blood vessels and a hematoma in the mesentery adjacent to the pancreas with vascular necrosis and inflammation. One mid dose male found dead on day 74 was observed with a large hematoma in the skeletal muscle of the hind limb and associated vascular and perivascular inflammation. Treatment related effects on clinical signs were limited to mice found dead or euthanized in extremis. A dose dependent increase in body weight gain was noted in low, mid and high dose females only (+8.5%, +10.1% and 16.3%, respectively, at week 26) compared to control females. A corresponding increase in food consumption was noted in mid and high dose females. No treatment related effects on ophthalmic findings or macroscopic findings were noted in this study.

Treatment related effects on hematologic parameters were noted in week 12 in mid and high dose males. These effects included decreased total white blood cell count (-33% compared to control), decreased percent large unstained cells, decreased percent lymphocytes (-12-17% compared to control), and increased percent neutrophils (+72-106% compared to control). Treatment related effects on serum chemistry parameters were noted in week 12 and/or 26 in low, mid and high dose animals. Increased total protein (+7.3-12.7% compared to control) and globulin (+18-20% compared to control) was noted in high dose males in week 12/26. Decreased albumin (-7.9% compared to control) was noted in high dose females in week 12,

decreased A/G (-24-28% compared to controls) in high dose females in week 12/26 and decreased chloride (-2.6% compared to control) in high dose females in week 26. An additional treatment related effect on serum chemistry parameters noted in low dose animals (week 12 only) and mid dose animals (week 26 only), included increased protein (+5.5% and 9.1%, respectively, compared to control). Increased haptoglobin levels were noted in mid and high dose animals in week 12 and/or 26 (+47-204% in males and +131-430% in females compared to control).

Treatment related effects on organ weights were noted in mid and high dose animals. Increased liver weights (corresponding to minimal hepatocellular hypertrophy) were noted in mid and high dose animals. Increased heart weight was noted in high dose females only which correlated with findings of inflammation and/or mineralization. Increased testes weights was noted in mid and high dose males and decreased brain weights were noted in mid and high dose females.

Microscopic lesions in the heart were noted in a few mid and high dose animals. These lesions involved inflammation of the aortic root or around other cardiac arteries and in the myocardium. Cartilaginous metaplasia of the aortic root, along with vascular mineralization was also noted. A loss of vascular integrity (i.e., vascular inflammation, hematoma formation and other lesions) was noted in animals found dead or euthanized in extremis. Centrilobular hepatocellular hypertrophy of the liver was noted in two-thirds of high dose mice. Additional lesions of vascular inflammation, hematoma in the mesentery adjacent to the pancreas were noted in one high dose female. Fibroplasia and inflammation in the gallbladder was noted in another high dose female. Vascular and perivascular inflammation of the liver and fibrosis around the bile ducts were noted in one mid dose male.

The toxicokinetic data for CC-10004 and two metabolites CC-16805 (M3) and CC-16166 (M12) are provided in the following table (copied from the briefing document).

Table 3: Mean CC-10004, CC-16085 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl CC-10004 glucuronide) Plasma Parameters in Male and Female Mice Following Daily Oral Administration of CC-10004 at 10, 100 and 1000

Dosing Day	Analyte	Dosage Group (mg/kg/day)	Gender	C_{max} (ng/mL)	T_{max} (hr)	AUC_{24h} (hr • ng/mL)	Ratio[a] Metabolite / Parent
Day 22	CC-10004	10	M	869	1.0	4876	NA
			F	1408	1.0	5703	NA
		100	M	2757	2.0	38528	NA
			F	2920	4.0	34929	NA
		1000	M	5494	4.0	88893	NA
			F	6377	2.0	108687	NA
Day 177	CC-10004	10	M	826	1.0	5614	NA
			F	902	2.0	5842	NA
	M3	10	M	2.79[a]	1.0[a]	5.29[a]	0.094
			F	4.14	2.0	15.2	0.260
	M12	10	M	128	1.0	1459	26.0
			F	155	8.0	1856	31.8
	CC-10004	100	M	2381	2.0	21289	NA
			F	2101	1.0	32491	NA
	M3	100	M	7.63	2.0	87.6	0.411
			F	8.33	8.0	132	0.406
	M12	100	M	1765	2.0	11144	52.3
			F	1987	12.0	27056	83.3
	CC-10004	1000	M	4640	12.0	72183	NA
			F	5874	2.0	76010	NA
	M3	1000	M	20.7	4.0	345	0.478
			F	29.7	4.0	416	0.547
	M12	1000	M	2698	4.0	48170	66.7
			F	6201	12.0	114619	151

[a] AUC_{24h} CC-10004/metabolite X 100
AUC_{24h} denotes $AUC_{0\text{-}24h}$
NA=Not applicable

A dose related increase (which was less than dose proportional) in systemic exposure was noted in males and females on days 22 and 177. No apparent dose accumulation was noted between days 22 and 177. No gender related difference in systemic exposure was noted in this study. (b) (4)

(b) (4) Systemic exposure to CC-10004 desmethyl glucuronide (M12) was dose related and ranged from approximately 16% to 151% of CC-10004. Systemic exposure to M12 was greater

in females compared to males. Systemic exposure to desmethyl CC-10004 (M3) was generally negligible relative to M12.

Study 3

Study title: CC-10004: 12-month oral toxicity study in cynomolgus monkeys

Key findings:

No treatment related effects on mortality, body weight, ophthalmic parameters, electrocardiographic parameters, urinalysis parameters, organ weights, macroscopic parameters or microscopic parameters were noted in this study. A higher incidence in the frequency of red vaginal discharge and red material on the cage floor was noted in low, mid and high dose females. Treatment related effects on hematologic parameters were noted in mid dose females and high dose animals. Increased absolute neutrophils, increased percentage neutrophils, increased total white blood cell count and decreased percent lymphocytes were noted in high dose animals. These changes in lymphocytes and neutrophils persisted through week 39 but were mostly resolved by week 51. Increased fibrinogen was noted in week 51 in high dose animals and mid dose females. No treatment related effects on hematologic parameters were noted in mid dose males and low dose animals.

A few relatively minor treatment related effects on serum chemistry parameters were noted in mid and high dose animals. Glucose was sporadically decreased in mid and high dose males. Decreased albumin was noted in mid and high dose females. No treatment related effects on C-reactive protein or haptoglobin were noted in this study. A minor alteration of the populations of T cells and NK cells (as measured by flow cytometry) was noted in mid and high dose males compared to control males. It is difficult to determine if this minor alteration can be considered a toxicological effect or not. No alterations of populations of T cells or NK cells were noted in treated females compared to control females.

If the effects noted on the hematologic parameters and serum chemistry parameters are considered relatively minor in the absence of any corresponding histopathological effects, then the NOAEL is identified as 600 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 42608 and 26936 ng·hr/ml for CC-10004 in males and females respectively, on day 358) in monkeys after 12 months of daily oral administration.

No overt toxicity was expressed in the 12 month oral monkey toxicology study. It would have been preferable if the sponsor had used a high dose that had expressed overt toxicity.

Study no.:	CC-10004-TOX-005
Volume #, and page #:	Volume 5, tab 7.2.15
Conducting laboratory:	[redacted] (b) (4)
Date of study initiation:	10/25/06
GLP compliance:	Yes (based on summary information)
QA reports:	No
Drug, lot #, and % purity:	CC-10004, Batch# 54560-05

Vehicle: 1% carboxymethycellulose

Methods

Oral (gavage) doses of 0 (vehicle), 60, 180 and 600 mg/kg/day CC-10004 were administered to cynomolgus monkeys (5/sex/group) for 12 months. Toxicologic parameters evaluated in this study included: mortality, clinical signs, body weight, food consumption, clinical pathology (hematology, serum/special {C-reactive protein and haptoglobin} chemistry and urinalysis), immunophenotyping, ophthalmic examination, electrocardiography, organ weights, macroscopic evaluation and microscopic examination of tissues (full array in all animals in all dose groups). Toxicokinetics of CC-10004 (S-isomer), two metabolites CC-16805 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl C-10004 glucuronide) were evaluated in this study. Blood samples were obtained on days 0 (1), 101 and 358 for toxicokinetic analysis of parent (days 0, 101 and 358) and metabolites (day 358).

Results:

No treatment related effects on mortality, body weight, ophthalmic parameters, electrocardiographic parameters, urinalysis parameters, organ weights, macroscopic parameters or microscopic parameters were noted in this study. A higher incidence in the frequency of red vaginal discharge and red material on the cage floor was noted in low, mid and high dose females. Treatment related effects on hematologic parameters were noted in mid dose females and high dose animals. Increased absolute neutrophils (+68-440% compared to controls), increased percentage neutrophils (+33-180% compared), increased total white blood cell count (+27-116% compared to control) and decreased percent lymphocytes (-51-62% compared to control) were noted in high dose animals. These changes in lymphocytes and neutrophils persisted through week 39 but were mostly resolved by week 51. Increased fibrinogen was noted in week 51 in high dose animals (+29-37% compared to controls) and mid dose females (+44% compared to controls). No treatment related effects on hematologic parameters were noted in mid dose males and low dose animals.

A few relatively minor treatment related effects on serum chemistry parameters were noted in mid and high dose animals. Glucose was sporadically decreased in mid and high dose males. Decreased albumin was noted in mid and high dose females. No treatment related effects on C-reactive protein or haptoglobin were noted in this study. A minor alteration of the populations of T cells and NK cells (as measured by flow cytometry) was noted in mid and high dose males compared to control males. It is difficult to determine if this minor alteration can be considered a toxicological effect or not. No alterations of populations of T cells or NK cells were noted in treated females compared to control females.

The toxicokinetic data for CC-10004 and two metabolites CC-16805 (M3) and CC-16166 (M12) are provided in the following table (copied from the briefing document).

Table 7: Mean CC-10004, CC-16085 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl CC-10004 glucuronide) Plasma Parameters in Male and Female Monkey Following Daily Oral Administration of CC-10004 at 60, 180 and 600 mg/kg/day

Dosing Day	Analyte	Dosage Group (mg/kg/day)	Gender	C_{max} (ng/mL)	T_{max} (hr)	AUC_{24h} (hr • ng/mL)	Ratio[a] Metabolite / Parent
Day 0[b]	CC-10004	60	M	774	2.3	9964	NA
			F	1159	3.3	12996	NA
		180	M	1613	5,3	19537	NA
			F	1653	7.3	22401	NA
		600	M	2158	9.3	34717	NA
			F	1622	8.0	25678	NA
Day 101	CC-10004	60	M	1213	2.3	9983	NA
			F	1509	3.0	10718	NA
		180	M	1528	3.3	14141	NA
			F	1371	2.7	12724	NA
		600	M	2554	3.0	23548	NA
			F	2757	4.0	23451	NA
Day 358	CC-10004	60	M	1265	3.3	16443	NA
			F	1596	4.0	17526	NA
	M3 (CC-16085)	60	M	23.5	8.0	452	2.75
			F	48.3	4.0	858	4.9
	M12 (CC-16166)	60	M	2573	12.0	50695	308
			F	2220	10.7	43629	249
	CC-10004	180	M	2413	3.3	23841	NA
			F	1833	2.7	22561	NA
	M3 (CC-16085)	180	M	54.9	4.0	804	3.37
			F	54.7	6.0	847	3.75
	M12 (CC-16166)	180	M	4224	14.7	71723	301
			F	1471	6.0	28234	125
	CC-10004	600	M	4533	3.3	42608	NA
			F	2365	3.7	26936	NA
	M3 (CC-16085)	600	M	187	5.3	2768	6.50
			F	61.5	1.3	1065	3.95
	M12 (CC-16166)	600	M	5788	12.0	90035	211
			F	3416	14.7	63662	236

[a] AUC_{24h} CC-10004/metabolite X 100
[b] The first day of dosing is designated Day 0 and the first week of dosing is designated Week 0
AUC_{24h} denotes $AUC_{0\text{-}24h}$
NA=Not applicable

A dose related increase (which was less than dose proportional) in systemic exposure was noted in males and females on days 0, 101 and 358. A slight dose accumulation was noted between days 101 and 358. No gender related difference in systemic exposure was noted in this

study (except a higher exposure in high dose males compared to high dose females on days 0 and 358). Systemic exposure to CC-10004 desmethyl glucuronide (M12) was dose related and ranged from approximately 211 – 308% in male monkeys 125 – 249% in female monkeys of CC-10004. Systemic exposure to M12 was greater in males compared to females. Systemic exposure to desmethyl CC-10004 (M3) was significantly lower than to M12. Systemic exposure to M3 ranged from 2.75% - 6.5% in male monkeys and 3.75% - 4.90% in females monkeys of CC-10004.

Study 4

Study title: CC-10004: Oral toxicity study in mice to investigate the time course for development and recovery of inflammatory lesions in multiple tissues

Key findings: The results of this study indicate that almost complete recovery from inflammatory lesions induced in the liver, thymus and mesenteric lymph node after 14 days of oral treatment with a high dose (1000 mg/kg/day) of CC-10004 is noted after a 31 day recovery period in mice. Complete recovery from inflammatory lesions induced in the liver, thymus and mesenteric lymph node after 14 days of oral treatment with a high dose (1000 mg/kg/day) of CC-10004 is noted after a 76 day recovery period in mice.

Study no.:	CC-10004-TOX-008
Volume #, and page #:	Volume 4, tab 7.2.8
Conducting laboratory:	(b) (4)
Date of study initiation:	9/7/06
GLP compliance:	Yes (based on summary information)
QA reports:	No
Drug, lot #, and % purity:	CC-10004, Batch# 54560-05
Vehicle:	1% carboxymethycellulose

Methods

This study was conducted to investigate recovery from inflammatory lesions noted in repeat dose toxicity studies conducted in mice. The sponsor states that based on the observation that the proinflammatory syndrome in rodents occurred early in the treatment period, the mice were administered a high dose (300-1000 mg/kg/day) for a short period (2 weeks) and allowed to recover for 31 or 76 days. The sponsor states that an additional group was treated for 90 days to determine if animals showed recovery while still receiving drug.

Oral (gavage) doses of 0 (vehicle), 300 and 1000 mg/kg/day CC-10004 were administered to female CD-1 mice (36/group) for 3 and 14 days and oral doses of 0 (vehicle) and 1000 mg/kg/day CC-10004 was administered for 45 or 90 days. A subset of animals dosed for 14 days were placed on a 31 or 76 day recovery to assess reversibility of treatment related effects associated with oral administration of CC-10004 in mice. Necropsies were conducted on days 3 and 14 (for animals continuously doses at 300 and 1000 mg/kg/day), on days 45 and 90 (for animals continuously receiving 1000 mg/kg/day or for the subset of recovery animals dosed for

14 days at 300 and 1000 mg/kg/day followed by a 31 day recovery {day 45} or for the subset of recovery animals dosed for 14 days at 300 and 1000 mg/kg/day followed by a 76 day recovery {day 90}).

Toxicologic parameters evaluated in this study included: mortality, clinical signs, body weight, food consumption, clinical pathology, organ weights, macroscopic evaluation and microscopic examination of tissues (heart with aortic root, kidney, liver, lung, mesenteric lymph node, pancreas, spleen, thymus, mesentery, femur with stifle join and all gross lesions for all animals in all dose groups).

Results:

Five animals died before their scheduled sacrifice dates. Early deaths included two low dose animals on days 5 and 13 and three high dose animals on days 12, 19 and 20. Summary information indicates that lesions from animals that died before the scheduled sacrifices were not included in the summary of liver and thymic lesions provided except where specifically noted.

Increased body weight was noted in high dose animals after administration for 90 days. Increased food consumption was noted in high dose animals during the first 2 weeks of dosing. No treatment related effects on hematology parameters were noted in this study. Treatment related effects on serum chemistry parameters induced higher globulin levels (in low and high dose animals on day 14 and in high dose animals on day 90) and urea nitrogen levels (in low and high dose animals on day 14) and lower A/G (in low and mid dose animals on day 14 and in high dose animals on day 90) when compared to control animals. No treatment related effects on serum chemistry parameters were noted in recovery animals treated for 14 days and allowed to recover for 35 or 76 days.

Increased liver weights were noted in high dose animals compared to control animals on day 14, 45 and 90. Liver weights in high dose recovery animals treated for 14 days and allowed to recover for 35 or 76 days were comparable to control animals. Increased heart weight was noted in high dose animals treated continuously for 90 days.

Treatment related effects on microscopic parameters were noted in the thymus, liver and mesenteric lymph node of low and high dose mice sacrificed on or before day 45. No treatment related effects on microscopic parameters were noted in animals sacrificed on day 90. Minimal to slight/mild hepatocellular hypertrophy was noted in several high dose animals on days 3, 14 and 45. This lesion was characterized histologically by enlargement of hepatocytes and nuclei with slightly increased cytoplasmic granularity that was most pronounced in the centrilobular area but also was present, to a lesser extent, in hepatocytes in other regions.

On day 3, minimal hepatocellular was present in 4/12 high dose animals (groups 3 and 4). One high dose group 4 animal sacrificed on day 3 also had moderate hepatocellular necrosis and was the only animal with this change. On day 14, minimal to slight/mild hepatocellular hypertrophy was noted in 7/20 high dose animals (groups 3 and 4). On day 45, minimal to slight/mild hepatocellular hypertrophy was noted in 7/10 animals treated continuously (group 4) and in one animal treated for 14 days followed by a 31 day recovery (group 3). No

hepatocellular hypertrophy was noted on day 90 in either group 3 (76 day recovery) animals or group 4 (continuous treatment) animals.

The incidences of selected liver lesions, not including early deaths are summarized in the following table (copied from the briefing document).

Table 4: Incidences of Selected Liver Lesions

	Day 3				Day 14			
	Group				Group			
	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg
Number Examined	6	6	6	6	10	10	10	10
Hepatocellular Hypertrophy	0	0	1	3	0	0	3	4
Hepatocellular Necrosis	0	0	0	1	0	0	0	0
	Day 45				Day 90			
	Group				Group			
	1 0 mg/kg	2* 300 mg/kg	3* 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg
Number Examined	10	10	10	10	10	8	10	7
Hepatocellular Hypertrophy	0	0	1	7	0	0	0	0
Hepatocellular Necrosis	0	0	0	0	0	0	0	0

Groups 2 and 3 were dosed daily for 14 days then allowed to recover to Day 45 or Day 90.

Histological changes in the thymus were noted in low and high dose animals on days 3, 14 and 45 but not on day 90. Thymic lesions were the most severe and occurred at the highest incidences on day 3. On Day 3, thymic lesions included moderate to severe/high lymphoid necrosis in 6/12 high dose animals (groups 3 and 4) and in 1/6 low dose animals (group 2). Minimal to slight/mild thymic lymphoid depletion was noted in 5/12 high dose animals (groups 3 and 4) and 5/6 low dose animals (group 2). Slight/mild to moderate subacute thymic inflammation was noted in 6/12 high dose animals (groups 3 and 4) and minimal to slight/mild subacute inflammation was noted in 3/6 low dose animals (groups 2).

On day 14, inflammatory and degenerative thymic lesions were decreased in severity and hyperplastic lesions were evident. Inflammatory thymic changes at this time point were diagnosed as chronic active and included small amounts of fibrous connective tissue in addition to the inflammatory cells. Minimal to slight/mild inflammation was noted in 5/12 high dose animals (groups 3 and 4) and 1/20 low dose animals (groups 2). Minimal to slight/mild lymphoid depletion was noted in 2/20 high dose animals and 1/10 low dose animals. Minimal to moderate lymphoid hyperplasia, affecting primarily the cortical lymphocytes, was noted in 6/20 high dose animals and minimal thymic lymphoid hyperplasia was noted in 1/20 low dose animals.

On day 45, minimal thymic lymphoid hyperplasia was noted in 2/20 high dose animals that were dosed continuously (group 4) and 1/10 high dose animals treated for 14 days followed by a 31 day recovery (group 3).

The incidences of selected thymic lesions, not including early deaths are summarized in the following table (copied from the briefing document).

Table 5: Incidences of Selected Thymic Lesions

	Day 3				Day 14			
	Group				Group			
	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg
Number Examined	6	6	6	6	10	10	10	10
Lymphoid Necrosis	0	1	4	2	0	0	0	0
Inflammation	0	3	4	2	0	1	2	3
Lymphoid Depletion	0	5	2	3	0	1	2	0
Lymphoid Hyperplasia	0	0	0	0	0	1	1	5
	Day 45				Day 90			
	Group				Group			
	1 0 mg/kg	2* 300 mg/kg	3* 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg
Number Examined	10	10	10	10	10	8	10	7
Lymphoid Necrosis	0	0	0	0	0	0	0	0
Inflammation	0	0	0	0	0	0	0	0
Lymphoid Depletion	0	0	0	0	1	0	0	0
Lymphoid Hyperplasia	0	0	1	2	0	0	0	0

Groups 2 and 3 were dosed daily for 14 days then allowed to recover to Day 45 or Day 90.

Histological changes in the mesenteric lymph node were noted in low and high dose animals on days 14 and 45 but not on day 3 or 90. On day 14, minimal acute inflammation was noted in 2/19 high dose animals (groups 3 and 4) and 1/10 low dose animals (group 2). On day 45, minimal to mild lymphoid hyperplasia was noted in 4/10 high dose animals treated continuously (group 4), in 3/7 high dose animals treated for 14 days followed by a 31 day recovery (group 3) and 1/10 low dose animals treated for 14 days followed by a 31 day recovery (group 2). No mesenteric lymph nodes lesions were noted on day 90 in any of the treatment groups.

The incidences of selected mesenteric lymph node lesions, not including early deaths are summarized in the following table (copied from the briefing document).

Table 6: Incidences of Selected Mesenteric Lymph Node Lesions

	Day 3				Day 14			
	Group				Group			
	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2 300 mg/kg	3 1000 mg/kg	4 1000 mg/kg
Number Examined	6	6	6	6	9	10	10	9
Acute Inflammation	0	0	0	0	0	1	1	1
Lymphoid Hyperplasia	0	0	0	0	0	1	0	0
	Day 45				Day 90			
	Group				Group			
	1 0 mg/kg	2* 300 mg/kg	3* 1000 mg/kg	4 1000 mg/kg	1 0 mg/kg	2* 300 mg/kg	3* 1000 mg/kg	4 1000 mg/kg
Number Examined	10	10	7	10	10	8	10	7
Acute Inflammation	0	0	0	0	0	0	0	0
Lymphoid Hyperplasia	0	1	3	4	1	0	0	0

Groups 2 and 3 were dosed daily for 14 days then allowed to recover to Day 45 or 90.

Summary of nonclinical toxicology information available for CC-10004:

A summary of the nonclinical toxicology studies conducted to support the safety of CC-10004 is provided below. The reader is referred to reviews entered in DFS under [redacted] (b) (4) if additional detail is needed.

Repeat dose oral dose toxicology summary:

Three 4 week oral mouse toxicology studies were conducted with CC-10004 (micronized; diameter = 19.8 microns). Oral (gavage) doses of 0 (vehicle), 250, 600 and 1500 mg/kg/day CC-10004 were administered in the first study. Oral (gavage) doses of 0 (vehicle), 5, 25, 75 and 150 mg/kg/day CC-10004 were administered in the second study. Oral (gavage) doses of 0 (vehicle), 1, 2, and 4 mg/kg/day CC-10004 were administered in the third study). The vehicle used for all three 4 week studies was 1% carboxymethylcellulose.

Arteritis was one of the primary toxicity findings noted in the 4 week oral mouse toxicology studies. Arteritis was noted at doses as low as 5 mg/kg in these studies. The NOEL was 4 mg/kg/day for both males and females. The arteritis occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. Neutrophil and globulin levels were also increased. Other findings included centrilobular liver hypertrophy, effects on the stomach and lymphoid tissue effects.

A 13 week oral mouse toxicology study was conducted with CC-10004 [redacted] (b) (4) Oral (gavage) doses of 0 (vehicle), 2, 4, 8 and 16 mg/kg/day CC-10004 were administered to mice for 13 weeks. The vehicle used in this study was 1% carboxymethylcellulose. Arteritis in the root of the aorta and the thymus and minor perivascular inflammatory cell infiltration in the lung were noted at 16 mg/kg/day. No arteritis or other toxicities were observed at 8 mg/kg/day or lower. The NOAEL for CC-10004 was identified as 8 mg/kg/day [24 mg/m^2; $AUC_{0\text{-}24\ hr}$ = 9608

ng·hr/ml (males); $AUC_{0\text{-}24\ hr}$ =8988 ng·hr/ml (females)] in mice after oral administration for 13 weeks.

A second 13 week oral mouse toxicology study was conducted with CC-10004 (milled; diameter = 64.2 microns) as a dose range finding study to support dose selection for a 2 year oral mouse carcinogenicity study. Oral (gavage) doses of 0 (vehicle), 100, 300 and 1000 mg/kg/day CC-10004 were administered to mice for 13 weeks. The vehicle used in this study was 1% carboxymethylcellulose. No treatment related mortality was noted in this study. A treatment related inflammation manifested by a neutrophilic leukocytosis, lymphopenia and increased acute phase proteins (haptoglobin and CRP) was noted in low, mid and high dose animals during week 1 but not during week 13. Treatment related effects on microscopic parameters included inflammatory lesions noted in the lung, heart and aortic root in mid and high dose animals. The NOAEL for this study could be identified as 100 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 24318 and 25478 ng·hr/ml in males and females, respectively) in mice after administration for 13 weeks, since the inflammatory effects induced by CC-10004 were transient.

A 13 week oral rat toxicology study was conducted with CC-10004 (milled; diameter = 64.2 microns) as a dose range finding study to support dose selection for a 2 year oral rat carcinogenicity study. Oral (gavage) doses of 0, 0.3, 3, 10 and 30 mg/kg/day were administered to female Sprague-Dawley rats (10/dose) for 90 days. Oral (gavage) doses of 0, 30, 100, 300 and 1000 mg/kg/day were administered to male Sprague-Dawley rats (10/dose) for 90 days. The vehicle used in this study was 1% carboxymethylcellulose. Due to the mortality noted in this study, dosing was discontinued in the following dose groups: 1) mid-low dose males on day 48, 2) mid-high dose males on day 11, 3) mid-high dose females on day 26 and 4) high dose animals on day 9.

Treatment related mortality was noted in the following dose groups: 1) mid-low dose males (10/10), 2) mid-high dose males (10/10), 3) mid-high dose females (10/10), 4) high dose males (7/10) and 5) high dose females (6/10). Mortality of all treated animals in the high dose groups was not noted due to very early dose discontinuation in these animals on day 9 and allowing the surviving animals to be maintained on an 82 day recovery period. Treatment related toxicity was noted in all dose groups tested in this study, which demonstrated a dose dependent increase in severity. CC-10004 caused acute inflammation and lymphoid depletion in multiple tissues in all dose groups manifested clinically by prostration and a neutrophilic leukocytosis, increased acute phase proteins (haptoglobin) and decreased albumin. Lethality was noted in all male dose groups and the mid-high and high dose females.

A NOAEL could not be identified in this study based on the microscopic findings of lymphoid depletion and/or subacute inflammation of the thymus, small intestines and/or mesentery noted in all dose groups. The maximum tolerated dose of CC-10004 after administration to rats for 90 days is identified as 30 mg/kg/day in male rats and 3 mg/kg/day in female rats, based on the results of this study.

A 4 week oral monkey toxicology study was conducted with CC-10004 (micronized). Oral (gavage) doses of 0 (vehicle), 50, 180 and 650 mg/kg/day CC-10004 were administered to monkeys for 4 weeks. The vehicle used in this study was 1% carboxymethylcellulose.

Increased neutrophil levels were noted in all CC-10004 dose groups. One high dose male had a body weight loss of 10%. Slight increases in liver weight were also observed in all drug treated groups. Several occurrences of vasculitis were noted in the mid and high dose groups although these were infrequent and did not follow a dose response. A NOEL was not identified, although the 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse.

A 13 week oral monkey toxicology study was conducted with CC-10004 [redacted] (b) (4) Oral (gavage) doses of 0 (vehicle), 25, 85 and 300 mg/kg/day CC-10004 were administered to monkeys for 13 weeks. The vehicle used in this study was 1% carboxymethylcellulose. Possible treatment related effects included salivation in low, mid and high dose groups and vomiting in the high dose group. An increase in hepatocyte vacuolation was noted that did not exhibit a dose dependent increase. No vasculitis was noted in this study. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug treated animals. A NOEL was not established in this study. The study report considered 300 mg/kg a NOAEL.

The following comments were relayed to the sponsor via fax on September 8, 2005 concerning nonclinical repeat dose toxicology studies for CC-10004.

"All clinical studies should be supported with nonclinical toxicity studies in two species (rodent and nonrodent) as per ICH M3. Psoriasis is a chronic indication and so drugs used to treat psoriasis should be supported by chronic toxicity studies (6 month rodent, 9-12 month nonrodents). It is recommended that more than 3 animals per sex per dose be used in the nonrodent studies. Carcinogenicity studies in two species would also be required for an NDA."

"Because of the concern about vasculitis with CC-10004, it is recommended that the rodent chronic toxicity study be conducted before expanded phase 2 studies and the reversibility of vasculitis be assessed."

Reviewer's comments: The sponsor has conducted a 6 month oral mouse toxicology study and a 12 month oral monkey toxicology study with CC-10004. The sponsor has submitted study protocols for oral mouse and rat carcinogenicity studies (refer to description provided below for details). The sponsor has conducted a study to evaluate the reversibility of vasculitis in mice.

Genetic toxicology:

CC-10004 did not induce mutations in the Ames test. CC-10004 did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. CC-10004 did not induce micronuclei in the bone marrow of mice after two daily oral gavage administrations of up to 2000 mg/kg. In summary, CC-10004 did not exhibit genotoxic potential in a battery of ICH genotoxicity studies.

Carcinogenicity:

Study protocols for oral mouse and rat carcinogenicity studies were included in Serial #030 (date: 8-18-06). An Exec CAC meeting was conducted on September 26, 2006 to discuss both study protocols. The following Exec CAC recommendations and conclusions were relayed to the sponsor via fax on September 27, 2006.

Rat protocol:

1) The Committee proposed the following doses for the oral (gavage) rat carcinogenicity study: 0 (vehicle control), 3, 10 and 20 mg/kg/day CC-10004 for males and 0 (vehicle control), 0.3, 1 and 3 mg/kg/day CC-10004 for females based on an MTD (death and pro-inflammatory syndrome). The sponsor's proposed high dose of 30 mg/kg/day for male rats slightly exceeds the MTD for male rats based on mortality and may not be tolerated in a 2 year oral rat carcinogenicity study. The sponsor's proposed high dose of 1 mg/kg/day for female rats is slightly less than the MTD for female rats based on mortality.

2) The Committee noted that the hematology and serum chemistry evaluations should not be conducted on main study animals in this study since the blood sampling may alter the study results.

3) The Committee noted that the sponsor should notify the Agency prior to early termination of any group based on mortality.

Mouse protocol:

1) The Committee concurred with the sponsor proposed doses for the oral (gavage) mouse carcinogenicity study of 0 (vehicle control), 100, 300, and 1000 mg/kg/day CC-10004, based on mouse/human AUC ratio.

2) The sponsor is cautioned that if the clinical dose rises such that the AUC ratio of rodent to human systemic exposure is no longer 25-fold, the study may not be acceptable.

3) The Committee noted that the hematology and serum chemistry evaluations should not be conducted on main study animals in this study since the blood sampling may alter the study results.

4) The Committee noted that the toxicokinetic analysis is probably not necessary for this study since toxicokinetic evaluation at the same doses was performed in a 13 week oral mouse toxicology study.

5) The Committee noted that the sponsor should notify the Agency prior to early termination of any group based on mortality.

Reviewer's comments: The doses for the oral mouse carcinogenicity study may come into question since the mouse/human AUC ratio was calculated based on a human dose of 40 mg/day. The sponsor is proposing to increase the dose to 60 mg/day and if the mouse/human AUC ratio for the high dose group should no longer be 25-fold at this dose, then the proposed high dose for this study may not be adequate.

Reproductive toxicology:

Oral embryofetal development studies have been conducted in mice and rabbits with CC-10004 [redacted] (b) (4) Oral (gavage) doses of 0 (vehicle), 250, 500 and 750 mg/kg/day CC-10004 were administered to pregnant female CD-1 mice from gestational days 6 - 15. The vehicle used in this study was 1% carboxymethylcellulose. Toxicokinetic analysis was not incorporated into this study. Administration of CC-10004 to pregnant CD-1 mice at doses up to 750 mg/kg (2250 mg/m^2) did not produce any teratogenic effects. Fetal growth was significantly reduced in a dose dependent manner as indicated by decreased fetal weight and delayed ossification. The high dose (750 mg/kg) in this study may not have been as high as desirable since this dose did not induce clear maternal toxicity. Decreased food consumption and decreased weight gain was observed in drug treated animals although the decreased weight gain appeared to be due to the decreased uterine weights. The sponsor appears to argue that 750 mg/kg is the highest feasible dose since this required a dose concentration of 75 mg/ml and a higher concentration of 100 mg/ml was too viscous to pass through the dosing catheter.

Oral (gavage) doses of 0 (vehicle), 250, 500 and 1000 mg/kg/day CC-10004 were administered to pregnant female New Zealand white rabbits from gestational days 7 - 19. The vehicle used in this study was 1% carboxymethylcellulose. Toxicokinetic analysis was incorporated into this study. However, CC-10004 was not quantifiable in any of the plasma samples. The reason for this is not clear. It may be possible that since the metabolism of CC-10004 appears to be very rapid in rabbits, that very little if any systemic exposure to CC-10004 occurred in this rabbit embryofetal development study. The study report noted that the samples were stored at -70°C for 8 months prior to analysis. Administration of CC-10004 to pregnant New Zealand white rabbits at doses up to 1000 mg/kg (12,000 mg/m^2) did not produce any teratogenic effects. A slight dose related decrease in maternal body weight gain and food consumption was observed. Fetal weight and growth did not appear to be affected. The report considered the high dose of 1000 mg/kg to be the limit dose and, therefore, adequate. Note that CC-10004 was not detected in plasma samples in this study. Therefore, this study may not be adequate if exposure was too low since little maternal toxicity was noted.

The following comments were relayed to the sponsor via fax on September 8, 2005 concerning nonclinical reproductive toxicology studies for CC-10004.

"Essentially no toxicity was noted in the rabbit embryofetal toxicity studies (range finding and definitive). In addition, no drug was detected in the plasma of these animals. These studies may not be an adequate assessment of embryofetal toxicity if no exposure to drug can be documented. It is recommended that either a new rabbit embryofetal study be conducted with higher maternally toxic doses and adequate toxicokinetics or, if the rabbit is not an appropriate species, then an embryofetal study should be conducted in another species."

"Other reproductive and developmental toxicity studies should be conducted as outlined in ICH M3 and related ICH guidances."

A final study report for a mouse fertility and reproduction toxicity study conducted with CC-10004 was submitted to the IND in Serial #032 (date: 10/23/06). Oral (gavage) doses of 0 (vehicle), 100, 300 and 1000 mg/kg/day CC-10004 were administered at 4 weeks prior to mating and during mating for males and 14 days prior to mating and through gestation day 7 for females. The vehicle used in this study was 1% carboxymethylcellulose.

Increased body weight gain was noted in high dose males over the treatment period compared to control animals. No treatment related effects on body weight gain were noted in low and mid dose males. Body weight gains were increased in low, mid and high dose females for the entire precohabitation period. Body weight gain was decreased in high dose females from gestation days 0 – 13.

Increased heart weights were noted in high dose males. Increased testis weight was noted in low, mid and high dose males. Decreased seminal vesicle weight was noted in mid and high dose males and decreased prostate weight was noted in high dose males.

Although no treatment related effects on sperm parameters were noted in this study, prolonged time to mating and decreased numbers of matings led to a decrease in fertility index in low, mid and high dose groups. Of the mice that did mate successfully, post-implantation loss was increased in low, mid and high dose groups. A NOAEL for effects on male and female fertility could not be established in this study. The male and female fertility NOAEL is less than 100 mg/kg/day CC-10004.

(b) (4)

Special toxicology:

A special study of CC-10004 was conducted in rats to assess possible biomarkers of inflammation and vasculitis. The animals were treated by oral gavage with 0 (vehicle), 6 or 10 mg/kg using a dose volume of 5 ml/kg for 7 consecutive days. Some animals were maintained for an additional 11 day recovery period and sacrificed on day 18 while other animals were sacrificed on days 3, 6, 8 and 14. CC-10004 caused an acute inflammatory reaction in female rats. This was characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment. Peritoneal fluid increased (ascites) and analysis of this fluid also showed markers of inflammation. Decreased leptin and increased lipase levels suggested that adipocytes may be affected.

Overall conclusion:

The NOAEL for the 6 month oral mouse toxicology study was 10 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 5614 and 5842 ng·hr/ml for CC-10004 in males and females respectively, on day 177). The NOAEL for the 12 month oral monkey toxicology study was 600 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 42608 and 26936 ng·hr/ml for CC-10004 in males and females respectively, on day 358). The human AUC for a 60 mg qd CC-10004 is 4347 ng·hr/ml after 14 days of oral administration. It is not anticipated that the AUC for a 60 mg qd and 30 mg bid (60 mg/day total dose) would be significantly different. Therefore, the human AUC value for the 60 mg qd dose will be used for calculation of multiples of human exposure.

The multiple of human exposure based on the 6 month oral mouse toxicology study is approximately one (1.3X; 5728 ng·hr/ml ÷ 4347 ng·hr/ml = 1.3). The multiple of human exposure based on the12 month oral monkey toxicology study is 8X (34772 ng·hr/ml ÷ 4347 ng·hr/ml = 8). Neither study provided for a 10 fold safety factor. The mouse may be a more sensitive species to the proinflammatory syndrome elicited by CC-10004. Therefore, monkey may be a more relevant species for determining a toxicity profile to support the safety of clinical studies with CC-10004. It would have been preferable if a higher dose had been used in the 12 month monkey study. However, the toxicities noted at 8X the dose proposed for the clinical study were relatively minor. The sponsor has proposed adequate safety monitoring for the clinical study which include monitoring for vasculitis. Taking all of the data into consideration, it is reasonably safe to initiate the proposed clinical studies from a Pharmacological/Toxicological perspective.

The 12 month monkey toxicology study probably would not need to be repeated at a higher dose if the sponsor does not evaluate a dose higher than 30 mg bid (60 mg/day) for a12 month duration in subsequent clinical studies. However, if the sponsor wishes to increase the dose further, then the 12 month monkey study may need to be repeated at a higher dose that elicits overt toxicity.

The study conducted in mice to evaluate the reversibility of pro-inflammatory lesions induced after 14 days of treatment with CC-10004 indicate that these lesions are reversible after removal of CC-10004. The 14-day treatment duration might have been interpreted as a duration that induced an acute syndrome which would have been different than if treatment had been continued to 90 days. However, this study included a treatment arm of 90 day continuous treatment which indicated that the induced pro-inflammatory syndrome resolved even after continuous treatment for 90 days. This may indicate that mice initially respond to treatment with CC-10004 by a severe acute pro-inflammatory syndrome but develop tolerance to CC-10004 with chronic dosing.

Pharmacology/Toxicology Question included in the Briefing Package:

Question 1

Celgene has recently completed the following nonclinical studies: in vitro plasma protein binding, toxicity studies in rodents treated up to 6 months, and monkeys for 12 months; and as

requested by the Agency, a study in mice to investigate the time course for development and recovery of inflammatory findings. The results of these studies are summarized in the nonclinical section of this briefing book.

Does the Agency wish to provide Celgene with any feedback regarding these data?

Pharmacology/Toxicology response

The summary data provided for the 6 month oral mouse toxicology study and 12 month oral monkey toxicology study conducted with CC-10004 appear to support increasing the dose from 20 mg bid to 30 mg bid and increasing the duration from 3 months to 12 months in clinical studies. However, the final study reports for both nonclinical studies should be submitted to the IND for evaluation prior to initiating the proposed clinical study modifications.

The Division notes that the high dose selected for the 12 month oral monkey toxicology study did not elicit overt toxicity. Typically, the high dose selected for repeat dose systemic toxicology studies should elicit overt toxicity or be the maximum feasible dose. The 12 month monkey toxicology study probably would not need to be repeated at a higher dose if the sponsor does not evaluate a dose higher than 30 mg bid (60 mg/day) for a 12 month duration in subsequent clinical studies. However, if the sponsor wishes to increase the dose further, then the 12 month monkey study may need to be repeated at higher doses including one that elicits overt toxicity.

The Division notes that the sponsor is currently conducting an intravenous rabbit range finding embryofetal development study with CC-10004. It is anticipated that this study is being conducted to determine doses for a repeat of the rabbit embryofetal study at doses that provide for adequate systemic exposure. The sponsor is reminded that the high dose selected for this study should elicit maternal toxicity or be the maximum feasible dose.

cc:
DDDP/ DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/CARR
DDDP/PM/OWENS

Appendix 7: December 10, 2007 [redacted] Review

Linked Applications	Sponsor Name	Drug Name
[redacted]	CELGENE CORP	CC-10004 [redacted]

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

/s/

BARBARA A HILL
12/10/2007
Non-Clinical Reviewer

PAUL C BROWN
12/10/2007
Non-Clinical Reviewer

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date:	2/1/08
SDN:	72
Submission type:	Nonclinical final study reports
Drug:	CC-10004 (S-enantiomer)
Drug class:	Phosphodiesterase type IV (PDE4) inhibitor
Indication:	Psoriasis
Route:	Oral
Sponsor:	Celgene Corporation, Summit, NJ

Review date: April 30, 2008

Clinical formulation: White capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose [redacted]	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has proposed to develop CC-10004 [redacted] for the treatment of psoriasis. The original IND was submitted on July 29, 2004. A guidance meeting was conducted with the sponsor on December 10, 2007. The briefing document for the guidance meeting contained summary information for a 6 month oral toxicity study and a 12 month oral monkey toxicity study. The sponsor asked if this data would be adequate to support increasing the dose in an ongoing Phase 2 clinical study from 20 mg bid to 30 mg bid and increasing the duration of this clinical study from 3 months to 12 months. The following Pharmacology/Toxicology response was relayed to the sponsor during the meeting.

"The summary data provided for the 6 month oral mouse toxicology study and 12 month oral monkey toxicology study conducted with CC-10004 appear to support increasing the dose from 20 mg bid to 30 mg bid and increasing the duration from 3 months to 12 months in clinical studies. However, the final study reports for both nonclinical studies should be submitted to the IND for evaluation prior to initiating the proposed clinical study modifications.

The Division notes that the high dose selected for the 12 month oral monkey toxicology study did not elicit overt toxicity. Typically, the high dose selected for repeat dose systemic toxicology studies should elicit overt toxicity or be the maximum feasible dose. The 12 month monkey toxicology study probably would not need to be repeated at a higher dose if the sponsor does not evaluate a dose higher than 30 mg bid (60 mg/day) for a 12 month duration in subsequent clinical studies. However, if the sponsor wishes to increase the dose further, then the 12 month monkey study may need to be repeated at higher doses including one that elicits overt toxicity."

The current submission contains two nonclinical toxicology final study reports (6 month mouse oral toxicity study and 12 month oral monkey toxicity study) which are reviewed in the following section.

Review of submitted nonclinical study reports:

Repeat dose toxicity study 1

Study title: CC-10004: A 6-month oral toxicity study in mice

Key study findings:

Treatment related mortality was noted in mid and high dose groups. Treatment related effects on hematological parameters were noted in mid and high dose males in week 12 only (decreases in total white blood cell count, large unstained cells and percent lymphocytes and increases in neutrophils). Treatment related effects on serum chemistry parameters were noted in mid and high dose animals in week 12 and/or week 26 (increases in total protein and globulin, decreases in albumin, A/G and chloride and increase in magnitude/incidence of haptoglobin level). Treatment related effects on organ weights were noted in mid and high dose groups and consisted of increases in liver weights (mid and high dose animals) correlating with minimal centrilobular hypertrophy, increases in heart weight (high dose females only) correlating with findings of inflammation and/or mineralization, increases in testes weight (mid and high dose males) and lower brain weight (mid and high dose females). Treatment related effects on microscopic parameters noted in mid and high dose animals included: lesions in the heart that involved inflammation of the aortic root or around the cardiac arteries and in the myocardium, cartilaginous metaplasia of the arotic root along with vascular mineralization, vascular inflammation, hematoma formation and centrilobular hepatocellular hypertrophy of the liver. Additional lesions included vascular inflammation and hematoma in the mesentery adjacent to the pancreas of one high dose female and necrosis, fibroplasia and inflammation in the gallbladder of another high dose female. Vascular and perivascular inflammation of the liver and fibrosis around the bile ducts was noted in one mid dose male.

The NOAEL is identified as 10 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 5614 and 5842 ng·hr/ml for CC-10004 in males and females respectively, on day 177) in mice after 6 months of daily oral administration, under the conditions of this study.

Study no.: [redacted]
Sponsor study no.: CC-10004-TOX-00
Volume #, and page #: Volume 1, Page 1
Conducting laboratory: [redacted]
Date of study initiation: 1-6-06
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: CC-10004 [redacted] Batch# 54560-05, 99.9% pure
Vehicle: 1% sodium carboxymethylcellulose

Methods

Doses: 0, 10, 100 and 1000 mg/kg/day
Species/strain: CD-1 mice
Number/sex/group or time point (main study): 15/sex/dose
Route, formulation, volume, and infusion rate: oral (gavage), 1% sodium caboxymethylcellulose, 10 ml/kg
Satellite groups used for toxicokinetics or recovery: TK (38/sex/dose; 6/sex/dose for vehicle control group)

Age: 10 weeks
Weight: males: 29.3-37.6 g; females: 22.5-29.3 g
Sampling times: N/A
Unique study design or methodology: Test article was orally (gavage) administered once daily, 7 days/week for 6 months.

Observation and Times:

Clinical signs: daily
Body weights: weekly
Food consumption: weekly
Hematology: weeks 12 and 26
Clinical chemistry: weeks 12 and 26
Ophthalmology: week 25
Gross pathology: necropsy at end of treatment
Organ weights: adrenals, brain, epididymis, heart, kidneys, liver, ovaries, spleen, testes, thymus
Histopathology: The following organs were preserved from all animals in all treatment groups: adrenals, aorta, bone (femur, sternum), bone marrow (femur, sternum), brain, cecum, colon, duodenum, epididymis, eyes with optic nerve, gallbladder, harderian gland, heart, ileum, jejunum, kidneys, lacrimal glands, liver, lungs, lymph nodes (mesenteric, popliteal), mammary gland (females only), nasal cavity, ovaries, pancreas, pituitary gland, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, stomach, stifle joint, testes, thymus, thyroid with parathyroid, tongue, trachea, urinary bladder, uterus with cervix, vagina, zymbal's glands and gross lesions/masses

Histological examination was performed for all preserved tissues for control and high dose animals only. Histological examination was performed for gross lesions in all animals. Histological examination was performed for heart, thymus, lungs, liver, uterus and kidneys in low and mid dose animals.

Toxicokinetics: Toxicokinetics of the parent [CC-10004 (S-isomer)] and two metabolites [CC-16805 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl C-10004 glucuronide)] were evaluated in this study. Blood samples were obtained on days 22 and 177 from TK animals for toxicokinetic analysis of parent (days 22 and 177) and metabolites (day 177). Blood was taken at 1, 2, 4, 8, 12 and 24 hours post dose (3/sex/timepoint). Animals in the vehicle group were only bled once at 2 hours post dosing.

Results:

Mortality: Treatment related mortality was noted in mid dose males (1/15), mid dose TK females (1/20) and high dose animals (2/15 males; 1/15 females) and high dose TK animals (3/20 males; 1/20 females). One high dose male that was found dead on day 103 was observed with a liver infarction with severe chronic active inflammation on the surrounding liver parenchyma, adhesions to body wall and fibrosis. One high dose male that was euthanized in extremis on day 128 was observed with a large hematoma with vascular and perivascular inflammation and pigment deposition in the dorsal abdominal wall. A high dose TK female that was found dead on day 168 was observed with a large hematoma in the mammary gland along with inflammation extending into the adjacent muscle and blood vessels and a hematoma in the mesentery adjacent to the pancreas with vascular necrosis and inflammation. One mid dose male found dead on day 74 was observed with a large hematoma in the skeletal muscle of the hind limb and associated vascular and perivascular inflammation.

Clinical signs: Treatment related effects on clinical signs were limited to mice found dead or euthanized in extremis. These effects included pale body or extremities, brown material on the anogenital area, impaired equilibrium, impaired use or swollen right forelimb, dermal atonia, labored respiration or decreased respiration rate and abnormal pupil position of the right eye.

Body weights: A dose dependent increase in body weight gain was noted in low, mid and high dose females only (+8.5%, +10.1% and 16.3%, respectively, at week 26) compared to control females. No treatment related effects on body weight were noted in males in this study.

Food consumption: A treatment related increase in food consumption, which corresponded with the increased body weight gain, was noted in mid and high dose females.

Hematology: Treatment related effects on hematologic parameters were noted in week 12 only in mid and high dose males. These effects included decreased total white blood cell count (-33% compared to control), decreased percent large unstained cells, decreased percent lymphocytes (-12 to -17% compared to control), and increased percent neutrophils (+72 to +106% compared to control).

Clinical chemistry: Treatment related effects on serum chemistry parameters were noted in week 12 and/or 26 in mid and high dose animals. Increased total protein (+7.3 to +12.7% compared to control) and globulin (+18 to +20% compared to control) was noted in high dose males in week 12/26. Decreased albumin (-7.9% compared to control) was noted in high dose females in week 12, decreased A/G (-24 to -28% compared to controls) in high dose females in week 12/26 and decreased chloride (-2.6% compared to control) in high dose females in week 26. An additional treatment related effect on serum chemistry parameters noted in mid dose animals (week 12 only) and high dose animals (week 26 only), included increased protein (+5.5% and +9.1%, respectively, compared to control). Increased haptoglobin levels were noted in mid and high dose animals in week 12 and/or 26 (+47 to +204% in males and +131 to +430% in females compared to control).

Ophthalmology: No treatment related effects on ophthalmologic parameters were noted in this study.

Gross pathology: No treatment related effects on macroscopic parameters were noted in this study (except for the macroscopic effects noted in animals that died during the study that were previously described under mortality).

Organ weights: Treatment related effects on organ weights were noted in mid and high dose animals. Increased liver weights (corresponding to minimal hepatocellular hypertrophy) were noted in mid and high dose animals (mid dose females: +24.9%; high dose females: +32.1%; mid dose males: +8.0%; high dose males: +9.8%). Increased heart weight was noted in high dose females only (+11.8%) which correlated with findings of inflammation and/or mineralization. Increased testes weights were noted in mid and high dose males (+21.6% and +20.8%, respectively) and decreased brain weights were noted in mid and high dose females (-2.9% and -2.1%, respectively).

Histopathology: Microscopic lesions in the heart were noted in a few mid and high dose animals. These lesions involved inflammation of the aortic root or around other cardiac arteries and in the myocardium. Cartilaginous metaplasia of the aortic root, along with vascular mineralization was also noted. A loss of vascular integrity (i.e., vascular inflammation, hematoma formation and

other lesions) was noted in animals found dead or euthanized in extremis. Centrilobular hepatocellular hypertrophy of the liver was noted in two-thirds of high dose mice. Additional lesions of vascular inflammation, hematoma in the mesentery adjacent to the pancreas were noted in one high dose female. Fibroplasia and inflammation in the gallbladder was noted in another high dose female. Vascular and perivascular inflammation of the liver and fibrosis around the bile ducts were noted in one mid dose male.

No treatment related effects on microscopic parameters were noted in low dose animals.

Toxicokinetics: The toxicokinetic data for CC-10004 and two metabolites CC-16805 (M3) and CC-16166 (M12) are provided in the following table (copied from the page 46 of the final study report).

Table T9: Mean CC-10004, CC-16085 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl CC-10004 glucuronide) Plasma Parameters in Male and Female Mice Following Daily Oral Administration of CC-10004 at 10, 100 and 1000 mg/kg/day

Dosing Day	Analyte	Dosage Group (mg/kg/day)	Gender	C_{max} (ng/mL)	T_{max} [b] (hr)	AUC_{24h} (hr • ng/mL)	Metabolite/Parent (%)[c]
Day 22	CC-10004	10	M	869	1.0	4876	NA
			F	1408	1.0	5703	NA
		100	M	2757	2.0	38528	NA
			F	2920	4.0	34929	NA
		1000	M	5494	4.0	88893	NA
			F	6377	2.0	108687	NA
Day 177	CC-10004	10	M	826	1.0	5614	NA
			F	902	2.0	5842	NA
	M3[a]	10	M	2.79[a]	1.0[a]	5.29[a]	0.094
			F	4.14	2.0	15.2	0.260
	M12[b]	10	M	128	1.0	1459	26.0
			F	155	8.0	1856	31.8
	CC-10004	100	M	2381	2.0	21289	NA
			F	2101	1.0	32491	NA
	M3[a]	100	M	7.63	2.0	87.6	0.411
			F	8.33	8.0	132	0.406
	M12[b]	100	M	1765	2.0	11144	52.3
			F	1987	12.0	27056	83.3
	CC-10004	1000	M	4640	12.0	72183	NA
			F	5874	2.0	76010	NA
	M3[a]	1000	M	20.7	4.0	345	0.478
			F	29.7	4.0	416	0.547
	M12[b]	1000	M	2698	4.0	48170	66.7
			F	6201	12.0	114619	151

[a] M3 = CC-16085 (desmethyl CC-10004)
[b] M12 = CC-16166 (desmethyl CC-10004 glucuronide)
[c] Metabolite/Parent x 100 based on AUC_{24h}
NA=Not applicable

A dose related increase (which was less than dose proportional) in systemic exposure was noted in males and females on days 22 and 177. No apparent dose accumulation was noted between days 22 and 177. No gender related difference in systemic exposure was noted in this study. Chiral inversion of CC-10004 to its [redacted] (b) (4) was not observed in this study. Systemic exposure to CC-10004 desmethyl glucuronide (M12) was dose related and ranged from approximately 16% to 151% of CC-10004. Systemic exposure to M12 was greater in females compared to males. Systemic exposure to desmethyl CC-10004 (M3) was generally negligible relative to M12.

No measurable levels of CC-10004 were noted in the vehicle control samples.

Repeat dose toxicity study 2

Study title: CC-10004: 12-month oral toxicity study in cynomolgus monkeys

Key study findings:

No treatment related effects on mortality, body weight, ophthalmic parameters, electrocardiographic parameters, urinalysis parameters, organ weights, macroscopic parameters or microscopic parameters were noted in this study. A higher incidence in the frequency of red vaginal discharge and red material on the cage floor was noted in low, mid and high dose females. Treatment related effects on hematologic parameters were noted in mid dose females and high dose animals. Increased absolute neutrophils, increased percentage neutrophils, increased total white blood cell count and decreased percent lymphocytes were noted in high dose animals. These changes in lymphocytes and neutrophils persisted through week 39 but were mostly resolved by week 51. Increased fibrinogen was noted in week 51 in high dose animals and mid dose females. No treatment related effects on hematologic parameters were noted in mid dose males and low dose animals.

A few relatively minor treatment related effects on serum chemistry parameters were noted in mid and high dose animals. Glucose was sporadically decreased in mid and high dose males. Decreased albumin was noted in mid and high dose females. No treatment related effects on C-reactive protein or haptoglobin were noted in this study. A minor alteration of the populations of T cells and NK cells (as measured by flow cytometry) was noted in mid and high dose males compared to control males. It is difficult to determine if this minor alteration can be considered a toxicological effect or not. No alterations of populations of T cells or NK cells were noted in treated females compared to control females.

If the effects noted on the hematologic parameters and serum chemistry parameters are considered relatively minor in the absence of any corresponding histopathological effects, then the NOAEL is identified as 600 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 42608 and 26936 ng·hr/ml for CC-10004 in males and females respectively, on day 358) in monkeys after 12 months of daily oral administration.

No overt toxicity was expressed in the 12 month oral monkey toxicology study. It would have been preferable if the sponsor had used a high dose that had expressed overt toxicity.

Study no.:	[redacted] (b) (4)
Sponsor study no.:	CC-10004-TOX-005
Volume #, and page #:	6, 1
Conducting laboratory:	[redacted] (b) (4)
Date of study initiation:	9-21-05
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, and % purity:	CC-10004 [redacted] (b) (4) Batch# 54560-05, 99.9% pure
Vehicle:	1% sodium carboxymethylcellulose

Methods

Doses:	0, 60, 180 and 600 mg/kg/day
Species/strain:	Cynomolgus monkeys
Number/sex/group or time point (main study):	5/sex/dose
Route, formulation, volume, and infusion rate:	oral (gavage), 1% sodium carboxymethylcellulose, 4 ml/kg

Satellite groups used for toxicokinetics or recovery: N/A
Age: 2 years
Weight: males: 1566-2169 g; females: 1675-2052 g
Sampling times: N/A
Unique study design or methodology: Test article was orally (gavage) administered once daily, 7 days/week for 12 months.

Observation and Times:

Clinical signs:	daily
Body weights:	weekly
Hematology:	baseline and during weeks 13, 26, 39 and 51
Clinical chemistry:	baseline and during weeks 13, 26, 39 and 51 (including C-reactive protein and haptoglobin as indicators of vasculitis)
Urinalysis:	baseline and during weeks 13, 26, 39 and 51
Ophthalmology:	baseline and during week 51
ECG:	baseline and during weeks 26 and 51 [ECGs were recorded for 2 – 4 hours post dose using a multi lead (I, II, II, aVR, aVL and aVF)]
FACS analysis:	baseline and during weeks 13 and 51
Gross pathology:	necropsy at end of treatment
Organ weights:	adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes, thymus
Histopathology:	The following organs were preserved from all animals in all treatment groups: adrenals, aorta, bone (femur, sternum), bone marrow (femur, sternum), brain, cecum, colon, duodenum, epididymis, esophagus, eyes with optic nerve, gallbladder, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mesenteric, mandibular), nasal cavity, ovaries with oviducts, pancreas, pituitary gland, rectum, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle, skin with mammary gland, spinal cord, spleen, stomach, testes, thymus, thyroid with parathyroid, trachea, urinary bladder, ureters, uterus with cervix, vagina and gross lesions/masses Histological examination was performed for all preserved tissues for all animals in all dose groups.
Toxicokinetics:	Toxicokinetics of the parent [CC-10004 (S-isomer)] and two metabolites [CC-16805 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl C-10004 glucuronide)] were evaluated in this study. Blood samples were obtained on days 0 (1), 101 and 358 for toxicokinetic analysis of parent

(days 0, 101 and 358) and metabolites (day 358). Blood was taken at 1, 2, 4, 8, 12 and 24 hours post dose.

Results:

Mortality: No treatment related effects on mortality were noted in this study.

Clinical signs: A higher incidence in the frequency of red vaginal discharge and red material on the cage floor was noted in low, mid and high dose females. No treatment related effects on clinical signs were noted in males in this study.

Body weights: No treatment related effects on body weights were noted in this study.

Hematology: Treatment related effects on hematologic parameters were noted in mid dose females and high dose animals. Increased absolute neutrophils (+68 to +440% compared to control), increased percentage neutrophils (+33 to +180% compared to control), increased total white blood cell count (+27 to +116% compared to control) and decreased percent lymphocytes (-51 to -62% compared to control) were noted in high dose animals. These changes in lymphocytes and neutrophils persisted through week 39 but were mostly resolved by week 51. Increased fibrinogen was noted in week 51 in high dose animals (+37 to +44% compared to control) and mid dose females (+29% compared to control). No treatment related effects on hematologic parameters were noted in mid dose males and low dose animals.

Clinical chemistry: A few relatively minor treatment related effects on serum chemistry parameters were noted in mid and high dose animals. Glucose was sporadically decreased in mid and high dose males. Decreased albumin was noted in mid and high dose females. No treatment related effects on C-reactive protein or haptoglobin were noted in this study.

Urinalysis: No treatment related effects on urinalysis parameters were noted in this study.

Ophthalmology: No treatment related effects on ophthalmologic parameters were noted in this study.

ECG: No treatment related effects on electrocardiographic parameters were noted in this study.

FACS: A minor alteration of the populations of T cells and NK cells (as measured by flow cytometry) was noted in mid and high dose males compared to control males during weeks 13 and 51. It is difficult to determine if this minor alteration can be considered a toxicological effect or not. No

alterations of populations of T cells or NK cells were noted in treated females compared to control females.

Gross pathology: No treatment related effects on macroscopic parameters were noted in this study.

Organ weights: No treatment related effects on organ weights were noted in this study.

Histopathology: No treatment related effects on microscopic parameters were noted in this study.

Toxicokinetics: The toxicokinetic data for CC-10004 and two metabolites CC-16805 (M3) and CC-16166 (M12) are provided in the following table (copied from page 45 of the study report).

Table T6: Mean CC-10004, CC-16085 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl CC-10004 glucuronide) Plasma Parameters in Male and Female Monkey Following Daily Oral Administration of CC-10004 at 60, 180 and 600 mg/kg/day

Dosing Day	Analyte	Dosage Group (mg/kg/day)	Gender	C_{max} (ng/mL)	T_{max} (hr)	AUC_{24h} (hr • ng/mL)	Metabolite/ Parent (%)[c]
Day 0	CC-10004	60	M	774	2.3	9964	NA
			F	1159	3.3	12996	NA
		180	M	1613	5.3	19537	NA
			F	1653	7.3	22401	NA
		600	M	2158	9.3	34717	NA
			F	1622	8.0	25678	NA
Day101	CC-10004	60	M	1213	2.3	9983	NA
			F	1509	3.0	10718	NA
		180	M	1528	3.3	14141	NA
			F	1371	2.7	12724	NA
		600	M	2554	3.0	23548	NA
			F	2757	4.0	23451	NA
Day 358	CC-10004	60	M	1265	3.3	16443	NA
			F	1596	4.0	17526	NA
	M3[a]	60	M	23.5	8.0	452	2.75
			F	48.3	4.0	858	4.9
	M12[b] (CC-16166)	60	M	2573	12.0	50695	308
			F	2220	10.7	43629	249

[a] M3 = CC-16085 (Desmethyl CC-10004)

[b] M12 = CC-16166 (Desmethyl CC-10004 glucuronide)

[c] Metabolite/CC-10004 x 100 based on AUC

NA = Not applicable

Table T6: Mean CC-10004, CC-16085 (M3, desmethyl CC-10004) and CC-16166 (M12, desmethyl CC-10004 glucuronide) Plasma Parameters in Male and Female Monkey Following Daily Oral Administration of CC-10004 at 60, 180 and 600 mg/kg/day (continued)

Dosing Day	Analyte	Dosage Group (mg/kg/day)	Gender	C_{max} (ng/mL)	T_{max} (hr)	AUC_{24h} (hr • ng/mL)	Metabolite/ Parent (%)[c]
Day 358	CC-10004	180	M	2413	3.3	23841	NA
			F	1833	2.7	22561	NA
	M3[a] (CC-16085)	180	M	54.9	4.0	804	3.37
			F	54.7	6.0	847	3.75
	M12[b] (CC-16166)	180	M	4224	14.7	71723	301
			F	1471	6.0	28234	125
	CC-10004	600	M	4533	3.3	42608	NA
			F	2367	3.7	26936	NA
	M3[a] (CC-16085)	600	M	187	5.3	2768	6.50
			F	61.5	1.3	1065	3.95
	M12[b] (CC-16166)	600	M	5788	12.0	90035	211
			F	3416	14.7	63662	236

[a] M3 = CC-16085 (Desmethyl CC-10004)

[b] M12 = CC-16166 (Desmethyl CC-10004 glucuronide)

[c] Metabolite/CC-10004 x 100 based on AUC

NA = Not applicable

A dose related increase (which was less than dose proportional) in systemic exposure was noted in males and females on days 0, 101 and 358. A slight dose accumulation was noted between days 101 and 358. No gender related difference in systemic exposure was noted in this study (except a higher exposure to CC-10004 in high dose males compared to high dose females on days 0 and 358). Systemic exposure to CC-10004 desmethyl glucuronide (M12) was dose related and ranged from approximately 211% – 308% in male monkeys 125% – 249% in female monkeys of CC-10004. Systemic exposure to M12 was greater in males compared to females.

Systemic exposure to desmethyl CC-10004 (M3) was significantly lower than to M12. Systemic exposure to M3 ranged from 2.75% - 6.5% in male monkeys and 3.75% - 4.90% in females monkeys of CC-10004.

Conclusions:

The sponsor submitted an amendment (amendment #2) to the clinical study protocol CC-1004-PSOR-004 titled "A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacodyamics, Pharmacokinetics, and Efficacy of CC-10004 in Subjects with Recalcitrant Plaque-type Psoriasis". This amendment was submitted in SDN 73 on February 4, 2008 to this IND. As was discussed during the guidance meeting conducted on December 10, 2007, the amendment includes an increase in dose from 20 mg BID to 30 mg BID and treatment duration from 12 weeks to 24 weeks (originally proposed for up to 12 months). The sponsor indicated that they intend to initiate this protocol amendment on March 3, 2008. The same safety parameters that were originally incorporated into this clinical study will be used for the amended clinical protocol.

The NOAEL for the 6 month oral mouse toxicology study was 10 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 5614 and 5842 ng·hr/ml for CC-10004 in males and females respectively, on day 177). The NOAEL for the 12 month oral monkey toxicology study was 600 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 42608 and 26936 ng·hr/ml for CC-10004 in males and females respectively, on day 358). The human AUC for a 60 mg qd CC-10004 is 4347 ng·hr/ml after 14 days of oral administration. It is not anticipated that the AUC for a 60 mg qd and 30 mg bid (60 mg/day total dose) would be significantly different. Therefore, the human AUC value for the 60 mg qd dose will be used for calculation of multiples of human exposure.

The multiple of human exposure based on the 6 month oral mouse toxicology study is approximately one (1.3X; 5728 ng·hr/ml ÷ 4347 ng·hr/ml = 1.3). The multiple of human exposure based on the12 month oral monkey toxicology study is 8X (34772 ng·hr/ml ÷ 4347 ng·hr/ml = 8). Neither study provided for a 10 fold safety factor. The mouse may be a more sensitive species to the proinflammatory syndrome elicited by CC-10004. Therefore, monkey may be a more relevant species for determining a toxicity profile to support the safety of clinical studies with CC-10004. It would have been preferable if a higher dose had been used in the 12 month monkey study. However, the toxicities noted at 8X the dose proposed for the clinical study were relatively minor. The sponsor has proposed adequate safety monitoring in the clinical study which include monitoring for vasculitis. Taking all of the data into consideration, it is reasonably safe to initiate the modified Phase 2 clinical study from a Pharmacological/Toxicological perspective.

The 12 month monkey toxicology study probably would not need to be repeated at a higher dose if the sponsor does not evaluate a dose higher than 30 mg bid (60 mg/day) for a 12 month duration in subsequent clinical studies. However, if the sponsor wishes to increase the dose further, then the 12 month monkey study may need to be repeated at a higher dose that elicits overt toxicity. This information was relayed to the sponsor during the guidance meeting

conducted on December 10, 2007. Therefore, this information does not need to be relayed to the sponsor again, at this time.

Recommendations:

No regulatory action is indicated for this submission from a Pharmacology/Toxicology perspective, at this time.

Appendix 8: April 30, 2008 [redacted] (b) (4) Review

Linked Applications	Sponsor Name	Drug Name
[redacted] (b) (4)	CELGENE CORP	CC-10004 [redacted] (b) (4)

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

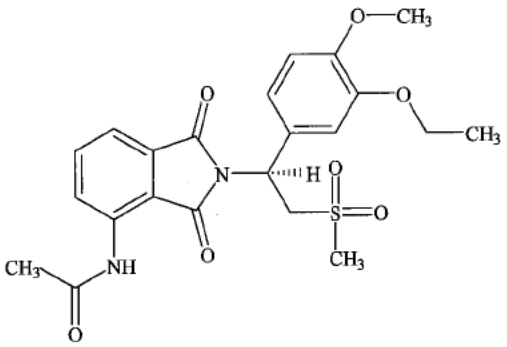
/s/

BARBARA A HILL
04/30/2008

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date: 7-11-08, 7-25-08, 1-30-09, 6-16-09
Serial No.: 85, 87, 106, 120
Submission type: Nonclinical, Investigational Brochure change, nonclinical, nonclinical safety report
Drug: CC-10004 (S-enantiomer)
Molecular formula: $C_{22}H_{24}N_2O_7S$
Molecular weight: 460.5
Structure:



Drug class: Phosphodiesterase type IV (PDE4) inhibitor
Indication: Psoriasis
Route: Oral
Sponsor: Celgene Corporation, Summit, NJ

Review date: July 20, 2009

Clinical formulation: White capsule [redacted] containing the following ingredients

Component	Quantity (mg)
CC-10004	10
[redacted] microcrystalline cellulose [redacted]	[redacted]
Lactose [redacted] monohydrate	
Croscarmellose sodium	
Magnesium stearate	

Introduction:

CC-10004 is a selective PDE4 inhibitor that inhibits TNF-α and IL-12 release from PBMC and increases IL-10 release. CC-10004 is a new molecular entity and the sponsor has proposed to develop CC-10004 [redacted] for the treatment of psoriasis. The original IND was submitted on July 29, 2004. Concern was raised about the vasculitis observed in the animal studies conducted to support the initial proposed clinical study contained in the original IND submission. Additional safety parameters to monitor for possible vasculitis were incorporated into the clinical study protocol. In addition, the initial dose was reduced to 20 mg/day and only patients with severe psoriasis were to be enrolled in the initial clinical study. The sponsor agreed to incorporate the changes into the initial clinical study and it was determined that the revised initial clinical study protocol was reasonably safe to initiate.

A guidance meeting was conducted on December 10, 2007. Following the conduct of the guidance meeting, the sponsor submitted the results from 6 month oral mouse and 12 month oral monkey toxicity studies on February 1, 2008 to support chronic Phase 3 clinical studies. The review of the submitted nonclinical studies supported a clinical dose up to 30 mg bid for a treatment duration up to 12 months. However, the sponsor was informed that if they decided to evaluate doses higher than 30 mg bid then they would need to repeat the 12 month monkey study at higher doses including one that elicits overt toxicity.

SDN 85 contains a nonclinical safety report that provides preliminary nonclinical findings for the oral mouse fertility and early embryonic study conducted with CC-10004. SDN 87 contains amended ongoing clinical protocols and an updated investigator's brochure that incorporates the preliminary findings of the oral mouse fertility and early embryonic study to reflect a potential reproductive risk for human subjects. SDN 120 contains a statement by the sponsor that their original interpretation of the preliminary nonclinical findings for the oral mouse fertility and early embryonic study was incorrect. SDN 106 contains seven nonclinical pharmacology and pharmacokinetic study reports.

Previous clinical experience:

Phase 2 clinical studies have been conducted with up to 20 mg bid for 12 weeks.

Proposed clinical studies: No clinical protocol was included in these submissions.

Review of submitted nonclinical toxicology study information:

SDN 85 (Date: 7-11-08)

This submission contained a summary of the preliminary nonclinical findings from the mouse fertility and early embryofetal development study titled "Oral (gavage) fertility and general reproduction toxicity study of CC-10004 in male mice (Study no. CC-10004-TOX-011)". The sponsor states that the final report for this study is expected to be available early 2009. To date, the final study report has not been submitted to the IND.

In a previously conducted fertility and early embryofetal development study conducted in male and female CD-1 mice (Study No. CC-10004-TOX-001; SDN 32; Date: 10/23/06), oral (gavage) doses of 0 (1% carboxymethylcellulose), 100, 300 and 1000 mg/kg/day CC-10004 were administered to male mice beginning 28 days before cohabitation and continuing through mating and to female mice 14 days prior to mating and through gestation day 7. Increased body weight gain was noted in low, mid and high dose animals. Increased testis weights were noted in low, mid and high dose males and decreased seminal vesicle and prostate weights were noted in mid and high dose males. Although no treatment related effects on sperm parameters were noted in this study, prolonged time to mating and decreased numbers of matings led to a decrease in fertility index in low, mid and high dose groups. Of the mice that did mate successfully, post-implantation loss was increased in low, mid and high dose groups. A NOAEL for effects on male and female fertility could not be established in this study.

The sponsor states that in order to establish a NOAEL for male and female fertility, and to determine whether the observed effects on fertility were related to treatment of male or female mice, repeat fertility assessments were done by conducting two additional studies with separate treatment of males (study CC-10004-TOX-011) and females (study CC-10004-TOX-012). The final study reports for both these studies have not been submitted to the IND, to date. The sponsor states that they are providing a report in this submission that summarizes significant new findings from tests in laboratory animals with apremilast (CC-10004) which may reflect a potential reproductive risk for human subjects, which include potentially test article related microscopic changes observed in the ongoing fertility study with treatment of male mice only.

The sponsor states that the purpose of the first follow up study was to test for toxic effects/disturbances resulting from CC-10004 treatment of CD1 male mice for a full cycle of spermatogenesis before cohabitation, through mating of untreated cohort mice and implantation and early embryonic development. Oral (gavage) doses of 0 (1% carboxymethylcellulose), 1, 10, 25 and 50 mg/kg/day were administered to male mice (25/group) beginning 70 days before cohabitation and continuing though mating with untreated females. The sponsor states that preliminary results form the male fertility study showed that apremilast treatment resulted in increased body weight gains at 10, 25 and 50 mg/kg/day. The absolute weights of the testes were increased in 25 and 50 mg/kg/day groups (+5% and +24%, respectively, compared to control). Treatment related microscopic changes were observed in the testes and epididymides of the mice in the 50 mg/kg/day group. These changes consisted of increased incidence and severity of necrotic spermatids and residual bodies in the lumen of seminiferous tubules in the testes and increased incidence of exfoliated spermatogenic cells in the epididymides. Number and percent motile/non-motile sperm, total sperm count, density from the cauda epididymis were unaffected up to 50 mg/kg/day. $AUC_{0\text{-}24\ hr}$ values were 427, 3309, 12100 and 17666 ng·hr/ml at doses levels of 1, 20, 25 and 50 mg/kg/day, respectively. The sponsor stated that no treatment related effects were noted in untreated females mated to treated males in this study. In addition, no treatment related effects on fertility and caesarean-sectioning parameters (corpora lutea, implantations, viable and nonviable embryos) were observed in these females.

The sponsor states that purpose of the second follow up study was to test for toxic effects/disturbances resulting from CC-10004 treatment of CD-1 female mice before cohabitation and through mating, implantation and closure of the hard palate. Oral (gavage)

doses of 0 (1% carboxymethylcellulose), 10, 20, 40 or 80 mg/kg/day were administered to females beginning 15 days before cohabitation and continuing through mating with untreated males until gestation day 15. The sponsor states that preliminary results indicate that the NOAEL for general maternal toxicity is 40 mg/kg/day. Heart weight was increased in 80 mg/kg/day treated females. Increased body weight gain was noted in all dose groups before the cohabitation period and reduced body weight gain was noted at the end of the gestation period in the 40 and 80 mg/kg/day groups. The decreased body weight gain correlated with increased litter resorptions in these groups.

The sponsor states that the NOAEL for female fertility was 10 mg/kg/day. Estrous cycling was altered at 20, 40 and 80 mg/kg/day with increased numbers of mice with 6 or more days of diestrus and reduced numbers of estrous cycles over 14 days in these groups. This lead to an increase in the average number of cohabitation days in these groups. The sponsor states that despite these changes, all mice were mated and pregnancy rates were unaffected. The sponsor states that the developmental NOAEL was 10 mg/kg/day. The numbers of early resorptions was increased in the 20, 40 and 80 mg/kg/day groups. AUC values were 9450, 16647, 17225 and 28215 ng·hr/ml at 10, 20, 40 and 80 mg/kg/day, respectively.

In summary, this report summarizes potentially treatment related effects in male and female mouse fertility studies conducted with apremilast that could suggest a potential reproductive risk for human subjects. The possible treatment related findings included microscopic changes consisting of increased incidence and severity of necrotic spermatids and residual bodies in the lumen of the seminiferous tubules in the testes and increased incidence of exfoliated spermatogenic cells in the epididymides of male mice treated with 50 mg/kg/day. These findings had not been noted in previously conducted mouse fertility studies. The NOAEL for this finding was identified as 25 mg/kg/day with a corresponding AUC value of 12100 ng·hr/ml. The sponsor states that this AUC value represents a 2 – 3 fold greater exposure compared to the anticipated clinical exposure of 4587 ng·hr/ml based on a daily clinical dose of 40 mg (CC-10004-PK-007). Furthermore, the sponsor states that based on linear kinetics of apremilast in humans, it is anticipated that the margin of safety at a clinical dose of 60 mg would be 1 – 2 fold.

The sponsor states that due to these significant new animal reproductive toxicology findings in male mice, they are notifying all relevant regulatory agencies, IRBs/ECs and investigators by this expedited non-clinical safety letter. In addition, the sponsor is revising informed consent documents for all ongoing studies and planned new studies to reflect these results (the effect of apremilast on male mice spermatogenesis). The sponsor indicated that the Investigator's Brochure will be updated to reflect this new information. The sponsor stated that they will be revising the ongoing protocols and include in future protocols a requirement for male subjects participating in all apremilast studies to use contraceptives during the studies and continuing for 84 days after the last dose of the study drug. The sponsor states that this period exceeds the generally accepted time for spermatogenesis in humans.

Reviewer's comments: The sponsor's proposal to address this new potentially treatment related safety signal appears reasonable.

SDN 87 (Date: 7-25-08)

This submission contained three revised documents based on the new potentially treatment related nonclinical safety signal noted in SDN 85. A list of the three revised documents with a corresponding summary of changes is provided below.

1) Amendment to protocol CC-10004-PSOR-004, A phase 2, open-label, multicenter study to evaluate the safety, pharmacodynamics, pharmacokinetics, and efficacy of CC-10004 in subjects with recalcitrant plaque-type psoriasis.

The protocol change that relates to the nonclinical safety signal noted in the follow up male fertility study increased the time that males should use barrier contraception (latex condoms) when engaging in sexual activity with FCBP for 28 days to 84 days after taking the last dose of study medication. This same increase in time for use of barrier contraception from 28 days to 84 days after taking the last dose of study medication was also included in the informed consent document associated with this clinical study protocol. This change appears acceptable. The other changes in the protocol were relatively small administrative changes.

2) Amendment to protocol CC-10004-PSOR-005, A phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque-type psoriasis.

The protocol change that relates to the nonclinical safety signal noted in the follow up male fertility study increased the time that males should use barrier contraception (latex condoms) when engaging in sexual activity with FCBP from 28 days to 84 days after taking the last dose of study medication. This same increase in time for use of barrier contraception from 28 days to 84 days after taking the last dose of study medication was also included in the informed consent document associated with this clinical study protocol. This change appears acceptable. The other changes in the protocol were relatively small administrative changes.

3) Updated Investigator Brochure, version 6.0.

The Investigator Brochure was updated with summary information from the follow up fertility studies conducted in male and female mice. The updated information appears acceptable.

SDN 120 (Date: 6/16/09)

The sponsor states that the purpose of this submission is to provide an update for the nonclinical safety report that was submitted to the IND on July 11, 2008 (SDN 85). Initially, the results from a follow up fertility study conducted in male CD-1 mice (CC-10004-TOX-011) indicated possible treatment related microscopic changes in the testes and epididymides of male mice. Based on this preliminary finding the sponsor modified the ongoing clinical study protocols and corresponding informed consent documents to increase the time of condom use for males from 28 days to 84 days after taking the last dose of study medication.

The sponsor states that a peer review of the data was conducted by an independent pathologist and an expert report was generated. The sponsor states that based on the review it was concluded that there were no drug related microscopic changes in the testes and epididymides of male mice. A copy of the Histopathology Expert Report was included in this submission.

During the peer review process, the incidence of the microscopic finding in the epididymides was revised and found to be comparable between males in the 50 mg/kg/day group compared to control animals. The microscopic finding originally recorded in the testis (necrosis, individual spermatid/residual bodies) was regarded to be cellular debris from residual bodies. The debris of normal spermatogenesis is known to stain deeply in virtually all sections and may be confused with degenerating cells. The Histopathology Expert Report states that although the incidence of the prominent cellular debris/residual bodies was slightly higher in male mice given 50 mg/kg/day compared to controls, this change graded minimal to mild in severity was interpreted to be a normal physiological process.

The peer review panel also re-evaluated the histopathological slides for the testes and epididymides from control and 1000 mg/kg/day animals from the 90 day and 6 month mouse toxicity studies (CC-10004-TOX-002 and CC-10004-TOX-004, respectively). The peer review concurred with the conclusion of the final report that there were to CC-10004 related microscopic findings in the testes of epididymides. The peer review panel also re-evaluated the histopathological slides from all the dose groups (0, 100, 300 and 1000 mg/kg/day) from the first mouse fertility study (CC-10004-TOX-001). In addition to the overall interpretation of the histopathological slides, the presence of cellular debris/residual bodies was recorded for all evaluated slides. The incidence of these findings was comparable between control and treated groups.

The peer review panel performed a selective review primarily focused on the histopathological observations made from the testes and epididymides from four oral (gavage) studies using mice which included two fertility studies, one 90 day toxicity study and one 6 month toxicity study. This peer review was conducted to assess the presence or absence of CC-10004 related effects on the testes and/or epididymides. The peer review panel determined that there were no microscopic findings attributed to the administration of CC-10004 in the testis and epididymis of animals examined in any of the fertility or toxicity studies reviewed and no effect on the sperm parameters was noted in either of the two fertility studies.

The sponsor states that given the artifactual nature of what had initially been interpreted as apremilast testicle toxicity, they intend to revert active protocols and informed consent documents and construct future protocols and informed consent documents with the original requirement that all male subjects use latex condom contraception for 30 days (instead of 84 days) after the last dose of the study drug. The requirement for condom use 30 days after the last dose of study drug was in effect before the preliminary testicle histopathology findings as a routine precaution. In addition, the investigator brochure will be updated to reflect the peer review conclusions and final data from all of these study reports.

Reviewer's comments: The sponsor's interpretation of the results from the peer review of the histopathology findings noted in male reproductive organs (testes and/or epididymides) appears acceptable. Since there was previous data from male mice treated with higher doses for longer periods of time that did not provide a safety signal for male reproductive organs, it seems reasonable to assume that the finding that was originally noted in the male fertility follow up study at the 50 mg/kg/day dose level were probably an artifact from misreading the histopathology slides rather that a true treatment related effect. The sponsor's proposal to revert active protocols and informed consent documents and construct future protocols and informed consent documents with the original requirement that all male subjects use latex condom contraception for 30 days (instead of 84 days) after the last dose of the study drug appears reasonable. The sponsor has not submitted the final study reports for the follow up male and female mouse fertility studies to the IND, to date. The sponsor will be asked to submit these final study reports to the IND for review.

SDN 106 (Date: 1-30-09)

This submission contained 7 nonclinical study reports (2 pharmacology study reports and 5 pharmacokinetic study reports). The submitted nonclinical study reports are listed below with a brief summary review of each study.

1) Analgesic assessment of test articles in the Bennett (CCI) model of neuropathic pain (Study No. [redacted]S07059)

CC-10004 did not exhibit any analgesic properties in this animal pain model.

2) The efficacy of CC-10004, CC-11050 and Tetomilast in a TNBS-induced colitis model: Further gene expression analysis (Study No. [redacted]07-163)

The results of this study did not provide any correlation between transcript levels of INF-γ, Cxcl-10 or Cxcl-9 with colitis severity or treatment related effects in this nonclinical colitis animal model.

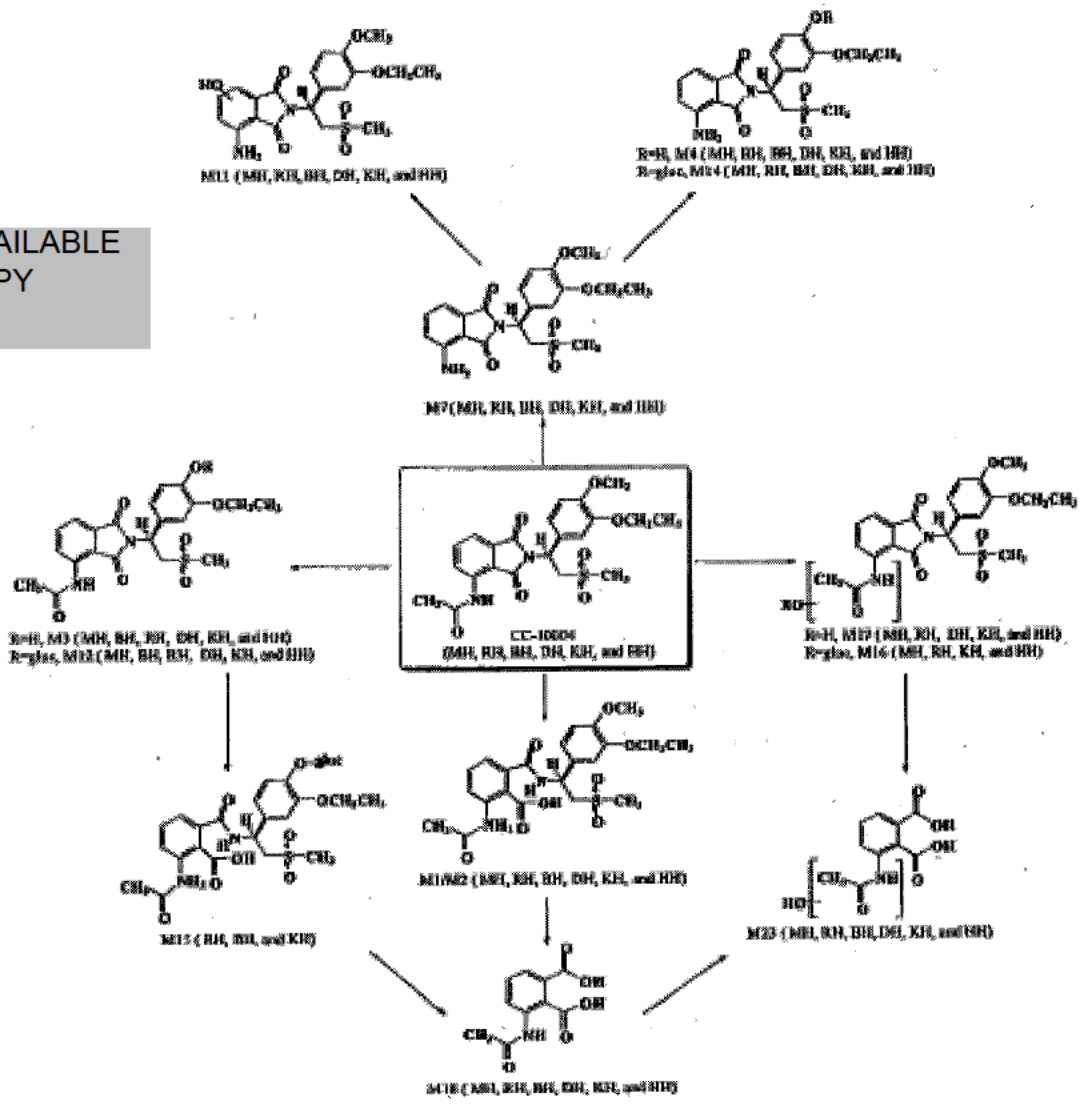
3) In vitro metabolism of [^{14}C]-CC-10004 in hepatocytes from the mouse, rat, rabbit, dog, monkey and human (Study No. CC-10004-DMPK-023)

[^{14}C]-CC-10004 (5 and 25 μM) was incubated with mouse rat, rabbit, dog, monkey and human hepatocytes for 4 hours. Metabolite radio profiling was accomplished by HPLC radio-chromatography. [^{14}C]-CC-10004 was not stable in the incubation media. After a 4 hour 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 in this study. M1/M2 and

M18 showed a similar or lower percent of the total radioactivity in all hepatocytes incubations compared to the negative control. A high concentration of M14 was observed in rabbit hepatocytes incubations, accounting for 25.4 – 29.7% of the total radioactivity. A much lower amount of M14 was observed, ranging from 0.8 – 2.6% of the total radioactivity in the hepatocytes incubations of the other five species. M3, M7 and M12 were observed in the hepatocyte incubations of all species. The other minor metabolites showing detectable radioactivity were M4 (only in mouse, rat and rabbit hepatocytes incubations), M15 (only in rat, rabbit and monkey hepatocytes incubations), M16 (only in mouse, rat, and human hepatocytes incubations), and M17 (only in mouse, rat and human hepatocytes incubations). Overall, all the metabolites formed in vitro by human hepatocytes were formed by hepatocytes from one or more animal species. The proposed metabolic pathway of CC-10004 in mouse, rat, rabbit, dog, monkey and human hepatocytes is provided in the figure below (copied from the submission).

Proposed Metabolic Pathways of CC-10004 in Mouse, Rat, Rabbit, Dog, Monkey and Human Hepatocytes:



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4) In vitro protein binding determination of CC-10004 in mouse, rat, rabbit, monkey and human plasma using ultrafiltration and LC/MS/MS analysis (Study No. CC-10004-DMPK-026)

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.

5) Assessment of interaction of CC-10004 with human organic anion transporters using influx transporter cRNA injected *Xenopus laevis* oocytes (Study No. CC-10004-DMPK-027)

The purpose of this study was to determine if CC-10004 inhibits uptake of probe substrates into *Xenopus laevis* oocytes expressing human solute-lined carrier uptake transporters hOAT1 and hOAT3. CC-10004 at 2.0 and 10 μM was assessed as an inhibitor of human OAT1-mediated uptake of probe substrate PAH (para aminohippuric acid) and human OAT3-mediated update of E-3-S (estrone-3-sulfate). CC-10004 at 2.0 μM did not inhibit human OAT1. At 10 μM, CC-10004 demonstrated slight inhibition (21%) of OAT1-mediated uptake activity. In comparison, control inhibitor probenicid inhibited OAT1 by 97%. The results suggest that CC-10004 is not a potent inhibitor of human OAT-1. CC-10004 did not demonstrate inhibition of human OAT3 at either concentration tested, which suggests that CC-10004 was not an inhibitor of human OAT3.

6) Elimination of radioactivity in bile, urine, and feces following oral and intravenous administration of ^{14}C-CC-10004 to mice (Study No. CC-10004-DMPK-030)

The absorption and excretion of ^{14}C-CC-10004 were determined after administration of a single oral (10 mg/kg) or intravenous dose (10 mg/kg or 5 mg/kg) of ^{14}C-CC-10004 to bile duct-intact and bile duct-cannulated (BDC) male mice. ^{14}C-CC-10004 derived radioactivity was readily excreted after oral or IV administration, primarily within the first 24 hours (approximately 75 – 87%) after dosing. The majority of the radioactive dose was eliminated in the bile of BDC mice after oral or IV dosing, which indicated that biliary excretion is the major route of elimination of ^{14}C-CC-10004 derived radioactivity.

7) Metabolite radio-profiling and identification after a single oral and IV dose of [^{14}C]-CC-10004 in male intact and BDC mice (Study No. CC-10004-DMPK-031)

The objective of this study was to investigate the metabolite profile and to characterize and/or identify prominent metabolites when present in the plasma from male intact mice and in the bile, urine and feces collected from male BDC mice administered a single 10 mg/kg oral or 5 or 10 mg/kg IV dose of ^{14}C-CC-10004. Metabolite characterization and identification were performed by LC/MS in conjunction with an appropriate radioactivity monitor.

CC-10004 was extensively metabolized by mice. The major metabolic route of CC-10004 in mice is *O*-demethylation, with 42 - 43% of the dose metabolized by this pathway. The other major metabolic pathway found in mice is *O*-deethylation. Minor pathways included *N*-deacetylation, hydroxylation (oxidative), hydrolysis of the imide ring, and combination of these pathways. The *O*-demethylated and deethylated metabolites in plasma, bile and urine are predominately glucuronide conjugates.

Plasma: Unchanged CC-10004 and M12 were the major circulating radioactive components in mouse plasma. Two minor metabolites, M13 and M14, and four trace metabolites M7, M16, M17 and M18 were also observed.

Bile: Unchanged ^{14}C-CC-10004 was a minor radioactive component, accounting for <1% of the administered dose. The major biliary metabolites were M12 and M13, accounting for 30% and 10% of the dose, respectively, in 0-48 hour mouse bile samples from oral and IV groups. Four minor metabolites, M14, M15, M18 and M21, were also detected, each accounting for 1 – 3.9% of the dose (except for M21 from oral group mouse bile, which accounted for only 0.54% of the dose). Five trace metabolites, M7, M11, M16, M17 and M23, each accounted for less than 0.37% of the dose.

Urine: Unchanged ^{14}C-CC-10004 was a minor radioactive component, accounting for 0.74% of the administered dose. The two most abundant urinary metabolites, M12 and M13, accounted for 4.0 – 7.1% of the dose. Seven trace metabolites, M11, M14, M15, M16, M17, M18 and M23, each accounted for <1% of the dose.

Feces: Unchanged ^{14}C-CC-10004 was a minor radioactive component, accounting for 2.6% and 4.5% of the administered dose in 0-48 hour male BDC mouse feces from oral and IV groups, respectively. The most abundant fecal metabolite, M3 (*O*-demethylated CC-10004), accounted for 4.6% and 3.0% of the dose in 0-48 hours male BDC mouse feces from oral and IV groups, respectively. Five trace metabolites, M7, M17, M18, M21 and M23 were also detected, each accounting for less than 0.4% of the dose.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

I agree that after a expert peer review of the histopathology findings noted in the male mouse reproductive organs from the oral male mouse fertility studies, 90 day oral mouse toxicity study and 6 month oral mouse toxicity study, there does not appear to be a cause for concern for a specific toxicity to male reproductive organs. The sponsor's proposal to use the original requirement in future protocols and informed consent documents that all male subjects use latex condom contraception for 30 days after the last dose of the study drug appears reasonable. The sponsor has not submitted the final study reports for the follow up male and female mouse fertility studies to the IND, to date. The sponsor will be asked to submit these final study reports to the IND for review.

The nonclinical study reports included in SDN 106 provide additional nonclinical information concerning the pharmacology and pharmacokinetics of CC-10004. This review serves to document the submission of these studies. No further action is indicated for this information, at this time.

External comments (to sponsor):

It is recommended that the following information be relayed to the sponsor for (b) (4) (b) (4)

You should submit the final study reports for all conducted male and female mouse fertility studies to the IND.

Appendix 9: July 21, 2009 (b) (4) Review

Linked Applications	Sponsor Name	Drug Name / Subject
(b) (4)	CELGENE CORP	CC-10004 (b) (4)

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

/s/

BARBARA A HILL
07/21/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	(b) (4)
Supporting document/s:	131, 140, 144, and 155
Sponsor's letter date:	October 28, 2009; January 7, 2010; February 3, 2010; and May 21, 2010
CDER stamp date:	October 28, 2009; January 7, 2010; February 3, 2010; and May 21, 2010
Product:	Apremilast (CC-10004)
Indication:	Psoriasis
Sponsor:	Celgene Corporation
Review Division:	Dermatology and Dental Products
Reviewer:	Carmen D Booker, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Susan Walker, MD
Project Manager:	Dawn Williams

Template Version: December 7, 2009

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Clinical Study (ies) Safe to Proceed: Yes

1.1.2 If Not Safe to Proceed, Recommendations to Allow Clinical Study (ies) to Proceed

N/A

1.1.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor)

Submit the final study report for Study Number CC-10004-TOX-013 (Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey) as soon as it is completed.

Please clearly identify [redacted] (b) (4) which was used in the submitted Ames assay (CC-10004-TOX-015).

1.2 Brief Discussion of Nonclinical Findings

Mice were orally administered CC-10004 for 3 or 14 days at a dose of 300 mg/kg/day or for 3, 14, 45 or 90 days at a dose of 1000 mg/kg/day. Inflammatory lesions were observed in multiple tissues at all terminal sacrifice timepoints; however, in those animals allowed to recover, complete recovery was noted at day 90.

In a bacterial reverse mutation assay, CC-10004 with [redacted] (b) (4) was not mutagenic.

Fertility studies in mice were conducted by the sponsor. Male mice orally administered 1, 10, 25 or 50 mg/kg CC-10004 for 70 days before and at least 25 days after cohabitation, no changes in mating and fertility parameters were observed. Increased testes weights were observed in mice given 25 or 50 mg/kg/day CC-10004; however, no corresponding changes in histopathology were observed. The NOAEL for this study was determined to be 50 mg/kg. In female mice orally administered 10, 20, 40 or 80 mg/kg CC-10004 for 15 days before cohabitation until gestation day 15, estrous cycling was altered at the 20, 40 and 80 mg/kg/day doses. The NOAEL for female fertility was determined to be 10 mg/kg/day. The numbers of early resorptions were increased and the number of ossified tarsals were reduced in the 20, 40 and 80 mg/kg/day dose groups. Fetal body weights were reduced at 40 and 80 mg/kg/day and retarded ossification of the supraoccipital bone of the skull occurred at these doses. The maternal and developmental NOAEL was determined to be 10 mg/kg/day.

Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 50, 200 or 1000 mg/kg experienced dose-related increases in fetal loss. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. A NOAEL may be determined when the final study report is submitted which evaluates a lower dose of CC-10004.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

608141-41-9

2.1.2 Generic Name

apremilast

2.1.3 Code Name

CC-10004

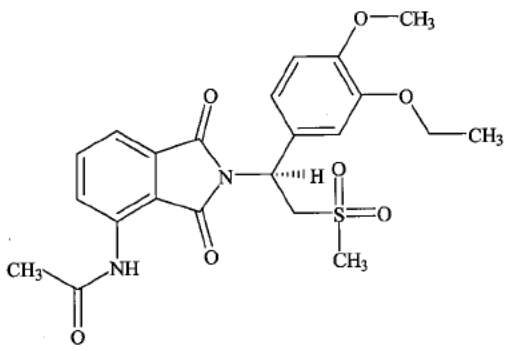
2.1.4 Chemical Name

N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]

2.1.5 Molecular Formula/Molecular Weight

$C_{22}H_{24}N_2O_7S$ / 460.5

2.1.6 Structure



2.1.7 Pharmacologic class

Phosphodiesterase type IV inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

INDs [redacted]

2.3 Clinical Formulation

2.3.1 Drug Formulation

White [redacted] containing the following ingredients: CC-10004 (10 mg), [redacted] microcrystalline cellulose [redacted] lactose [redacted] monohydrate [redacted] croscarmellose sodium [redacted] and magnesium stearate [redacted]

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

The sponsor's proposed clinical population is patients with psoriasis. The sponsor has completed Phase II studies [redacted] their dosing regimen is [redacted]

2.5 Regulatory Background

2.5.1 Previous Clinical Experience

Phase 2 clinical studies have been conducted with up to 20 mg b.i.d for 12 weeks.

2.5.2 History of Regulatory Submission

The sponsor has completed Phase 2 clinical studies. At an end of Phase 2 meeting on May 12, 2010 the sponsor asked if an audited draft report of their embryofetal development study in cynomolgus monkeys could be submitted before the final draft was available so that they could proceed to Phase 3 studies. The Agency agreed that an audited draft report could be submitted provided that individual animal data was

included and that each dose group contained an adequate number of pups for assessment.

3 Studies Submitted

3.1 Studies Reviewed

SD 131: CC-10004: Oral Toxicity Study in Mice to Investigate the Time Course for Development and Recovery of Inflammatory Lesions in Multiple Tissues. Study Number CC-10004-TOX-008. September 2009.

Oral (Gavage) Fertility and General Reproduction Toxicity Study of CC-10004 in Male Mice. Study Number CC-10004-TOX-011. September 2009.

Combined Oral (Gavage) Fertility and Developmental Toxicity Study of CC-10004 in Female Mice. Study Number CC-10004-TOX-012. September 2009.

SD 140: Intravenous Dosage-Range Finding Developmental Toxicity Study of CC-10004 in Rabbits. Study Number CC-10004-TOX-009. November 2009.

SD 144: Bacterial Reverse Mutation Assay. Study Number CC-10004-TOX-015. December 2009.

SD 155: Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey. Study Number CC-10004-TOX-013. March 2010.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Apremilast is a phosphodiesterase type IV inhibitor and has been shown to inhibit the production of TNF-α, IL-6, IL-8, IL-17, IL-23 and IFN-γ. It also inhibits neutrophil infiltration.

4.2 Secondary Pharmacology

No new data was submitted.

4.3 Safety Pharmacology

Behavioral effects of a single oral dose of CC-10004 at doses up to 2000 mg/kg were evaluated in male CD-1 mice. The NOAEL was determined to be 500 mg/kg. Higher doses produced minor effects including lacrimation, ptosis and apathy.

The cardiovascular and pulmonary effects of CC-10004 were evaluated after single intravenous dose administration at doses up to 5 mg/kg in anesthetized dogs. CC-10004 induced a dose related increase in blood pressure and heart rate. Corrected QT interval was not affected in this study. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in this study.

CC-10004 appears to be a very low potency inhibitor of the hERG channel with an IC_{50} of 184.2 µM. The mean maximum inhibition produced by CC-10004 was 59.0% and occurred at the high dose of 249.7 µM.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new data was submitted.

5.2 Toxicokinetics

See toxicology study summary.

6 General Toxicology

6.1 Single-Dose Toxicity

No new data was submitted.

6.2 Repeat-Dose Toxicity

Study title: CC-10004: Oral Toxicity Study in Mice to Investigate the Time Course for Development and Recovery of Inflammatory Lesions in Multiple Tissues

Study no.:	CC-10004-TOX-008
Study report location:	SD 131 - electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 10, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, 54560-05, 99.9%

Key Study Findings: Mice were orally administered CC-10004 for 3 or 14 days at a dose of 300 mg/kg/day or for 3, 14, 45 or 90 days at a dose of 1000 mg/kg/day. Inflammatory lesions were observed in multiple tissues at all terminal sacrifice timepoints; however, in those animals allowed to recover, complete recovery was noted at Day 90.

Methods

Doses:	0, 300 or 1000 mg/kg/day
Frequency of dosing:	once daily for 3 and 14 days at 300 and 1000 mg/kg/day, and 45 or 90 days at 1000 mg/kg/day
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	1% (w/v) sodium carboxymethylcellulose in deionized water
Species/Strain:	Crl:CD1[ICR] mice
Number/Sex/Group:	36 females/group
Age:	44 days
Weight:	20.4 – 28.3 g
Satellite groups:	A subset of animals (≤10/group) dosed for 14-days at 300 and 1000 mg/kg/day were placed on a 31- or 76-day recovery to assess reversibility of test article-related effects associated with the oral administration of CC-10004 in mice
Unique study design:	None
Deviation from study protocol:	None

Observations and Results

Mortality

Daily. Five animals died before their scheduled necropsies including two LD animals and three HD animals. One HD animal found dead had pleural hemorrhage and dilatation of the heart which may have been secondary to gavage trauma and terminal congestion, respectively. One LD animal that was euthanized had acute lung and nasal hemorrhage that also may have been secondary to acute gavage trauma. One LD early death had moderately severe thymic lymphoid depletion. No specific causes for early death were evident in the examined tissues from this animal or from the other two HD early deaths.

Clinical Signs

Daily. No treatment-related effects were observed.

Body Weights

Weekly. Statistically significant increases in body weight were observed in LD and HD animals when compared to controls on day 6 and continued throughout the study.

Feed Consumption

Weekly. Feed consumption was increased in LD and HD animals starting on day 6 and continued for approximately two weeks.

Hematology

Days 3, 14, 45 or 90. No treatment-related effects were observed.

Clinical Chemistry

Days 3, 14, 45 or 90. Mean globulin levels were statistically significantly higher than the control group on study day 14 in LD and HD animals and on study day 90 in the HD group administered CC-10004 for 90 days. A/G ratio was lower in LD and HD animals on study day 14 and in the HD group administered CC-10004 for 90 days on study day 90 when compared to the control group. Mean urea nitrogen levels in the 300 and 1000 mg/kg/day groups were generally statistically significantly higher than the control group on study day 14.

Gross Pathology

Days 3, 14, 45 or 90. No treatment-related effects were observed.

Organ Weights

Days 3, 14, 45 or 90. Adrenal glands, brain, heart, kidneys, liver, ovaries with oviducts, spleen and thymus. Increased heart and liver weights were observed in HD animals on days 14 and 90.

Histopathology

Adequate Battery: Yes

Histological Findings: Days 3, 14, 45 or 90. Minimal to slight/mild hepatocellular hypertrophy was present in several HD animals on study days 3, 14, and 45. This lesion was characterized histologically by enlargement of hepatocytes and nuclei with slightly increased cytoplasmic granularity that was most pronounced in the centrilobular area but also was present, to a lesser extent, in hepatocytes in other regions. On study day 3, minimal hepatocellular hypertrophy was present in 4/12 HD animals. One HD animal euthanized on study day 3 also had moderate hepatocellular necrosis and was the only animal in the study with this change. On study day 14, minimal to slight/mild hepatocellular hypertrophy was observed in 7/20 HD animals. At study day 45, minimal to slight/mild hepatocellular hypertrophy was

present in HD 7/10 animals treated for 45 days and in 1 HD animal for 14 days followed by recovery to study day 45. No hepatocellular hypertrophy was evident in any of the continuously treated or recovery animals euthanized on study day 90. Histological changes in the thymus were present in CC-10004-treated animals from all 3 groups on study days 3, 14, and 45 but not on study day 90. On study day 3, test article-related thymic lesions included lymphoid necrosis, subacute inflammation, and lymphoid depletion. Thymic lesions were the most severe and occurred at the highest incidence on study day 3. Study day 3 thymic lesions included moderate to severe/high lymphoid necrosis in 6/12 HD animals and in 1/6 LD animals. Minimal to slight/mild thymic lymphoid depletion was present in 5/12 HD animals and in 5/6 LD animals on study day 3. Subacute thymic inflammation graded as slight/mild to moderate was present on study day 3 in 6/12 HD animals, and minimal to slight/mild subacute inflammation was present in 3/6 LD animals. By study day 14, inflammatory and degenerative thymic lesions were decreased in severity and hyperplastic lesions were evident. Inflammatory thymic changes at this time point were diagnosed as chronic-active and included small amounts of fibrous connective tissue in addition to the inflammatory cells. Minimal to slight/mild inflammation was present in 5/20 HD animals, and in 1/10 LD animals. Minimal to slight/mild lymphoid depletion was diagnosed in only 2/20 HD animals and in 1/10 LD animals. Lymphoid hyperplasia, affecting primarily the cortical lymphocytes, was evident in 6/20 HD animals on study day 14 and graded as minimal to moderate; minimal thymic lymphoid hyperplasia was present in 1/10 LD animals. At study day 45, minimal thymic lymphoid hyperplasia was present in 2/10 HD animals dosed continuously. One of 10 HD animals dosed for 14 days and allowed to recover to study day 45 had this change. Minimal thymic lymphoid hyperplasia was present in 4 of the early deaths. In the mesenteric lymph node on study day 14, minimal acute inflammation was present in 2/19 HD animals and in 1/10 LD animals. On study day 45, minimal to mild lymphoid hyperplasia was present in the mesenteric lymph nodes in 4/10 HD animals dosed continuously, in 3/7 HD animals treated for 14 days and allowed to recover to Day 45, and in 1/10 LD animals treated for 14 days and allowed to recover to Day 45.

Stability and Homogeneity

The dosing formulations were formulated within -6.2 to 1.1% differences of their targeted concentrations of 30 and 100 mg/mL. Vehicle control samples were devoid of test article.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.:	CC-10004-TOX-015
Study report location:	SD144 - electronic
Conducting laboratory and location:	[redacted]
Date of study initiation:	August 5, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004 spiked with [redacted]

Key Study Findings: Under the conditions of this assay, CC-10004 with [redacted] was not mutagenic.

Methods

Strains:	*Salmonella typhimurium* tester strains TA98, TA100, TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A
Concentrations in definitive study:	50, 150, 500, 1500 and 5000 mcg per plate
Basis of concentration selection:	Preliminary assay with maximum concentration of 5000 mcg per plate (precipitate observed at highest concentration)
Negative control:	DMSO
Positive control:	2-aminoanthracene (1, 2 or 20 mcg/plate), 2-nitrofluorene (1 mcg/plate), sodium azide (1 mcg/plate), 9-aminoacridine (75 mcg/plate) and methyl methanesulfonate (1000 mcg/plate)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	12 hours & 48 to 72 hours

Study Validity

For the test article to have been positive, it must have caused a dose-related increase in the mean revertants per plate of at least one tester strain over a minimum of two increasing concentrations of test article. An equivocal response was a biologically relevant increase in a revertant count that partially meets the criteria for evaluation as positive. A response would be evaluated as negative, if it was neither positive nor equivocal. The mean of each positive control must exhibit at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control. This study was valid as judged by these criteria.

Results

No toxicity was observed but precipitate was observed at 5000 µg per plate with most test conditions. No increases in the number of mean revertants per plate were observed, except in the positive control plates.

Reviewer note: The chemical identity of (b) (4) is unclear as well as its purpose in this assay. A comment will be sent to the sponsor asking for identification of (b) (4)

8 Carcinogenicity

No new data was submitted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study #1

Study title: Oral (Gavage) Fertility and General Reproduction Toxicity Study of CC-10004 in Male Mice

Study no.:	CC-10004-TOX-011
Study report location:	SD131 - electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 1, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-1004, 54560-05, 99.9%

Key Study Findings: Male mice orally administered 1, 10, 25 or 50 mg/kg CC-10004 for 70 days before and at least 25 days after cohabitation, no changes in mating and fertility parameters were observed. Increased testes weights were observed in mice given 25 or 50 mg/kg/day CC-10004; however, no corresponding changes in histopathology were observed. The NOAEL for this study was determined to be 50 mg/kg.

Methods

Doses:	0, 1, 10, 25 and 50 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	1% w/v aqueous carboxymethylcellulose
Species/Strain:	Crl:CD1(ICR) male mice
Number/Sex/Group:	25 males/group

Satellite groups: 36 males/group for toxicokinetics
Study design: Male mice were given the test article and/or vehicle once daily beginning 70 days before cohabitation (maximum of 14 days) and continuing through the day before sacrifice (totals of 95 to 98 daily dosages).
Deviation from study protocol: None

Observations and Results

Mortality

Daily. One animal each from the 1 and 50 mg/kg groups was euthanized early due to dosing error.

Clinical Signs

Daily. No treatment-related effects were observed.

Body Weight

Weekly. Body weight gains for the entire study period were significantly increased in the 10, 25 and 50 mg/kg dose groups.

Toxicokinetics

Days 1, 2, 70 and 71. CC-10004 was readily absorbed following oral administration in mice. Peak plasma concentrations were reached between 0.50 and 2.00 hours following oral gavage dosing. On day 1, the C_{max} values ranged from 122 to 1690 ng/mL, the $AUC_{(0\text{-}24h)}$ values were 473, 4257, 12100 and 17666 ng•h/mL for males given 1, 10, 25 or 50 mg/kg/day CC-10004, respectively. On day 70, C_{max} values ranged from 132 to 1337 ng/mL and $AUC_{(0\text{-}24h)}$ values were 564, 5901, 12848 and 21040 ng•h/mL for males given 1, 10, 25 or 50 mg/kg/day CC-10004, respectively. Over the dose range studied, increases in CC-10004 C_{max} were less than dose proportional. On both days 1 and 70, AUC values increased in an approximate dose proportional manner in the 1 to 25 mg/kg/day dose range, but the increase was slightly less than dose-proportional at 50 mg/kg/day. There was negligible to minor accumulation of CC-10004 between day 1 and day 70, as the accumulation ratio (R_c) for $AUC_{(0\text{-}24h)}$ values ranged from 1.06 to 1.39 between the two sampling days.

Stability and Homogeneity

Dosing formulations were formulated within -11.3 to -0.6% of their targeted concentrations of 0.1, 1, 2.5 and 5 mg/mL. Homogeneity of dosing formulations was

verified, with % CV of the dosing formulations ranging from 1.4 to 3.8%. Vehicle control samples were devoid of test article.

Necropsy

Day 71 or 72. All mating and fertility parameters [numbers of days in cohabitation, mice that mated, the fertility index (number of pregnancies per number of mice that mated), mice with confirmed mating dates during the first week of cohabitation and number of pregnancies per number of mice in cohabitation] were unaffected by doses as high as 50 mg/kg/day. All values were comparable among the five dosage groups and did not significantly differ.

The absolute weights of the right and left testes and the ratios of these organ weights to terminal body weight were increased or significantly increased in the 25 and 50 mg/kg/day dosage groups; values ranged from 5% to 24% greater than the control group values.

Values for number and percent motile sperm, number of nonmotile sperm and total sperm count and density from the cauda epididymis were unaffected by dosages of CC-10004 as high as 50 mg/kg/day.

Study #2

Study title: Combined Oral (Gavage) Fertility and Developmental Toxicity Study of CC-10004 in Female Mice

Study no.:	CC-10004-TOX-012
Study report location:	SD131 - electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 24, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CC-1004, 54560-05, 99.9%

Key Study Findings: In female mice orally administered 10, 20, 40 or 80 mg/kg CC-10004 for 15 days before cohabitation until gestation day 15, estrous cycling was altered at the 20, 40 and 80 mg/kg/day doses. All mice were mated and pregnancy rates were unaffected. The NOAEL for female fertility was determined to be 10 mg/kg/day. The numbers of early resorptions were increased and the number of ossified tarsals were reduced in the 20, 40 and 80 mg/kg/day dose groups. Fetal body weights were reduced at 40 and 80 mg/kg/day and retarded ossification of the supraoccipital bone of the skull occurred at these doses. The maternal and developmental NOAEL was determined to be 10 mg/kg/day. Fetal plasma drug levels suggested that CC-10004 traverses the maternal blood-placental barrier in mice.

Methods

Doses:	0, 10, 20, 40 and 80 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	1% w/v aqueous carboxymethylcellulose
Species/Strain:	Crl:CD1(ICR) mice
Number/Sex/Group:	25 females / group
Satellite groups:	36 females/group for toxicokinetics
Study design:	Female mice were dosed once daily beginning 15 days before cohabitation (maximum of 21 days) and continuing through DG 15 (totals of 31 to 48 daily dosages).
Deviation from study protocol:	Due to reduced estrous cycles, the average number of days in cohabitation was increased in the 20, 40 and 80 mg/kg/day dose groups.

Observations and Results

Mortality

Daily. Two mice in the 10 mg/kg/day dosage group were sacrificed because of adverse clinical observations and one mouse in the 20 mg/kg/day dosage group was found dead. The cause of death for all early deaths was dosing error.

Clinical Signs

Daily. No treatment-related effects were observed.

Body Weight

Weekly. Body weight gains were significantly increased in the 20, 40 and 80 mg/kg/day dosage groups on days 1 to 8, in the 10 mg/kg/day dosage group on days 8 to 15 and, as a result, body weight gains for the entire precohabitation period (days 1 to 15) were significantly increased in all test article-treated groups.

Toxicokinetics

Days 14, 15 and 16. CC-10004 was readily absorbed following oral administration in mice. On day 14, the Cmax values were 814, 1283, 2047 and 2469 ng/mL and the AUC(0-24h) values were 7407, 13089, 19225 and 29035 ng•h/mL at 10, 20, 40 and 80 mg/kg/day respectively. On gestation day 15, Cmax values were 875, 1842, 1308 and 2626 ng/mL, and the AUC(0-24h) values were 9450, 16647, 17225 and 29215 ng•h/mL at 10, 20, 40 and 80 mg/kg/day respectively. Less than dose- proportional increases in Cmax and AUC(0-24h) were observed with increasing dose in female mice. The Cmax

and AUC(0-24h) values were generally comparable between day 14 nonpregnant mice and gestation day 15 pregnant mice. The plasma concentrations of CC-10004 in the pooled fetal plasma 24 hours after dose on gestation day 15 were highly variable. In six of the ten litters evaluated, CC-10004 levels were below the limit of quantification. In four of the ten litters evaluated, fetal plasma concentrations of CC-10004 ranged from 14.5 to 2813 ng/mL, and the fetal to maternal plasma ratio of CC-10004 ranged from 0.35 to 2.85. These data suggest that CC-10004 crosses the maternal blood-placental barrier in mice.

Stability and Homogeneity

The dose formulations were within -11.7 to 0.8% of their targeted concentrations of 1, 2, 4 and 8 mg/mL. Homogeneity of dosing formulations was verified, with % CV for each homogeneity group ranging from 0.7 to 5.0%. Vehicle control samples were devoid of test article.

Necropsy

Day 14, 15 or 16. The number of estrous stages per 14 days was comparable among the five dosage groups before the start of administration. During the precohabitation dosage period, the number of estrous stages per 14 days was significantly reduced in the 40 and 80 mg/kg/day dose groups. The numbers of mice with six or more days of diestrus were significantly increased in the 80 mg/kg/day dose group. The average number of days in cohabitation was increased in the 20, 40 and 80 mg/kg/day dosage groups; however, the increases were not statistically significant. The number of days in cohabitation were 1.9, 1.9, 3.4, 2.8 and 4.3 in the five respective dose groups. The values in these three groups were increased over the average number of days in cohabitation observed historically at the Testing Facility, but only the value at 80 mg/kg/day was outside the range of days observed historically. All other mating and fertility parameters [mice that mated, the Fertility Index (number of pregnancies per number of mice that mated), mice with confirmed mating dates during the first or second week of cohabitation and number of pregnancies per number of mice in cohabitation] were unaffected in all dose groups. All female mice were mated.

Average heart weight was significantly increased in the 20 and 80 mg/kg/day dose groups.

The average numbers of total and early resorptions and the percentage of mice with dead or resorbed conceptuses were increased in the 40 and 80 mg/kg/day dose groups. Litter sizes and the average number of live fetuses were significantly reduced in the HD group. Two mice in each of the 40 and 80 mg/kg/day dose groups had completely resorbed litters. Fetal body weights were reduced at 40 and 80 mg/kg/day. Although these reductions were not statistically significant, as compared with the vehicle control group values, the reductions, which were more severe in male fetuses than in female fetuses, were associated with reversible delays in ossification.

The average numbers of ossified tarsals in the 20, 40 and 80 mg/kg/day dose groups were reduced below the averages observed historically at the testing facility. Additionally the numbers of litters and fetuses with incompletely ossified supraoccipitals were increased in a dose-dependent manner in the 40 and 80 mg/kg/day dose groups.

Variations in skull ossification, including an interfrontal ossification site, incompletely ossified supraoccipital, nasal, frontal and/or parietal bones and not ossified supraoccipital bones, occurred in 15, 9, 7, 8 and 8 fetuses from 11, 6, 6, 7 and 6 litters in the 0, 10, 20, 40 and 80 mg/kg/day dose groups, respectively. The most prevalent of these variations was an interfrontal ossification site, which occurred in 14, 9, 6, 5 and 4 fetuses from 10, 6, 5, 5 and 2 litters in the five respective dosage groups. The litter and fetal incidences of one of these variations in ossification, incompletely ossified supraoccipitals, were increased in a dose related manner in the 40 and 80 mg/kg/day dose groups; however, these increases were not statistically significant.

Variations in sternal ossification (asymmetric, duplicate, irregularly shaped and/or fused) occurred in 5, 3, 11, 7 and 4 fetuses from 5, 2, 9, 7 and 3 litters in the five respective dose groups. The litter incidence of the most common of these variations in sternal ossification, asymmetric sternal centra, was significantly increased in the 20 and 40 mg/kg/day dose groups.

The average numbers of ossified tarsals were significantly reduced in a dose related manner in the 10, 20, 40 and 80 mg/kg/day dose groups, respectively. Values in the 20, 40 and 80 mg/kg/day dosage group were below the averages observed historically at the testing facility.

9.2 Embryonic Fetal Development

The sponsor conducted a dose range finding study in rabbits with CC-10004. CC-10004 was administered as a one hour intravenous infusion in doses of 5 and 50 mg/kg. All HD animals had to be sacrificed on dosing day 2 due to moribundity. All vehicle and LD animals were sacrificed on dosing day 5. The sponsor subsequently tried infusing rabbits with 15 mg/kg CC-10004 with a slower infusion rate. These rabbits became moribund and were sacrificed on dosing day 2. The results from this study indicate that conduct of the rabbit embryofetal development study by the intravenous route of administration would not be tolerated in rabbits. Previous conduct of an oral rabbit embryofetal development study did not demonstrate adequate systemic exposure to CC-10004. It appears that rabbit may not be an appropriate nonrodent model to evaluate embryofetal development effects of CC-10004. Therefore, the sponsor decided to conduct an oral monkey embryofetal development study.

Study title: Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey

Study no.:	CC-10004-TOX-013
Study report location:	Electronic
Conducting laboratory and location:	[redacted]
Date of study initiation:	December 10, 2008
GLP compliance:	Yes; draft study report
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, 59692-07, not given

Key Study Findings: Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 50, 200 or 1000 mg/kg experienced dose-related increases in fetal loss. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. A NOAEL may be determined when the final study report is submitted which will include data from a lower dose evaluated in the oral monkey embryofetal development study.

Methods

Doses:	50, 200 and 1000 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	5 mL/kg/day
Route of administration:	Oral
Formulation/Vehicle:	1.0% carboxymethylcellulose sodium salt
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	16/group
Satellite groups:	None
Study design:	Control and test articles were administered orally once daily from gestation day 20 to gestation day 50. Cesarean section was conducted on gestation day 100.
Deviation from study protocol:	None

Observations and Results

Mortality

Daily. No deaths were observed.

Clinical Signs

Daily. A dose-related increase in emesis was observed in CC-10004-treated animals.

Body Weight

Weekly. Decreased individual body weights were observed in several females that aborted. No overall mean group body weight changes were observed at termination. It is unclear if the decrease in body weights in those animals that aborted is due to the drug or a secondary effect of the abortion process.

Toxicokinetics

Gestation days 20 and 50 at 0, 1, 2.5, 5, 8, 12 and 24 hours after dosing. Data not included in this draft report.

Stability and Homogeneity

Not provided. Sponsor states it will be included in final report.

Necropsy

Gestation day 100. No treatment-related effects were observed.

Cesarean Section Data

Gestation day 100. The incidence of embryonic/fetal loss was 2 of 16 (12.5%) in group 1 (0 mg/kg/day), 6 of 16 (37.5%) in group 2 (50 mg/kg/day), 8 of 16 (50%) in group 3 (200 mg/kg/day), and 13 of 16 (81.3%) in group 4 (1000 mg/kg/day). The reference fetal loss rate at this facility is 12.9%.

On gestation day 100, fetuses were removed by cesarean section in 14 control (0 mg/kg/day), 10 group 2 (50 mg/kg/day), 8 group 3 (200 mg/kg/day), and 3 group 4 (1000 mg/kg/day) females. No treatment-related changes in fetal body weights, body measurements or placental weights were observed.

Offspring

Gestation day 100. External findings such as small tissue ball at tail end, hematoma, or not completely opened prepuces were observed in single fetuses of all groups. Adrenal size was bilaterally reduced in one single group 4 fetus (1000 mg/kg/day). Minor skeletal abnormalities were observed in all fetuses of the CC-10004-treated groups and the control group. The findings included variations in the ossification or misaligned vertebrae especially in the tail region. The type, incidence and pattern of the findings was not dose-related and was not considered by the sponsor to be related to treatment with CC-10004. Scoliosis caused by different vertebral anomalies was observed in one HD (1000 mg/kg/day) fetus. These multifactorial anomalies included hemicentric and/or asymmetrically ossified vertebrae. In addition, vertebral bodies of vertebrae 20 and 21 were misshapen and fused.

9.3 Prenatal and Postnatal Development

No new data was submitted.

10 Special Toxicology Studies

No new data was submitted.

11 Integrated Summary and Safety Evaluation

Inflammatory lesions were previously observed in mice treated with CC-10004. The sponsor conducted an additional study to determine the reversibility of these effects. Mice were orally administered CC-10004 for 3 or 14 days at a dose of 300 mg/kg/day or for 3, 14, 45 or 90 days at a dose of 1000 mg/kg/day. Inflammatory lesions were observed in multiple tissues at all terminal sacrifice timepoints; however, in those animals allowed to recover, complete recovery was noted at Day 90.

The sponsor conducted a bacterial reverse mutation assay using a formulation of CC-10004 with an increased concentration of (b) (4) Under the conditions of the assay, CC-10004 with (b) (4) was not mutagenic. The chemical identity of (b) (4) is unclear.

Fertility studies in mice were conducted by the sponsor. Male mice orally administered 1, 10, 25 or 50 mg/kg CC-10004 for 70 days before and at least 25 days after cohabitation, no changes in mating and fertility parameters were observed. Increased testes weights were observed in mice given 25 or 50 mg/kg/day CC-10004; however, no corresponding changes in histopathology were observed. The NOAEL for this study was determined to be 50 mg/kg. In female mice orally administered 10, 20, 40 or 80 mg/kg CC-10004 for 15 days before cohabitation until gestation day 15, estrous cycling was altered at the 20, 40 and 80 mg/kg/day doses. All mice were mated and pregnancy rates were unaffected. The NOAEL for female fertility was determined to be 10 mg/kg/day. The numbers of early resorptions were increased and the number of ossified tarsals were reduced in the 20, 40 and 80 mg/kg/day dose groups. Fetal body weights were reduced at 40 and 80 mg/kg/day and retarded ossification of the supraoccipital bone of the skull occurred at these doses. The maternal and developmental NOAEL was determined to be 10 mg/kg/day. Fetal plasma drug levels suggested that CC-10004 traverses the maternal blood-placental barrier in mice.

The sponsor submitted a draft study report for a developmental toxicity study conducted in cynomolgus monkeys. This draft report does not include an additional low dose group added to the study after substantial fetal loss was observed in other dose groups. Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 50, 200 or 1000 mg/kg experienced dose-related increases in fetal loss. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. A NOAEL may be determined when the final study report is submitted.

In the cover letter to SDN 155 (submitted 5/21/10), the sponsor proposed the following contraception language for planned Phase 3 clinical studies.

- Female subjects of child bearing potential (FCBP) who engage in activity in which contraception is possible must use 2 forms of contraception while on study medication and for at least 28 days after taking the last dose of study medication: one highly effective form (i.e., hormonal, intrauterine device [IUD], tubal ligation, vasectomized parter) and one additional form (condom, diaphragm, sponge). If one highly effective form of contraception cannot be used, then 2 forms of barrier contraception must be used, (i.e., condom with either of the following: sponge with spermicide or diaphragm with spermicide).

- Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (condom) while on study medication and for a least 28 days after the last dose of study medication.

The proposed wording for contraception for Phase 3 study protocols appears reasonable from a Pharmacology/Toxicology perspective. The results of the oral monkey embryofetal development study have identified an embryofetal development hazard for CC-10004 (i.e., embryofetal lethality). Due to the limited number of monkeys that can be evaluated in an oral monkey embryofetal development study, it may not be possible to identify a teratogenic signal but an increase in embryofetal lethality in an oral monkey embryofetal development study is cause for concern. Therefore, it would be prudent to incorporate appropriate birth control methods in Phase 3 clinical studies.

Appendix 10: Aug 26 2010 [redacted] (b) (4) Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
[redacted] (b) (4)	ORIG-1	CELGENE CORP	CC-10004 [redacted] (b) (4)

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

/s/

CARMEN D BOOKER
08/26/2010

BARBARA A HILL
08/26/2010
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	[redacted] (b) (4)
Supporting document/s:	166 and 169
Sponsor's letter date:	October 19, 2010 and October 28, 2010
CDER stamp date:	October 19, 2010 and October 28, 2010
Product:	Apremilast (CC-10004)
Indication:	Psoriasis
Sponsor:	Celgene Corporation
Review Division:	Dermatology and Dental Products
Reviewer:	Carmen D Booker, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Susan Walker, MD
Project Manager:	Dawn Williams

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Apremilast is a phosphodiesterase type IV inhibitor. The sponsor has completed Phase 2 studies in psoriasis patients with doses up to 30 mg bid for up to 12 weeks. The sponsor is preparing a Phase 3 protocol for evaluation. A Type A guidance meeting is being conducted with the sponsor on December 8, 2010.

1.2 Brief Discussion of Nonclinical Findings

Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 50, 200 or 1000 mg/kg experienced dose-related increases in fetal loss. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. An additional dosing group of 20 mg/kg was added to the study and determined to be the NOAEL.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

1.3.2 If Not Safe to Proceed

N/A

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor)

The following pharm/tox comment will be included in the Agency's responses for the Type A meeting on December 8, 2010.

While the Agency agrees that the NOAEL for the monkey embryofetal development study is 20 mg/kg/day, we do not agree with your statement that "there were no test-related malformations detected at any dose". Fetuses lost before cesarean section were not evaluated for malformations; therefore, it is impossible to know if teratogenicity was present in those fetuses.

2 Drug Information

2.1 Drug

CAS Registry Number: 608141-41-9

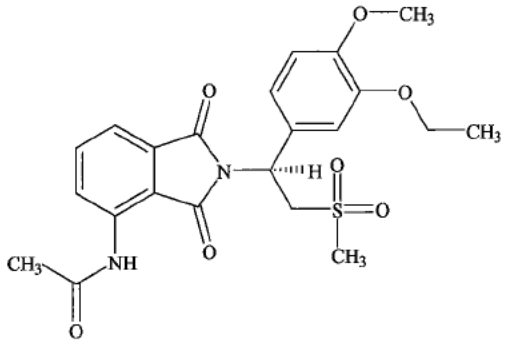
Generic Name: Apremilast

Code Name: CC-10004

Chemical Name: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]

Molecular Formula/Molecular Weight: $C_{22}H_{24}N_2O_7S$ / 460.5

Structure



Pharmacologic Class: Phosphodiesterase type IV inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

INDs [redacted]

2.3 Drug Formulation

White [redacted] containing the following ingredients: CC-10004 (10 mg), [redacted] microcrystalline cellulose [redacted] lactose [redacted] monohydrate [redacted] croscarmellose sodium [redacted] and magnesium stearate [redacted]

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Protocol

The sponsor's proposed clinical population is patients with psoriasis. The sponsor has completed Phase II studies [redacted]

2.7 Previous Clinical Experience

Phase 2 clinical studies have been conducted with up to 30 mg b.i.d for 12 weeks.

2.8 Regulatory Background

The sponsor has completed Phase 2 clinical studies. At an end of Phase 2 meeting on May 12, 2010 the sponsor asked if an audited draft report of their embryofetal development study in cynomolgus monkeys could be submitted before the final draft was available so that they could proceed to Phase 3 studies. The Agency agreed that an audited draft report could be submitted provided that individual animal data was included and that each dose group contained an adequate number of pups for

assessment. The sponsor initially submitted the draft report and has now submitted the final report for the monkey embryofetal study.

3 Studies Submitted

3.1 Studies Reviewed

SD 169: Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey. Study Number CC-10004-TOX-013. March 2010.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Apremilast is a phosphodiesterase type IV inhibitor and has been shown to inhibit the production of TNF-α, IL-6, IL-8, IL-17, IL-23 and IFN-γ. It also inhibits neutrophil infiltration.

4.2 Secondary Pharmacology

No new data was submitted.

4.3 Safety Pharmacology

Behavioral effects of a single oral dose of CC-10004 at doses up to 2000 mg/kg were evaluated in male CD-1 mice. The NOAEL was determined to be 500 mg/kg. Higher doses produced minor effects including lacrimation, ptosis and apathy.

The cardiovascular and pulmonary effects of CC-10004 were evaluated after single intravenous dose administration at doses up to 5 mg/kg in anesthetized dogs. CC-10004 induced a dose related increase in blood pressure and heart rate. Corrected QT interval was not affected in this study. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in this study.

CC-10004 appears to be a very low potency inhibitor of the hERG channel with an IC_{50} of 184.2 μM. The mean maximum inhibition produced by CC-10004 was 59.0% and occurred at the high dose of 249.7 μM.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new data was submitted.

5.2 Toxicokinetics

See toxicology study summary.

6 General Toxicology

6.1 Single-Dose Toxicity

No new data was submitted.

6.2 Repeat-Dose Toxicity

No new data was submitted.

7 Genetic Toxicology

Previously the sponsor had submitted an Ames assay study report in which CC-10004 with [redacted] was evaluated. The results of the study were negative; however, the chemical identity of [redacted] was not clear. In SD 166, the sponsor clarified that [redacted] is a process impurity that had been detected in their product at levels of up to [redacted] The sponsor states that [redacted] is now controlled at [redacted] in accordance with ICH Q3A. The chemical name and structure below were copied from the sponsor's electronic submission.

[redacted]

[redacted]

8 Carcinogenicity

No new data was submitted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Male mice orally administered 1, 10, 25 or 50 mg/kg CC-10004 for 70 days before and at least 25 days after cohabitation, no changes in mating and fertility parameters were observed. Increased testes weights were observed in mice given 25 or 50 mg/kg/day CC-10004; however, no corresponding changes in histopathology were observed. The NOAEL for this study was determined to be 50 mg/kg.

In female mice orally administered 10, 20, 40 or 80 mg/kg CC-10004 for 15 days before cohabitation until gestation day 15, estrous cycling was altered at the 20, 40 and 80 mg/kg/day doses. All mice were mated and pregnancy rates were unaffected. The NOAEL for female fertility was determined to be 10 mg/kg/day. The numbers of early resorptions were increased and the number of ossified tarsals were reduced in the 20, 40 and 80 mg/kg/day dose groups. Fetal body weights were reduced at 40 and 80 mg/kg/day and retarded ossification of the supraoccipital bone of the skull occurred at these doses. The maternal and developmental NOAEL was determined to be 10 mg/kg/day. Fetal plasma drug levels suggested that CC-10004 traverses the maternal blood-placental barrier in mice.

9.2 Embryonic Fetal Development

The sponsor conducted a dose range finding study in rabbits with CC-10004. CC-10004 was administered as a one hour intravenous infusion in doses of 5 and 50 mg/kg. All HD animals had to be sacrificed on dosing day 2 due to moribundity. All vehicle and LD animals were sacrificed on dosing day 5. The sponsor subsequently tried infusing rabbits with 15 mg/kg CC-10004 with a slower infusion rate. These rabbits became moribund and were sacrificed on dosing day 2. The results from this study indicate that conduct of the rabbit embryofetal development study by the intravenous route of administration would not be tolerated in rabbits. Previous conduct of an oral rabbit embryofetal development study did not demonstrate adequate systemic exposure to CC-10004. It appears that rabbit may not be an appropriate nonrodent model to evaluate embryofetal development effects of CC-10004. Therefore, the sponsor decided to conduct an oral monkey embryofetal development study.

Study title: Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey

Study no.:	CC-10004-TOX-013
Study report location:	Electronic
Conducting laboratory and location:	[redacted]
Date of study initiation:	December 10, 2008
GLP compliance:	Yes; draft study report
QA statement:	Yes
Drug, lot #, and % purity:	CC-10004, 59692-07, 99.6%

Key Study Findings: Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 50, 200 or 1000 mg/kg experienced dose-related increases in fetal loss. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. An additional dose group of 20 mg/kg/day was added. No fetal loss or abnormalities were observed in the 20 mg/kg/day group; therefore, the NOAEL for this study was 20 mg/kg/day.

Methods

Doses:	20, 50, 200 and 1000 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	5 mL/kg/day
Route of administration:	Oral
Formulation/Vehicle:	1.0% carboxymethylcellulose sodium salt
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	16/group
Satellite groups:	None
Study design:	Control and test articles were administered orally once daily from gestation day 20 to gestation day 50. Cesarean section was conducted on gestation day 100.
Deviation from study protocol:	Due to an increase in prenatal loss at 50, 200 and 1000 mg/kg/day an additional dose group of 20 mg/kg was added to the study after it had already begun.

Observations and Results

Mortality

Daily. No deaths were observed.

Clinical Signs

Daily. A dose-related increase in emesis was observed in CC-10004-treated animals.

Body Weight

Weekly. Decreased individual body weights were observed in several females that aborted. No overall mean group body weight changes were observed at termination. It is unclear if the decrease in body weights in those animals that aborted is due to the drug or a secondary effect of the abortion process.

Toxicokinetics

Gestation days 20 and 50 at 0, 1, 2.5, 5, 8, 12 and 24 hours after dosing. Exposure increased in a less than dose-proportional manner. No significant time-dependent changes were observed except at the high dose where a 2.8-fold increase in AUC was observed. The ratios of fetal to maternal apremilast concentrations at the time of cesarean section were between 0.3 and 0.4. The following table was copied from the sponsor's electronic submission.

The mean toxicokinetic parameters are provided in the following table:

	Group (Dosage)			
	Group 5 (20 mg/kg/day)	**Group 2 (50 mg/kg/day)**	**Group 3 (200 mg/kg/day)**	**Group 4 (1000 mg/kg/day)**
	Gestation Day 20			
C_{max} (ng/mL)	971	1140	2050	1780
AUC_τ (ng·hr/mL)	11700	14700	29200	25700
	Gestation Day 50			
C_{max} (ng/mL)	1390	1950	3020	4400
AUC_τ (ng·hr/mL)	10100	15400	33700	62400
	Gestation Day 100 ± 1[a]			
Maternal Conc. (ng/mL)	650	748	421	429
Fetal Conc. (ng/mL)	176	253	165	130
Fetal: Maternal Conc. Ratio	0.3	0.4	0.4	0.4

[a] Samples collected at 5 hours after dosing on Gestation Day 100 ± 1.

Abbreviations: AUC_τ = Area under the curve from the time of dosing (time zero) to the last quantifiable concentration; C_{max} = maximum plasma concentration

C_{max}, AUC_τ and plasma concentrations are shown to 3 significant figures.

Dosing Solution Analysis

Mean values of all analyzed formulations met the acceptance criteria for concentration and homogeneity.

Necropsy

Gestation day 100. No treatment-related effects were observed.

Cesarean Section Data

Gestation day 100. The incidence of embryonic/fetal loss was 3 of 20 (15%) in group 1 (0 mg/kg/day), 6 of 16 (37.5%) in group 2 (50 mg/kg/day), 8 of 16 (50%) in group 3 (200 mg/kg/day), 13 of 16 (81.3%) in group 4 (1000 mg/kg/day) and 2 of 16 (12.5%) in group 5 (20 mg/kg). The reference fetal loss rate at this facility is 12.9%. The sponsor states that at this facility prenatal loss rates of 10-30% were observed in about 50% of studies and prenatal loss rates of 0% or more than 45% occurred in 5% of studies. Following table copied from the sponsor's electronic submission.

Table 3: Percentage of Pre-Natal Loss

Group number	Group description	Dose level (mg/kg/day)	Percentage of pre-natal loss (%)
1	control	0	15
2	low 2	50	37.5
3	intermediate	200	50.0
4	high	1000	81.3
5	low 1	20	12.5

On gestation day 100, fetuses were removed by cesarean section in 14 control (0 mg/kg/day), 10 group 2 (50 mg/kg/day), 8 group 3 (200 mg/kg/day), and 3 group 4 (1000 mg/kg/day) females. No treatment-related changes in fetal body weights, body measurements or placental weights were observed. A dose-related increased incidence of emesis occurred at doses of 200 and 1000 mg/kg/day.

Offspring

On GD 100 ± 1, fetuses were removed by cesarean-section in 17/20 control (0 mg/kg/day), 10/16 Group 2 (50 mg/kg/day), 8/16 Group 3 (200 mg/kg/day), 3/16 Group 4 (1000 mg/kg/day), and 14/16 Group 5 (20 mg/kg/day) females. External findings such as small tissue ball at tail end, hematoma, or not completely opened prepuces were observed in single fetuses of all groups. Adrenal size was bilaterally reduced in one single group 4 fetus (1000 mg/kg/day). Minor skeletal abnormalities were observed in all fetuses of the CC-10004-treated groups and the control group. The findings included variations in the ossification or misaligned vertebrae especially in the tail region. The type, incidence and pattern of the findings was not dose-related and was not considered by the sponsor to be related to treatment with CC-10004. Scoliosis caused by different vertebral anomalies was observed in one HD (1000 mg/kg/day) fetus. These multifactorial anomalies included hemicentric and/or asymmetrically ossified vertebrae. In addition, vertebral bodies of vertebrae 20 and 21 were misshapen and fused.

The sponsor states in their report that no signs of teratogenicity were observed at doses up to 1000 mg/kg/day. This statement is misleading in that lost fetuses were not evaluated for teratogenicity; therefore, it is unknown if there was teratogenicity present at those doses.

The NOAEL for this study was 20 mg/kg/day. Mean C_{max} and AUC_t at this dose were 1390 ng/mL and 10100 ng-hr/mL, respectively.

9.3 Prenatal and Postnatal Development

No new data was submitted

10 Special Toxicology Studies

No new data was submitted.

11 Integrated Summary and Safety Evaluation

Pregnant cynomolgus monkeys orally administered CC-10004 at doses of 20, 50, 200 or 1000 mg/kg from gestation day 20 to gestation day 50 experienced dose-related increases in fetal loss at doses of 50 mg/kg/day and higher. In those fetuses delivered by c-section, a variety of fetal abnormalities were observed; however, none appeared to be dose-related. An effect on maternal body weight was observed in several females that aborted. In the fetuses evaluated, no external, visceral or skeletal examinations revealed treatment-related findings. The NOAEL for this study is 20 mg/kg/day. The sponsor states that this NOAEL is 1.5-fold the therapeutic systemic exposures attained following 30 mg BID apremilast administration to psoriasis patients.

A type A guidance meeting has been scheduled with the sponsor on December 8, 2010. In the briefing document for this meeting, the sponsor proposes the following birth control measures be used for phase 3.

- Females of child bearing potential (FCBP) must use one highly effective contraception method (IUD, hormonal, tubal ligation or partner's vasectomy) or two effective forms of contraception (male condom, diaphragm, cervical cap or vaginal contraceptive ring).

- Male subjects must use one form of contraception.

The sponsor has also proposed that apremilast be classified as Pregnancy Category C.

The adequacy of the proposed contraception for Phase 3 is a clinical decision. The results of the oral monkey embryofetal development study have identified an embryofetal development hazard for CC-10004 (i.e., embryofetal lethality). Due to the limited number of monkeys that can be evaluated in an oral monkey embryofetal development study, it may not be possible to identify a teratogenic signal but an increase in embryofetal lethality in an oral monkey embryofetal development study is cause for concern. It would be prudent to incorporate appropriate birth control methods in Phase 3 clinical studies. Pregnancy Category C appears to be appropriate for this drug product.

The following pharm/tox comment will be included in the Agency's responses for the Type A meeting on December 8, 2010.

While the Agency agrees that the NOAEL for the monkey embryofetal development study is 20 mg/kg/day, we do not agree with your statement that "there were no test-related malformations detected at any dose". Fetuses lost before cesarean section were not evaluated for malformations; therefore, it is impossible to know if teratogenicity was present in those fetuses.

12 Appendix/Attachments

None

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

/s/

CARMEN D BOOKER
11/23/2010

BARBARA A HILL
11/24/2010
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	(b) (4)
Supporting document/s:	180
Sponsor's letter date:	January 14, 2011
CDER stamp date:	January 18, 2011
Product:	Apremilast (CC-10004)
Indication:	Psoriasis
Sponsor:	Celgene Corporation
Review Division:	Dermatology and Dental Products
Reviewer:	Carmen D Booker, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Susan Walker, MD
Project Manager:	Dawn Williams

Template Version: September 1, 2010

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Apremilast is a phosphodiesterase type IV inhibitor. The sponsor has completed Phase 2 studies in psoriasis patients with doses up to 30 mg bid for up to 12 weeks. The sponsor is preparing a Phase 3 protocol for evaluation.

1.2 Brief Discussion of Nonclinical Findings

Cotreatment of apremilast and methotrexate provided only a modest therapeutic benefit in a human NK cell-driven model of psoriasis utilizing human skin xenotransplanted onto immunodeficient mice.

Apremilast metabolite M14 (N-deacetylated O-desmethylated glucuronide) was 40,000-fold less potent than apremilast at inhibiting PDE4. Compared with apremilast, the M14 metabolite was relatively inactive for the inhibition of TNF-α production.

In synovial fibroblasts stimulated with IL-1, IL-6 and IL-6R, apremilast significantly inhibited IL-7 gene expression, while methotrexate, etanercept, and prednisone had no significant effect. In stimulated RA synovial fibroblasts, apremilast in combination with etanercept and methotrexate significantly inhibited IL-7 expression more than apremilast treatment alone. The combination of apremilast with prednisone enhanced IL-7 expression compared with apremilast alone.

Apremilast inhibited IFN-α and TNF-α protein production at 0.25, 0.5, and 1 μM as measured from the culture supernatants. Apremilast significantly inhibited HEKa intracellular MxA protein expression at 0.25 - 1 μM.

The effect of apremilast on the gout-like inflammation and gouty-like peritonitis models in mice was evaluated. No significant anti-inflammatory effects were observed.

Apremilast is present in the milk of lactating mice following a single oral dose of 10 mg/kg.

CC-10004 did not inhibit ATP-dependent BCRP, MRP1, MRP2, and MRP4 mediated transport. Although CC-10004 exhibited inhibition of MRP3 mediated transport, 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.

In vitro, apremilast does not significantly inhibit CYP2A6 or CYP2B6 activity. CC-10004 does inhibit CYP2C8-catalyzed paclitaxel 6a-hydroxylation with an estimated IC_{50} value of 56.1 μM.

CC-10004 did not inhibit OATP1B3-mediated uptake of [^{3}H]-estradiol glucuronide nor OCT2-mediated uptake of [^{14}C]-tetraethylammonium bromide. CC-10004 (20 μmol/L)

did show slight inhibition (approximately 26%) of OATP1B1-mediated uptake of [^{3}H]-estradiol glucuronide.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

1.3.2 If Not Safe to Proceed

N/A

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor)

None.

2 Drug Information

2.1 Drug

CAS Registry Number: 608141-41-9

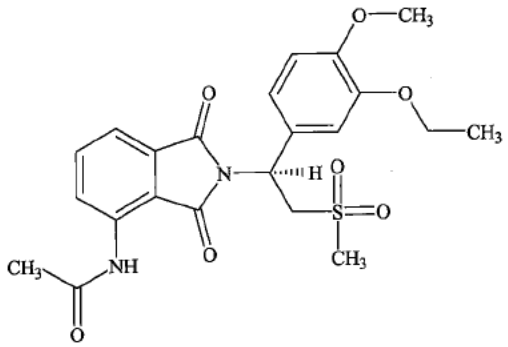
Generic Name: Apremilast

Code Name: CC-10004

Chemical Name: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]

Molecular Formula/Molecular Weight: $C_{22}H_{24}N_2O_7S$ / 460.5

Structure



Pharmacologic Class: Phosphodiesterase type IV inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

INDs (b) (4)

2.3 Drug Formulation

White [redacted] containing the following ingredients:CC-10004 (10 mg), [redacted] microcrystalline cellulose [redacted] lactose [redacted] monohydrate [redacted] croscarmellose sodium [redacted] and magnesium stearate [redacted]

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Protocol

The sponsor's proposed clinical population is patients with psoriasis. The sponsor has completed Phase II studies and is preparing to draft their Phase III protocol.

2.7 Previous Clinical Experience

Phase 2 clinical studies have been conducted with up to 30 mg b.i.d for 12 weeks.

2.8 Regulatory Background

The sponsor has completed Phase 2 clinical studies.

The following comment was relayed to the sponsor during a Type A meeting on December 8, 2010.

While the Agency agrees that the NOAEL for the monkey embryofetal development study is 20 mg/kg/day, we do not agree with your statement that "there were no test-related malformations detected at any dose". Fetuses lost before cesarean section were not evaluated for malformations; therefore, it is impossible to know if teratogenicity was present in those fetuses.

3 Studies Submitted

3.1 Studies Reviewed

Effect of PDE4 Inhibitors CC-11050 and Apremilast and JNK Inhibitor CC-930 on Type I Interferon Pathophysiology in Cellular Models of Cutaneous Lupus. Study Number 3252-910. September 2010.

Phosphodiesterase 4 and Tumor Necrosis Factor-alpha Inhibitory Activity of CC-10004 (Apremilast) Metabolite M14 (N-deacetylated O-desmethylated glucuronide). Study Number 5638-96. February 2010.

In Vitro Effects of CC-10004 and CC-11050 alone and in Combination with Anti-Rheumatic Agents on Synovial Markers in Primary Chondrocytes and Rheumatoid Arthritis Synovial Fibroblasts. Study Number 5673-140. March 2010.

Evaluation of Two Testing Items, CC-10004 and CC-11050 in the Air Pouch Gout-Like Inflammation Model in Mice. Study Number MD-2-2-005-1168. January 2010.

Evaluation of Two Testing Items, CC-10004 and CC-11050 in the Gout-Like Peritonitis Model in Mice. Study Number MD-2-2-005-1169. January 2010.

Treatment of Psoriasiform with Methotrexate in Combination with Apremilast. Study Number TECH10282009. December 2009.

Determination of Lacteal Transfer of CC-10004 following a Single Oral Dose to Lactating CD-1 Mice. Study Number CC-10004-DMPK-034. February 2010.

In Vitro Assessment of Inhibition Potential of CC-10004 for Efflux Transporters. Study Number CC-10004-DMPK-036. May 2010.

In Vitro Evaluation of CC-1004 as an Inhibitor of Human Cytochrome P450 Enzymes CYP2A6, CYP2B6 and CYP2C8. Study Number CC-10004-DMPK-039. April 2010.

CC-10004: Inhibition Potential in OCT2, OATP1B1 and OATP1B3 expressing HEK293 cells. Study Number CC-10004-DMPK-040. December 2010.

3.2 Studies Not Reviewed

A 104-Week Oral Carcinogenicity Study of CC-10004 in Mice. Study Number CC-10004-TOX-006. August 2010.

CC-10004: A 104-Week oral Carcinogenicity Study in Rats. Study Number CC-10004-TOX-007. November 2010.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

Apremilast is a phosphodiesterase type IV inhibitor and has been shown to inhibit the production of TNF-α, IL-6, IL-8, IL-17, IL-23 and IFN-γ. It also inhibits neutrophil infiltration.

4.2 Secondary Pharmacology

No new data submitted.

4.3 Safety Pharmacology

The sponsor conducted a study in a human NK cell-driven model of psoriasis utilizing human skin xenotransplanted onto immunodeficient mice to assess the benefit of cotreatment of apremilast with methotrexate. Only a modest therapeutic effect was observed in 2 out of 5 mice.

The sponsor conducted a study to assess the PDE4 enzyme activity and TNF-α production following exposure to the apremilast metabolite M14 (N-deacetylated O-desmethylated glucuronide). In the PDE4 enzyme assay, the M14 metabolite showed significant 22% inhibition at 80 μM (IC_{50} > 80 μM) compared with untreated controls (approximately 40,000-fold less potent than apremilast). For the LPS-stimulated PBMC TNF-α production assay, the M14 metabolite displayed minimal but significant inhibition of TNF-α production of approximately 8% - 13% between the 0.001 - 10 μM concentrations (IC_{50} > 10 μM), compared with untreated controls. Compared with apremilast, the M14 metabolite was relatively inactive for the inhibition of TNF-α production.

In synovial fibroblasts stimulated with IL-1, IL-6 and IL-6R, apremilast and CC-11050 significantly inhibited IL-7 gene expression in a dose-dependent manner within the concentration range of 0.1 - 10 μM, while methotrexate, etanercept, and prednisone had no significant effect. Also in stimulated RA synovial fibroblasts, apremilast in combination with etanercept and methotrexate significantly inhibited IL-7 expression greater than apremilast treatment alone. Also, CC-11050 in combination with etanercept, but not methotrexate significantly inhibited IL-7 expression greater than CC-11050 treatment alone. In contrast, the combination of apremilast or CC-11050 with prednisone enhanced IL-7 expression compared with apremilast or CC-11050 treatment alone. In primary human normal chondrocytes stimulated with IL-1, IL-6 and IL-6R, apremilast slightly inhibited intercellular adhesion molecule 1 (ICAM-1) and alpha-v-beta-3 (αvβ3) integrin expression in a dose-dependent manner (not statistically significant). Similarly, apremilast also showed a trend toward inhibition of CXCL8/IL-8 expression, MMP-3 expression and pro-MMP-13 expression in the stimulated primary human normal chondrocytes (did not reach significance).

CC-11050 and apremilast, at their approximate C_{max} concentration of 0.5 μM, showed significant inhibition of CXCL9, CXCL10, and CXCL11 chemokine gene expression. CC-930 showed inhibitory effects on CXCL9, CXCL10, and CXCL11 chemokines at the 10 μM concentration. CC-11050 inhibited STAT1 at 0.5 μM and at 5 μM inhibited the genes LY6E, OAS1, and OASL. CC-930 inhibited gene expression of STAT1, LY6E, OAS1, and OASL at 10 μM. In a second set of pDC/HEKa coculture experiments, CC-11050 and apremilast inhibited IFN-α and TNF-α protein production at 0.25, 0.5, and 1 μM as measured from the culture supernatants. Apremilast significantly inhibited HEKa intracellular MxA protein expression at 0.25 - 1 μM.

The effect of apremilast on the gout-like inflammation and gouty-like peritonitis models in mice was evaluated. No significant anti-inflammatory effects were observed.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Lacteal transfer of apremilast following a single oral dose was evaluated in lactating mice. Apremilast (10 mg/kg) was administered to 15 lactating CD-1 mice. Milk and plasma were collected at approximately 1, 6 and 24 hours post-dose. Following a single oral dose, the peak average concentration of CC-10004 occurred at 1 h postdose, and were 984 and 1441 ng/mL in plasma and milk, respectively. The average concentrations of CC-10004 declined rapidly to 138 ng/mL and 186 ng/mL at 6 h in plasma and milk, respectively, and the concentrations were below the limit of quantitation (3 ng/mL) by 24 h post-dose. The average milk to plasma concentration ratios were 1.46 and 1.62 at 1 and 6 h postdose, respectively. This data indicates that apremilast does partition into milk.

The ability of apremilast to inhibit transport of transporter-selective substrates in membrane vesicles was evaluated by the sponsor. CC-10004 did not inhibit ATP-dependent BCRP, MRP1, MRP2, and MRP4 mediated transport at concentrations of 2 or 20 µM. Although CC-10004 exhibited inhibition of MRP3 mediated transport, the inhibition was not concentration-dependent 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.

In vitro, apremilast does not significantly inhibit CYP2A6 or CYP2B6 activity. CC-10004 does inhibit CYP2C8-catalyzed paclitaxel 6a-hydroxylation with an estimated IC_{50} value of 56.1 µM.

A study was conducted to assess the inhibition potential of apremilast (2 and 20 µmol/L) using OCT2, OATP1B1 and OATP1B3 expressing cells. CC-10004 did not inhibit OATP1B3-mediated uptake of [^{3}H]-estradiol glucuronide nor OCT2-mediated uptake of [^{14}C]-tetraethylammonium bromide. CC-10004 (20 µmol/L) did show slight inhibition (approximately 26%) of OATP1B1-mediated uptake of [^{3}H]-estradiol glucuronide.

5.2 Toxicokinetics

No new data submitted.

6 General Toxicology

6.1 Single-Dose Toxicity

No new data submitted.

6.2 Repeat-Dose Toxicity

No new data submitted.

7 Genetic Toxicology

No new data submitted.

8 Carcinogenicity

Two carcinogenicity study reports were submitted with this supporting document. These studies will be reviewed when the NDA for this product is submitted.

9 Reproductive and Developmental Toxicology

No new data submitted.

10 Special Toxicology Studies

No new data submitted.

11 Integrated Summary and Safety Evaluation

The sponsor submitted several new pharmacology and pharmacokinetic study reports. Cotreatment of apremilast and methotrexate provided only a modest therapeutic benefit in a human NK cell-driven model of psoriasis utilizing human skin xenotransplanted onto immunodeficient mice.

Apremilast metabolite M14 (N-deacetylated O-desmethylated glucuronide) was 40,000-fold less potent than apremilast at inhibiting PDE4. Compared with apremilast, the M14 metabolite was relatively inactive for the inhibition of TNF-α production.

In synovial fibroblasts stimulated with IL-1, IL-6 and IL-6R, apremilast significantly inhibited IL-7 gene expression, while methotrexate, etanercept, and prednisone had no significant effect. In stimulated RA synovial fibroblasts, apremilast in combination with etanercept and methotrexate significantly inhibited IL-7 expression more than apremilast treatment alone. The combination of apremilast with prednisone enhanced IL-7 expression compared with apremilast alone.

Apremilast inhibited IFN-α and TNF-α protein production at 0.25, 0.5, and 1 μM as measured from the culture supernatants. Apremilast significantly inhibited HEKa intracellular MxA protein expression at 0.25 - 1 μM.

The effect of apremilast on the gout-like inflammation and gouty-like peritonitis models in mice was evaluated. No significant anti-inflammatory effects were observed.

Apremilast is present in the milk of lactating mice following a single oral dose of 10 mg/kg.

CC-10004 did not inhibit ATP-dependent BCRP, MRP1, MRP2, and MRP4 mediated transport. Although CC-10004 exhibited inhibition of MRP3 mediated transport, 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.

In vitro, apremilast does not significantly inhibit CYP2A6 or CYP2B6 activity. CC-10004 does inhibit CYP2C8-catalyzed paclitaxel 6a-hydroxylation with an estimated IC_{50} value of 56.1 µM.

CC-10004 did not inhibit OATP1B3-mediated uptake of [^{3}H]-estradiol glucuronide nor OCT2-mediated uptake of [^{14}C]-tetraethylammonium bromide. CC-10004 (20 µmol/L) did show slight inhibition (approximately 26%) of OATP1B1-mediated uptake of [^{3}H]-estradiol glucuronide.

Pharm/tox has no new concerns based on this new data and still believes the proposed clinical study is safe to proceed.

12 Appendix/Attachments

None.

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/s/

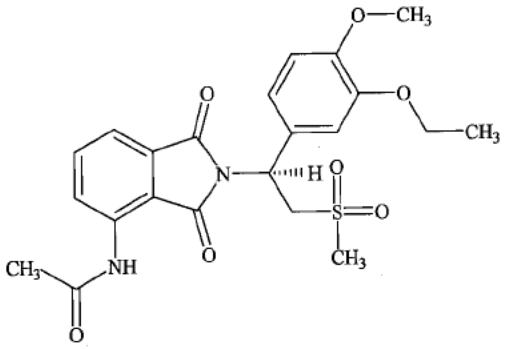
CARMEN D BOOKER
05/13/2011

BARBARA A HILL
05/13/2011

Memorandum
To: [redacted]
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date: March 7, 2012
SDN: 242
Submission type: Nonclinical study reports
Drug: Apremilast (CC-10004)
Molecular formula: $C_{22}H_{24}N_2O_7S$
Molecular weight: 460.5
Structure:



Drug class: Phosphodiesterase type IV (PDE4) inhibitor
Indication: Psoriasis
Route: Oral
Sponsor: Celgene Corporation, Summit, NJ

Review date: April 4, 2012

Drug formulation:

White [redacted] containing the following ingredients: CC-10004 (10 mg), [redacted] microcrystalline cellulose [redacted] lactose [redacted] monohydrate [redacted] croscarmellose sodium [redacted] and magnesium stearate [redacted]

Introduction:

Apremilast is a PDE4 inhibitor and has been shown to inhibit the production of TNF-α, IL-6, IL-8, IL-17, IL-23 and IFN-γ. Apremilast also inhibits neutrophil infiltration. The sponsor is developing apremilast [redacted] for the treatment of psoriasis.

This submission contains three nonclinical study reports which are listed in the table below. These nonclinical studies are reviewed in this document.

Study Number	Study Title
MD-3-2-005-1220	Evaluation of the Effect of Apremilast Treatment on the TH-17 Cells in the Murine Model of Collagen Induced Arthritis
CC-10004-DMPK-038	In Vitro Metabolism of CC-10004 in Adult and Juvenile Human Cryopreserved Hepatocytes, Human Microsomes and CD-1 Mouse Microsomes
CC-10004-TOX-014	Two-Week Oral (Gavage) Dosage Range Finding Repeated-dose Toxicity Study of CC-10004 in Neonatal Mice

Previous clinical experience:

Two Phase 3 clinical studies are currently active, CC-10004-PSOR-008 and CC-1004-PSOR-009. The Phase 3 clinical studies will evaluate the clinical efficacy and safety of apremilast 30 mg BID compared to placebo in adult subjects (≥18 years) with moderate to severe plaque psoriasis. The placebo controlled period is 16 weeks (primary efficacy time point). Randomized withdrawal period is week 32 – 52 with a long-term extension of up to an additional 4 years.

Proposed clinical studies: No clinical protocol was included in this submission.

Review of submitted nonclinical toxicology study information:

Study 1 – Evaluation of the effect of apremilast treatment on the TH-17 cells in the murine model of collagen induced arthritis (Study Number MD-3-2-005-1220)

The objective of this study was to determine the effect of 10 mg/kg Apremilast on TH-17 cells in the collagen induced murine arthritis model. Apremilast did not significantly inhibit arthritis in this mouse arthritis model. Some minor reductions in mean total score, fore paw and rear paw score and rear paw measurements were observed over the course of the study. Treatment with apremilast did not significantly alter the percentage of IL-17 producing cells present in inguinal lymph nodes *ex vivo* or after a 5 day culture with bovine type II collagen. Apremilast treatment did result in significantly increased levels of IFNγ in the serum on study day 14 and significantly increased IL-6 on days 14 and 28, but no significant differences on cytokine mRNA expression were noted in the joints.

Study 2 – In vitro metabolism of CC-1004 in adult and juvenile human cryopreserved hepatocytes, human microsomes and CD-1 mouse microsomes (Study Number CC-10004-DMPK-038)

The objective of this study was to investigate the in vitro comparative metabolic profiles of [^{14}C]-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.

[^{14}C]-CC-10004 was hydrolyzed in control incubations without microsomes or hepatocytes to produce M1 and M2 (hydrolysis products), as well as M18 (3-acetamidephthalic acid). 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) (refer to table 1 below, copied from submission). 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. In adult and juvenile mouse liver microsomes there were no notable differences between the profiles generated, except for M7, which was formed by adult to a very minor extent.

Table 1: Percent Distribution of Radioactive Metabolites from Incubations of [^{14}C]-CC-10004 (10 µM) with Human and Mouse Liver Microsomes and Human Hepatocytes

Metabolite ID (RT, min)	Biotransformation	Matrix Incubated with [^{14}C]-CC-10004: Percent of Metabolite Formed							
		Human Hepatocytes			Human Liver Microsomes			Mouse Liver Microsomes	
		Adult	Juvenile male	Juvenile female	Adult	Juvenile male (average, 6/10 yr)	Juvenile female (average 7/10 yr)	Adult	Juvenile male
CC-10004 (65.5)	Parent	34	66	45	83	86	75	88	87
M1/M2 (38.5)	Hydrolysis product of CC-10004	8.7	12	12	3.5	2.8	4.2	5.5	4.0
M1/M2 (42.1)	Hydrolysis product of CC-10004	6.1	7.4	7.5	2.6	1.8	2.6	3.6	2.6
M3 (58.4)	*O*-Demethylated	3.7	1.9	8.0	2.5	3.9	3.1	ND	ND
M7 (64.3)	*N*-Deacetylated	[1]ND	ND	ND	0.3	ND	0.20	0.8	ND
M11 (54.4)	Hydroxylated *N*-deacetylated	1.1	ND	1.1	0.4	0.3	0.70	0.2	0.80
M12 (44.1)	*O*-Demethylated glucuronide	31	6.9	19	5.7	3.7	11	1.8	4.6
M13 (43.2)	*O*-Deethylated glucuronide	3.7	1.2	1.4	0.50	0.20	0.80	ND	0.70
M14 (43.0)	*N*-Deacetylated *O*-demethylated glucuronide								
M15 (22.7)	Hydrolysis product of *O*-demethylated glucuronide	4.4	1.4	2.1	0.30	0.10	0.90	ND	ND
M17 (60.4)	Hydroxylated acetamide	2.7	1.1	2.2	0.80	0.70	1.3	ND	ND
M18 (17.6)	3-Acetamide-phthalic acid	4.8	2.3	2.8	0.50	0.40	2.0	0.60	0.80

[1] ND = not detected

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

Study 3 – Two week oral (gavage) dosage range finding repeated-dose toxicity study of CC-10004 in neonatal mice (Study Number CC-10004-TOX-014)

The purpose of this study was to determine the tolerability of CC-10004 administered by oral gavage for up to 14 days to neonatal through juvenile Crl:CD1(ICR) mice beginning on postpartum day (PPD) 7.

Oral (gavage) doses of 0 (1% carboxymethylcellulose), 10, 100, and 1000 mg/kg/day CC-10004 (batch number 82633-09) were administered to neonatal male and female Crl:CD1(ICR) mice (8/sex/group) on PPD 7 through 20.

The following treatment related effects were noted in this study.

- Mortality occurred in 2 male pups at 10 mg/kg/day on PPD 9 and 10. The remaining 6 males and all 8 female pups at this dose survived to scheduled necropsy. Mortality occurred in 7 males and 7 females at 100 mg/kg/day and in all pups at 1000 mg/kg/day on PPD 9 to 12.

- Clinical signs at 10 mg/kg/day included dehydration (males and females) and thin appearance (females only). Dehydration, thin body condition, cold to touch, and decreased motor activity occurred in males and females at 100 and 1000 mg/kg/day.

- Body weight gain in the 10 mg/kg/day dose group was reduced after the first two doses (PPD 7 to 8 and 8 to 9) and then was generally comparable to control group values after PPD 10. The surviving pups in the 100 mg/kg/day dose group tended to gain weight after PPD 10. Consistent body weight loss prior to death occurred in the 1000 mg/kg/day group.

- Average body weights for males and females on PPD 21 were 8% and 17% below control, respectively, at 10 mg/kg/day and 46% and 43% below control, respectively, at 100 mg/kg/day.

No treatment related effects on macroscopic parameters were noted during the necropsy.

A dose dependent increase in toxicity (i.e., increased mortality, increased clinical signs and decreased body weight/body weight gain) was elicited in this study. A NOAEL was not established in this study.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The nonclinical study reports included in this submission provide additional nonclinical information concerning the pharmacology, pharmacokinetics and toxicology of apremilast. This review serves to document the submission of these nonclinical studies. No regulatory action is indicated for this submission.

External comments (to sponsor): None at this time.

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/s/

BARBARA A HILL
04/04/2012

Executive CAC
Date of Meeting: September 26, 2006

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Joseph Contrera, Ph.D., OPS, Member
C. Joseph Sun, Ph.D., DPAP, Alternate Member
Paul Brown, Ph.D., DDDP, Pharm Tox Supervisor
Barbara Hill, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND# (b) (4)
Drug Name: CC-10004 (b) (4)
Sponsor: Celgene Corporation, Summit, NJ

Background:

CC-10004 is a phosphodiesterase type IV (PDE4) inhibitor. The sponsor is developing CC-10004 (b) (4) for the treatment of psoriasis. An oral rat carcinogenicity study protocol and an oral mouse carcinogenicity study protocol, along with supporting dose range finding studies, were submitted to the IND with a request for Special Protocol Assessment.

Oral (Gavage) Rat Carcinogenicity Study Protocol and Dose Selection:

Species/strain:	Sprague-Dawley rats
Number/sex/dose:	70/sex/dose for main study animals
	9/sex/dose for TK animals
Duration:	**104 weeks**
Route:	Oral (gavage)
Dose volume:	10 ml/kg
Doses proposed:	Males: 0 (vehicle control), 3, 10 and 30 mg/kg/day
	Females: 0 (vehicle control), 0.1, 0.3 and 1 mg/kg/day
Vehicle:	0.5% methylcellulose
Dosing procedure:	Test article will be administered daily, seven days/week for 104 weeks.

Justification for Dose Selection:

Dose selection proposed by the sponsor was based on the results of a 3 month oral (gavage) rat dose range finding study. Oral (gavage) doses of 0, 0.3, 3, 10 and 30 mg/kg/day were administered to female Sprague-Dawley rats (10/dose) for 90 days. Oral (gavage) doses of 0, 30, 100, 300 and 1000 mg/kg/day were administered to male Sprague-Dawley rats (10/dose) for 90 days. The vehicle used in this study was 1% carboxymethylcellulose. Due to the mortality noted in this study, dosing was discontinued in the following dose groups: 1) mid-low dose males on day 48, 2) mid-high dose males on day 11, 3) mid-high dose females on day 26 and 4) high dose animals on day 9.

Treatment related mortality was noted in the following dose groups: 1) low dose males (1/10), 2) mid-low dose males (10/10), 3) mid-high dose males (10/10), 4) mid-high dose females (10/10), 5) high dose males (7/10) and 6) high dose females (6/10). Mortality of all treated animals in the high dose groups was not noted due to very early dose discontinuation in these animals on day 9 and allowing the surviving animals to be maintained on an 82 day recovery period. Treatment related toxicity was noted in all dose groups tested in this study, which demonstrated a dose dependent increase in severity. CC-10004 caused acute inflammation and lymphoid depletion in multiple tissues in all dose groups manifested clinically by prostration and a neutrophilic leukocytosis, increased acute phase proteins (haptoglobin) and decreased albumin. Lethality was noted in all male dose groups and the mid-high and high dose females.

A NOAEL could not be identified in this study based on the microscopic findings of lymphoid depletion and/or subacute inflammation of the thymus, small intestines and/or mesentery noted in all dose groups. The maximum tolerated dose for CC-10004 after administration to rats for 90 days is identified as less than 30 mg/kg/day in male rats and 3 mg/kg/day in female rats, based on mortality noted in this study. The sponsor proposed a high dose of 30 mg/kg/day for male rats and 1 mg/kg/day for female rats.

Oral (Gavage) Mouse Carcinogenicity Study Protocol and Dose Selection:

Species/strain:	CD-1 mice
Number/sex/dose:	70/sex/dose for main study animals 9/sex/dose for TK animals
Duration:	**104 weeks**
Route:	Oral (gavage)
Dose volume:	10 ml/kg
Doses proposed:	0 (vehicle control), 100, 300 and 1000 mg/kg/day
Vehicle:	0.5% methylcellulose
Dosing procedure:	Test article will be administered daily, seven days/week for 104 weeks.

Justification for Dose Selection:

Dose selection proposed by the sponsor was based on the results of a 3 month oral (gavage) mouse dose range finding study. Oral (gavage) doses of 0, 100, 300 and 1000 mg/kg/day CC-10004 were administered to CD-1 mice (10/sex/dose) for 90 days. The vehicle used in this study was 1% carboxymethylcellulose.

No treatment related mortality was noted in this study. A treatment related inflammation manifested by a neutrophilic leukocytosis, lymphopenia and increased acute phase proteins (haptoglobin and CRP) was noted in low, mid and high dose animals during week 1 but not during week 13. Treatment related effects on microscopic parameters included inflammatory lesions noted in the lung, heart and arotic root in mid and high dose animals. The NOAEL for this study could be identified as 100 mg/kg/day CC-10004 ($AUC_{0\text{-}24\ hr}$ = 24318 and 25478 ng·hr/ml in males and females, respectively) in mice after administration for 13 weeks, since the inflammatory effects induced by CC-10004 were transient.

CC-10004 induced a systemic inflammatory response in multiple organs in all dose groups tested in the 90 day oral mouse toxicology study. However, a maximum tolerated dose was not identified in the 90 day oral mouse toxicology study. The sponsor proposed a high dose of 1000 mg/kg/day CC-10004 for the oral mouse carcinogenicity study, which is a dose that induced inflammation in multiple tissues in the 90 day oral mouse toxicology study. The proposed high dose of 1000 mg/kg/day for males and females provides for a slightly greater that 25 fold exposure to CC-10004 (actual multiple is 26 fold), based on mouse/human AUC comparisons assuming use of a clinical dose of 40 mg/day CC-10004. CC-10004 exhibits slightly higher binding to human plasma proteins compared to mouse plasma proteins (99.5% versus 96.5%, respectively).

Executive CAC Recommendations and Conclusions:

Rat protocol:

1) The Committee proposed the following doses for the oral (gavage) rat carcinogenicity study: 0 (vehicle control), 3, 10 and 20 mg/kg/day CC-10004 for males and 0 (vehicle control), 0.3, 1 and 3 mg/kg/day CC-10004 for females based on an MTD (death and pro-inflammatory syndrome). The sponsor's proposed high dose of 30 mg/kg/day for male rats slightly exceeds the MTD for male rats based on mortality and may not be tolerated in a 2 year oral rat carcinogenicity study. The sponsor's proposed high dose of 1 mg/kg/day for female rats is slightly less than the MTD for female rats based on mortality.

2) The Committee noted that the hematology and serum chemistry evaluations should not be conducted on main study animals in this study since the blood sampling may alter the study results.

3) The Committee noted that the sponsor should notify the Agency prior to early termination of any group based on mortality.

Mouse protocol:

1) The Committee concurred with the sponsor proposed doses for the oral (gavage) mouse carcinogenicity study of 0 (vehicle control), 100, 300, and 1000 mg/kg/day CC-10004, based on mouse/human AUC ratio.

2) The sponsor is cautioned that if the clinical dose rises such that the AUC ratio of rodent to human systemic exposure is no longer 25-fold, the study may not be acceptable.

3) The Committee noted that the hematology and serum chemistry evaluations should not be conducted on main study animals in this study since the blood sampling may alter the study results.

4) The Committee noted that the toxicokinetic analysis is probably not necessary for this study since toxicokinetic evaluation at the same doses was performed in a 13 week oral mouse toxicology study.

5) The Committee noted that the sponsor should notify the Agency prior to early termination of any group based on mortality.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DDDP
/P. Brown/Supervisor, DDDP
/B. Hill/Reviewer, DDDP
/M. Owens/Project Manager, DDDP
/A. Seifried, OND IO

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/s/

Abby Jacobs
9/27/2006 12:47:52 PM

Executive CAC
Date of Meeting: July 2, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Alex Jordan, Ph.D., DRUP, Alternate Member
Presenting: Marcie Wood, Ph.D., DPARP, Team Leader
L. Steven Leshin, D.V.M., Ph.D., DPARP, Presenting Reviewer

Also attending: Barbara Hill, Ph.D., DDDP
Lynnda Reid, Ph.D., DRUP

Author of Draft: L. Steven Leshin, D.V.M., Ph.D., DPARP

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA	205437
Drug Name	Apremilast (Otezla, CC-10004)
Sponsor	Celgene Corp.

Background:

Two-year mouse and rat carcinogenicity studies with CC-10004 were conducted by (b) (4) (b) (4) The sponsor received ECAC concurrence for doses used with mice and rats (see Meeting Minutes dated September 26, 2006).

CC-10004 was negative in the bacterial reverse mutation and human peripheral blood lymphocyte chromosomal aberration assays and in the in vivo micronucleus assay in mice.

Mouse Carcinogenicity Study:

Crl:CD-1 (ICR) Mice (n=70/sex/dose) were dosed once daily by gavage with CC-10004 at doses of 0 (vehicle:1.0% sodium carboxymethylcellulose in deionized water), 100, 300, and 1000 mg/kg/day. Due to morbidity and deaths in the latter part of the study, dosing of the high dose males was terminated and dosing of the high dose females was reduced to 500 mg/kg/day during week 73 (month 18). The dose of the 300 mg/kg/day group was also lowered to 200 mg/kg/day at this time and maintained through weeks 98 and 96 in males and females, respectively. Dosing was then stopped and the remaining

animals were maintained until the scheduled necropsy (study weeks 103 and 102 in males and females, respectively).

There were no definitive CP-10004-related malignancies in either male or female rats. For combined osteomas and osteosarcomas in females, there was a statistically significant trend of increasing incidence with dose ($p = 0.0128$). However these tumors were only present in the high dose group and pairwise comparison with the control group was not significant due to the low incidences in the control and high dose groups (0 and 3, respectively; $p= 0.0918$).

Rat Carcinogenicity Study:

CC-10004 was administered once daily by gavage to Crl:CD(SD) rats (n=70/sex/dose) at 0 (vehicle, 1.0% methocellulose), 2, 10 or 20 mg/kg/day in males and at 0 (vehicle, 1.0% methocellulose), 0.3, 1, or 3 mg/kg/day in females. In study week 66 (16.5 months), dosing of the 20 mg/kg/day males was stopped and the mid group dose of 10 mg/kg/day was reduced to 6 mg/kg/day due to animal morbidity and deaths. All dose groups were terminated between study week 91 and 104.

There were no malignancies related to CC-10004 treatment in either male or female rats. In female rats, there was a significant trend ($p=0.046$) for a dose-related increase in the incidence of ovarian Sertoli cell tumors. However with the low incidences of only 1 at the mid dose and 2 at the high dose of 70 animals per dose group, the pairwise comparison with control incidences of 0 were not significant.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DPARP
/Team leader, MWood
/Reviewer, LSLeshin
/CSO/PM, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/10/2013

DAVID JACOBSON KRAM
07/10/2013

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/s/

LAWRENCE S LESHIN
11/21/2013

MARCIE L WOOD
11/21/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205437 **Applicant: Celgene** **Stamp Date: March 21 2013**

Drug Name: Apremilast **NDA Type: 505(b)(1)**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		oral gavage administration of drug substance formulated differently than the marketed tablet
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		expressed as (b) (4) will need to be rewritten, defer till labeling sessions, since substantial changes are often made after studies are reviewed
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		(b) (4) a major impurity and which is also a metabolite were qualified
11	Has the applicant addressed any abuse potential issues in the submission?			not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

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

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

No review issues were identified at this time.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

LAWRENCE S LESHIN
05/21/2013

MARCIE L WOOD
05/21/2013