

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**NON-CLINICAL REVIEW(S)**

**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration**

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**Division of Neurology 2  
Division of Pharmacology/Toxicology  
Office of Neuroscience  
Center for Drug Evaluation and Research**

Date: March 24, 2020

From: Lois M. Freed, Ph.D.  
Supervisory Pharmacologist

Subject: NDA 209-899 (Zeposia, ozanimod, RPC1063)

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NDA 209-899 was submitted by Celgene International II Sarl on December 22, 2017, to support marketing approval of Zeposia for treatment of adult patients with relapsing forms of multiple sclerosis (RMS). A Refusal to File letter was issued on February 23, 2018, based on the lack of adequate nonclinical and clinical pharmacology data on RP112273 (CC112273), an active metabolite that was stated to account for the majority ((b)(4)%) of drug-related material in human circulation. The NDA was resubmitted on March 25, 2019. Clinical development of ozanimod for RMS was conducted under IND 109159.

A standard battery of nonclinical studies was conducted on ozanimod, with additional studies to directly assess major human metabolites. These studies were reviewed in detail by Dr. Toscano (Pharmacology/Toxicology NDA Review and Evaluation, NDA 209-899, Christopher D. Toscano, Ph.D., March 10, 2020), who has concluded that the data support approval of the NDA; however, Dr. Toscano finds the pre- and postnatal development (PPND) study in rat to be deficient (lack of adequate exposure to a major human metabolite, CC1084037) and recommends a PPND study of CC1084037 as a post-marketing requirement.

Ozanimod is a sphingosine-1-phosphate (S1P) receptor agonist and functional antagonist, which binds with high affinity to human S1P receptors 1 and 5. Binding of ozanimod to the S1P<sub>1</sub> receptor causes internalization of the receptor, which results in inhibition of egress of lymphocytes from lymph nodes, decrease in circulating lymphocytes, and reduced migration of lymphocytes into the central nervous system (CNS). It is through this mechanism that ozanimod is thought to be therapeutic in adult patients with RMS.

Following oral administration of ozanimod in humans, two major metabolites are formed, CC112273 and CC1084037; both are active at S1P<sub>1</sub> and S1P<sub>5</sub> receptors. Following multiple oral doses, ozanimod and these metabolites account for ((b)(4)%) of total drug-related material. (According to a single-dose mass balance study, RP101124, an inactive metabolite, was found to account for ((b)(4)%) of total circulating drug-related material in humans; however, because of the

long  $t_{1/2}$  of CC112273 and CC1084037, RP101124 was determined, following multiple doses, to account for only 10% of total circulating material in humans, which is just below the threshold for a major metabolite according to ICH M3(R2) [January 2010].)

While both metabolites are formed in mouse, rat, rabbit, and monkey, there were quantitative differences in exposure among species. In vitro binding data ( $EC_{50}$ ) for mouse, rat, and human receptors are summarized below:

CMPD	S1P <sub>1</sub> (nM)			S1P <sub>5</sub> (nM)		
	mouse	rat	human	mouse	rat**	human
ozanimod	0.90±0.21	1.02±0.14	1.03±0.16	1048.80±160.22		10.66±0.29
CC112273	2.77±0.30	2.82±0.27	2.99±0.17	310.60±28.93		29.32±1.98
CC1084037*	0.16±0.01	0.17±0.02	0.20±0.01	164.07±35.71		3.02±0.16

\*CC1084037 is a racemate; both enantiomers have similar binding affinity; \*\*rat S1P<sub>5</sub> receptor not available

According to the sponsor, “Recombinant receptors for the cynomolgus monkey were not available...but in silico analysis of amino acid sequences suggests that the pharmacology will likely be similar to human.”

At the time of the original NDA submission, there were concerns regarding the lack of systemic exposure data for CC112273, in the animal species used in the pivotal nonclinical studies and for human, because of the abundance of this metabolite in human circulation. Additional information was provided in the NDA resubmission to address these concerns, although the nonclinical pharmacokinetic/toxicokinetic data were presented in a manner (e.g., different units or animal strains, combining males and females) that made them unnecessarily burdensome to evaluate.

### Toxicology

The pivotal oral (gavage) toxicology studies were conducted in Sprague-Dawley rat (28-day + 14-day recovery, 13-week, and 26-week) and cynomolgus monkey (28-day + 14-day recovery, 13-week, and 39-week + 6-week recovery).

Rat: In rat, findings reported in all studies included reductions in total wbc and lymphocyte counts (all doses), increased lung weight and alveolar changes (edema, foamy macrophage accumulation), and increased spleen weight and lymphoid depletion. Kidney findings (tubular epithelium degeneration/regeneration, anisocytosis) observed in the 28-day and 13-week studies were not detected in the 26-week study. Overall, the no-effect dose was 0.2 mg/kg/day, based primarily on lung findings at higher doses.

Plasma ozanimod AUCs (ng\*hr/mL) at the last sampling time are summarized below:

DOSES (mg/kg/day)	MALES			FEMALES		
	28-day	13-week	26-week	28-day	13-week	26-week
0.2	37.2	53.5	27.2	91.2	97.5	57.8
2	701	561	616	1130	1330	750
30	13300	13800	8847	22900	21700	14676

Plasma exposures to the major human metabolites, CC112273 and CC1084037, were not quantitated in the toxicity studies. In a 14-day bridging study, plasma AUCs (ng\*hr/mL) for these metabolites were as follows:

DOSES (mg/kg/day)	MALES		FEMALES	
	CC112273	CC1084037	CC112273	CC1084037
0.2	2.31	0.069	2.25	<LLOQ
2	43.2	2.80	40.4	1.8
30	1100	49.3	879	32.7

**Monkey:** In monkey, findings reported in the 28-day and 13-week studies included reductions in total wbc and lymphocyte counts at all doses, and increased lung weight and alveolar changes (multifocal macrophage accumulation) and increased spleen weight and lymphoid depletion at the mid and high doses. Findings observed only at the high dose included clinical signs (e.g., trembling, vomiting, dehydration), decreases in rbc parameters, renal histopathology (basophilia of collecting duct epithelium or anisocytosis/anisokaryosis and basophilia of the proximal tubule), and adrenal cortex hypertrophy. The NOAEL in both studies was 0.15 mg/kg/day.

Because of the findings at the high dose, ozanimod was administered at lower doses in the 39-week study. No clinical signs were observed; however, effects on wbc and lymphocyte counts, lung, and spleen were similar to those that occurred in the shorter duration studies. The NOAEL was 0.1 mg/kg/day.

Plasma ozanimod AUCs (ng\*hr/mL) at the last sampling time are summarized below:

DOSES (mg/kg/day)	MALES			FEMALES		
	28-day	13-week	39-week	28-day	13-week	39-week
0.15	26.3	39.8	16.5	35.3	44.5	19.1
1			199.9			193.7
3	681	769		765	968	
15			3556			2988
30	8070	12400		9560	13600	

Plasma exposures to the major human metabolites, CC112273 and CC1084037, were not quantitated in the toxicity studies. In a 14-day bridging study, plasma AUCs (ng\*hr/mL) for these metabolites were as follows (males and females combined):

DOSES (mg/kg/day)	CC112273	CC1084037
0.15	21.2	4.83
1	203	42.9
15	4100	947

### Reproductive and Developmental Toxicology

A standard battery of reproductive and developmental toxicology studies was conducted for ozanimod (fertility and early embryonic development (to implantation) in rat, embryofetal

development in Sprague Dawley rat and New Zealand White rabbit, and pre- and postnatal development in Sprague Dawley rat). In all studies, ozanimod was administered by oral gavage.

Fertility: In the fertility study, ozanimod was administered to male and female rats at doses of 0, 0.2, 2, and 30 mg/kg/day, prior to and during mating and continuing in females through gestation day (GD) 7. There were no adverse effects on a standard battery of fertility parameters.

Toxicokinetic (TK) data were not collected during the study. Data from a 28-day toxicity study indicate plasma ozanimod exposures (AUC) at 30 mg/kg/day of 13300-22900 ng\*hr/mL; data from a 14-day bridging study indicate plasma AUCs at 30 mg/kg/day for metabolites, CC112273 and CC1084037, of 1100-879 and 49.3-41.0 ng\*hr/mL, respectively.

Embryofetal Development: In rat, oral administration of ozanimod at doses of 0, 0.2, 1, and 5 mg/kg/day during organogenesis (GD 6 through GD 17) resulted in embryoletality (primarily late resorptions), reduced fetal body weight, malformations (anasarca in 3 fetuses from 2 litters; malpositioned testes in 2 fetuses from 2 litters; 1 fetus with local (neck) edema and cleft palate), and skeletal variations (abnormal/delayed ossification) at the high dose. In dams, there were no drug-related deaths or clinical signs; the lower body weight in HD dams was considered to reflect the lower litter size at that dose. At the no-effect dose for embryofetal toxicity (mid dose of 1 mg/kg/day), plasma ozanimod exposure (AUC) was 284 ng\*hr/mL; TK data were not collected for CC112273 or CC1084037. In a 14-day bridging study, Day 14 plasma AUCs for these metabolites in females at 1 mg/kg/day were 17.2 and 0.678 ng\*hr/mL, respectively.

In rabbit, oral administration of ozanimod at doses of 0, 0.2, 0.6, and 2.0 mg/kg/day during organogenesis (GDs 6-19) resulted in embryoletality (early and late resorptions) at the high dose and increased malformations (malformed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, ozanimod was not detectable in rabbit plasma; plasma exposure data were not available for the major human metabolites, CC112273 and CC1084037. In a bridging study in pregnant rabbit, plasma ozanimod exposure (AUC on GD19) at 0.2 mg/kg/day was determined to be 40.4 nM\*hr or 17.8 ng\*hr/mL (MW = 440.92 Da); the sponsor provided a value of 21.20 ng\*hr/mL. In a separate 14-day bridging study in pregnant rabbit, plasma AUCs for CC112273 and CC1084037 at 0.2 mg/kg/day (GD19) were 6.77 and 3.78 ng\*hr/mL, respectively.

Pre- and postnatal development: Oral administration of ozanimod (0, 0.2, 0.7, and 2 mg/kg/day) to female rats from GD 6 to lactation day (LD) 20 resulted in reduced male and female offspring body weight at the HD, which persisted during the postweaning period. In female offspring, there was an increase in estrus cycle length (5.2 vs 4.2 days in controls) and reduced (~18%) body weight during gestation at the HD. The only effect on neurobehavioral function was an increase in locomotor activity in female offspring at the HD; however, effects on learning and memory were not evaluated using a complex task, such as the Morris or Cincinnati water maze. Plasma ozanimod exposures (AUC) in dams at the LD, MD, and HD were <LOQ, 142, and 431 ng\*hr/mL. Plasma exposures for metabolites, CC112273 and CC1084037, were not quantitated. In a 14-day bridging study, plasma AUCs for CC112273 at 0.2 and 2 mg/kg/day were 2.25 and 40.4 ng\*hr/mL, respectively, and for CC1084037 at 0.2 and 2 mg/kg/day were <LOQ and 1.82 ng\*hr/mL, respectively.

Plasma exposures (AUC; ng\*hr/mL) at the highest doses tested in each study are summarized below. The data are from the reproductive and developmental studies, from other (e.g., toxicity) studies, TK bridging studies, or are estimated (in parentheses) based on available data.

STUDY	DOSE (mg/kg)	OZANIMOD	CC112273	CC1084037
<b>RAT</b>				
fertility	30	8847-22900	1100-879	49.3-32.7
EFD	5	1903	(100)	(5)
PPND	2	431	40.0	1.82
<b>RABBIT</b>				
EFD	2	130	(60)	(40)
<b>HUMAN</b>				
RPC01-1001	0.92 mg	4.776	67.097	(13.292 )

Distribution: In pregnant Sprague Dawley rat, distribution of ozanimod into fetal plasma and milk was demonstrated following oral doses of 0.2, 0.7, and 2 mg/kg/day throughout gestation (GDs 6-18) or throughout gestation and lactation (GD 6 to LD 20). At the high dose, fetal plasma exposure (AUC) was 181.58 ng\*hr/mL, with a fetal-to-maternal ratio of 0.23, on GD 18. AUC for ozanimod in milk at 2 mg/kg/day was 937.40 ng\*hr/mL, with a milk-to-maternal plasma ratio of 1.99.

In pregnant New Zealand White rabbit, distribution of ozanimod into fetal plasma was assessed only at the lowest dose (0.2 mg/kg/day) tested in the embryofetal development study. At that dose, the fetal plasma AUC for ozanimod was 16.30 ng\*hr/mL; the fetal-to-maternal plasma AUC ratio was 1.21.

Juvenile animal toxicology: the potential for adverse effects of ozanimod on postnatal development was assessed in two pivotal juvenile animal studies.

In a 10-week (+ 2-week recovery) study, ozanimod was administered to juvenile rats at doses of 0, 0.3, 3, and 10 mg/kg/day, starting on postnatal (PND) 21. However, this study was inadequate by design, particularly regarding the assessment of CNS effects. The neurobehavioral evaluation did not include a complex task (e.g., Morris or Cincinnati water maze) and was assessed in too few animals, and there was no indication that an expanded neurohistopathological evaluation was conducted. These deficiencies are of particular importance considering the expression of the S1P<sub>5</sub> receptor in the brain and its reported role in development and maturation of oligodendrocytes (Novgorodov AS et al. FASEB J. 21: 1503-1514, 2007).

In a separate (+ 2-week recovery) study, ozanimod was administered to juvenile rats at doses of 0, 0.3, 3, and 10 mg/kg/day for 33 days, starting on PND 21. Wbc and lymphocyte cts were reduced at all doses at the end of the dosing and recovery periods. T-dependent antibody response (TDAR) was evaluated on Days 25 and 33 using KLH. Primary (IgM) and secondary (IgG) antibody responses were significantly inhibited at the mid and high doses; however, reversibility was not assessed.

## Genetic Toxicology

Ozanimod was negative in a standard battery of OECD-compliant in vitro (Ames, mouse lymphoma *tk*) and in vivo (rat micronucleus) assays. Metabolite CC112273 was negative in an Ames assay and an in vitro chromosomal aberration assay in human peripheral blood lymphocytes, with and without metabolic activation. Metabolite CC1084037 was negative in an Ames assay (with and without metabolic activation) and positive in an in vitro mammalian cell micronucleus assay in TK6 cells (human lymphoblastoid cell line), primarily in the absence of metabolic activation, but negative in an in vivo rat micronucleus/comet assay.

## Carcinogenicity

The carcinogenic potential of ozanimod was tested in a 26-week study in Tg.rasH2 mouse (0, 8, 25, and 80 mg/kg/day) and a 2-year study in Sprague-Dawley rat (0, 0.2, 0.7, and 2 mg/kg/day). In both studies, ozanimod was administered daily by oral gavage.

In Tg.rasH2 mouse (CByB6F1-Tg(HRAS)2.Jic), there was an increase in combined hemangioma and hemangiosarcoma in males and females at the mid and high doses (males: 0/25, 5/25, 17/25, and 10/25 in C, LD, MD, and HD groups, respectively; females: 0/25, 3/25, 8/25, and 11/25 in C, LD, MD, and HD groups, respectively). TK analysis was conducted for ozanimod but not for CC112273 or CC1084037. On Day 177, plasma AUCs for ozanimod were 9423-6592, 29966-19694, and 89372-65513 ng\*hr/mL for control, LD, MD, and HD groups, respectively. CC112273 was quantitated in a 28-day bridging study in CByB6F1 mouse; at doses of 10, 30, and 100 mg/kg/day, plasma AUCs on Day 27 were 47.6-56.2, 117-181, and 192-245 ng\*hr/mL, respectively. In CByB6F1 mouse, plasma exposure data for CC1084037 were collected only at 8 mg/kg/day in a 14-day study; plasma AUCs on Day 14 were 13.8-23.6 ng\*hr/mL.

In rat, no drug-related increase in tumors was observed. At the high dose, plasma exposures (AUC) for ozanimod and CC112273, were 517-685 and 131-92.6 ng\*hr/mL, respectively, on Day 185. CC1084037 was not quantitated in the 2-year study; in a 14-day bridging study, plasma CC1084037 exposures (AUC) at 2 mg/kg/day were 2.8-1.82 ng\*hr/mL.

## Metabolites

Because CC112273 is the most abundant drug-related material in human circulation (66% at steady-state), the sponsor conducted studies in which CC112273 was administered directly by oral gavage to CByB6F1 mouse (28-day toxicity), Sprague Dawley rat (96-day toxicity), and pregnant New Zealand White rabbit (dose-ranging/TK) at doses up to 100 mg/kg/day.

In mouse, the only finding was a slight decrease in body weight gain at the high dose in males; no effects on wbc or lymphocyte counts were evident. In rat, the only finding was a decrease (~25%) in wbc and lymphocyte counts in males at the high dose. In pregnant rabbit (0, 10, 30, 60 and 100 mg/kg/day), complete abortion occurred in two females, one at 60 mg/kg/day and one at 100 mg/kg/day; the high dose was also associated with a decrease in fetal body weight. At 100 mg/kg/day, plasma CC112273 exposures (AUC) were 180-253, 61.8-50.1, and 13.9 ng\* hr/mL

in mouse, rat, and rabbit, respectively. Therefore, higher exposures were not achieved with direct oral administration of CC112273.

### Conclusions and Recommendations

Overall, the nonclinical studies are adequate to support approval of ozanimod for the proposed indication, although systemic exposures to the two major (and active) human metabolites (CC112273 and CC1084037) were lower in several pivotal studies than in humans at the maximum recommended human dose (0.92 mg/day). Specifically, CC112273 and CC1084037 exposures in the pre- and postnatal development (PPND) study and CC1084037 exposures in the embryofetal development and carcinogenicity studies in rat were lower than those in humans at the MRHD. However, for the most abundant metabolite (CC112273), the sponsor demonstrated that higher exposures were not achieved with direct oral administration (doses up to 100 mg/kg) and that wbc and lymphocyte counts were not affected (rat), as would have been expected based on the in vitro binding affinity of CC112273 for the S1P<sub>1</sub> receptor. Studies with direct administration of CC1084037 were not conducted.

Dr. Toscano concluded that the PPND study is inadequate because of the lack of sufficient exposure to CC1084037 and recommended the metabolite be assessed in a PPND study as a post-marketing requirement. However, the available data demonstrate that ozanimod, administered to pregnant animals, has clear adverse effects on the developing organism, including teratogenicity, which are consistent with the critical role of the S1P<sub>1</sub> and S1P<sub>5</sub> receptors in embryogenesis (including vascular and neural development) and should discourage use during pregnancy. Therefore, I do not believe the sponsor needs to conduct such a study.

A juvenile animal toxicology study is not needed to support use of ozanimod in adult patients with relapsing forms of multiple sclerosis; however, a study in juvenile animals, to include an adequate assessment of effects on neurobehavioral development and an expanded neurohistopathological evaluation, should be conducted as a post-marketing requirement to support development in pediatric patients <12 years of age, if ozanimod is approved.

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/s/  
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LOIS M FREED  
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**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: NDA 209-899  
Supporting document: 13  
Sponsor's letter date: 3/25/2019  
CDER stamp date: 3/25/2019  
Product: ZEPOSIA (ozanimod)  
Indication: Treatment of adults with relapsing forms of  
multiple sclerosis (MS)  
Sponsor: Celgene International II Sarl; Couvet,  
Switzerland  
Review Division: Neurology 2  
Reviewer: Christopher D. Toscano, Ph.D., DABT  
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Project Manager: Susan Daugherty, R.N., B.S.N.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209-899 are owned by Celgene International II Sarl or are data for which Celgene International II Sarl has obtained a written right of reference. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 209-899.

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# 1 Executive Summary

## 1.1 Introduction

Zeposia (ozanimod, RPC1063) is a small molecule that exhibits potent agonism at sphingosine 1-phosphate (S1P) 1 and 5 receptors. Zeposia has been developed for the treatment of relapsing forms of multiple sclerosis (MS) in adults.

## 1.2 Brief Discussion of Nonclinical Findings

Agonism of lymphocytic S1P receptors inhibits the release of T-cells and B-cells from peripheral lymphoid organs, subsequently decreasing the available pool of autoreactive circulating lymphocytes available for entry into the central nervous system. Consistent with the known pharmacology of S1P agonists, ozanimod induced leukopenia in every nonclinical species used in the nonclinical program. Ozanimod (RPC1063) is extensively metabolized, with three metabolites, CC112273, CC1084037, and RP101124, considered to be major human metabolites. The parent and the major human metabolites, with the exception of RP101124, were demonstrated to be agonists at S1P<sub>1</sub> and S1P<sub>5</sub> receptors.

In the general toxicology studies, spleen, thymus, and lung were determined to be targets of ozanimod in both rat and monkey. Ozanimod and its major human metabolites (except for CC1084037) were negative for mutagenicity or clastogenicity in a genotoxicity battery. When assessed in vitro in TK6 cells, CC1084037 increased the number of micronuclei by up to 4-fold in the absence of metabolic activation. RP101124 was not assessed in an in vitro chromosomal aberration assay. In carcinogenicity studies, ozanimod increased the combined incidence of hemangioma and hemangiosarcoma in transgenic mice dosed daily for 6 months; there was no drug-related neoplasia detected in the two-year carcinogenicity study conducted in rats. There were no effects on fertility in male or female animals dosed with ozanimod. Embryolethality and developmental effects (e.g., incomplete skeletal ossification, malpositioned vertebrae, malformed or absent arteries, anasarca, malpositioned testes, and cleft palate) occurred in pregnant rats and/or rabbits exposed to ozanimod and its metabolites during gestation. Hyperactivity (increased motor activity in the open field assessment) and increased sensitivity to touch were the only ozanimod-related findings in the pre- and postnatal development study. While not required to support the use of ozanimod in adult MS patients, the sponsor assessed toxicity in juvenile rats; there were no ozanimod-related findings at the highest dose studied.

Given the extensive metabolism of ozanimod, the sponsor conducted toxicokinetic (TK) analyses of ozanimod and the three major human metabolites, including several bridging studies assessing the two major human metabolites discovered late in development, CC112273 and CC1084037. Based on these TK data, it was determined that ozanimod and its three major human metabolites were adequately assessed in the nonclinical studies with the following exceptions:

- RP101124 was not assessed in an in vitro chromosomal aberration assay.
- CC1084037 was not adequately assessed in the pre- and postnatal development study conducted in rat.

### 1.3 Recommendations

#### 1.3.1 Approvability

The nonclinical data provided in the NDA support approval, with one recommended postmarketing requirement (PMR). The sponsor should determine, as a PMR, if CC1084037 adversely impacts the pre- and postnatal developmental period. Although not assessed in this application, conducting an in vitro chromosomal aberration assay with RP101124 as a PMR or prior to approval would not substantially add to the current understanding of the carcinogenic potential of this metabolite because it was adequately tested in the 6-month carcinogenicity assay, which was positive.

#### 1.3.2 Additional Nonclinical Recommendations

None.

#### 1.3.3 Labeling

<b><u>Sponsor's Proposed Labeling</u></b>	<b><u>Recommended Labeling</u></b>
<p>-----INDICATIONS AND USAGE-----</p> <p>ZEPOSIA is indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS) (1).</p>	<p>-----INDICATIONS AND USAGE-----</p> <p>ZEPOSIA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS) (1).</p>
<p><b>8.1. Pregnancy</b>  <b>Risk Summary</b>                      There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women (b) (4).                      (b) (4)                      In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown. (b) (4)                      (b) (4)</p>	<p><b>8.1. Pregnancy</b>  <b>Risk Summary</b>                      There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women.                      Based on animal data, ZEPOSIA can cause fetal harm when administered to a pregnant woman (see Data). Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ZEPOSIA-induced embryotoxicity and teratogenicity in rats and rabbits. Increased incidences of post-implantation loss, fetal lethality, and fetal abnormalities (skeletal, urogenital) occurred in rat with a no-effect dose that was 2-times the maximum recommended human dose of 1 mg, on a mg/m<sup>2</sup> basis. Skeletal fetal abnormalities were present at all doses tested in the pregnant rabbit, with the lowest dose being 4-fold higher than the maximum recommended human dose of 1 mg, on a mg/m<sup>2</sup> basis. Higher</p>

	<p>doses in the pregnant rabbit were associated with vascular abnormalities, abortion and embryoletality.</p> <p>In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown. If the patient becomes pregnant or plans to become pregnant while taking ZEPOSIA, she should be informed of the potential hazards and discontinuation of therapy should be considered.</p>
<p><u>Data</u> <i>Animal Data</i></p> <div style="background-color: #cccccc; width: 100%; height: 300px; position: relative;"> <span style="position: absolute; top: 5px; right: 5px; font-size: small;">(b) (4)</span> </div>	<p><u>Data</u> <i>Animal Data</i></p> <p>When ozanimod (0, 0.2, 1, or 5 mg/kg) was orally administered to pregnant rats during the period of organogenesis, malformations (skeletal and urogenital), postimplantation loss, and fetal lethality occurred at &gt; 0.2 mg/kg, a dose that is 2-times higher than the maximum recommended human dose of 1 mg, on a mg/m<sup>2</sup> basis. At the no-effect level of 0.2 mg/kg, exposure to ozanimod and RP101124, was 8.9- and 13.7-times higher than the exposure at the maximum recommended human dose of 1 mg; exposure to the other two major human metabolites, CC112273 and CC1084037, was less than the exposure at the maximum recommended human dose.</p> <p>When ozanimod (0, 0.2, 0.6, or 2 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, a no-effect dose could not be determined because skeletal malformations were observed at all doses. Vascular malformations, with a no-</p>

	<p>effect dose of 0.2 mg/kg, and spontaneous abortion and embryoletality, with a no-effect dose of 0.6 mg/kg, occurred at higher doses. The lowest dose, 0.2 mg/kg, represented a dose that is 4-fold higher than the maximum recommended human dose. Exposure to ozanimod at the lowest dose of 0.2 mg/kg was 2.2-fold higher than exposure at the maximum recommended human dose; the level of the three major human metabolites did not exceed exposure at the maximum recommended human dose.</p> <p>When ozanimod (0, 0.2, 0.7, or 2 mg/kg) was orally administered to female rats throughout pregnancy and lactation, offspring exhibited an increase in activity and reactivity to touch with a no-effect dose of 0.7 mg/kg, which is 7-times higher than the maximum recommended human dose, on a mg/m<sup>2</sup> basis. Exposure to ozanimod and RP101124, a major human metabolite, at the no-effect dose was 30- and 40-times higher than at the maximum recommended human dose; exposure to the other two major human metabolites, CC112273 and CC1084037, was less than the exposure at the maximum recommended human dose.</p>
<p><b>8.2. Lactation</b>  <u>Risk Summary</u>                  There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.</p> <div data-bbox="181 1543 803 1732" style="background-color: #cccccc; height: 90px; width: 100%;"></div>	<p><b>8.2. Lactation</b>  <u>Risk Summary</u>                  There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.</p> <p>A study in lactating rats has shown excretion of ozanimod and its metabolites in milk.</p> <p>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPOSIA and any potential adverse</p>

	<p>effects on the breastfed infant from ZEPOSIA or from the underlying maternal condition.</p>
<p><b>8.3 Females and Males of Reproductive Potential</b>  <u>Contraception</u>                  Women of childbearing age should use effective contraception (b) (4) for 3 months after stopping ZEPOSIA.</p>	<p><b>8.3 Females and Males of Reproductive Potential</b>  <u>Contraception</u>                  Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with ZEPOSIA [see <i>Use in Specific Populations (8.1)</i>]. Women of childbearing age should use effective contraception (b) (4) for 3 months after stopping ZEPOSIA.</p>
<p><b>8.4. Pediatric Use</b>                  Safety and effectiveness in pediatric patients have not been established.</p>	<p><b>8.4. Pediatric Use</b>                  Safety and effectiveness in pediatric patients have not been established.</p> <p><u>Juvenile Animal Toxicity Data</u>                  Juvenile rats were given a daily oral dose of 0, 0.3, 3, or 10 mg/kg/day ozanimod for 10 weeks beginning on postnatal day 21. There were no drug-related effects observed on development up to the highest dose tested (10 mg/kg) which was 97-fold higher than the MRHD of 1 mg on a body surface area basis. Systemic exposure to ozanimod and the three major human metabolites (RP101124, CC112273, and CC1084037) at the highest dose tested, 10 mg/kg/day, was 582-, 1131-, 3-, and 1.1-fold greater, respectively, than exposure at the maximum recommended human dose of 1 mg.</p>
<p><b>12.1. Mechanism of Action</b>                  Ozanimod is a sphingosine 1-phosphate receptor modulator, which binds with high affinity (b) (4) to sphingosine 1-phosphate receptor (b) (4) 1 and 5. (b) (4). The (b) (4).</p>	<p><b>12.1. Mechanism of Action</b>                  Ozanimod is a highly metabolized sphingosine 1-phosphate receptor modulator. In humans, approximately 94% of circulating total active drug exposure is represented by ozanimod</p>

<p>mechanism by which ozanimod exerts therapeutic effects in multiple sclerosis (b) (4) is unknown but may involve the reduction of lymphocyte migration into the central nervous system.</p> <p>(b) (4)</p>	<p>(6%), CC112273 (73%), and CC1084037 (15%). Ozanimod and its major metabolites bind with high affinity to sphingosine 1-phosphate receptor (b) (4) 1 and 5. (b) (4). The mechanism by which ozanimod exerts therapeutic effects in multiple sclerosis (b) (4) is unknown but may involve the reduction of lymphocyte migration into the central nervous system.</p>
<p><b>13 Nonclinical Toxicology</b>  <b>13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>(b) (4)</p>	<p><b>13 Nonclinical Toxicology</b>  <b>13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility</b>  <u>Carcinogenesis</u>  Oral carcinogenicity studies of ozanimod were conducted in transgenic mice and rats.</p> <p>In Tg.rasH2 mice administered ozanimod (0, 8, 25, or 80 mg/kg/day) by oral gavage for 6 months, the incidence of hemangiosarcoma and hemangioma was increased in males at all doses and in females at doses &gt; 8 mg/kg. Systemic exposure to ozanimod and the three major human metabolites (RP101124, CC112273, and CC1084037) at the lowest dose of 8 mg/kg/day was 1680-, 106-, 3-, and 1.4-fold greater, respectively, than exposure at the maximum recommended human dose of 1 mg.</p> <p>In rats, ozanimod was administered at oral doses of 0, 0.2, 0.7, or 2 mg/kg/day. No increase in tumors was observed.</p>

	<p>(b) (4) Systemic exposure to ozanimod and one of the major human metabolites, RP101124, at the high dose of 2 mg/kg/day was 126- and 212-fold greater, respectively, than exposure at the maximum recommended human dose of 1 mg. Systemic exposure to the other major human metabolites, CC112273 and CC1084037, at the high dose of 2 mg/kg/day in rats did not exceed the clinical exposure at the maximum recommended human dose of 1 mg.</p>
	<p><u>Mutagenesis</u> Except for the major human metabolite CC1084037, which was positive in an in vitro chromosomal aberration assay, and RP101124, which was not assessed in an in vitro mammalian cell assay, ozanimod and its major human metabolites were negative in a battery of in vitro (Ames, gene mutation assay in mammalian cells, and chromosomal aberration in mammalian cells) and in vivo (micronucleus in rat) assays. CC1084037 was negative in in vivo micronucleus and comet assays conducted in mouse.</p>
	<p><u>Impairment of Fertility</u> When ozanimod was administered orally (0, 0.2, 2, or 30 mg/kg/day) to male and female rats 14 days prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested (30 mg/kg) which is approximately 291-times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis (assuming a 60 kg human). Exposure to ozanimod and the three major human metabolites (RP101124, CC112273, and CC1084037) at the high dose of 30 mg/kg were 2460-, 4290-, 14.7-, and 3.1-fold</p>

	higher, respectively, than exposure at the MRHD.
<b>13.2 Animal Toxicology and/or Pharmacology</b>  <small>(b) (4)</small>	<b>13.2 Animal Toxicology and/or Pharmacology</b>  <i>This section should be eliminated.</i>

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: Base: 1306760-87-1; HCl salt: 1618636-37-5

Generic Name: Ozanimod

Code Name: RPC1063

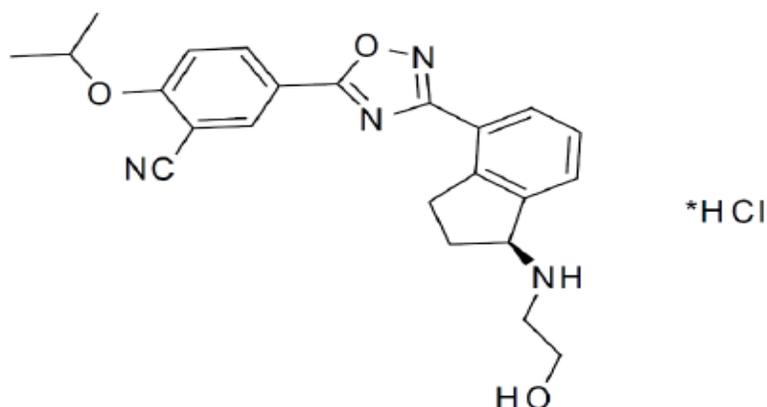
Chemical Name: 5-(3-((1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl)-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride

Molecular Formula: C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>•HCl

Molecular Weight: 440.92 Da

Pharmacologic Class: Sphingosine 1-phosphate receptor (S1P) agonist

Structure: Sponsor's figure, below



### 2.2 Relevant INDs and NDAs:

The following applications were submitted by the current sponsor:

- INDs: 109,159 (Multiple sclerosis, DN2), (b) (4)  
(b) (4)
- NDAs: 209-899 (Multiple sclerosis, DNP), 209-902 (Multiple Sclerosis, Presubmission, DN2)

### 2.3 Drug Formulation:

ZEPOSIA is formulated in gelatin capsules for oral administration. Dosage strengths and dosing formulations are provided in the sponsor's tables, below. There are no nonclinical concerns regarding the formulation. All of the excipients are listed in the Inactive Ingredient Database and are present in the drug product at levels equal to or less than those of previously approved drugs formulated for oral administration.

**Table 1: Expression of Dosage Strengths**

Ozanimod HCl/RPC1063	Ozanimod (active moiety)
0.25 mg	0.23 mg
0.5 mg	0.46 mg
1 mg	0.92 mg

**Table 2: Composition of Ozanimod HCl Capsules**

Component	Reference to Quality Standard	Function	Amount per Unit (mg)		
			0.25 mg	0.5 mg	1.0 mg
Ozanimod HCl	3.2.S.4.1 Specifications	Active	0.25	0.50	1.00
Microcrystalline cellulose, (b) (4)	NF/Ph.Eur./JP	(b) (4)			
(b) (4)	NF/Ph.Eur./JP				
Colloidal silicon dioxide	NF/Ph.Eur./JP				
Croscarmellose sodium	NF/Ph.Eur./JP				
Magnesium stearate	NF/Ph.Eur./JP				

## 2.5 Comments on Impurities/Degradants of Concern:

Except for (b) (4), all identified impurities are controlled below the qualification threshold of 0.15%. (b) (4)

(b) (4) is controlled at (b) (4) % and is qualified at levels of (b) (4) % in the chronic studies conducted in rat and monkey. Except for (b) (4), all potentially genotoxic impurities were negative in an adequate in silico assessment. (b) (4) was positive for mutagenicity using the CASE Ultra program; follow-up testing in an adequately conducted bacterial reverse mutation assay demonstrated that (b) (4) was not mutagenic (AE81YV.502ICH, (b) (4)).

## 2.6 Proposed Clinical Population and Dosing Regimen:

ZEPOSIA is indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS). The sponsor recommends dose escalation over an 8-day period from 0.23 mg QD to the maximum recommended human dose (MRHD) of 0.92 mg QD. The sponsor proposes that QD dosing at 0.92 mg should continue unless treatment has been interrupted for > 14 days. In this case, the sponsor states that the titration period should be repeated.

## 2.7 Regulatory Background:

The protocols for the rat and mouse carcinogenicity studies were assessed by the

Executive Carcinogenicity Assessment Committee on December 16, 2014, and January 20, 2015 under IND 109159. In the preliminary responses to questions provided in the Pre-NDA meeting package, the Division informed the sponsor that it would be necessary to demonstrate that adequate exposure to a major human metabolite, RP112273, was achieved in the full battery of nonclinical studies (e.g., chronic toxicity, reproductive and developmental, and carcinogenicity studies). RP112273, estimated to account for (b) (4) % of total drug-related exposure, was identified late in clinical development. The sponsor was informed that toxicokinetic data documenting adequate assessment of RP112273 would need to be provided in the NDA. The face-to-face pre-NDA meeting was cancelled by the sponsor on November 22, 2017. NDA 209-899 was submitted for review on December 22, 2017. The Division refused to file the application on February 26, 2018, based on the lack of nonclinical studies demonstrating coverage of RP112273. The sponsor was informed of the need to conduct additional nonclinical PK studies to bridge to the existing battery of nonclinical studies. At the follow-up Type A meeting held on April 3, 2018, the sponsor was told that the proposed bridging strategy appeared to be sufficient to allow for review. In written responses to a Type C meeting request (November 9, 2018), the sponsor was reminded of the Division's concern regarding the lack of exposure coverage to RP112273 in the rat carcinogenicity study as well as the determination that insufficient exposure to this metabolite also occurred in the embryofetal development study conducted in rat.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

All nonclinical studies provided in the sponsor's resubmission (March 25, 2019) and initial submission (December 26, 2017) were reviewed.

#### **3.2 Studies Not Reviewed**

N/A

#### **3.3 Previous Reviews/Memos Referenced**

- Gautam, DC, Nonclinical Review, January 22, 2015, (b) (4)
- Seifried, AS, SPA Agreement Memo, December 18, 2014, IND 109,159
- Seifried AS, SPA Agreement Memo, January 21, 2015, IND 109,129
- Siarey RJ, Nonclinical Filing Review, February 26, 2018, NDA 209-899
- Toscano CD, Nonclinical Filing Review, May 2, 2018, NDA 209-899

## 4 Pharmacology

### 4.1 Primary Pharmacology

Ozanimod (RPC1063) is extensively metabolized to nine different circulating metabolites, with three of these metabolites, CC112273, CC1084037, and RP101124, considered to be major human metabolites because they circulate at > 10% of the total drug-related exposure. The parent and all major metabolites, except for RP101124, were demonstrated to be agonists at the sphingosine-1-phosphate (S1P) receptor, a G protein-coupled receptor.

The sponsor assessed activation of the human, mouse, and rat S1P receptor isoforms by each of the metabolites in an in vitro model of radiolabeled GTP binding activity (RP-PH-001, RP-PH-002, RP-PH-010, RP-PH-014; sponsor's Tables 2, 3, and 4, below). Recombinant receptors for cynomolgus monkey were not available for assessment in vitro. Ozanimod and metabolites, CC112273, CC1084037 (also known as RP100798), RP101075, RP101988, RP101442, RP112289, and RP112509, exhibited agonist activity at the human S1P<sub>1</sub> and S1P<sub>5</sub> receptors, the mouse S1P<sub>1</sub> receptor, and the rat S1P<sub>1</sub> receptor (sponsor's Tables 2, 3, and 4, below). RP101124 exhibited no activity at the human, mouse, or rat S1P receptors. CC1084037, a major human metabolite, and RP101988 exhibited some activity at the human S1P<sub>3</sub> receptor.

**Table 2: Human Sphingosine 1-phosphate Receptor Binding Data**

Compound	Human S1P <sub>1</sub>		Human S1P <sub>2</sub>		Human S1P <sub>3</sub>		Human S1P <sub>4</sub>		Human S1P <sub>5</sub>	
	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA
S1P	33.18 ± 0.83	100	213.06 ± 12.21	100	1.56 ± 0.11	100	550.90 ± 25.24	100	7.32 ± 0.83	100
Ozanimod	1.03 ± 0.16	91.9 ± 1.9	>10,000	<i>28.1 ± 0.7</i>	2618 ± 203	47.5 ± 2.7	>10,000	<i>37.1 ± 0.5</i>	10.66 ± 0.29	97.4 ± 5.0
CC112273	<b>2.99 ± 0.17</b>	<b>85.9 ± 2.9</b>	>10,000	NR	>10,000	NR	>10,000	NR	<b>29.32 ± 1.98</b>	<b>69.8 ± 5.0</b>
CC1084037*	<b>0.20 ± 0.01</b>	<b>85.3 ± 1.6</b>	>10,000	NR	<b>2414 ± 749</b>	41.0 ± 13.0	>10,000	NR	<b>3.02 ± 0.16</b>	<b>86.5 ± 6.8</b>
RP101124	>10,000	<i>11.8 ± 1.7</i>	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	<i>15.8 ± 3.7</i>
RP101075	0.35 ± 0.01	85.6 ± 1.9	>10,000	<i>36.8 ± 2.1</i>	>10,000	NR	1801 ± 317	54.1 ± 4.3	4.49 ± 0.67	74.8 ± 6.4
RP101988	0.33 ± 0.01	85.8 ± 3.8	>10,000	NR	2773 ± 379	44.2 ± 9.0	>10,000	<i>21.2 ± 1.3</i>	29.15 ± 1.25	79.9 ± 5.3
RP101442	3.30 ± 0.25	87.0 ± 2.9	>10,000	NR	>10,000	NR	>10,000	NR	44.77 ± 5.10	69.0 ± 6.8
RP112289	9.28 ± 0.79	68.2 ± 1.8	>10,000	NR	>10,000	NR	>10,000	NR	43.51 ± 3.66	38.4 ± 2.0
RP112509	10.51 ± 1.53	87.6 ± 0.9	>10,000	NR	>10,000	NR	>10,000	NR	68.98 ± 5.67	54.2 ± 1.4

EC<sub>50</sub> = concentration at which 50% of maximal activity is observed; IA = intrinsic activity (% relative to S1P response); NR = no response (Mean %E<sub>max</sub> < 10% where E<sub>max</sub> is the maximal response achieved relative to the internal positive control, sphingosine 1-phosphate); S1P = sphingosine 1-phosphate; S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub>, or S1P<sub>5</sub> = sphingosine 1-phosphate receptor 1, 2, 3, 4, or 5, respectively. Data are expressed as mean and standard error of the mean (SEM), N = 3 to 6 independent experiments.

*Italic = response achieved at the top test compound concentration of 10,000 nM.*

**Bold = major human metabolites that contribute > 10% of the total drug-related exposure in the plasma.**

\* CC1084037 is a racemate. R and S enantiomers of CC1084037 are equally potent in in vitro assays (Report RP-PH-014).

Source: Report RP-PH-010.

**Table 3: Mouse Sphingosine 1-phosphate Receptor Binding Data**

Compound	Mouse S1P <sub>1</sub>		Mouse S1P <sub>2</sub>		Mouse S1P <sub>3</sub>		Mouse S1P <sub>4</sub>		Mouse S1P <sub>5</sub>	
	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA
S1P	26.26 ± 2.38	100	35.84 ± 1.40	100	9.19 ± 0.97	100	455.6 ± 124.2	100	21.73 ± 2.13	100
Ozanimod	0.90 ± 0.21	92.0 ± 2.1	>10,000	<i>11.9 ± 0.6</i>	>10,000	NR	>10,000	48.5 ± 4.5	1048.80 ± 160.22	<i>86.4 ± 1.3</i>
CC112273	<b>2.77 ± 0.30</b>	<b>86.1 ± 4.1</b>	>10,000	NR	>10,000	NR	>10,000	NR	310.60 ± 28.93	<b>15.0 ± 1.8</b>
CC1084037*	<b>0.16 ± 0.01</b>	<b>83.2 ± 2.5</b>	>10,000	NR	>10,000	NR	>10,000	NR	164.07 ± 35.71	<b>70.3 ± 2.2</b>
RP101124	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	NR
RP101075	0.28 ± 0.02	85.8 ± 3.5	>10,000	<i>11.7 ± 0.8</i>	>10,000	<i>11.0 ± 1.2</i>	>3,333	77.0 ± 6.6	380.98 ± 125.24	67.9 ± 4.1
RP101988	0.38 ± 0.02	87.3 ± 2.3	>10,000	NR	>10,000	<i>12.0 ± 2.2</i>	>10,000	NR	>3,333	55.2 ± 8.6
RP101442	2.86 ± 0.13	86.5 ± 1.2	>10,000	NR	>10,000	NR	>10,000	NR	453.23 ± 240.61	9.2 ± 0.7
RP112289	8.43 ± 1.12	71.8 ± 1.3	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	NR
RP112509	10.59 ± 1.82	86.7 ± 3.3	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	NR

EC<sub>50</sub> = concentration at which 50% of maximal activity is observed; IA = intrinsic activity (% relative to S1P response); NR = no response (Mean %E<sub>max</sub> < 10%, where E<sub>max</sub> is the maximal response achieved relative to the internal positive control, sphingosine 1-phosphate); S1P = sphingosine 1-phosphate; S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub>, or S1P<sub>5</sub> = sphingosine 1-phosphate receptor 1, 2, 3, 4, or 5, respectively. Data are expressed as mean and standard error of the mean (SEM), N = 3 to 6 independent experiments.

*Italic* = response achieved at the top test compound concentration of 10,000 nM.

**Bold** = major human metabolites that contribute > 10% of the total drug-related exposure in the plasma.

\* CC1084037 is a racemate. R and S enantiomers of CC1084037 are equally potent in in vitro assays ([Report RP-PH-014](#)).

Source: [Report RP-PH-010](#).

**Table 4: Rat Sphingosine 1-phosphate Receptor Binding Data**

Compound	Rat S1P <sub>1</sub>		Rat S1P <sub>2</sub>		Rat S1P <sub>3</sub>		Rat S1P <sub>4</sub>	
	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA
S1P	21.72 ± 0.90	100	10.60 ± 0.57	100	3.30 ± 0.98	100	163.65 ± 23.66	100
Ozanimod	1.02 ± 0.14	90.9 ± 2.7	>10,000	<i>13.3 ± 1.0</i>	>10,000	NR	>3,333	70.3 ± 5.2
<b>CC112273</b>	<b>2.82 ± 0.27</b>	<b>83.8 ± 3.0</b>	>10,000	NR	>10,000	NR	>10,000	NR
<b>CC1084037*</b>	<b>0.17 ± 0.02</b>	<b>81.2 ± 3.5</b>	>10,000	NR	>10,000	NR	>10,000	NR
<b>RP101124</b>	>10,000	NR	>10,000	NR	>10,000	NR	>10,000	NR
RP101075	0.31 ± 0.02	88.7 ± 6.1	>10,000	<i>13.6 ± 1.1</i>	>10,000	NR	>3,333	72.6 ± 9.0
RP101988	0.40 ± 0.02	85.5 ± 0.4	>10,000	NR	>10,000	<i>20.8 ± 6.0</i>	>10,000	32.0 ± 7.3
RP101442	3.49 ± 0.23	89.2 ± 1.1	>10,000	NR	>10,000	NR	>10,000	NR
RP112289	9.20 ± 0.48	71.7 ± 3.9	>10,000	NR	>10,000	NR	>10,000	NR
RP112509	10.89 ± 1.61	86.2 ± 3.5	>10,000	NR	>10,000	NR	>10,000	NR

EC<sub>50</sub> = concentration at which 50% of maximal activity is observed; IA = intrinsic activity (% relative to S1P response); NR = no response (Mean %E<sub>max</sub> < 10%, where E<sub>max</sub> is the maximal response achieved relative to the internal positive control, sphingosine 1-phosphate; S1P = sphingosine 1-phosphate; S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, or S1P<sub>4</sub>, = sphingosine 1-phosphate receptor 1, 2, 3, or 4, respectively. Data are expressed as mean and standard error of the mean (SEM), N = 3 to 4 independent experiments.

*Italic = response achieved at the top test compound concentration of 10,000 nM.*

**Bold = major human metabolites that contribute > 10% of the total drug-related exposure in the plasma.**

\* CC1084037 is a racemate. R and S enantiomers of CC1084037 are equally potent in in vitro assays ([Report RP-PH-014](#)).

Source: [Report RP-PH-010](#).

S1P<sub>1</sub> receptor internalization occurs upon activation of the receptor. Internalization of the receptor was studied in HEK293 cells that were incubated with ozanimod or its nine circulating metabolites (RP-PH-013, RP-PH-003). The parent and all metabolites, except for RP101124, caused receptor internalization (sponsor's Table 5, below). Similar internalization of the S1P<sub>5</sub> receptor was not observed when CHO cells overexpressing the receptor were incubated with 1 μM ozanimod (RP-PH-003).

**Table 5: Potency and Intrinsic Activity of Ozanimod and Metabolites to Induce Sphingosine 1-phosphate Receptor Subtype 1 Internalization**

Compound	1 Hour		3 Hour		6 Hour		24 Hour	
	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA	EC <sub>50</sub> (nM)	IA
Ozanimod	17.38 ± 3.12	72.08 ± 7.13	7.56 ± 1.21	75.57 ± 3.17	4.40 ± 1.04	73.18 ± 1.68	1.45 ± 0.23	64.72 ± 0.61
<b>CC112273</b>	<b>5.16 ± 1.37</b>	<b>77.83 ± 9.08</b>	<b>3.74 ± 1.21</b>	<b>77.03 ± 7.73</b>	<b>1.69 ± 0.75</b>	<b>86.64 ± 4.04</b>	<b>1.03 ± 0.27</b>	<b>54.71 ± 4.98</b>
<b>CC1084037</b>	<b>4.35 ± 1.04</b>	<b>67.08 ± 15.88</b>	<b>2.84 ± 0.48</b>	<b>83.06 ± 0.83</b>	<b>1.21 ± 0.33</b>	<b>77.60 ± 3.79</b>	<b>1.04 ± 0.16</b>	<b>58.23 ± 6.98</b>
<b>RP101124</b>	NR		NR		NR		NR	
RP101075	12.34 ± 3.13	76.88 ± 3.81	5.61 ± 0.75	76.68 ± 34.57	3.99 ± 0.83	69.73 ± 3.28	1.01 ± 0.08	65.25 ± 3.85
RP101988	3.69 ± 1.33	66.64 ± 1.55	1.53 ± 0.21	69.36 ± 8.96	1.10 ± 0.32	65.42 ± 8.31	0.41 ± 0.07	65.53 ± 3.55
RP101442	6.08 ± 0.96	66.97 ± 4.68	3.70 ± 0.95	81.27 ± 4.91	3.22 ± 0.63	83.11 ± 10.35	1.28 ± 0.15	57.12 ± 6.75
RP112289	24.65 ± 10.36	60.17 ± 8.86	11.09 ± 4.40	76.92 ± 6.63	7.88 ± 0.36	74.73 ± 0.68	3.79 ± 0.29	59.06 ± 4.10
RP112509	18.44 ± 1.70	64.78 ± 6.14	9.99 ± 3.05	87.76 ± 3.74	5.50 ± 7.60	73.18 ± 1.68	1.49 ± 0.47	55.33 ± 7.29

EC<sub>50</sub> = concentration at which 50% of maximal activity is observed; IA = intrinsic activity; NR= no response (no observed loss of sphingosine 1-phosphate receptor 1 expression from the plasma membrane); SEM = standard error of the mean.

Data are shown as mean ± SEM (n = 3 or 4 for metabolites and n = 7 for ozanimod as it was included in all experimental runs) for EC<sub>50</sub> for internalization of sphingosine 1-phosphate receptor 1 (S1P<sub>1</sub>) as measured by flow cytometry analysis and for IA, which is the difference between maximum and minimum percentage of internalization for each compound relative to dimethyl sulfoxide (DMSO) vehicle control.

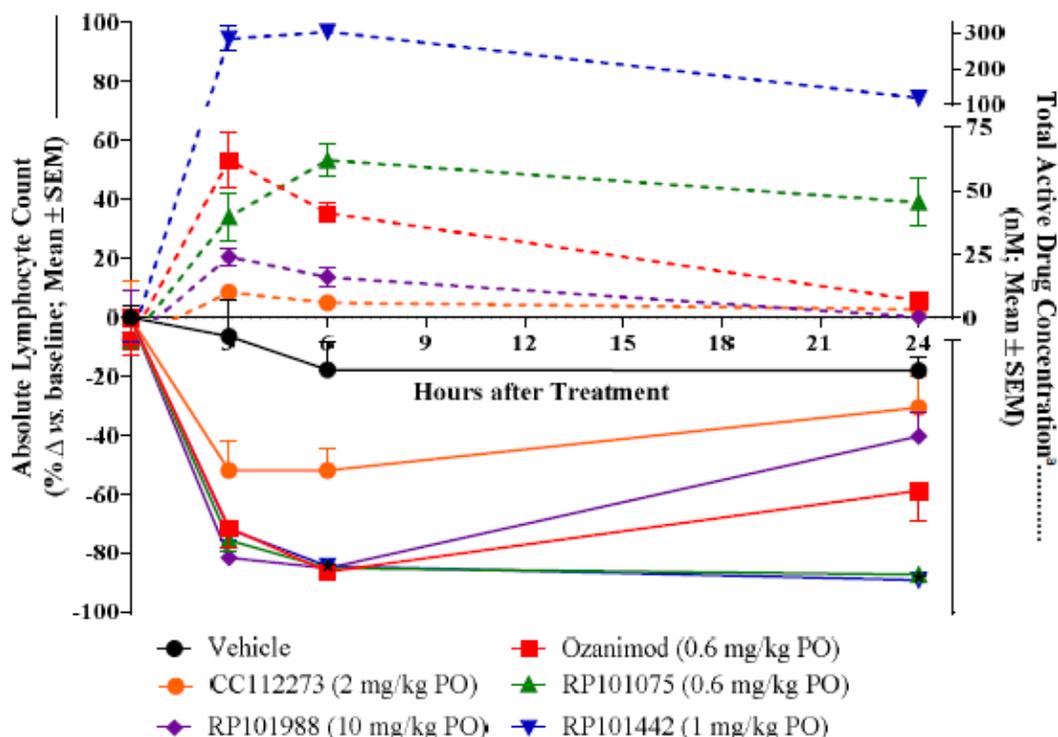
**Bold = major human metabolites that contribute > 10% of the total drug-related exposure in the plasma.**

Source: Report RP-PH-013.

In vitro studies were conducted with primary astrocyte cultures from mouse, rat, and human that were incubated with ozanimod, CC112273, or RP101988 for 10 minutes, after which cells were lysed and assessed for phosphorylation of protein kinase B (AKT) and extracellular-signal-regulated kinase activity (ERK; RP-PH-004, RP-PH-009, RP-PH-12). Ozanimod and the two metabolites exhibited potent stimulation of AKT and ERK phosphorylation in astrocytes from all three species. An additional study conducted with mouse primary astrocytes demonstrated that signaling through the S1P<sub>1</sub>, not S1P<sub>5</sub>, was responsible for the increased phosphorylation (RP-PH-011).

The reduction in the number of circulating lymphocytes is an established pharmacodynamic effect of S1P receptor agonism. Ozanimod (0.6 mg/kg) and its

metabolites (2 mg/kg CC112273, 0.6 mg/kg RP101075, 1 mg/kg RP101442, 10 mg/kg RP101988) decreased the number of circulating CD4+, CD8+, and B220+ lymphocyte subtypes by 52 to 89%, relative to pre-dose levels, after a single oral dose in Sprague Dawley rats (RP-PH-005, sponsor's figure, below). Ozanimod also decreased circulating lymphocytes in C57BL/6 mice, beagle dogs, and cynomolgus monkeys (RP-PH-006, RP-PK-002). In all species tested, the reduction in circulating lymphocytes was reversible upon cessation of treatment.



PO = oral; SEM = standard error of the mean; %Δ = percent change.

<sup>a</sup> Total active drug = administered compound plus active metabolite[s].

The sponsor conducted several in vivo efficacy studies of ozanimod and its metabolites in the mouse (C57BL/6) experimental autoimmune encephalomyelitis model, the results of which are summarized in the sponsor's table, below (20091001-1d, 20091203-2b, and RP-PH-006). Ozanimod, RP101442, RP101075, and RP101988 markedly decreased circulating lymphocyte counts and disease score. CC112273 decreased the disease score but was not as effective as the parent or other tested metabolites in causing circulating lymphocyte reduction in study RP-PH-006. However, in a follow-up study (RP-PH-016), CC112273 reduced circulating lymphocytes by > 70% after 5 days of dosing at 10 mg/kg.

**Table 7: Summary of Ozanimod and Active Metabolites in the Mouse Experimental Autoimmune Encephalomyelitis Model**

Treatment	Dose(s) (mg/kg/day)	Disease Score	Body Weight Loss	Absolute Lymphocyte Counts <sup>a</sup>
FTY720 <sup>b</sup>	3	Significantly attenuated (~ 55%)	Significantly attenuated	~ 64% ↓
Ozanimod	0.2, 0.6	Significantly attenuated (≤ 44%)		~ 50% ↓
RP101442	0.2, 0.4, 0.8			≤ 69% ↓
RP101075	0.05, 0.1, 0.3			≤ 45% ↓
RP101988	2, 6, 20			≤ 43% (NS)
CC112273	2, 6, 10	Significantly attenuated (≤ 43%) <sup>c</sup>	Trend for attenuation	5% (NS) <sup>d</sup>
CC1084037	CC1084037 was not tested directly but present at clinically relevant levels (≤ 16 nM) as a metabolite and likely contributed to efficacy in the CC112273 EAE study (Report RP-PH-006-1.0-Addendum#1). Similarly, CC1084037 is anticipated to contribute to the PD effect in the mouse CC112273 study (Report RP-PH-016).			

EAE = experimental autoimmune encephalomyelitis; NS – not significantly different.

<sup>a</sup> absolute lymphocyte counts assessed 24 hours after final dose and compared with EAE vehicle control animals

<sup>b</sup> In all 4 experimental autoimmune encephalomyelitis model studies, 64% was the average lymphocyte reduction induced by FTY720.

<sup>c</sup> during the first 7 days of treatment

<sup>d</sup> a separate study (Report RP-PH-016) demonstrated significant (≤ 72 %) decrease in lymphocyte counts in C57BL/6J mice after 5 days of dosing at 10 mg/kg, an efficacious dose in the EAE model.

Source: Report RP-PH-006-1.0-Addendum#1.

The efficacy of ozanimod was also assessed in a mouse model of cuprizone-induced demyelination (RP-PH-015). Mice were given a daily oral dose of 5 mg/kg ozanimod both during the 6-week cuprizone treatment period and the following 12-week recovery period during which cuprizone was not administered. Ozanimod decreased circulating lymphocytes by 99.5% at week 6 and 86% at week 18. Concurrent treatment with ozanimod and cuprizone decreased the rate of demyelination, compared to control; however, there was no effect of ozanimod treatment on remyelination during the 12-week recovery period when compared to controls.

## 4.2 Secondary Pharmacology

In vitro binding of ozanimod and its metabolites, CC112273, CC1084037, RP101075, RP101442, RP101988, and RP101124, was assessed using a high-throughput screening assay (CEREP Express Profile; 10040667, CC-DISC-ET-2289, 16603, 16829, 17638, 100032946). When tested at 1 μM, CC112273, RP101075, RP101988, RP101442, and RP101124 did not exhibit binding in the screening assays. When tested at concentrations of up to 10 μM, ozanimod inhibited the human 5-HT transporter by 73%; an IC<sub>50</sub> of 3.6 μM and Ki 600 nM was determined in a follow-up assay (CC-DISC-ET-2926). When tested at concentrations of up to 10 μM, CC1084037 bound to the human adenosine 3 (A3), melatonin (MT1), sigma, and GABA-gated chloride channel receptors; a follow-up study demonstrated an IC<sub>50</sub> of 300 and 1500 nM at the A3 and MT1 receptors, respectively. There was no discussion regarding any functional assessments of the GABA-gated chloride channel and sigma receptor binding of CC1084037.

Several of the metabolites, CC112273, RP101075, and CC1084037, were determined to be in vitro inhibitors of monoamine oxidase (MAO). CC1084037 inhibited human recombinant MAO-B ( $IC_{50}$ = 43 to 57 nM) but not MAO-A ( $IC_{50}$  > 10  $\mu$ M; RPC-1063-DMPK-2859). MAO-B was inhibited in vitro by RP112273 ( $IC_{50}$ = 5.7 nM) and RP101075 ( $IC_{50}$ = 56 nM; RP-PK-026). MAO-A was inhibited by RP101075 ( $IC_{50}$ = 1322 nM) but not RP112273. When assessed in two separate studies conducted in the mouse, there was no evidence of serotonin syndrome caused by ozanimod or RP112273 (PH-008; RP-PH-017).

### 4.3 Safety Pharmacology

CNS: A functional observational battery was conducted as part of the 28-day study (026004) and is reviewed in the General Toxicology section of this review.

Cardiovascular: In a GLP in vitro hERG assay, ozanimod and the major human metabolite, CC112273, were determined to be potent hERG inhibitors ( $IC_{50}$  of 0.2 and 0.6  $\mu$ M, respectively; 100503.SJD, 170531.SFD). CC1084037 inhibited hERG by 15%, when tested at a concentration of up to 3  $\mu$ M; precipitates prevented assessment at higher concentrations (CC-DISC-ET-2880).

In a non-GLP study, cynomolgus monkeys dosed with 0.15, 3 or 10 mg/kg ozanimod exhibited an 18-26% increase in PR interval between 0.5 and 3.5 hours after dosing; no other ECG parameters were affected (1840-002).

A GLP cardiovascular safety pharmacology study of ozanimod was conducted in telemetered cynomolgus monkeys (026002). In monkeys given a single oral dose of 0, 0.15, 3, or 30 mg/kg, ECG and hemodynamic parameters were monitored for up to 24 hours after dosing. Diastolic blood pressure was decreased by 20%, relative to pretest values, at the MD and HD at 30 minutes after dosing but normalized by 2-3 hours after dosing. Heart rate (27%) was decreased and R-R interval (37%) was increased, both relative to pretest, at the HD for up to 24 hours after dosing. QTc interval (Bazett's correction) was not affected. The NOAEL was the LD of 0.15 mg/kg, with decreased diastolic blood pressure and heart rate observed at higher doses.

Respiratory: Sprague Dawley rats (n=2/sex/group) were given a daily oral dose of 0, 0.1, 2, or 8 mg/kg ozanimod for 5 days and subjected to head-out plethysmography on days 1 and 5 of dosing for up to 24 hours post-dose on each day (non-GLP; 1275rr32-011). There were no ozanimod-related effects on respiratory parameters. In the GLP pivotal respiratory safety pharmacology study, male SD rats (n=18/group) were given a daily dose of 0, 0.2, 2, or 30 mg/kg ozanimod for seven days. Whole-body plethysmography was conducted for up to 24 hours after dosing on the first and last day of dosing. At 12 and 24 hours after dosing, respiratory rate was increased (Day 1: 16 to 23%; Day 7: 13 to 15%) and tidal volume was decreased (Day 1: 12 to 15%; Day 7: 12 to 14%). Lung weight was increased by 34% and 86% in MD and HD rats, respectively, at the end of the 7-day dosing period.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

Analytical Methods and Validation Reports: The sponsor developed and validated LC-MS/MS methods for detecting and quantifying ozanimod and its circulating metabolites in mouse, rat, rabbit, and monkey plasma, except for RP101124 in rabbit plasma. The lower limits (LLOQ) and upper limits of quantification (ULOQ) for these assays are provided in the sponsor's table, below.

**Table 2: Bioanalytical Method Validations for the Measurement of Plasma Concentrations of Ozanimod and Metabolites**

Report Number	Analyte	Species	LLOQ (ng/mL)	ULOQ (ng/mL)
181882 <sup>a</sup>	Ozanimod	Mouse	0.400	100
	RP101075			
	RP101442			
	RP101988			
	RP101124			
RPC1063-DMPK-2886 (CEL-R8871) <sup>a</sup>	CC112273	Mouse	0.040	8.000
	CC1084037		0.020	4.000
	RP112289		0.020	4.000
185698 <sup>a</sup>	CC112273	Mouse	0.200	100
180264 <sup>a</sup>	Ozanimod	Rat	0.400	100
	RP101075			
	RP101442			
	RP101988			
	RP101124			
025996 <sup>a</sup>	Ozanimod	Rat	0.400	300
	RP101442			
	RP101075			
185687 <sup>a</sup>	CC112273	Rat	0.100	50.0
187239 <sup>a</sup>	CC112273	Rat	20.0	3200
	CC1084037		10.0	1600
	RP112289		10.0	1600
AB03213 <sup>a</sup>	Ozanimod	Rabbit	0.800	300
	RP101442			
	RP101075			

**Table 2: Bioanalytical Method Validations for the Measurement of Plasma Concentrations of Ozanimod and Metabolites (Continued)**

Reference Number	Analyte	Species	LLOQ (ng/mL)	ULOQ (ng/mL)
RPC1063-DMPK-2887 (CEL-R8989) <sup>a</sup>	CC112273	Rabbit	0.040	8.000
	CC1084037		0.020	4.000
	RP112289		0.020	4.000
1840-035 <sup>a</sup>	CC112273	Rabbit	0.0500	20.0
030550 <sup>a</sup>	Ozanimod	Monkey	0.400	300
	RP101442			
	RP101075			
180262 <sup>a</sup>	Ozanimod	Monkey	0.400	100
	RP101442			
	RP101075			
	RP101988			
	RP101124			
185684 <sup>a</sup>	CC112273	Monkey	0.0500	125
187236 <sup>a</sup>	CC112273	Monkey	20.0	3200
	CC1084037		10.0	1600
	RP112289		10.0	1600

LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

<sup>a</sup> Study conducted in compliance with the US Food and Drug Administration: Guidance for Industry: Bioanalytical Method Validation, May 2001.

**Absorption:** When assessed in Caco-2 cells, the cellular permeability of ozanimod was high and was mainly due to passive diffusion (16RECEP1R1, 16RECEP3R1, 16RECEP3R1GLP372). The half-life and  $T_{max}$  of ozanimod and its metabolites in mice, rats, and monkeys dosed orally with ozanimod are summarized in the table below.

	Half-life (hr)			Tmax (hr)		
	Mouse	Rat	Monkey	Mouse	Rat	Monkey
<b>Ozanimod</b>	5-25	10-14	6-10	1	2-6	4
<b>RP101124</b>	11	8	11	2-4	24	13
<b>CC112273</b>	8	8-31	11	2	4	7
<b>CC1084037</b>	NA	8-12*	NA	NA	6	8
<b>RP101075</b>	13	38-52	7-10	4-24	2-6	4-11
<b>RP101442</b>	NA	18-30	NA	24	24	8
<b>RP101988</b>	4-11	8-10	10	1	2	4

*Table:* Half-life and Tmax values for ozanimod and its metabolites (summarized from 1840-027, 1840-028, 1840-033, 1840-040, 1840-043, 1840-044, 1840-047, 1840-054, RPC1063-dmpk-2836, PK-001, PK-015, PK-023) \*= calculated from available data (1840-047). NA= not available.

The half-life of ozanimod in pregnant NZW rabbits was 5-6 hours after oral dosing (1840-024); circulating levels of RP101988, RP101075, and RP101124 were quantitated, but PK parameters were not provided.

Because CC112273 and CC1084037 were not determined to be major human metabolites until late in clinical development, the sponsor conducted bridging studies to determine if adequate exposure had been achieved in the chronic toxicity, carcinogenicity, and embryofetal development studies (summarized in the sponsor's tables, below).

**Table 9: Mean Steady-State Exposure of Ozanimod and its Major Metabolites in Repeat-Dose Studies in Rats**

Species Study Type (Study Number)	Dose (mg/kg/day)	Steady State Exposure <sup>a</sup> AUC <sub>t</sub> (ng·hr/mL)							
		Ozanimod (ng·hr/mL)		RP101124 (ng·hr/mL)		CC112273 (ng·hr/mL)		CC1084037 (ng·hr/mL)	
		M	F	M	F	M	F	M	F
Rat 26-week Repeated Dose (71357) <sup>b</sup>	0.2 (NOAEL)	31.5	59.9	27.2	57.8	--	--	--	--
	2	649	805	616	750	--	--	--	--
	30	9340	15100	8847	14676	--	--	--	--
Rat Carcinogenicity 2-year Carcinogenicity (b)(4)-72515) <sup>b</sup>	0.2	32.9	49.7	104	120	--	--	--	--
	0.7	138	393	328	393	--	--	--	--
	2 (NOAEL)	517	685	570	1050	--	--	--	--
Rat (maternal) Embryo-fetal Development (AB03215) <sup>b</sup>	0.2	--	42.3	--	--	--	--	--	--
	1 (NOAEL)	--	209	--	--	--	--	--	--
	5	--	1420	--	--	--	--	--	--
Rat 14-Day Bridging PK Study (1840-047) <sup>b</sup>	0.2	--	--	--	--	2.31	2.25	0.069	NC
	1	--	--	--	--	20.3	17.2	1.13	0.678
	2	--	--	--	--	43.2	40.4	2.80	1.82
	30	--	--	--	--	1100	879	49.3	32.7

AUC<sub>t</sub> = area under the concentration-time curve calculated from 0 to the last quantified time point post dosing;

GLP = good laboratory practices; -- = not available; NC = not calculated; NOAEL = no observed adverse effect level.

<sup>a</sup> Steady-state exposures were measured on Day 178 for Study 71357, Day 185 for Study (b)(4)-72515, Day G17 for Study AB03215, and Day 14 for Study 1840-047.

<sup>b</sup> Study is GLP compliant.

**Table 11: Mean Steady-State Exposure of Ozanimod and its Major Metabolites in Repeat-Dose Studies in Mice**

Species Study (Study number)	Dose Mouse Strain (mg/kg/day)	Steady-State Exposure <sup>a</sup> (ng·hr/mL)							
		Ozanimod (ng·hr/mL)		RP101124 (ng·hr/mL)		CC112273 (ng·hr/mL)		CC1084037 (ng·hr/mL)	
		M	F	M	F	M	F	M	F
Mouse 28-Day Toxicity Study (72207) <sup>b</sup>	0.4	192	168	8.68	17.0	--	--	--	--
	4	2030	1790	126	186	--	--	--	--
	80	41200	32300	3210	3960	--	--	--	--
Mouse 6-month Carcinogenicity (AE18BZ.7G8R. <sup>(b)(4)</sup> ) <sup>b</sup>	8 (NOAEL)	9410	6590	--	--	--	--	--	--
	25	29900	19700	--	--	--	--	--	--
	80	89323	65500	--	--	--	--	--	--
Mouse 14-Day Bridging GLP-Compliant PK Study (1840-040) <sup>b</sup>	0.4 (CD1)	--	--	--	--	9.37	11.3	9.86	8.46
	8 (CByB6F1/J)	--	--	--	--	267	245	25.3	20.2
	8 (CD1)	--	--	--	--	200	196	13.8	23.6
	25 (CD1)	--	--	--	--	735	876	70.9	58.2
	80 (CD1)	--	--	--	--	2560	2410	211	201

F = female; M = male; -- = not available; NOAEL = no observed adverse effect level.

<sup>a</sup> Steady-state exposure was measured at Day 28 for Study 72207, Week 26 for Study AE18BZ.7G8R<sup>(b)(4)</sup>, and Day 14 for Study 1840-040.<sup>b</sup> Study is GLP compliant.**Table 14: Mean Steady-State Exposure of Ozanimod and its Major Active Human Metabolites in Repeat-Dose Studies of Ozanimod in Cynomolgus Monkey**

Study/Species	Dose (mg/kg/day)	Steady State Exposure <sup>a</sup> (ng·hr/mL)							
		Ozanimod (ng·hr/mL)		RP101124 (ng·hr/mL)		CC112273 (ng·hr/mL)		CC1084037 (ng·hr/mL)	
		M	F	M	F	M	F	M	F
Monkey 39-week Repeated Dose (30477) <sup>b</sup>	0.1 (NOAEL)	19.8	25.4	0.578	2.81	--	--	--	--
	1	208	199	61.4	56.1	--	--	--	--
	15	3530	3730	774	827	--	--	--	--
Monkey 14-Day Bridging PK Study (1840-043) <sup>b</sup>	0.1	--	--	--	--	20.9	21.5	5.3	4.37
	1	--	--	--	--	212	194	45.4	40.5
	15	--	--	--	--	3670	4520	736	1160

F = female; M = male; -- = not applicable.

<sup>a</sup> Steady-state exposure was measured at Day 274 for Study 30477 and Day 14 for Study 1840-043.<sup>b</sup> Study is GLP compliant.

**Table 16: Mean Toxicokinetic Parameters for Ozanimod Metabolites CC112273 and CC1084037 on Day 14 in New Zealand White Rabbits**

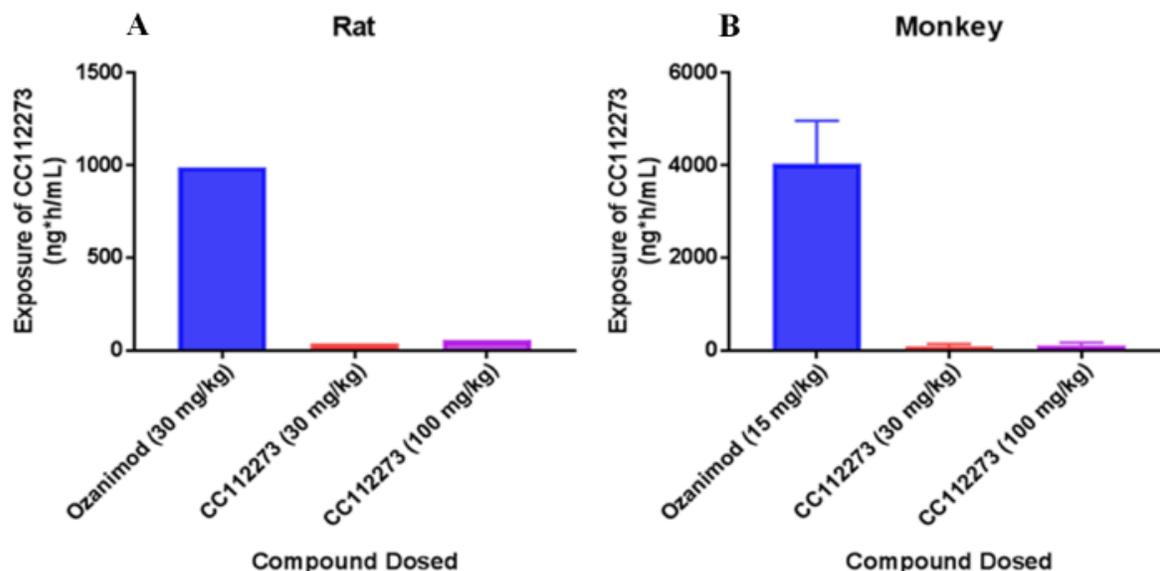
Species Study Report Number	Dose (mg/kg/day)	Steady State Exposure (ng·hr/mL)					
		CC112273			CC1084037		
		C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·hr/mL)	R <sup>a</sup>	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·hr/mL)	R <sup>a</sup>
Rabbit 14-day Repeated Dose (1840-054)	0.2	0.386	6.77	1.51	0.206	3.78	1.87
	0.6	1.040	18.0	1.18	0.590	10.8	1.51

AUC<sub>0-24</sub> = area under concentration versus time curve from time of dosing to 24 hours; C<sub>max</sub> = maximum concentration of drug in plasma.

<sup>a</sup> R = AUC<sub>0-24</sub> Day 14/AUC<sub>0-24</sub> Day 1.

To achieve higher exposure to the major human metabolites in nonclinical studies, additional studies were conducted in which mice, rats, and monkeys were dosed orally with ozanimod metabolites. Increasing the systemic exposure to CC112273 could not be achieved by direct dosing with CC112273 in rats or monkeys, mainly due to extensive clearance after oral dosing with the metabolite (sponsor's figure, below). CC1084037, which is in equilibrium with CC112273 in vivo, was not detected in monkey plasma after oral dosing with CC112273.

**Figure 5: Comparison of Steady-State Exposures of CC112273 Dosed Via Direct Administration and With Ozanimod to (A) Rats and (B) Monkeys**



Source: [Report 1840-047](#), [Report 1840-032](#), [Report 1840-043](#), and [Report RPC1063-DMPK-3001](#).

In a single dose study conducted in male rat, it was determined that an oral dose of 1000 mg/kg CC1084037 was necessary to achieve a similar systemic exposure in rats given a single oral dose of 800 mg/kg ozanimod (sponsor's table, below).

**Table 19: Mean Pharmacokinetic Parameters of CC1084037 in CD-IGS Male Rats Following Single Oral Doses of CC1084037 at 10, 50, 500, or 1000 mg/kg or Ozanimod at 800 mg/kg.**

Compound Dosed	Dose mg/kg	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>last</sub> (ng·hr/mL)
CC1084037	10	1.49 ± 0.232	2.3 ± 1.5	10.3 ± 6.85
	50	3.06 ± 1.11	9.0 ± 13.0	38.8 ± 24.8
	500	5.97 ± 2.83	4.6 ± 3.1	69.2 ± 45.5
	1000	6.90 ± 1.66	6.0 ± 3.5	103 ± 65.4
Ozanimod	800	6.39 ± 2.04	10.7 ± 11.5	103 ± 47.9

AUC<sub>last</sub> = area under concentration versus time curve from time of dosing to last dose; C<sub>max</sub> = maximum concentration of drug in plasma; t<sub>max</sub> = time to maximum plasma concentration.  
Source: Report RPC1063-DMPK-2975.

In C57BL/6 mice dosed orally with CC112273, exposure to CC112273 was slightly lower when compared to mice dosed with ozanimod (sponsor's Table 20 below and sponsor's Table 11, above). Exposure to RP101124 was much higher in mice after oral dosing with CC112273 compared to oral dosing with ozanimod (sponsor's Table 21, below and sponsor's Table 11, above).

**Table 20: Mean Pharmacokinetic Parameters for CC112273 in Male Mice after Single and Repeated Administration**

CC112273 Dose (mg/kg)	Route (frequency)	t <sub>1/2</sub> (hr)		t <sub>max</sub> (hr)		C <sub>max</sub> (ng/mL)		AUC <sub>0-24</sub> (ng·hr/mL)	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
0.3	IV (single)	10	NA	0.2	NA	108	NA	73	NA
3	Oral (single and repeated dose for five days)	8	8	1	2	19	53	93	207
10		9	13	1	0.5	46	64	232	371
30		20	13	6	0.5	45	139	469	677
100		12	24	2	0.5	59	88	610	1084

AUC<sub>last</sub> = area under concentration versus time curve from time of dosing to last dose; AUC<sub>0-24</sub> = area under concentration versus time curve from time of dosing to 24 hours; C<sub>max</sub> = maximum concentration of drug in plasma; IV = intravenous; NA = not applicable; t<sub>1/2</sub> = half-life; t<sub>max</sub> = time to maximum plasma concentration.  
Source: Report RP-PK-022.

**Table 21: Mean Pharmacokinetic Parameters for RP101124 in Male Mice after and Single and Repeated Administration of CC112273**

CC112273 Dose (mg/kg)	Route (frequency)	t <sub>1/2</sub> (hr)		t <sub>max</sub> (hr)		C <sub>max</sub> (ng/mL)		AUC <sub>0-24</sub> (ng·hr/mL)	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
0.3	IV (single)	8	NA	0.2	NA	7	NA	28	NA
3	Oral (single and repeated dose for five days)	4	4	4	4	473	525	4602	4813
10		5	3	4	4	1220	1443	13276	16960
30		7	4	6	12	2520	4360	32169	51429
100		3	6	12	12	4017	4840	44679	57324

AUC<sub>last</sub> = area under concentration versus time curve from time of dosing to last dose; AUC<sub>0-24</sub> = area under concentration versus time curve from time of dosing to 24 hours; C<sub>max</sub> = maximum concentration of drug in plasma; IV = intravenous; NA = not applicable; t<sub>1/2</sub> = half-life; t<sub>max</sub> = time to maximum plasma concentration.  
Source: Report RP-PK-022.

**Distribution:** Plasma binding of ozanimod (97-98%) and its metabolites (89-99%) was similar among CD-1 mouse, SD rat, cynomolgus monkey, and human (RP-PK-004, RP-PK-013, RP-PK-019, RP-PK-025, RPC1063-DMPK2860). Ozanimod and the major metabolite, CC112273, both exhibited binding to lipoproteins (CEL-R7743). Brain distribution was high for ozanimod (> 3-fold brain to plasma ratio) and metabolites (> 10-fold brain to plasma ratio) in mice (RP-PK-016-1) and in rat (~2-fold brain to plasma ratio; RP-PK-023-1). Tissue distribution was assessed for up to 504 hours (21 days) after a single oral dose of [<sup>14</sup>C]-ozanimod in Lister Hooded pigmented rats (RCT/01). The highest levels of radioactivity were detected in the GI tract, uveal tract, lachrymal gland, pituitary gland, liver, and kidney. At the final time point, radioactivity was still detected in the hippocampus and uveal tract; radioactivity was BLQ in all other tissues. Placental transfer of ozanimod and its metabolites in pregnant SD rats given a daily dose of up to 2 mg/kg from gestational day (GD) 6 through GD 18 was low (0.08 to 0.62 fetal to maternal plasma ratio); milk to plasma ratio for ozanimod was 2-fold (1840-023). RP101988, was highly concentrated in the milk of lactating rats dosed with up to 2 mg/kg ozanimod (22- to 24-fold, milk to plasma ratio; sponsor's table, below).

Test Article: RPC1063									
Study Number: 1840-023 (continued)									
Ozanimod Dose (mg/kg/day)	Day	Age/Sample	Analyte	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>∞</sub> (ng·hr/mL)	AUC <sub>0-24</sub> (ng·hr/mL)	t <sub>1/2</sub> (hr)	Milk/Plasma AUC <sub>0-24</sub> Ratio
0.2	LD12	Maternal Milk	Ozanimod	10.8	4	83.71	82.50	3.62	1.98
			RP101075	1.01	4	10.67	9.23	8.05	2.35
			RP101124	0.68	4	149.59	14.26	157	0.33
			RP101442	0.44	4	48.29	8.89	75.3	0.68
			RP101988	104.18	4	1000.81	918.81	6.59	24.3
0.7	LD12	Maternal Milk	Ozanimod	26.25	2	237.38	230.51	4.31	1.65
			RP101075	1.84	8	DNS	28.08	DNS	1.83
			RP101124	3.18	8	DNS	45.76	DNS	0.32
			RP101442	2.09	8	DNS	41.04	DNS	1.28
			RP101988	254.81	8	DNS	3020.01	DNS	22.0
2.0	LD12	Maternal Milk	Ozanimod	108.38	4	950.74	937.40	3.63	1.99
			RP101075	7.86	4	138.39	113.53	8.85	2.49
			RP101124	9.11	12	DNS	151.03	DNS	0.29
			RP101442	11.67	24	DNS	175.45	DNS	1.61
			RP101988	804.58	2	11540.73	11290.11	3.79	24.5
<b>Additional Information:</b>			Abbreviations: AUC <sub>0-24</sub> = area under the blood concentration versus time curve from time 0 to 24 hours; AUC <sub>∞</sub> = area under concentration versus time curve from time of dosing and extrapolated to infinity; C <sub>max</sub> = maximum blood concentration; DNS = data not sufficient; GD18 = Gestation Day 18; GLP = Good Laboratory Practice; LC-MS/MS = liquid chromatographic tandem mass spectrometric method; LD12 = Lactation Day 12; NA = not applicable; t <sub>1/2</sub> = terminal phase half-life; t <sub>max</sub> = time to maximum blood concentration.						

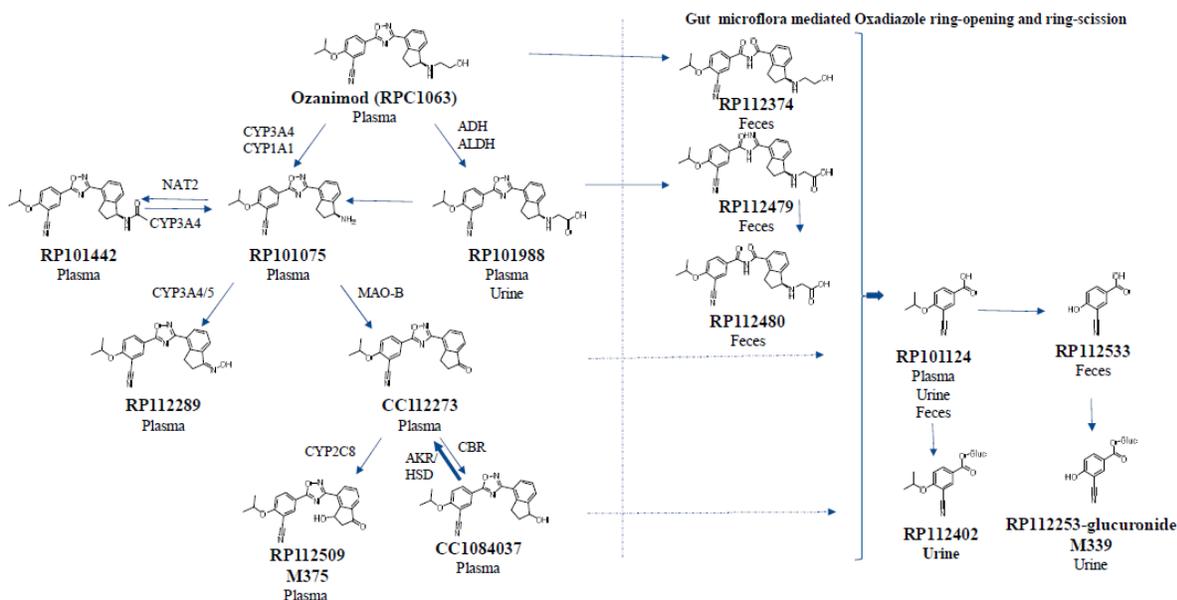
Note: Data is converted to ng from the reported nM. Molecular weights used to convert were Ozanimod = 404.4, RP101075 = 360.4, RP101124 = 205.2, RP101442 = 402.4, RP101988 = 418.4.

Ozanimod, RP101075, and RP101988 were detected in the fetuses of pregnant New Zealand white rabbits dosed with 0.2 mg/kg ozanimod from GD 6 to GD 19 (1840-025). The fetal-to-maternal ratio for these compounds was 1.2, 2.6, and 0.07, respectively.

**Metabolism:** Ozanimod is extensively metabolized in animals and humans with the major human metabolites being CC112273 (RP112273), CC1084037 (RP100798), and RP101124 (sponsor's figure, below). Metabolism of ozanimod is primarily mediated through alcohol dehydrogenase (ALD) and aldehyde dehydrogenase (ALDH) to form

RP101988, CYP3A4 and CYP1A1 mediated metabolism to form RP101075, and intestinal microbiota ring scission to form RP101124. CC112273 is formed via MAO-B-mediated oxidative deamination of RP101075. The formation of CC1084037 is the result of CC112273 undergoing carbonyl reduction; the formation of CC112273 and CC1084037 is reversible.

**Figure 6: Proposed Metabolic Pathway of Ozanimod**



**Excretion:** The majority of dosed radioactivity was excreted via feces (83%), with urinary excretion (5-8%) being a minor component, when [ $^{14}\text{C}$ ]-ozanimod was administered at 0.5 mg/kg in SD rat (RCT/01). The excreted radioactivity was composed predominantly of ozanimod metabolites.

**Pharmacokinetic Drug Interactions:** When assessed in vitro with pooled human hepatic microsomes, ozanimod and its metabolites (RP101075, RP101442, RP101124, RP101988, RP112273, CC1084037) were not potent inhibitors of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 (RP-PK-003-3.0, XT165054, RP-PK-012-01, XT175040, RPC1063-DMPK-2863). RP101124 was not a potent inhibitor of uridine 5'-diphosphoglucuronosyltransferase (UGT) isoforms 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15, 2B17 in human liver microsomes (XT175076). The major human metabolites, CC112273 and CC1084037, were potent inhibitors of human recombinant MAO-B ( $\text{IC}_{50}$ : 5.7 nM and 58 nM, respectively; RP-PK-026, RPC1063-DMPK-2859); the two metabolites did not inhibit MAO-A. CC112273 and CC1084037 are both potent inhibitors ( $\text{IC}_{50}$ : 22 to 25 nM) of the breast cancer resistance protein (BCRP; XT178045 and RPC1063-DMPK-2841). MATE1, MATE2-K, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 were not inhibited by ozanimod or its metabolites (XS-0983, XS-1052, DMPK-2841, XT148054, XT178045).

## 6 General Toxicology

### 6.2 Repeat-Dose Toxicity

#### Mouse

TX-003-01: “Multiple Dose Toxicology Study of RPC1063 in the CByB6F1-Tg (HRAS) 2Jic-Wild Type (CByB6F1) Mouse.” Wild-type (WT) mice (5 females/group) were given a daily oral dose of 0, 0.2, 2, 10, or 50 mg/kg ozanimod for 3 days or 0, 0.2, 2, or 40 mg/kg ozanimod (Lot #024) for 14 days, in 0.5% carboxymethylcellulose (CMC). Total lymphocyte count was decreased on Day 3 by 12%, 81%, 86%, and 85% in mice dosed with 0.2, 2, 10 or 50 mg/kg, respectively. In the second group of mice, lymphocytes were reduced by 7%, 50%, and 69%, respectively on Day 14. There were no ozanimod-related histology findings on Day 14. Based on the lack of toxicity at the highest dose tested, the sponsor selected a high dose of 80 mg/kg for the 28-day dose range-finding study to support selection of doses for the pivotal 6-month carcinogenicity study in Tg.rasH2 mouse.

72207:” RPC1063: A 28-day oral dose range-finding toxicity study in CByB6F1 mice.” This study was conducted to support the selection of doses for the 6-month carcinogenicity study. CByB6F1 WT mice (Main: 10/sex/group; TK: 20/sex/group, except 4/sex/group for control) were given a daily oral dose of 0, 0.4, 4, or 80 mg/kg ozanimod (Lot AJ506FP-11-001) in 0.5% CMC for 28 days. On day 29, WBC and lymphocyte count was decreased at all dose levels in males and in MDF and HDF (sponsor’s table, below).

Percentage (%) Change in Hematology Parameters Compared to Mean Concurrent Control Values

	0.4 mg/kg/day		4 mg/kg/day		80 mg/kg/day	
WBC	-45%	-	-71%	-32%	-61%	-18%
LYMPH	-58%	-	-86%	-57%	-78%	-46%
%LYMPH	-20%	-	-51%	-37%	-43%	-32%

Absolute lung weight was increased (11% to 42%) and spleen weight was decreased (17% to 26%) in a dose-dependent manner. Minimal to mild accumulation of foamy macrophages occurred in the lung of 4/10 MDM, 5/10 MDF, and all HD animals. A minimal to mild decrease in splenic cellularity occurred in 4/10 LDM, 1/10 LDF, 7/10 MDM, 9/10 MDF, and all HD animals. TK parameters for ozanimod and several of its metabolites are provided in the sponsor’s tables, below.

Gender	Analyte	Formulation (RPC1063)	T <sub>max</sub> (h)	C <sub>max</sub> (uM)	C <sub>max</sub> (SE) (uM)	AUC <sub>0-24</sub> (uM <sup>h</sup> )	AUC <sub>0-24</sub> (SE) (uM <sup>h</sup> )	% of Total Agonist AUC <sup>a</sup>	% of Total AUC <sup>b</sup>	
Female	RPC1063	Low Dose - 0.4 mg/kg/day	6.00	0.0409	0.0144	0.412	0.0655	36.79	34.40	
		Mid Dose - 4 mg/kg/day	6.00	0.442	0.138	4.43	0.627	41.79	38.51	
		High Dose - 80 mg/kg/day	3.00	4.78	0.258	79.9	2.50	55.10	48.66	
	RP101075	Low Dose - 0.4 mg/kg/day	6.00	0.00678	0.00472	0.0431 <sup>c</sup>	0.0212 <sup>c</sup>	3.85	3.60	
		Mid Dose - 4 mg/kg/day	6.00	0.0591	0.0319	0.623	0.144	5.88	5.42	
		High Dose - 80 mg/kg/day	12.00	0.992	0.0777	18.9	0.822	13.03	11.51	
	RP101442	Low Dose - 0.4 mg/kg/day	NC	NC	NC	NC	NC	NC	NC	NC
		Mid Dose - 4 mg/kg/day	12.00	0.000867	0.000537	0.0135	0.00552	0.13	0.12	
		High Dose - 80 mg/kg/day	1.00	0.0571	0.00640	1.28	0.0583	0.88	0.78	
	RP101988	Low Dose - 0.4 mg/kg/day	6.00	0.132	0.126	0.634 <sup>c</sup>	0.566 <sup>c</sup>	56.61	52.93	
		Mid Dose - 4 mg/kg/day	6.00	1.07	0.993	5.50	4.47	51.89	47.81	
		High Dose - 80 mg/kg/day	1.00	3.35	0.323	45.3	6.33	31.24	27.59	
	Total Agonist	Low Dose - 0.4 mg/kg/day	6.00	0.179	0.145	1.12	0.652	N/AP	93.51	
		Mid Dose - 4 mg/kg/day	6.00	1.57	1.16	10.6	5.23	N/AP	92.14	
		High Dose - 80 mg/kg/day	3.00	8.82	0.238	145	7.56	N/AP	88.31	
	RP101124	Low Dose - 0.4 mg/kg/day	6.00	0.0107	0.00202	0.0777 <sup>c</sup>	0.0107 <sup>c</sup>	N/AP	6.49	
		Mid Dose - 4 mg/kg/day	6.00	0.0971	0.0295	0.904	0.158	N/AP	7.86	
		High Dose - 80 mg/kg/day	6.00	1.57	0.254	19.2	1.75	N/AP	11.69	

NC: Not Calculated, N/AP: Not Applicable  
<sup>a</sup> Total agonist AUC = combined AUC for pharmacologically active species (i.e. RPC1063, RP101075, RP101442 and RP101988).  
<sup>b</sup> Total AUC = combined AUC for all analytes (i.e. including inactive metabolite RP101124).  
<sup>c</sup> AUC<sub>0-T</sub> reported (analyte was BQL at 24 hours)

Gender	Analyte	Formulation (RPC1063)	T <sub>max</sub> (h)	C <sub>max</sub> (uM)	C <sub>max</sub> (SE) (uM)	AUC <sub>0-24</sub> (uM <sup>h</sup> )	AUC <sub>0-24</sub> (SE) (uM <sup>h</sup> )	% of Total Agonist AUC <sup>a</sup>	% of Total AUC <sup>b</sup>	
Male	RPC1063	Low Dose - 0.4 mg/kg/day	3.00	0.0407	0.00259	0.475	0.0261	69.75	65.68	
		Mid Dose - 4 mg/kg/day	3.00	0.413	0.0139	5.01	0.221	68.44	63.16	
		High Dose - 80 mg/kg/day	12.00	5.10	0.386	102	4.10	60.00	54.96	
	RP101075	Low Dose - 0.4 mg/kg/day	12.00	0.00473	0.000376	0.0854	0.00428	12.54	11.81	
		Mid Dose - 4 mg/kg/day	12.00	0.0615	0.00341	1.07	0.0354	14.62	13.49	
		High Dose - 80 mg/kg/day	12.00	2.10	0.241	40.1	2.41	23.59	21.61	
	RP101442	Low Dose - 0.4 mg/kg/day	NC	NC	NC	NC	NC	NC	NC	NC
		Mid Dose - 4 mg/kg/day	12.00	0.00247	0.000120	0.0435	0.00317	0.59	0.55	
		High Dose - 80 mg/kg/day	12.00	0.0989	0.00732	2.20	0.0998	1.29	1.19	
	RP101988	Low Dose - 0.4 mg/kg/day	6.00	0.0169	0.0128	0.106 <sup>c</sup>	0.0575 <sup>c</sup>	15.57	14.66	
		Mid Dose - 4 mg/kg/day	3.00	0.232	0.150	1.20	0.377	16.39	15.13	
		High Dose - 80 mg/kg/day	3.00	1.72	0.233	25.5	1.10	15.00	13.74	
	Total Agonist	Low Dose - 0.4 mg/kg/day	6.00	0.0561	0.0140	0.681	0.0660	N/AP	94.16	
		Mid Dose - 4 mg/kg/day	3.00	0.692	0.164	7.32	0.487	N/AP	92.28	
		High Dose - 80 mg/kg/day	12.00	8.34	0.497	170	5.28	N/AP	91.59	
	RP101124	Low Dose - 0.4 mg/kg/day	6.00	0.00451	0.000404	0.0422 <sup>c</sup>	0.00548 <sup>c</sup>	N/AP	5.84	
		Mid Dose - 4 mg/kg/day	6.00	0.0490	0.00816	0.612	0.0854	N/AP	7.72	
		High Dose - 80 mg/kg/day	6.00	1.33	0.568	15.6	2.69	N/AP	8.41	

NC: Not Calculated, N/AP: Not Applicable  
<sup>a</sup> Total agonist AUC = combined AUC for pharmacologically active species (i.e. RPC1063, RP101075, RP101442 and RP101988).  
<sup>b</sup> Total AUC = combined AUC for all analytes (i.e. including inactive metabolite RP101124).  
<sup>c</sup> AUC<sub>0-T</sub> reported (analyte was BQL at 24 hours)

AF00PS.2G3R. (b) (4): “RP-112273: 28-day repeated dose oral toxicity and toxicokinetic study in CByB6F1 mice.” CByB6F1 mice [CByB6F1-Tg(HRAS)2Jic (-/-homozygous c-Haras)] (Main: 10/sex/group; TK: 20/sex/group) were given a daily oral dose of 0, 10, 30, or 100 mg/kg RP-112273 (Lot 5), a major human metabolite of ozanimod, in 0.5% CMC for 28 days. There were no RP-112273-related effects observed on BW, clinical chemistry and hematology parameters, or histology assessment. TK parameters are provided in the sponsor’s table below.

**Text Table 3: RP-112273 Toxicokinetic Parameters (Males and Females Combined)**

Dose (mg/kg)	Day	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	R <sup>a</sup>
10	1	6.27	0.627	1	24	48.2	4.82	NA
	27	7.94	0.794	1	24	51.9	5.19	1.08
30	1	11.5	0.383	1	24	127	4.25	NA
	27	16.5	0.551	1	24	149	4.95	1.17
100	1	21.3	0.213	1	24	216	2.16	NA
	27	16.9	0.169	1	24	219	2.19	1.01

NA = Not applicable

<sup>a</sup> R = AUC<sub>0-24hr Day 27</sub>/AUC<sub>0-24hr Day 1</sub>

## Rat

026004: “28-day oral toxicity study in rats with a 14-day recovery period.” CrI:CD(SD) rats (15/sex/group) were given a daily oral dose, by gavage, of 0, 0.2, 2, or 30 mg/kg RPC1063 (Lot AJ501FPRP-10-001; 99.2%) in 0.5% carboxymethylcellulose for 28 days with a 14-day recovery period. One HDF was found dead on Day 29 (#255146). Absolute BW was decreased at all dose levels in males by up to 8%, relative to control, at the end of the dosing and recovery periods. Lymphocyte count was decreased in all dose groups (LDM: 28%, MDM: 31%, HDM 35%; LDF: 57%, MDF: 23%, HDF 30%) at the end of the dosing period; count was similar to controls at the end of the recovery period. Minimal to mild anisocytosis and anisokaryosis of the proximal tubules occurred in all HDM and HDF; coagulative necrosis (minimal) was observed in the proximal tubules of 2 HDM. Minimal to moderate multifocal alveolar edema occurred in 1 MDF, 1 HDM, and 4 HDF. Moderate multifocal perivascular edema of the lung occurred in 6 HDM and 4 HDF. Depletion of the periarterial lymphoid elements occurred in the spleen of a majority of the MD and HD rats. At the end of the recovery period, the only drug-related histopathology finding occurred in the kidney of HDM and HDF and consisted of minimal diffuse anisocytosis and minimal regeneration of the epithelium of the proximal convoluted tubules in all HD animals. TK parameters for RPC1063 and two metabolites (RP-101075 and RP-101442) are provided in the sponsor’s tables, below. The NOAEL was the LD of 0.2 mg/kg, based on histology findings.

**RPC1063 Toxicokinetic Parameters**

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	6	0.2	M	4	8.9	3.21	0.008	37.0	0.091
1	6	0.2	F	4	5.5	3.99	0.010	55.9	0.138
1	7	2	M	4	4.6	40.3	0.100	453	1.120
1	7	2	F	2	5.8	53.4	0.132	632	1.563
1	8	30	M	4	6.6	595	1.471	8,740	21.612
1	8	30	F	4	10.3	787	1.946	11,100	27.448
28	6	0.2	M	4	9.7	3.00	0.007	37.2	0.092
28	6	0.2	F	2	6.3	7.94	0.020	91.2	0.226
28	7	2	M	4	5.7	47.4	0.117	701	1.733
28	7	2	F	2	8.7	98.2	0.243	1,130	2.794
28	8	30	M	12	NC <sup>1</sup>	773	1.911	13,300	32.888
28	8	30	F	4	9.1	1,460	3.610	22,900	56.627

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

**RP-101075**

Toxicokinetic parameters for RP-101075 are presented in the table below.

**RP-101075 Toxicokinetic Parameters**

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	6	0.2	M	4	8.9	3.14	0.009	36.3	0.101
1	6	0.2	F	4	5.5	3.88	0.011	53.8	0.149
1	7	2	M	12	NC <sup>1</sup>	4.54	0.013	81.9	0.227
1	7	2	F	12	NC	3.89	0.011	71.7	0.199
1	8	30	M	12	NC	94.6	0.262	1,790	4.967
1	8	30	F	24	NC	53.0	0.147	1,030	2.858
28	6	0.2	M	4	14.7	0.768	0.002	14.5	0.040
28	6	0.2	F	12	NC	0.928	0.003	17.2	0.048
28	7	2	M	12	NC	11.0	0.031	200	0.555
28	7	2	F	8	20.9	8.62	0.024	163	0.452
28	8	30	M	12	NC	264	0.733	4,900	13.596
28	8	30	F	12	NC	195	0.541	3,920	10.877

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

## RP-101442 Toxicokinetic Parameters

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	6	0.2	M	NC <sup>1</sup>	NC <sup>1</sup>	0	0	0	0
1	6	0.2	F	NC <sup>1</sup>	NC <sup>1</sup>	0	0	0	0
1	7	2	M	24	NC <sup>2</sup>	4.72	0.012	71.4	0.177
1	7	2	F	24	NC <sup>2</sup>	3.95	0.010	49.1	0.122
1	8	30	M	24	NC <sup>2</sup>	162	0.403	2,080	5.169
1	8	30	F	24	NC <sup>2</sup>	84.0	0.209	902	2.242
28	6	0.2	M	1	48.7	0.694	0.002	14.7	0.037
28	6	0.2	F	12	NC <sup>2</sup>	0.929	0.002	16.4	0.041
28	7	2	M	0	NC <sup>2</sup>	19.1	0.047	401	0.997
28	7	2	F	0	NC <sup>2</sup>	11.1	0.028	237	0.589
28	8	30	M	4	NR <sup>3</sup>	649	1.613	13,200	32.803
28	8	30	F	0	NR <sup>3</sup>	615	1.528	13,200	32.803

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin; RP-101442 below limit of quantitation in all Group 6 samples on Day 1.

<sup>2</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

<sup>3</sup>NR = Not reported, due to poor goodness-of-fit ( $R^2 < 0.8$ ) for the elimination phase.

026636: "RPC1063: 13-week oral toxicity and toxicokinetics study in rats." Sprague-Dawley rats (10/sex/group) were given a daily dose, by oral gavage, of 0, 0.2, 2, or 30 mg/kg RPC1063 (Lot AJ501FPRP-10-001; 99.2%) in 0.5% CMC for 13 weeks. Absolute BW in males was decreased in a dose-dependent manner, up to 8% at the HD. Absolute lymphocyte count was decreased at all dose levels (LDM: 50%, MDM: 60%, HDM 50%; LDF: 53%, MDF: 74%, HDF 73%). Absolute lung weight was increased in MDM and HDM by ~18% and in HDF by 26%. Spleen weight was decreased by 21-24% in MD and HD animals. Minimal, diffuse lymphoid depletion of the spleen occurred in all LD animals, 2 MDF, 10 MDM, 2 HDM, and 6 HDF; moderate lymphoid depletion occurred in 8 HDM and 4 HDF. Mild, diffuse anisocytosis and anisokaryosis of the proximal renal tubules occurred in all HD animals; minimal bilateral tubular degeneration/regeneration occurred in 9/10 HDM and 10/10 HDF. Minimal to moderate, bilateral hypertrophy of the zona fasciculata of the adrenal was evident in most HD animals. Minimal to moderate diffuse hypertrophy of the mammary gland occurred in all HDM. The NOAEL was 0.2 mg/kg. TK parameters for RPC1063, RP-101075, and RP-101442 are provided in the sponsor's table, below.

Toxicokinetic Parameters									
				RPC1063		RP-101075		RP-101442	
				C <sub>max</sub>	AUC <sub>0-24</sub>	C <sub>max</sub>	AUC <sub>0-24</sub>	C <sub>max</sub>	AUC <sub>0-24</sub>
Occasion	Group	RPC1063 Dose (mg/kg)	Sex	ng/mL	hr*ng/mL	ng/mL	hr*ng/mL	ng/mL	hr*ng/mL
Day 1	6	0.2	M	4.03	44.2	0.465	5.98	NC <sup>1</sup>	NC <sup>1</sup>
Day 1	6	0.2	F	5.57	63.1	0.515	8.38	NC <sup>1</sup>	NC <sup>1</sup>
Day 1	7	2	M	40.8	424	3.40	60.0	4.52	70.2
Day 1	7	2	F	52.2	556	3.06	53.7	2.81	37.0
Day 1	8	30	M	747	9,790	53.3	1,120	160	1,750
Day 1	8	30	F	948	13,500	43.7	818	96.7	965
Week 13	6	0.2	M	4.23	53.5	1.01	16.7	1.13	24.5
Week 13	6	0.2	F	7.35	97.5	0.833	15.7	1.16	21.9
Week 13	7	2	M	54.0	561	11.1	189	21.2	422
Week 13	7	2	F	109	1,330	8.95	171	16.5	349
Week 13	8	30	M	837	13,800	285	5,520	1,320	24,400
Week 13	8	30	F	1,170	21,700	203	4,050	902	19,300

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin; RP-101442 below limit of quantitation in all Group 6 samples on Day 1.

1840-032: "RP112273: A 96-day oral toxicity study in rats with a 29-day recovery period." Sprague-Dawley rats (16/sex/group with 6 reserved for a 29-day recovery period) were given a daily oral dose of 0, 10, 30, or 100 mg/kg RP112273 (Lots 5 and 7), a major human metabolite of RPC1063, in 0.5% CMC and 0.1% Tween 80. Absolute lymphocyte count was decreased by 25% in HDM. Based on the lack of RP112273-related adverse findings at the end of the dosing and recovery periods, the NOAEL was 100 mg/kg. The TK parameters for RP112273 are provided in the sponsor's table, below.

**Table 8: Summary of Mean Toxicokinetic Parameters for Males and Females Combined**

	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Day 1			
C <sub>max</sub> (ng/mL)	2.91	3.12	5.81
AUC <sub>0-24hr</sub> (hr*ng/mL)	12.9	21.9	42.4
Day 94			
C <sub>max</sub> (ng/mL)	4.12	6.01	7.20
AUC <sub>0-24hr</sub> (hr*ng/mL)	20.2	37.8	55.9

AUC<sub>0-24hr</sub> = area under the plasma concentration-time curve from time 0 to 24 hours postdose;  
C<sub>max</sub> = maximum plasma concentration.

**Study title: A 26-Week Oral Toxicity Study of RPC1063 with a 6-Week Recovery Period in Sprague-Dawley Rats**

Study no.: 71357  
Study report location: EDR  
Conducting laboratory and location: (b) (4)  
Date of study initiation: May 11, 2011  
GLP compliance: Yes, OECD  
QA statement: Yes, signed Oct. 31, 2013  
Drug, lot #, and % purity: RPC1063, AJ506FP-11-001, 99.5%

**Key Study Findings**

- **Target organs were spleen, thymus, and lung. Leukopenia was observed at all dose levels.**

**Methods**

Doses: 0, 0.2, 2, 30 mg/kg  
Frequency of dosing: Once daily for 26 weeks  
Route of administration: Oral gavage  
Dose volume: 5 mL/kg  
Formulation/Vehicle: 0.5% CMC in water  
Species/Strain: Sprague-Dawley CrI: CD (SD) rat  
Number/Sex/Group: Main: 20/sex/group; Recovery: 5/sex/group; TK: 12/sex/group.  
Age: 7 weeks  
Weight: M: 240 to 328 g; F: 170 to 244 g  
Deviation from study protocol: Deviations did not impact the validity of the study

Dosing Solution Analysis: Dosing formulations were within +/- 15% of the nominal concentration.

Mortality: Four rats were found dead (CM #1002A, LDM #2013C, MDM #3021D, HDF #4522D); the cause of death for each was undetermined but was not attributed to RPC1063.

Clinical Signs: There were no RPC1063-related clinical signs.

Body Weights & Food Consumption: There were no RPC1063-related effects on BW or food consumption.

Ophthalmoscopy: There were no RPC1063-related findings when funduscopy and biomicroscopic assessment was conducted at the end of the dosing period.

Hematology: Leukopenia was observed in all RPC1063 treatment groups at Weeks 13 and 26, but not at the end of the recovery period (sponsor's tables, below).

## Week 13 - Males

Groups	RBC	WBC	LYMPH	MONO	EOS	BASO	LUC
1	9.46	11.84	9.97	0.42	0.16	0.04	0.13
2	9.67	9.52	7.39	0.29	0.18	0.03	0.07
% diff	2%	-20%	-26%	-31%	13%	-25%	-46%
3	8.96	4.05	2.49	0.27	0.13	0.01	0.02
% diff	-5%	-66%	-75%	-36%	-19%	-75%	-85%
4	8.78	3.79	1.75	0.29	0.10	0.01	0.02
%diff	-7%	-68%	-82%	-31%	-38%	-75%	-85%

## Week 13 - Females

Groups	RBC	WBC	LYMPH	MONO	EOS	BASO	LUC
1	9.15	7.04	6.06	0.17	0.11	0.02	0.07
2	8.65	5.73	4.65	0.15	0.11	0.01	0.04
% diff	-5%	-19%	-23%	-12%	0%	-50%	-43%
3	8.37	1.9	1.00	0.10	0.09	0.00	0.01
% diff	-9%	-73%	-83%	-41%	-18%	-100%	-86%
4	7.91	2.24	1.07	0.17	0.09	0.00	0.01
%diff	-14%	-68%	-82%	0%	-18%	-100%	-86%

## Week 26 - Males

Groups	RBC	WBC	LYMPH	MONO	EOS	BASO	LUC
1	8.80	8.64	6.79	0.39	0.12	0.02	0.20
2	8.59	6.87	5.04	0.29	0.10	0.01	0.12
% diff	-2%	-20%	-26%	-26%	-17%	-50%	-40%
3	8.72	3.68	1.94	0.28	0.10	0.00	0.06
% diff	-1%	-57%	-71%	-28%	-17%	-100%	-70%
4	8.32	3.43	1.58	0.29	0.06	0.00	0.06
%diff	-5%	-60%	-77%	-26%	-50%	-100%	-70%

## Week 26 - Females

Groups	RBC	WBC	LYMPH	MONO	EOS	BASO	LUC
1	8.07	4.16	3.31	0.20	0.06	0.01	0.08
2	8.27	3.29	2.38	0.16	0.07	0.01	0.05
% diff	2%	-21%	-28%	-20%	17%	0%	-38%
3	8.01	1.44	0.74	0.11	0.06	0.00	0.02
% diff	-1%	-65%	-78%	-45%	0%	-100%	-75%
4	7.77	1.66	0.73	0.15	0.05	0.00	0.03
%diff	-4%	-60%	-78%	-25%	-17%	-100%	-63%

Clinical Chemistry & Urinalysis: There were no RPC1063-related findings at the end of the dosing or recovery periods.

Gross Pathology: Lungs of 5/20 HDM and 1/20 HDF exhibited pale areas.

Organ Weights: Absolute lung weight was increased in MD (5 to 10%) and HD (32 to 36%) animals at the end of the dosing period but not after the recovery period.

Histopathology: Adequate battery: Yes; Peer Review: Yes; Signed and dated: Yes  
Decreased lymphoid cellularity of the spleen, loss of thymic corticomedullary differentiation, pulmonary edema, and accumulation of foamy macrophages in the alveoli were observed at the end of the dosing period, but not at the end of recovery (sponsor's table, below).

Sex			Males				Females				
Dose Level (mg/kg/day)			0	0.2	2	30	0	0.2	2	30	
Number of animals examined			18	20	19	20	20	20	20	20	
Organ	Finding	Severity									
Spleen	Decreased cellularity, lymphoid		2	3	18	19	0	1	10	18	
		minimal	2	3	9	2	0	1	5	2	
		mild	0	0	9	1	0	0	5	5	
		moderate	0	0	0	16	0	0	0	9	
		severe	0	0	0	0	0	0	0	2	
Thymus	Loss of corticomedullary differentiation		0	1	20	20	0	5	20	20	
		Present	0	1	20	20	0	5	20	20	
Lungs	Accumulation, foamy macrophages, alveolar		0	0	0	11	0	0	0	11	
		minimal	0	0	0	7	0	0	0	1	
		mild	0	0	0	3	0	0	0	2	
		moderate	0	0	0	1	0	0	0	8	
		Edema		0	0	0	4	0	0	0	5
		minimal	0	0	0	1	0	0	0	3	
		mild	0	0	0	2	0	0	0	1	
		moderate	0	0	0	1	0	0	0	1	

**Toxicokinetics:** TK parameters were reassessed after the discovery of the major human metabolites of RPC1063. The TK parameters provided in the following sponsor's tables are from the reanalysis performed and reported in RP-TX-004-01.

**Table 2: Composite RPC1063 Toxicokinetic Parameters**

Day	RPC1063 (mg/kg/day)	Sex	Current Analysis <sup>a</sup>				Original Analysis <sup>b</sup>	
			T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (µM)	AUC <sub>0-24hr</sub> (µM×hr)	C <sub>max</sub> (µM)	AUC <sub>0-24hr</sub> (µM×hr)
1	0.2	M	4.0	DNS	0.0053	0.040 <sup>c</sup>	0.00539	0.0409
1	0.2	F	4.0	DNS	0.0067	0.060 <sup>c</sup>	0.00687	0.0838
1	2.0	M	4.0	4.9	0.0583	0.7808	0.0611	0.828
1	2.0	F	4.0	DNS	0.0738	0.9717	0.0804	1.08
1	30.0	M	4.0	6.6	0.9125	14.3678	0.942	13.8
1	30.0	F	2.0	12.7	1.2426	18.3265	1.23	18.1
178	0.2	M	4.0	DNS	0.0089	0.080 <sup>c</sup>	0.00979	0.0779
178	0.2	F	4.0	6.4	0.0115	0.1489	0.0108	0.148
178	2.0	M	4.0	5.4	0.1392	1.5223	0.118	1.60
178	2.0	F	4.0	5.8	0.1337	1.8549	0.130	1.99
178	30.0	M	4.0	6.8	1.4404	21.8775	1.51	23.1
178	30.0	F	4.0	8.4	2.1184	36.2916	2.13	37.3

DNS = data not sufficient to estimate TK parameter

<sup>a</sup>A new LC-MS/MS method validated to measure RPC1063, RP101075, RP101988, RP101442 and RP101124 was used; this analysis was conducted 3.4 years after the earliest sample collection using samples stored at -80°C.

<sup>b</sup>A previous LC-MS/MS method validated to measure RPC1063, RP101075, and RP101442 was used; this analysis was conducted at the time the toxicology study was completed.

<sup>c</sup>AUC<sub>last</sub> was used because RPC1063 was below limit of assay quantification at 24 hours

**Table 3: Composite RP101075 Toxicokinetic Parameters**

Day	RPC1063 (mg/kg/day)	Sex	Current Analysis <sup>a</sup>				Original Analysis <sup>b</sup>	
			T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)
1	0.2	M	BQL	BQL	BQL	BQL	BQL	BQL
1	0.2	F	BQL	BQL	BQL	BQL	BQL	BQL
1	2.0	M	12.0	DNS	0.0052	0.0939	0.00608	0.107
1	2.0	F	12.0	DNS	0.0044	0.0853	0.00455	0.0927
1	30.0	M	24.0	DNS	0.1162	1.9989	0.0988	1.80
1	30.0	F	24.0	DNS	0.1055	1.7019	0.0821	1.69
178	0.2	M	12.0	DNS	0.0015	0.010 <sup>c</sup>	0.00181	0.0106
178	0.2	F	4.0	DNS	0.0015	0.020 <sup>c</sup>	0.00166	0.0116
178	2.0	M	8.0	DNS	0.0197	0.3598	0.0234	0.421
178	2.0	F	12.0	DNS	0.0164	0.3488	0.0206	0.414
178	30.0	M	4.0	44.6	0.3135	6.8612	0.361	7.61
178	30.0	F	1.0	53.5	0.5198	9.2683	0.466	9.32

BQL = below assay limit of quantitation; DNS = data not sufficient to estimate TK parameter

<sup>a</sup>A new LC-MS/MS method validated to measure RPC1063, RP101075, RP101988, RP101442 and RP101124 was used; this analysis was conducted 3.4 years after the earliest sample collection using samples stored at -80°C.

<sup>b</sup>A previous LC-MS/MS method validated to measure RPC1063, RP101075, and RP101442 was used; this analysis was conducted at the time the toxicology study was completed.

<sup>c</sup>AUC<sub>last</sub> was used because RP101075 was below limit of assay quantification at 24 hours

**Table 4: Composite RP101442 Toxicokinetic Parameters**

Day	RPC1063 (mg/kg/day)	Sex	Current Analysis <sup>a</sup>				Original Analysis <sup>b</sup>	
			T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)
1	0.2	M	BQL	BQL	BQL	BQL	BQL	BQL
1	0.2	F	BQL	BQL	BQL	BQL	BQL	BQL
1	2.0	M	24.0	DNS	0.0085	0.1435	0.00835	0.137
1	2.0	F	24.0	DNS	0.0085	0.1104	0.00833	0.106
1	30.0	M	24.0	DNS	0.2959	3.5967	0.266	3.28
1	30.0	F	24.0	DNS	0.2242	2.7863	0.206	2.48
178	0.2	M	4.0	DNS	0.0040	0.0752	0.00408	0.0597
178	0.2	F	8.0	DNS	0.0031	0.0636	0.00331	0.0598
178	2.0	M	8.0	DNS	0.0673	1.2870	0.0815	1.45
178	2.0	F	2.0	DNS	0.0427	0.9895	0.0495	1.07
178	30.0	M	4.0	DNS	1.2811	29.0333	1.38	31.9
178	30.0	F	4.0	74.6	2.5099	51.8265	2.58	56.0

BQL = below assay limit of quantitation; DNS = data not sufficient to estimate TK parameter

<sup>a</sup>A new LC-MS/MS method validated to measure RPC1063, RP101075, RP101988, RP101442 and RP101124 was used; this analysis was conducted 3.4 years after the earliest sample collection using samples stored at -80°C.

<sup>b</sup>A previous LC-MS/MS method validated to measure RPC1063, RP101075, and RP101442 was used; this analysis was conducted at the time the toxicology study was completed.

**Table 5: Composite RP101988 Toxicokinetic Parameters**

Day	RPC1063 (mg/kg/day)	Sex	Current Analysis <sup>a</sup>				Original Analysis <sup>b</sup>	
			T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)
1	0.2	M	4/0	DNS	0.0028	0.020 <sup>c</sup>	NA	NA
1	0.2	F	4.0	DNS	0.0040	0.060 <sup>c</sup>	NA	NA
1	2.0	M	8.0	DNS	0.0415	0.5225	NA	NA
1	2.0	F	2.0	7.0	0.0378	0.4311	NA	NA
1	30.0	M	8.0	DNS	0.9138	12.3660	NA	NA
1	30.0	F	4.0	6.5	1.2261	14.2772	NA	NA
178	0.2	M	4.0	DNS	0.0119	0.090 <sup>c</sup>	NA	NA
178	0.2	F	4.0	5.2	0.0123	0.1334	NA	NA
178	2.0	M	4.0	6.1	0.1590	2.1712	NA	NA
178	2.0	F	4.0	5.7	0.1533	1.6168	NA	NA
178	30.0	M	4.0	7.0	1.7292	23.5696	NA	NA
178	30.0	F	2.0	7.0	2.5414	30.8153	NA	NA

BQL = below assay limit of quantitation; DNS = data not sufficient to estimate TK parameter; NA = not applicable

<sup>a</sup>A new LC-MS/MS method validated to measure RPC1063, RP101075, RP101988, RP101442 and RP101124 was used; this analysis was conducted 3.4 years after the earliest sample collection using samples stored at -80°C.

<sup>b</sup>A previous LC-MS/MS method validated to measure RPC1063, RP101075, and RP101442 was used; this analysis was conducted at the time the toxicology study was completed; RP10988 was not an analyte in the original method

<sup>c</sup>AUC<sub>last</sub> was used because RP101988 was below limit of assay quantification at 24 hours

**Table 6: Composite RP101124 Toxicokinetic Parameters**

Day	RPC1063 (mg/kg/day)	Sex	Current Analysis <sup>a</sup>				Original Analysis <sup>b</sup>	
			T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)	C <sub>max</sub> (μM)	AUC <sub>0-24hr</sub> (μM×hr)
1	0.2	M	12.0	DNS	0.0135	0.1767	NA	NA
1	0.2	F	12.0	DNS	0.0122	0.1696	NA	NA
1	2.0	M	8.0	DNS	0.1191	1.7338	NA	NA
1	2.0	F	12.0	DNS	0.1208	1.9412	NA	NA
1	30.0	M	12.0	DNS	2.2123	31.6628	NA	NA
1	30.0	F	12.0	DNS	2.5829	40.5372	NA	NA
178	0.2	M	8.0	DNS	0.0187	0.3461	NA	NA
178	0.2	F	8.0	DNS	0.0189	0.3409	NA	NA
178	2.0	M	8.0	DNS	0.1751	3.3858	NA	NA
178	2.0	F	12.0	DNS	0.2656	4.8263	NA	NA
178	30.0	M	4.0	DNS	4.4960	68.7391	NA	NA
178	30.0	F	24.0	15.2	5.0885	91.1396	NA	NA

BQL = below assay limit of quantitation; DNS = data not sufficient to estimate TK parameter; NA = not applicable

<sup>a</sup>A new LC-MS/MS method validated to measure RPC1063, RP101075, RP101988, RP101442 and RP101124 was used; this analysis was conducted 3.4 years after the earliest sample collection using samples stored at -80°C.

<sup>b</sup>A previous LC-MS/MS method validated to measure RPC1063, RP101075, and RP101442 was used; this analysis was conducted at the time the toxicology study was completed; RP101124 was not an analyte in the original method

## Monkey

**026005:** "RPC1063: 14-day oral toxicity study in *Cynomolgus* monkeys." *Cynomolgus* monkeys (1/sex/group) were given a daily oral dose of 0, 0.15, 3, or 15 mg/kg RPC1063 (Lot 068-146-HRD) in 0.5% CMC for 14 days or 45 mg/kg RPC1063 for 7 days. At the end of the 14-day dosing period, absolute BW in the HDF was decreased by 6.2%, compared to baseline. Absolute lymphocyte count was decreased in a dose-dependent manner at all doses (M: 42% to 61%; F: 24% to 72%). Thymus weight was decreased in the HDM, and lung weight was decreased at all dose levels. Minimal multifocal

hepatocellular apoptosis, mild thymic atrophy, and moderate bilateral follicular hypertrophy of the thyroid as well as marked hepatocyte vacuolation and mild vacuolation of the pulmonary macrophages occurred in the HDM.

026006: “RPC1063: 28-day oral toxicity study in Cynomolgus monkeys with a 14-day recovery period.” Cynomolgus monkeys (Main: 3/sex/group; Recovery: 2/sex/group) were given a daily oral dose of 0, 0.15, 3, or 30 mg/kg RPC1063 (Lot AJ501FPRP-10-001) in 0.5% CMC. Food consumption was decreased at the HD but was not associated with a change in body weight. Absolute lymphocyte and absolute basophil counts were decreased at all dose levels at the end of the dosing period (sponsor’s table, below). At the end of the recovery period, lymphocyte and basophil count was similar to the predose period at the LD and MD: counts were still decreased at the HD (lymphocytes: 37%, basophils: up to 62%)

		White Blood Cell Parameters Percent of Control (Day 29)		
Group	Dose (mg/kg)	White Blood Cell	Absolute Lymphocyte	Absolute Basophil
<b>Male</b>				
2	0.15	60	48	42
3	3.0	45	16	8
4	30	34	10	12
<b>Female</b>				
2	0.15	95	44	50
3	3.0	54	18	13
4	30	48	9	19

Absolute weight of spleen in males (reduced by 31% to 58%) and lung in both sexes (increased by 10% to 39% in males and 11% to 55% in females) was affected at all dose levels. Absolute organ weights were similar to control at the end of the recovery period.

Mild depletion of splenic lymphoid elements occurred in 3/3 MDM, 2/3 MDF, 2/3 HDM, and 3/3 HDF; the depletion in the remaining HDM was moderate. Mild bilateral hypertrophy and basophilia of the renal collecting tubules was observed in 3/3 HDM. Pulmonary findings consisted of minimal to moderate vacuolated alveolar macrophages in all MD and HD animals. There were no RPC1063-related histology findings at the end of the recovery period.

TK parameters for RPC1063, RP101075, and RP101442 are provided in the sponsor’s tables, below. The NOAEL was considered to be the LD of 0.15 mg/kg based on histology findings at higher doses.

## Mean RPC1063 Toxicokinetic Parameters

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.15	M	3.5	7.4	2.76	0.00682	32.8	0.0811
1	2	0.15	F	5.6	8.7	2.81	0.00694	37.3	0.0923
1	3	3	M	5.1	6.6	61.4	0.152	862	2.13
1	3	3	F	3.0	5.9	66.1	0.163	952	2.35
1	4	30	M	7.2	10.8	429	1.06	6,830	16.9
1	4	30	F	8.0	11.4	424	1.05	6,590	16.3
28	2	0.15	M	4.8	5.9	2.35	0.00580	26.3	0.0651
28	2	0.15	F	4.0	6.4	3.22	0.00796	35.3	0.0873
28	3	3	M	4.0	7.0	55.3	0.137	681	1.68
28	3	3	F	4.0	7.6	60.5	0.150	765	1.89
28	4	30	M	4.8	13.1	515	1.27	8,070	20.0
28	4	30	F	5.6	12.4	609	1.51	9,560	23.6

## Mean RP-101075 Toxicokinetic Parameters

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.15	M	6.7	NC <sup>1</sup>	0.340	0.000943	3.34	0.00930
1	2	0.15	F	4.0	NC	0.116	0.000322	0.711	0.00197
1	3	3	M	10.4	5.3	9.71	0.0269	147	0.408
1	3	3	F	11.2	4.5	11.0	0.0306	154	0.428
1	4	30	M	12.0	NC	130	0.359	2,180	6.04
1	4	30	F	16.8	NC	158	0.437	2,710	7.52
28	2	0.15	M	6.0	8.2	0.462	0.00128	3.76	0.0104
28	2	0.15	F	5.0	NC	0.415	0.00115	2.55	0.00707
28	3	3	M	8.0	5.8	10.1	0.0281	130	0.360
28	3	3	F	8.0	6.0	8.27	0.0230	111	0.307
28	4	30	M	7.2	22.2	183	0.508	3,440	9.56
28	4	30	F	6.4	21.3	352	0.976	6,870	19.1

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to no non-zero concentration values or to insufficient data points for the elimination phase.

## Mean RP-101442 Toxicokinetic Parameters

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.15	M	NC <sup>1</sup>	NC	0.00	0.00	0.00	0.00
1	2	0.15	F	NC	NC	0.00	0.00	0.00	0.00
1	3	3	M	12.0	NC	0.295	0.000734	4.50	0.0112
1	3	3	F	12.0	NC	0.103	0.000255	0.821	0.00204
1	4	30	M	24.0	NC	11.5	0.0286	163	0.406
1	4	30	F	24.0	NC	9.18	0.0228	127	0.316
28	2	0.15	M	NC	NC	0.00	0.00	0.00	0.00
28	2	0.15	F	NC	NC	0.00	0.00	0.00	0.00
28	3	3	M	10.0	NC	0.558	0.00139	8.03	0.0199
28	3	3	F	10.7	NC	0.384	0.000954	5.81	0.0144
28	4	30	M	10.4	28.1	18.1	0.0450	366	0.910
28	4	30	F	6.4	38.7	37.2	0.0925	736	1.83

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to no non-zero concentration values or to insufficient data points for the elimination phase.

026715: "RPC1063: 13-week oral toxicokinetics and toxicity study in Cynomolgus monkeys." Cynomolgus monkeys (n=3/sex/group) were given a daily oral dose of 0, 0.15, 3, or 30 mg/kg RPC1063 (Lot AJ501FPRP-10-001) in 0.5% CMC for 13 weeks. Trembling occurred in one HDF and one HDM; both monkeys exhibited a decrease in food intake and decreased body weight. Absolute BW was 4% and 24% lower in HDM and HDF, respectively, compared to baseline. Food consumption was also decreased in HD animals. Mean WBC and absolute lymphocyte count were decreased in all dose groups (sponsor's tables, below).

	Mean White Blood Cell Count (% of pretest)					
	Male			Female		
Group	2	3	4	2	3	4
Day 38	53	69	33	60	50	39
Day 60	60	61	26	54	47	36
Day 87	48	65	32	72	45	29

	Mean Lymphocyte Count (% of pretest)					
	Male			Female		
Group	2	3	4	2	3	4
Day 38	62	35	14	66	34	15
Day 60	87	38	14	92	45	17
Day 87	57	23	14	58	26	9

Test article-related findings were observed in the adrenal gland, sternal and femoral bone marrow, intestine, kidney, liver, lung, and spleen. Mild to moderate hypertrophy of the adrenal cortex occurred in 2/3 MDM, 2/3 MDF, and all HD animals. An increase in myeloid elements occurred in the bone marrow of all animals dosed with RPC1063. Vacuolated macrophages were observed in the intestinal lamina propria of the duodenum, jejunum, and ileum of 1/3 HDF and 1/3 HDM. Minimal anisokaryosis and anisocytosis of the renal proximal tubules occurred in 1/3 MDF and all HD animals; there were no associated changes in clinical chemistry or urinalysis. Minimal to moderate accumulation of vacuolated macrophages was observed in the alveoli of 1/3 MDM, 2/3 HDM, and 2/3 HDF. Moderate depletion of the lymphoid elements of the spleen was evident in 2/3 HDM and 2/3 HDF.

TK parameters for RPC1063, RP101075, and RP101442 are provided in the sponsor's tables, below. The NOAEL was considered to be the LD of 0.15 mg/kg based on histology findings at higher doses.

#### Mean RPC1063 Toxicokinetic Parameters

Day/Week	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
Day 1	2	0.15	M	5.3	7.1	3.94	0.00974	52.1	0.129
Day 1	2	0.15	F	4.6	7.7	3.60	0.00890	46.1	0.114
Day 1	3	3	M	2.5	6.6	72.9	0.180	884	2.19
Day 1	3	3	F	3.3	6.7	74.2	0.183	984	2.43
Day 1	4	30	M	5.3	19.7	428	1.06	7,260	18.0
Day 1	4	30	F	9.3	8.9	374	0.925	5,850	14.5
Week 13	2	0.15	M	5.3	7.2	3.36	0.00831	39.8	0.0984
Week 13	2	0.15	F	4.0	7.0	3.91	0.00967	44.5	0.110
Week 13	3	3	M	4.0	7.2	65.6	0.162	769	1.90
Week 13	3	3	F	6.7	7.8	81.6	0.202	968	2.39
Week 13	4	30	M	8.0	NC <sup>1</sup>	790	1.95	12,400	30.7
Week 13	4	30	F	5.3	18.9	754	1.86	13,600	33.6

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

**Mean RP-101075 Toxicokinetic Parameters**

Day/Week	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
Day 1	2	0.15	M	8.0	NC <sup>1</sup>	0.347	0.000963	1.39	0.00386
Day 1	2	0.15	F	NC	NC	0.000	0.000	0.000	0.000
Day 1	3	3	M	8.0	6.3	13.6	0.0377	175	0.486
Day 1	3	3	F	8.0	6.7	17.0	0.0472	247	0.685
Day 1	4	30	M	20.0	NC	127	0.352	2,010	5.58
Day 1	4	30	F	24.0	NC	135	0.375	2,450	6.80
Week 13	2	0.15	M	4.0	NC	0.316	0.000877	1.62	0.00450
Week 13	2	0.15	F	4.0	NC	0.467	0.00130	1.59	0.00441
Week 13	3	3	M	4.0	5.9	16.3	0.0452	205	0.569
Week 13	3	3	F	10.7	4.0	22.5	0.0624	292	0.810
Week 13	4	30	M	8.0	NC	813	2.26	11,900	33.0
Week 13	4	30	F	8.0	NR <sup>2</sup>	590	1.64	11,700	32.5

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to no non-zero concentration values or to insufficient data points for the elimination phase.

<sup>2</sup>NR = Not reported, due to extensive extrapolation or poor goodness-of-fit ( $R^2 < 0.8$ ) for the elimination phase.

**Mean RP-101442 Toxicokinetic Parameters**

Day/Week	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
Day 1	2	0.15	M	NC <sup>1</sup>	NC	0.000	0.000	0.000	0.000
Day 1	2	0.15	F	NC	NC	0.000	0.000	0.000	0.000
Day 1	3	3	M	12.0	NC	0.477	0.00119	4.97	0.0124
Day 1	3	3	F	10.7	NC	0.881	0.00219	14.4	0.0358
Day 1	4	30	M	24.0	NC	11.9	0.0296	152	0.378
Day 1	4	30	F	24.0	NC	15.9	0.0395	206	0.512
Week 13	2	0.15	M	NC	NC	0.000	0.000	0.000	0.000
Week 13	2	0.15	F	NC	NC	0.000	0.000	0.000	0.000
Week 13	3	3	M	5.3	18.8	0.952	0.00237	12.9	0.0321
Week 13	3	3	F	10.7	NC	1.86	0.00462	20.5	0.0509
Week 13	4	30	M	8.0	NC	187	0.465	2,650	6.59
Week 13	4	30	F	8.0	NC	91.2	0.227	1,920	4.77

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to no non-zero concentration values or to insufficient data points for the elimination phase.

**Study title: A 39-week oral toxicity study of RPC1063 with a 6-week recovery period in Cynomolgus monkeys**

Study no.: 30477  
 Study report location: (b) (4)  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: May 18, 2010  
 GLP compliance: Yes, OECD  
 QA statement: Yes, signed.  
 Drug, lot #, and % purity: RPC1063, AJ506FP-11-001, 99.5%

**Key Study Findings**

- **Based on findings in the thymus, spleen, and lung at the MD and HD, the NOAEL was the LD of 0.1 mg/kg.**

**Methods**

Doses: 0, 0.1, 1, 15 mg/kg  
 Frequency of dosing: Once daily for 39 weeks  
 Route of administration: Oral gavage  
 Dose volume: 5 mL/kg  
 Formulation/Vehicle: 0.5% CMC in water  
 Species/Strain: Cynomolgus monkey; (b) (4)  
 Number/Sex/Group: Interim (26 weeks): 3/sex/group; Main (39 weeks): 4/sex/group; Recovery: 2/sex/group  
 Age: 2 to 3 years  
 Weight: M: 2 to 2.5 kg; F: 2.1 to 2.6 kg  
 Deviation from study protocol: Deviations did not impact the validity of the study.

Dosing Solution Analysis: Dosing solutions were within +/- 15% of the nominal concentration.

Mortality & Clinical Signs: All animals survived to planned sacrifice, and there were no RPC1063-related clinical signs.

Body Weights: There were no RPC1063-related effects on absolute BW or BW gain during the dosing or recovery periods.

Ophthalmoscopy: When conducted with funduscopy and biomicroscopic assessment during Weeks 26 and 39, there were no RPC1063-related findings.

ECG: There were no RPC1063-related effects on ECG parameters on Day 1, and during Weeks 26 and 39.

Hematology: At Weeks 13, 26, and 39, a dose-dependent leukopenia was evident, with a majority of the effect due to decreases in neutrophils and lymphocytes (sponsor's tables, below). An effect on WBC count was still evident in males at the end of the 6-week recovery period (sponsor's tables, below).

**Week 13 - Males**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	10.57	2.5	7.26	0.05	0.06
2	6.7	2.28	3.85	0.03	0.03
% diff	-37%	-9%	-47%	-40%	-50%
3	4.51	2.08	1.91	0.01	0.04
% diff	-57%	-17%	-74%	-80%	-33%
4	3.66	1.21	1.78	0.01	0.03
% diff	-65%	-52%	-75%	-80%	-50%

**Week 13 - Females**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	11.74	2.82	8.05	0.07	0.08
2	6.51	2.68	3.17	0.02	0.04
% diff	-45%	-5%	-61%	-71%	-50%
3	5.64	2.62	2.45	0.02	0.05
% diff	-52%	-7%	-70%	-71%	-38%
4	4.57	2.21	1.68	0.01	0.03
% diff	-61%	-22%	-79%	-86%	-63%

**Week 26 - Males**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	9.06	3.29	5.26	0.04	0.07
2	6.00	3.18	2.43	0.01	0.04
% diff	-34%	-3%	-54%	-75%	-43%
3	4.45	2.61	1.43	0.01	0.05
% diff	-51%	-21%	-73%	-75%	-29%
4	3.09	1.57	1.08	0.01	0.06
% diff	-66%	-52%	-79%	-75%	-14%

**Week 26 - Females**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	10.52	4.04	5.74	0.04	0.1
2	6.14	3.83	1.81	0.01	0.04
% diff	-42%	-5%	-68%	-75%	-60%
3	5.36	3.37	1.51	0.01	0.05
% diff	-49%	-17%	-74%	-75%	-50%
4	3.86	2.33	1.01	0.01	0.05
% diff	-63%	-42%	-82%	-75%	-29%

**Week 39 - Males**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	9.81	3.07	6.23	0.07	0.07
2	7.04	4.10	2.49	0.03	0.03
% diff	-28%	+33%	-60%	-57%	-57%
3	3.70	1.54	1.79	0.03	0.03
% diff	-62%	-49%	-71%	-57%	-57%
4	2.70	1.62	0.66	0.01	0.02
% diff	-72%	-47%	-89%	-86%	-71%

**Week 39 - Females**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	10.10	3.85	5.49	0.05	0.09
2	6.65	3.57	2.58	0.02	0.04
% diff	-34%	-7%	-53%	-60%	-55%
3	4.58	2.35	1.76	0.01	0.03
% diff	-55%	-39%	-68%	-80%	-66%
4	3.81	2.32	1.03	0.01	0.03
% diff	-62%	-40%	-81%	-80%	-66%

**Week 45 - Males**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	12.70	3.06	8.71	0.09	0.08
2	6.42	3.06	2.85	0.02	0.02
% diff	-49%	0%	-67%	-78%	-75%
3	8.65	4.26	4.01	0.04	0.04
% diff	-32%	39%	-54%	-56%	-50%
4	9.02	4.79	3.58	0.04	0.03
% diff	-29%	57%	-59%	-56%	-63%

**Week 45 - Females**

Group	WBC (10 <sup>9</sup> /L)	NEUT (10 <sup>9</sup> /L)	LYMPH (10 <sup>9</sup> /L)	BASO (10 <sup>9</sup> /L)	LUC (10 <sup>9</sup> /L)
1	7.71	2.70	4.62	0.03	0.04
2	7.96	2.33	4.82	0.05	0.07
% diff	3%	-14%	4%	67%	75%
3	11.44	3.98	6.67	0.07	0.07
% diff	48%	47%	44%	133%	75%
4	10.90	3.46	6.90	0.05	0.05
% diff	41%	28%	49%	67%	25%

Clinical Chemistry & Urinalysis: There were no RPC1063-related findings during Weeks 13, 26, or 39.

Gross Pathology: There were no RPC1063-related findings at the end of the dosing or recovery periods.

Organ Weights: There was a 19% increase in absolute lung weight in MDM and HDM at Week 39 but not at the end of the recovery period.

Histopathology: Adequate Battery: Yes; Peer Review: No; Signed/Dated: Yes  
RPC1063-related findings were evident in the thymus, lung, and spleen (sponsor's tables, below). At the interim sacrifice (Week 26), there was a decreased ratio of cortex to medulla in the thymus and minimal to mild alveolar histiocytosis at the MD and HD. Similar findings were evident in the lung and thymus at the end of the dosing period. Decreased splenic size and cellularity was also evident at the MD and HD (sponsor's table, below). At the end of the 6-week recovery period, minimal alveolar histiocytosis was observed in 1 HDM.

*Incidence and severity of RPC1063-related microscopic findings in Interim animals.*

Tissue/Finding/Severity	Incidence of Finding			
	Control 0 mg/kg/day	Low Dose 0.1 mg/kg/day	Mid Dose 1.0 mg/kg/day	High Dose 15 mg/kg/day
<b>Thymus</b>				
Cortex/medulla ratio, decreased	0/6	0/6	2/6	4/6
minimal	0	0	0	3
mild	0	0	2	1
<b>Lung</b>				
Alveolar histiocytosis	0/6	0/6	3/6	5/6
minimal	0	0	0	5
mild	0	0	3	0

*Incidence and severity of RPC1063-related microscopic findings in Terminal and Recovery animals*

Tissue/Finding/Severity	Incidence of Finding							
	Terminal				Recovery			
	Control 0 mg/kg/day	Low Dose 0.1 mg/kg/day	Mid Dose 1.0 mg/kg/day	High Dose 15 mg/kg/day	Control 0 mg/kg/day	Low Dose 0.1 mg/kg/day	Mid Dose 1.0 mg/kg/day	High Dose 15 mg/kg/day
<b>Thymus</b>								
Cortex/medulla ratio, decreased	0/8	0/8	6/8	6/8	0/4	0/4	0/4	0/4
minimal	0	0	5	2	0	0	0	0
mild	0	0	1	4	0	0	0	0
<b>Spleen</b>								
Decreased size/cellularity, white pulp	0/8	0/8	3/8	7/8	0/4	0/4	0/4	0/4
minimal	0	0	3	6	0	0	0	0
<b>Lung</b>								
Alveolar histiocytosis	1/8	0/8	5/8	5/8	0/4	0/4	0/4	1/4
minimal	1	0	5	2	0	0	0	1
mild	0	0	0	3	0	0	0	0

**Toxicokinetics:** TK parameters for RPC1063, RP101075, and RP101442 are provided in the sponsor's tables, below.

**Mean RPC1063 Toxicokinetic Parameters**

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.1	M	4.00	NC <sup>1</sup>	2.29	0.00567	16.8	0.0417
1	2	0.1	F	3.67	6.58	2.26	0.00560	16.9	0.0419
1	3	1	M	4.44	5.30	18.1	0.0448	181	0.448
1	3	1	F	4.00	5.61	16.5	0.0408	163	0.404
1	4	15	M	4.00	7.17	294	0.728	3270	8.08
1	4	15	F	4.44	7.97	247	0.611	2840	7.02
183	2	0.1	M	4.00	7.46	1.96	0.00484	16.8	0.0415
183	2	0.1	F	4.00	NC	2.22	0.00548	18.2	0.0450
183	3	1	M	4.44	8.54	18.2	0.0450	202	0.499
183	3	1	F	3.67	6.94	16.4	0.0405	177	0.437
183	4	15	M	4.00	10.4	271	0.669	3640	8.99
183	4	15	F	4.44	9.10	252	0.622	3280	8.10
274	2	0.1	M	4.67	8.95	2.23	0.00551	19.8	0.0491
274	2	0.1	F	4.00	7.57	2.51	0.00620	25.4	0.0629
274	3	1	M	4.00	7.09	17.0	0.0420	208	0.514
274	3	1	F	4.00	6.29	18.5	0.0457	199	0.491
274	4	15	M	4.67	8.76	251	0.621	3530	8.73
274	4	15	F	5.33	8.45	263	0.651	3730	9.23

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

**Mean RP-101075 Toxicokinetic Parameters**

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.1	M	NC <sup>1</sup>	NC	0.00	0.00	0.00	0.00
1	2	0.1	F	NC	NC	0.00	0.00	0.00	0.00
1	3	1	M	4.89	NC	2.23	0.00618	15.3	0.0426
1	3	1	F	4.00	NC	1.68	0.00466	11.8	0.0326
1	4	15	M	8.89	NC	62.8	0.174	954	2.65
1	4	15	F	8.44	NC	54.7	0.152	825	2.29
183	2	0.1	M	4.00	NC	0.0623	0.000173	0.0935	0.000259
183	2	0.1	F	4.00	NC	0.107	0.000297	0.160	0.000445
183	3	1	M	4.44	17.4	2.78	0.00771	28.3	0.0784
183	3	1	F	4.00	8.64	2.23	0.00620	19.0	0.0526
183	4	15	M	7.56	10.8	58.1	0.161	1010	2.79
183	4	15	F	7.56	10.2	60.9	0.169	1000	2.78
274	2	0.1	M	4.00	NC	0.0905	0.000251	0.453	0.00126
274	2	0.1	F	4.00	NC	0.0897	0.000249	0.135	0.000373
274	3	1	M	6.67	6.59	2.45	0.00679	29.9	0.0831
274	3	1	F	4.00	NC	2.68	0.00742	21.1	0.0586
274	4	15	M	8.00	NC	52.2	0.145	826	2.29
274	4	15	F	8.67	NC	62.0	0.172	957	2.66

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

## Mean RP-101442 Toxicokinetic Parameters

Day	Group Number	RPC1063 Dose (mg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub>		AUC <sub>0-24</sub>	
						ng/mL	μM	hr*ng/mL	hr*μM
1	2	0.1	M	NC <sup>1</sup>	NC	0.00	0.00	0.00	0.00
1	2	0.1	F	NC	NC	0.00	0.00	0.00	0.00
1	3	1	M	NC	NC	0.00	0.00	0.00	0.00
1	3	1	F	NC	NC	0.00	0.00	0.00	0.00
1	4	15	M	12.4	NC	3.75	0.00932	64.2	0.160
1	4	15	F	11.1	NC	2.97	0.00737	51.5	0.128
183	2	0.1	M	NC	NC	0.00	0.00	0.00	0.00
183	2	0.1	F	NC	NC	0.00	0.00	0.00	0.00
183	3	1	M	NC	NC	0.00	0.00	0.00	0.00
183	3	1	F	NC	NC	0.00	0.00	0.00	0.00
183	4	15	M	8.89	43.2	4.20	0.0104	80.8	0.201
183	4	15	F	8.00	18.4	3.15	0.00782	56.1	0.139
274	2	0.1	M	NC	NC	0.00	0.00	0.00	0.00
274	2	0.1	F	NC	NC	0.00	0.00	0.00	0.00
274	3	1	M	NC	NC	0.00	0.00	0.00	0.00
274	3	1	F	NC	NC	0.00	0.00	0.00	0.00
274	4	15	M	8.00	NC	3.84	0.00954	64.6	0.160
274	4	15	F	8.67	NC	2.80	0.00695	47.0	0.117

<sup>1</sup>NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

## 7 Genetic Toxicology

### 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Ozanimod (RPC1063) and its three major human metabolites, RP-101124 (Lot 3), RP-112273 (Lot 3), CC1084037 (Lot S00L01), were demonstrated to be non-mutagenic in adequately-designed, GLP-compliant bacterial reverse mutation assays conducted in the presence or absence of rat hepatic S9 fraction (Study reports 025999, AE86da-502ICH. (b) (4), AF00PS.502ICH. (b) (4), AF40JJ.502ICH. (b) (4)). Minor human metabolites of ozanimod, RP-110351 and RP-101988, were also negative in adequately-designed, GLP-compliant bacterial reverse mutation assays (AE81YV.502ICH. (b) (4), AE86CZ.502ICH. (b) (4)). Other minor human metabolites of ozanimod, RP101075, RP101063, and RP101442, were negative when tested in bacterial mutagenicity assays (Study reports AC31AY-850- (b) (4), AD03BC-850- (b) (4), AD03BD-850- (b) (4)).

### 7.2 *In Vitro* Assays in Mammalian Cells

RPC1063 (Lot AJ501FPRP-10-001) was not mutagenic in an adequately conducted, OECD GLP-compliant *in vitro* mouse lymphoma TK gene mutation assay in the presence and absence of rat hepatic S9 fraction (Study report AA93888). CC112273 was negative in an adequately conducted *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes (AF00PS.341ICH. (b) (4)). CC1084037, a major human metabolite, increased the number of micronuclei in TK6 cells by up to 4-fold when incubated for 4 hours or 27 hours in the absence of bioactivation (RPC1063-TOX-2844).

### 7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

In an adequately conducted and GLP compliant *in vivo* assay, RPC1063 was negative for induction of bone marrow micronuclei in Sprague-Dawley rat (n=5/sex/group) given two daily oral doses of 0, 251, 448, and 800 mg/kg/day RPC1063 (Lot AJ506FP-11-001) administered 6 hours apart in 0.5% CMC for two days (AA99751). The high dose represented a maximum feasible dose and marrow collection occurred 24 hours after administration of the final dose. Based on available TK data for rat, there was adequate exposure to the major human metabolites CC112273, CC1084037, and RP101124 occurred at the doses tested. The sponsor conducted an *in vivo* erythrocyte micronucleus and mammalian alkaline comet assay in rat dosed with CC1084037 (n=6/sex/group; RPC1063-TOX-2957). CC1084037 (0, 250, 500, or 1000 mg/kg; Lot S00L02) was administered by oral gavage once per day for three days; bone marrow and liver were harvested 3 to 4 hours after the final dose. There was no CC1084037-related increase in micronucleated cells in the bone marrow, and the comet assay was negative.

## 8 Carcinogenicity

**Study title: RPC1063: 26-week repeated dose oral carcinogenicity study in Tg.rasH2 mice.**

Study no.:	AE18BZ.7G8R. (b) (4)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 3, 2015
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes, signed
Drug, lot #, and % purity:	RPC1063, Lot AJ506FP-11-001, 99.6%
CAC concurrence:	ExecCAC SPA recommendations: January 21, 2015

### Key Study Findings

- **The combined incidence of hemangioma and hemangiosarcoma was increased in males at all dose levels and in females at doses > 8 mg/kg RPC1063. The incidence of skin hemangiosarcoma was increased at doses > 8 mg/kg. Multicentric hemangiosarcoma was increased in females at 80 mg/kg.**

### Adequacy of Carcinogenicity Study

- **Although all major metabolites were not assessed in this study, other PK studies have demonstrated that mice produce all major human metabolites at levels that exceed those in humans when tested at the dose levels used in this study. Overall, the carcinogenicity study was adequately conducted.**

### Methods

Doses:	0, 8, 25, 80 mg/kg/day RPC1063; 1000 mg/kg/day urethane (positive control)
Frequency of dosing:	RPC1063: once daily for 26 weeks; urethane: once daily on Days 1, 3, and 5
Dose volume:	5 mL/kg
Route of administration:	RPC1063: Oral gavage Urethane: intraperitoneal
Formulation/Vehicle:	RPC1063: 0.5% CMC in water, pH 2.2 Urethane: 0.9% saline
Basis of dose selection:	The ExecCAC recommended the doses of 0, 8, 25, and 80 mg/kg based on effects in the lung (e.g., increased weight and accumulation of foamy macrophages) at 80 mg/kg in a dose-ranging study.
Species/Strain:	Tg.rasH2 mice [CByB6F1-Tq(HRAS)2Jic (+/- hemizygous c-Ha-ras)]; (b) (4), (b) (4)
Number/Sex/Group:	Main: 25/sex/group; TK: Control 8/sex/group, Dose Groups 38/sex/group; Positive control: 10/sex/group

Age: 5 weeks  
 Animal housing: Individually housed  
 Paradigm for dietary restriction: Ad libitum food and water  
 Dual control employed: No  
 Interim sacrifice: No  
 Deviation from study protocol: Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: Dosing solutions were within 92% to 102% of the nominal concentration.

Mortality: Early deaths occurred in 1 LDM, 1 LDF, 3 MDF, 10 MDM, 9 HDM and 9 HDF; cause and date of death for each animal is provided in the sponsor's tables, below.

Text Table 9A: Male Mortality

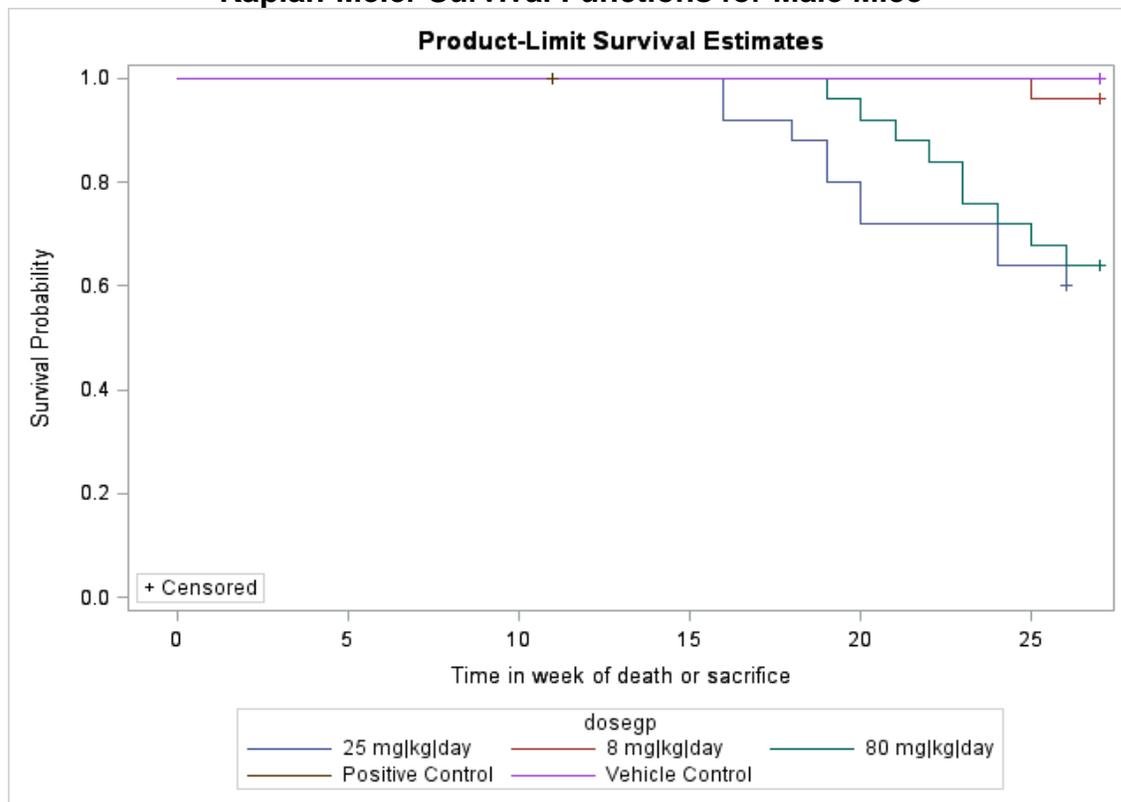
Group	Dose Levels (mg/kg/day)	Animal Number	Day of Removal	Mode of Death	Cause of Death
2	8	2734	169	Natural Death	Multicentric mesothelioma Lung, carcinoma Lung, hemangiosarcoma
3	25	2751	112	Moribund Sacrifice	Undetermined
		2753	127	Natural Death	Multicentric hemangiosarcoma
		2756	127	Natural Death	Multicentric hemangiosarcoma
		2758	165	Natural Death	Multicentric hemangiosarcoma
		2764	112	Moribund Sacrifice	Multicentric hemangiosarcoma
		2765	139	Natural Death	Skin, hemangiosarcoma
		2766	140	Natural Death	Duodenal abscess and granulopoiesis, multiple tissues
		2767	124	Natural Death	Hind limb (skin), hemangiosarcoma
		2770	176	Natural Death	Multicentric hemangiosarcoma
		2773	164	Natural Death	Multicentric hemangiosarcoma
4	80	2779	173	Natural Death	Undetermined
		2781	155	Natural Death	Undetermined
		2786	166	Natural Death	Multicentric hemangiosarcoma
		2787	160	Natural Death	Jejunal abscess and granulopoiesis, multiple tissues
		2789	129	Natural Death	Undetermined
		2790	139	Natural Death	Undetermined
		2792	150	Natural Death	Skeletal muscle, hemangiosarcoma
		2794	144	Moribund Sacrifice	Ileum abscess and granulopoiesis, multiple tissues
		2798	182	Natural Death	Hind limb (skin), hemangiosarcoma

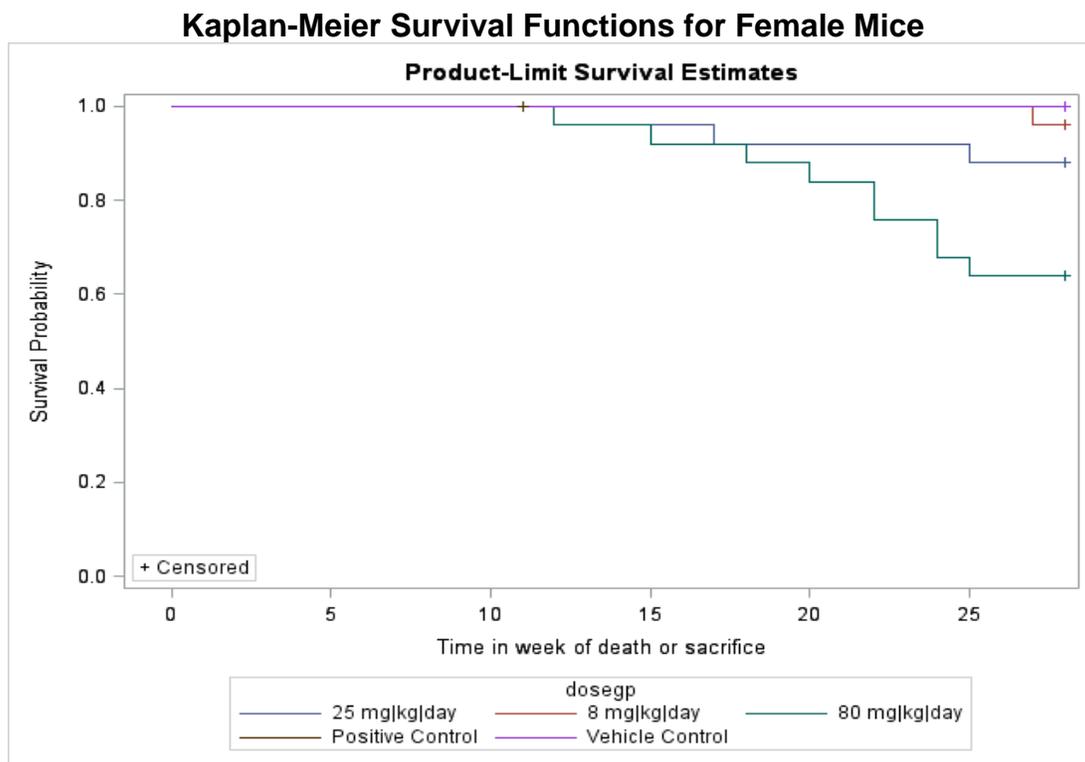
Text Table 9B: Female Mortality

Group	Dose Levels (mg/kg/day)	Animal Number	Day of Removal	Mode of Death	Cause of Death
2	8	2839	184	Natural Death	Kidneys, mesothelioma
3	25	2863	117	Natural Death	Mediastinum, mesothelioma
		2870	174	Natural Death	Skin, hemangiosarcoma
		2878	78	Natural Death	Spleen, hemangiosarcoma
		2886	153	Moribund Sacrifice	Multicentric hemangiosarcoma
4	80	2890	101	Natural Death	Multicentric hemangiosarcoma
		2895	175	Natural Death	Multicentric hemangiosarcoma
		2900	162	Natural Death	Thymus, mesothelioma
		2904	148	Natural Death	Skin, hemangiosarcoma
		2906	79	Natural Death	Undetermined
		2908	162	Natural Death	Undetermined
		2910	122	Natural Death	Skin, hemangiosarcoma
		3166	136	Natural Death	Undetermined

Survival at the terminal sacrifice was 100%, 96%, 0% (because of early termination on Day 177) and 64% at 8, 25 and 80 mg/kg/day in males and 100%, 96%, 88% and 64% in females, respectively. The remaining MDM were sacrificed on Day 177 (5 days prior to the planned terminal sacrifice) because of “high mortality (10/25 early deaths).” Survival curves provided below are from the FDA Statistical Review (Miao Z, Zhou F, Lin K).

**Kaplan-Meier Survival Functions for Male Mice**





**Clinical Signs:** Decreased motor activity, ruffled fur, and hunched posture were common in MD and HD males. Thin appearance occurred in a dose-related manner in males but only correlated with BW effect at the HD.

**Body Weights:** Absolute BW was decreased by up to 9%, relative to control, in HDM beginning on Day 169.

**Food Consumption:** Food consumption was increased in HD animals by 14% to 18%.

**Hematology:** Blood was sampled at terminal sacrifice and hematology parameters were assessed (sponsor's tables, below). Absolute lymphocyte count was decreased markedly (a known pharmacodynamic effect of RPC1063) in males and females. RBC, hemoglobin, and hematocrit were decreased and platelets were increased in males and females.

**Text Table 11A: Males, Week 27 Hematology**

Parameter	Dose Level (mg/kg/day)	Statistically Significant Difference Compared to Control
Red Blood Cells	8 & 80	↓(13.7%) & ↓(21.8%)
Hemoglobin	8 & 80	↓(11.0%) & ↓(21.5%)
Hematocrit	8 & 80	↓(11.3%) & ↓(18.4%)
Absolute Reticulocytes	80	↑(44.9%)
Platelets	8 & 80	↑(53.4%) & ↑(77.6%)
Absolute Neutrophils	8 & 80	↑(91.8%) & ↑(291.1%)
Absolute Lymphocytes	8 & 80	↓(44.8%) & ↓(54.9%)

↑ = Statistically significant increase ( $p < 0.05$ ) compared to Group 1 (vehicle control).

↓ = Statistically significant decrease ( $p < 0.05$ ) compared to Group 1 (vehicle control).

**Text Table 11B: Females, Week 27 Hematology**

Parameter	Dose Level (mg/kg/day)	Statistically Significant Difference Compared to Control
Red Blood Cells	8, 25 & 80	↓(12.2%), ↓(11.8%) & ↓(16.4%)
Hemoglobin	8, 25 & 80	↓(12.5%), ↓(12.2%) & ↓(17.6%)
Hematocrit	8, 25 & 80	↓(11.1%), ↓(10.5%) & ↓(15.0%)
Platelets	25 & 80	↑(63.1%) & ↑(42.4%)
Mean Platelet Volume	8 & 25	↓(11.0%) & ↓(8.1%)
Absolute Lymphocytes	8, 25 & 80	↓(51.9%), ↓(51.3%) & ↓(64.1%)

↑ = Statistically significant increase ( $p < 0.05$ ) compared to Group 1 (vehicle control).

↓ = Statistically significant decrease ( $p < 0.05$ ) compared to Group 1 (vehicle control).

**Gross Pathology:** Skin masses, some identified as hemangiosarcoma were observed sporadically in RPC1063-treated rats. Enlarged heart was observed in 8 LDM, 7 MDM, 13 HDM, and 4 HDF.

**Organ Weight:** Absolute weight was increased in heart (HDM 54%, MDF 18%, and HDF 39%), adrenals (HDM 27%), kidneys (HDM 10%), lungs (HDM 27%), liver (HDM 11%, LDF 14%, MDF 26%, and HDF 26%).

**Histopathology:** Peer Review: Yes; Signed/Dated Report: Yes

**Neoplastic:** Multiple lung adenomas (10/10 males and 10/10 females) and splenic hemangiosarcoma (7/10 males and 4/10 females) were evident in the positive control group. The increase in hemangiosarcoma and hemangioma (combined for the whole body) at all doses in males and at the MD and HD in females (sponsor's table, below) was considered to be RPC1063-related. The incidence of hemangiosarcoma in the skin of MDM, HDM, and HDF was increased in a dose-dependent manner. Multicentric hemangiosarcoma incidence was increased in HDF.

**Text Table 15A: Incidence of Hemangiosarcomas and Hemangiomas in Multiple Organs (Including Spleen), Males**

Dose Level (mg/kg/day)	0	8	25	80	HCR Incidence Range
Number Examined	25	25	25	25	
Spleen	0	1	0	0	0-4
Multicentric, Hemangioma	0	0	0	1	NPO
Multicentric	0	1	7*	2	0-1
Femur, Bone Marrow	0	1	0	0	0-1
Ileum	0	0	2	0	NPO
Jejunum	0	0	1	0	NPO
Rectum	0	0	1	0	NPO
Lung	0	1	0	0	0-1
Skin	0	0	4	4	0-1
Lumbar, Spinal Cord	0	1	0	0	0-1
Skeletal Muscle	0	0	2	2	0-1
Skin, Hemangioma	0	0	0	1	NPO
<b>Combined Incidence</b>	<b>0</b>	<b>5*</b>	<b>17*</b>	<b>10*</b>	<b>0-6<sup>1</sup></b>

**Text Table 15B: Incidence of Hemangiosarcomas and Hemangiomas in Multiple Organs (Including Spleen), Females**

Dose Level (mg/kg/day)	0	8	25	80	HCR Incidence Range
Number Examined	25	25	25	25	
Spleen	0	0	1	1	0-4
Multicentric	0	1	1	4*	0-1
Femur, Bone Marrow	0	0	1	0	0-1
Ileum	0	0	1	0	NPO
Mammary Gland, Hemangioma	0	1 <sup>#</sup>	0	0	NPO
Ovaries, Hemangioma	0	0	1	0	0-1
Ovaries	0	1	0	0	0-1
Pancreas	0	1 <sup>#</sup>	1	0	NPO
Skin	0	0	1	5	0-1
Stomach	0	0	1	0	NPO
Skeletal Muscle	0	0	0	1	0-1
<b>Combined Incidence</b>	<b>0</b>	<b>3</b>	<b>8*</b>	<b>11*</b>	<b>0-7<sup>1</sup></b>

\* = Statistically significant when compared to the vehicle control.

HCR =  $\frac{(b)(4)}{(b)(4)}$  Historical Control Incidence Range/25 control mice; 40 studies.

NPO = Not Previously Observed in the  $\frac{(b)(4)}{(b)(4)}$  Historical Control Database.

Note: Hemangiomas are explicitly noted above; all others tumors are hemangiosarcomas.

<sup>#</sup> = A benign tumor (mammary gland) and a malignant tumor (pancreas) were observed in animal no. 2840; therefore, these tumors are counted as one in the combined incidence.

<sup>1</sup> = Indicates Historical Incidence Range calculated as the combined incidence of splenic hemangiosarcomas (0-4), non-splenic hemangiosarcomas (0-2) and hemangiomas (0-1) in females, noted in the  $\frac{(b)(4)}{(b)(4)}$  Historical Control Database.

*Non Neoplastic*: Non-neoplastic lesions consisted of cardiomyopathy, lung infiltration of foamy macrophages, pigmented macrophage infiltration and lymphoid necrosis in the mesenteric lymph node, and mucosal hyperplasia of the glandular stomach in both sexes (table, below). In males, adrenal cortical hypertrophy and vacuolation, liver necrosis, epididymal interstitial inflammation, and testicular degeneration were observed (table below).

Histology Finding	Control		8 mg/kg		25 mg/kg		80 mg/kg	
	M	F	M	F	M	F	M	F
<b>Heart, Cardiomyopathy</b>	<b>0</b>	<b>0</b>	<b>5</b>	<b>1</b>	<b>14</b>	<b>12</b>	<b>6</b>	<b>15</b>
Minimal	0	0	0	1	0	11	0	9
Mild	0	0	5	0	9	0	6	6
Moderate	0	0	0	0	5	1	0	0
<b>Lung, Foamy Macrophage</b>	<b>0</b>	<b>0</b>	<b>3</b>	<b>0</b>	<b>25</b>	<b>12</b>	<b>25</b>	<b>25</b>
Minimal	0	0	1	0	9	9	0	5
Mild	0	0	2	0	13	3	5	17
Moderate	0	0	0	0	3	0	20	3
<b>Lymph Node (mesenteric), Pigmented Macrophage</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>22</b>	<b>7</b>
Minimal	0	0	0	0	0	0	0	4
Mild	0	0	0	0	0	0	20	3
Moderate	0	0	0	0	0	0	2	0
<b>Lymph Node (mesenteric), Lymphoid Necrosis</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>7</b>	<b>8</b>
Minimal	0	0	0	0	0	1	2	1
Mild	0	0	0	1	1	0	4	7
Moderate	0	0	0	0	0	0	1	0
<b>Glandular Stomach, Hyperplasia</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>18</b>	<b>21</b>
Minimal	0	0	0	0	0	0	4	11
Mild	1	0	0	0	0	0	14	9
Moderate	0	0	0	0	0	0	0	1
<b>Adrenal Cortex, Hypertrophy</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>11</b>	<b>0</b>	<b>24</b>	<b>0</b>
Minimal	0	0	0	0	2	0	5	0
Mild	0	0	0	0	9	0	19	0
<b>Adrenal Cortex, Vacuolation</b>	<b>1</b>	<b>0</b>	<b>7</b>	<b>0</b>	<b>9</b>	<b>0</b>	<b>6</b>	<b>0</b>
Minimal	1	0	4	0	2	0	10	0
Mild	0	0	3	0	7	0	16	0
<b>Liver, Necrosis</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>5</b>	<b>0</b>
Minimal	1	0	1	0	0	0	2	0
Mild	0	0	0	0	1	0	2	0
Moderate	0	0	0	0	1	0	1	0
<b>Epididymis, Inflammation</b>	<b>3</b>	<b>-</b>	<b>6</b>	<b>-</b>	<b>8</b>	<b>-</b>	<b>8</b>	<b>-</b>
Minimal	2	-	3	-	3	-	0	-
Mild	0	-	1	-	4	-	4	-
Moderate	1	-	2	-	1	-	3	-
Marked	0	-	0	-	0	-	1	-
<b>Testes, Degeneration</b>	<b>5</b>	<b>-</b>	<b>1</b>	<b>-</b>	<b>6</b>	<b>-</b>	<b>8</b>	<b>-</b>
Minimal	3	-	0	-	2	-	1	-
Mild	0	-	0	-	2	-	2	-
Moderate	2	-	1	-	1	-	3	-
Marked	0	-	0	-	1	-	2	-

**Toxicokinetics:** TK parameters for RPC1063 and metabolites, RP101075, RP101442, RP101988, and RP101124, on Day 1 and Week 26 are provided in the sponsor's tables, below. Two of the three major human metabolites, CC112273 and CC1084037, were not assessed.

**Text Table 10A: Mean Plasma TK Exposure Parameters in CByB6F1 Mice, Day 1**

RPC1063 Dose ( $\mu\text{mol/kg/day}$ ) Day 1	Sex	RPC1063		RP101075		RP101442	
		AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>
		(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )
19.78 (8 mg/kg/day)	Males	18.4	1.32	3.17	0.191	0.0781	0.00536
	Females	12.5	1.07	1.15	0.0643	0.0245	0.00157
	Combined	15.4	1.20	2.16	0.128	0.0513	0.00342
	Ratio (M/F)	1.47	1.23	2.76	2.97	3.19	3.41
61.82 (25 mg/kg/day)	Males	52.5	3.69	6.57	0.389	0.158	0.00956
	Females	45.0	3.02	4.64	0.273	0.103	0.00611
	Combined	48.7	3.25	5.61	0.331	0.130	0.00753
	Ratio (M/F)	1.17	1.22	1.42	1.42	1.53	1.56
197.82 (80 mg/kg/day)	Males	79.0	5.87	11.3	0.633	0.322	0.0254
	Females	86.8	5.38	9.01	0.571	0.230	0.0167
	Combined	82.9	5.62	10.2	0.602	0.276	0.0211
	Ratio (M/F)	0.910	1.09	1.25	1.11	1.40	1.52
RPC1063 Dose ( $\mu\text{mol/kg/day}$ ) Day 1	Sex	RP101988		RP101124		Total Agonist	
		AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>
		(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h <sup>+</sup> $\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )
19.78 (8 mg/kg/day)	Males	1.88	0.197	0.666	0.0421	23.5	1.54
	Females	1.97	0.208	1.98	0.121	15.6	1.30
	Combined	1.92	0.203	1.32	0.0809	19.6	1.42
	Ratio (M/F)	0.954	0.947	0.336	0.348	1.51	1.18
61.82 (25 mg/kg/day)	Males	6.43	0.583	1.62	0.110	65.6	4.37
	Females	8.78	0.793	5.01	0.333	58.6	3.95
	Combined	7.61	0.688	3.31	0.221	62.1	4.09
	Ratio (M/F)	0.732	0.735	0.323	0.330	1.12	1.11
197.82 (80 mg/kg/day)	Males	12.1	1.36	3.40	0.291	103	7.38
	Females	21.3	2.05	14.6	0.876	117	7.55
	Combined	16.7	1.71	8.98	0.487	110	7.46
	Ratio (M/F)	0.568	0.663	0.233	0.332	0.880	0.977

AUC<sub>0-last</sub> = area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration;

C<sub>max</sub> = maximum plasma concentration; F = females; h = hour(s); M = males;

Combined data represent the C<sub>max</sub> and AUC<sub>0-last</sub> values estimated from the composite TK profiles of the male and female animals.

**Text Table 10B: Mean Plasma TK Exposure Parameters in CByB6F1 Mice, Week 26**

RPC1063 Dose ( $\mu\text{mol/kg/day}$ ) Week 26	Sex	RPC1063		RP101075		RP101442	
		AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>
		(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )
19.78 (8 mg/kg/day)	Males	23.3	1.86	4.66	0.225	0.182	0.00861
	Females	16.3	1.51	2.00	0.115	0.0936	0.00478
	Combined	19.8	1.68	3.33	0.164	0.138	0.00669
	Ratio (M/F)	1.43	1.23	2.33	1.96	1.94	1.80
61.82 (25 mg/kg/day)	Males	74.1	5.27	17.1	0.788	0.690	0.0314
	Females	48.7	3.94	6.97	0.369	0.363	0.0173
	Combined	61.4	4.55	12.0	0.566	0.527	0.0244
	Ratio (M/F)	1.52	1.34	2.45	2.14	1.90	1.82
197.82 (80 mg/kg/day)	Males	221	11.1	62.6	3.16	2.79	0.128
	Females	162	10.5	31.4	1.70	1.82	0.0869
	Combined	192	10.2	47.0	2.34	2.31	0.105
	Ratio (M/F)	1.36	1.06	1.99	1.86	1.53	1.47
RPC1063 Dose ( $\mu\text{mol/kg/day}$ ) Week 26	Sex	RP101988		RP101124		Total Agonist	
		AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>	AUC <sub>0-last</sub>	C <sub>max</sub>
		(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )	(h $\cdot\mu\text{mol/L}$ )	( $\mu\text{mol/L}$ )
19.78 (8 mg/kg/day)	Males	2.72	0.237	1.36	0.111	30.8	2.32
	Females	3.97	0.433	2.58	0.148	22.3	1.98
	Combined	3.34	0.304	1.97	0.113	26.6	2.15
	Ratio (M/F)	0.685	0.547	0.527	0.750	1.38	1.17
61.82 (25 mg/kg/day)	Males	11.0	0.871	3.26	0.219	103	6.93
	Females	14.5	1.59	7.79	0.490	70.5	5.89
	Combined	12.8	1.18	5.52	0.320	86.7	6.19
	Ratio (M/F)	0.759	0.548	0.418	0.447	1.46	1.18
197.82 (80 mg/kg/day)	Males	43.0	2.20	11.3	0.612	329	16.5
	Females	67.6	5.36	22.4	1.16	263	17.7
	Combined	55.3	3.78	16.8	0.841	296	15.8
	Ratio (M/F)	0.636	0.410	0.504	0.528	1.25	0.932

AUC<sub>0-last</sub> = area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration;

C<sub>max</sub> = maximum plasma concentration; F = females; h = hour(s); M = males;

Combined data represent the C<sub>max</sub> and AUC<sub>0-last</sub> values estimated from the composite TK profiles of the male and female animals.

**Study title: A 24-month oral (gavage) carcinogenicity study of RPC1063 in rats**

Study no.: (b) (4) 72515  
 Study report location: EDR  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: January 12, 2015  
 GLP compliance: Yes, US FDA GLP  
 QA statement: Yes, signed  
 Drug, lot #, and % purity: RPC1063, AJ506FP-11-001, 99.5%  
 CAC concurrence: ExecCAC SPA recommendations:  
 December 18, 2014

**Key Study Findings**

- **There were no RPC1063-related neoplasia in rats dosed daily with RPC1063 for two years.**
- **Mineralization of the thalamus was increased in males at all dose levels and in females at doses > 0.2 mg/kg.**

**Adequacy of Carcinogenicity Study**

- **The study included the design recommendations of the ExecCAC (SPA meeting minutes dated December 18, 2014). The doses recommended by the ExecCAC were based on the metabolism information available at the time. Two of the major human metabolites, CC112273 and CC1084037, were not yet characterized at the time of submission of the SPA or study initiation. As such, TK assessment for these metabolites was not conducted.**

**Methods**

Doses: 0, 0.2, 0.7, 2 mg/kg  
 Frequency of dosing: Once daily  
 Dose volume: 5 mL/kg  
 Route of administration: Oral gavage  
 Formulation/Vehicle: 0.5% CMC in water, pH= 2.2  
 Basis of dose selection: Coverage (>25-fold) of parent and human metabolites (RP101075, RP101124, RP101442, RP101988)  
 Species/Strain: Crl:CD(SD) rat  
 Number/Sex/Group: Main: n=65/sex/group; TK: n=9/sex/group  
 Age: 1 month  
 Animal housing: Pair housed  
 Paradigm for dietary restriction: None, ad libitum food and water  
 Dual control employed: No  
 Interim sacrifice: None  
 Deviation from study protocol: The deviations did not impact the validity of the study.

**Dosing Solution Analysis:** Dosing solutions were 97% to 107% of the nominal concentration.

**Mortality:** Survival rates were 28%, 32%, 45%, and 27% in males (control, LD, MD, HD, respectively) and 26%, 34%, 37%, and 38% in females (control, LD, MD, HD, respectively; sponsor's tables and figures, below). The main identified cause of unscheduled death in all dose groups was pituitary adenoma (Males: 24, 23, 19, 23; Females: 33, 27, 21, 20, Control, LD, MD, HD, respectively). Group size remained above 20/sex/group through Week 100 for both sexes.

Text Table 10  
Survival - Number and Percentage of Animals Surviving (N = 65/group)<sup>a</sup>

Group (mg/kg/day)	Males				Females			
	0	0.2	0.7	2	0	0.2	0.7	2
<b>Study Week</b>								
60	58/65 89%	60/65 92%	61/64 95%	58/64 91%	59/65 91%	59/65 91%	63/65 97%	63/65 97%
80	48/65 74%	50/65 77%	49/64 77%	45/64 70%	42/65 65%	48/65 74%	46/65 71%	55/65 85%
88 (survival >50% for males)	41/65 63%	40/65 62%	41/64 64%	33/64 52%	NA	NA	NA	NA
89 (survival >50% for females)	NA	NA	NA	NA	34/65 52%	32/65 49%	34/65 52%	36/65 55%
104 (End of Study)	18/65 28%	21/65 32%	29/64 45%	17/64 27%	17/65 26%	22/65 34%	24/65 37%	25/65 38%

<sup>a</sup> Mortality data corrected for accidental deaths.

NA = not applicable

Text Table 11  
Kaplan-Meier Estimates of Survival<sup>a</sup>

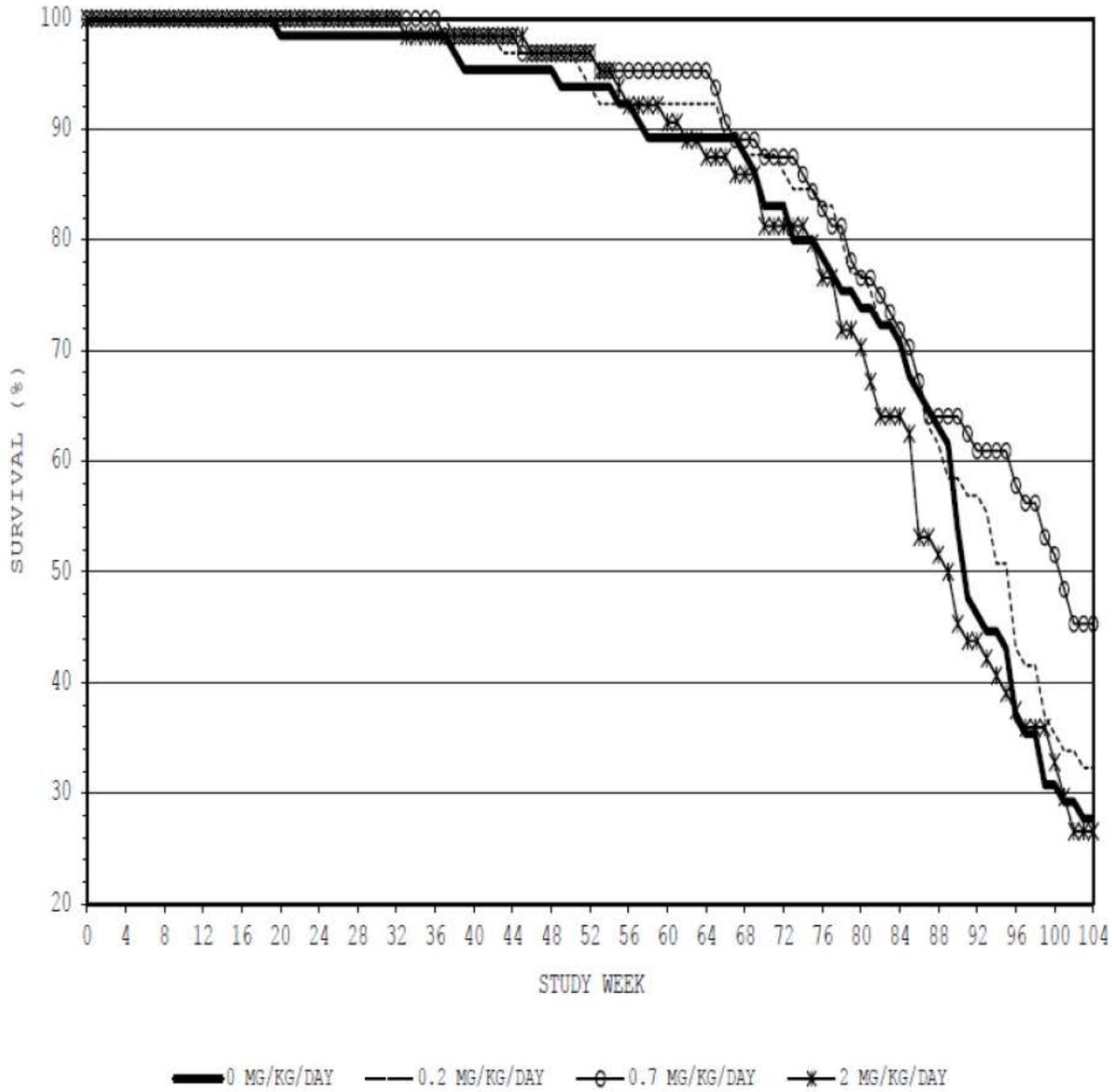
Study Week	Dosage Level (mg/kg/day)				Overall	Trend
	0	0.2	0.7	2		
<b>Males</b>						
60	89%	92%	95%	91%		
80	74%	77%	77%	70%		
End of Study	28%	32%	45%	27%		
p-value		NT	NT	NT	0.1724	0.8824
<b>Females</b>						
60	91%	91%	97%	97%		
80	65%	74%	71%	85%		
End of Study	26%	34%	37%	38%		
p-value		NT	NT	NT	0.3607	0.1019

p-values (p): Comparisons using vehicle group

NT = Not tested per protocol statistical methodology

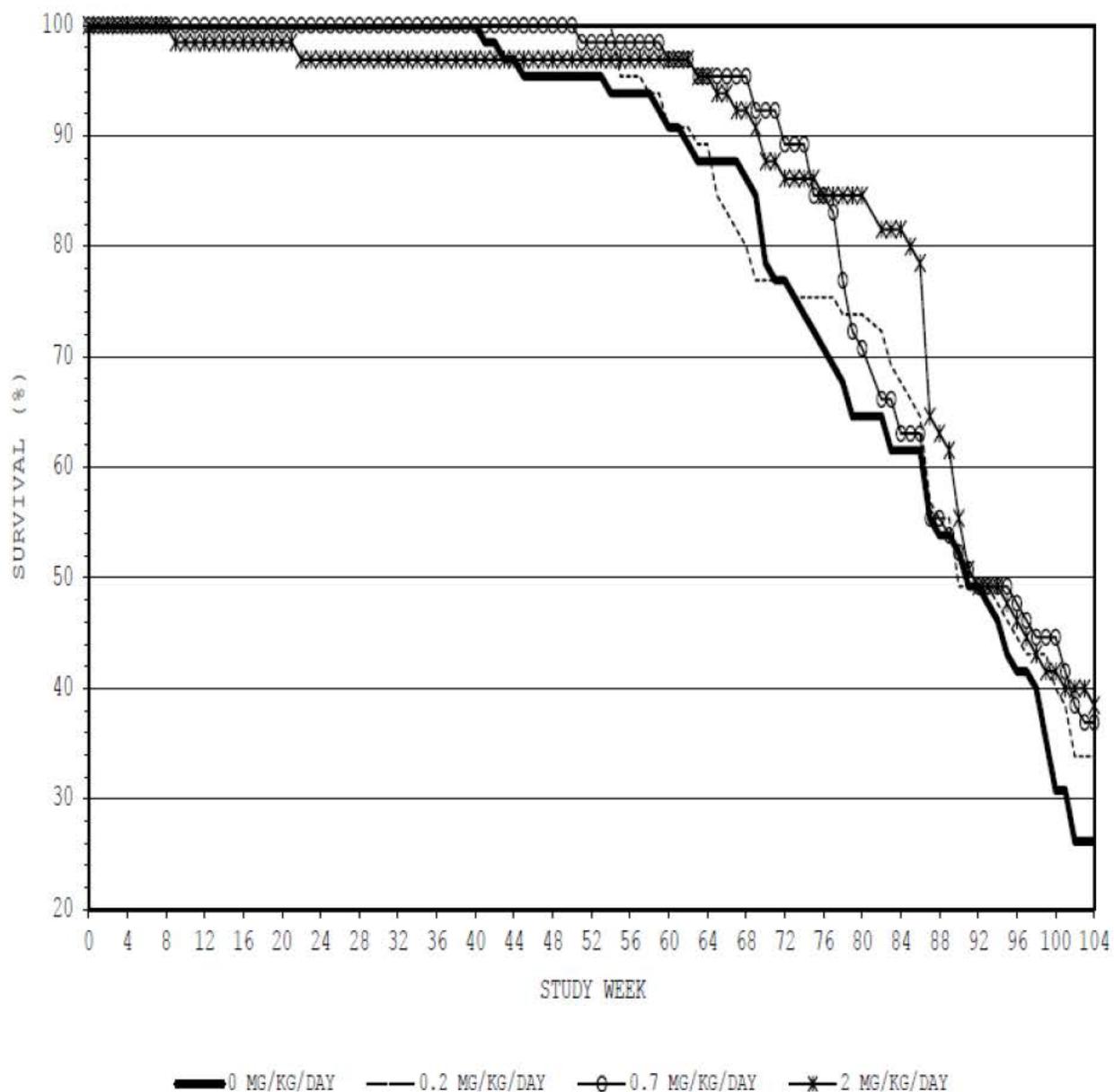
PROJECT NO. (b) (4) 72515M  
SPONSOR: RECEPTOS INC.

FIGURE 1 (MALES)  
SUMMARY OF SURVIVAL [%]



PROJECT NO. (b) (4) 72515F  
 SPONSOR: RECEPTOS INC.

FIGURE 2 (FEMALES)  
 SUMMARY OF SURVIVAL [%]

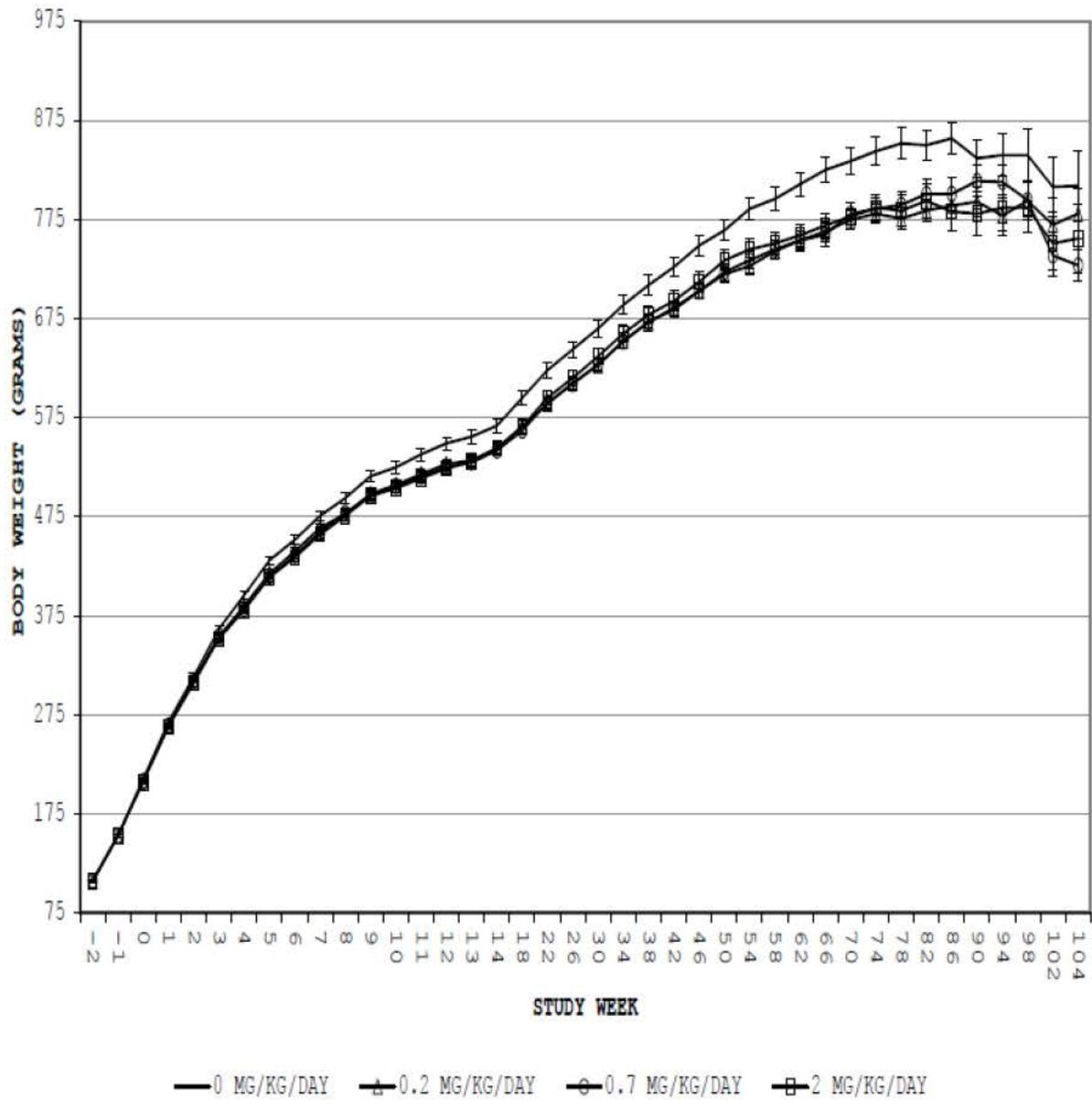


Clinical Signs: There were no RPC1063-related clinical signs.

Body Weights: Beginning at Week 4 and Week 8 for males and females, respectively, mean body weights were decreased in all RPC1063 dose groups, relative to control. At study termination, mean body weight was 3.5%, 9.9%, and 6.6% lower than controls in males and 12.5%, 9%, and 9.9% lower than controls in females.

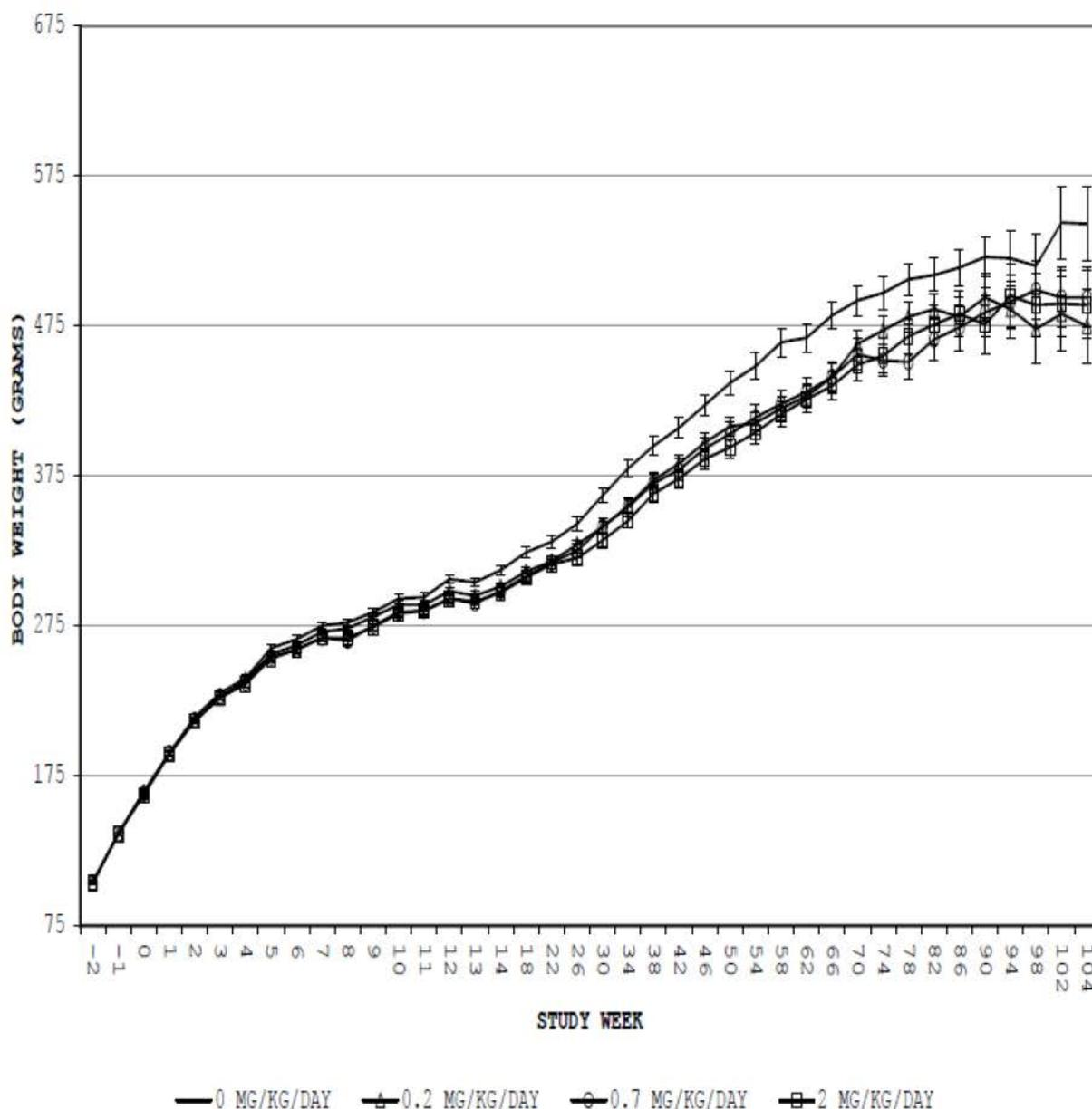
PROJECT NO. (b)(4) 72515M  
SPONSOR: RECEPTOS INC.

FIGURE 3 (MALES)  
SUMMARY OF BODY WEIGHTS [G]  
DATA PRESENTED AS MEAN ± S.E.



PROJECT NO. (b) (4) 72515F  
 SPONSOR: RECEPTOS INC.

FIGURE 4 (FEMALES)  
 SUMMARY OF BODY WEIGHTS [G]  
 DATA PRESENTED AS MEAN  $\pm$  S.E.



Food Consumption: There were no RPC1063-related effects on food consumption.

Gross Pathology: There were no RPC1063-related findings.

Histopathology: Peer Review: Yes; Signed/Dated: Yes

Neoplastic: There were no RPC1063-related neoplastic findings.

Non-Neoplastic: Bilateral accumulation of basophilic aggregates in the thalamus, characterized as mineralization, was increased in incidence and severity with dose at  $\geq$  8

mg/kg in males and  $\geq 25$  mg/kg in females (sponsor's table, below). The study pathologist states that this lesion is a known spontaneous lesion that occurs with age in rat; RPC1063 increased the incidence and severity of this finding. There was no necrosis or inflammation associated with this finding. Although the incidence was not specifically dose-related, an increase in hepatic eosinophilic and basophilic foci occurred at all dose levels of RPC1063.

Histology Finding	Control		8 mg/kg		25 mg/kg		80 mg/kg	
	M	F	M	F	M	F	M	F
<b>Brain, Mineralization (Thalamus)</b>	<b>2</b>	<b>2</b>	<b>10</b>	<b>2</b>	<b>32</b>	<b>15</b>	<b>47</b>	<b>42</b>
Minimal	2	2	9	2	16	12	21	27
Mild	0	0	1	0	10	3	16	6
Moderate	0	0	0	0	6	0	10	9
<b>Liver, Eosinophilic foci</b>	<b>9</b>	<b>7</b>	<b>20</b>	<b>14</b>	<b>28</b>	<b>21</b>	<b>19</b>	<b>19</b>
Minimal	2	7	7	9	11	14	5	15
Mild	4	0	6	3	3	5	10	1
Moderate	3	0	6	2	11	1	4	2
Marked	0	0	1	0	3	1	0	1
<b>Liver, Basophilic foci</b>	<b>18</b>	<b>39</b>	<b>29</b>	<b>48</b>	<b>28</b>	<b>55</b>	<b>32</b>	<b>52</b>
Minimal	13	25	22	14	14	9	17	10
Mild	4	7	7	15	9	15	10	14
Moderate	1	5	0	11	5	17	5	14
Marked	0	1	0	8	0	14	0	14
Severe	0	1	0	0	0	0	0	0

Toxicokinetics: TK parameters for the parent (RPC1063) and four metabolites, RPC101075, RP101124, RP101442, and RP101988, are provided in the sponsor's tables, below. Metabolites CC112273 and CC1084037 were not assessed.

Text Table 12  
Toxicokinetic Parameters for RPC1063 in Rats

Analyte	Study Day	Dose	Sex	Group	Tmax	Cmax	AUClast	AUClast/D	AUClast
		mg/kg/day			(h)	(ng/mL)	(h*ng/mL)	(h*ng/mL)/(mg/kg)	RAUC
RPC1063	0	0.2	M	2A	4	1.96	11.8	58.8	NA
			F	2A	2	2.32	15.1	75.5	NA
		0.7	M	3A	4	7.60	45.1	64.4	NA
			F	3A	4	9.19	122	175	NA
		2	M	4A	4	19.0	269	134	NA
			F	4A	4	26.8	385	192	NA
RPC1063	185	0.2	M	2A	4	2.88	32.9	164	2.80
			F	2A	2	5.09	49.7	248	3.29
		0.7	M	3A	4	10.5	138	197	3.05
			F	3A	2	19.0	214	305	1.74
		2	M	4A	2	37.3	517	259	1.92
			F	4A	2	64.5	685	342	1.78

NA = Not applicable

Text Table 13  
Toxicokinetic Parameters for RPC101075 in Rats

Analyte	Study Day	Dose	Sex	Group	Tmax	Cmax	AUClast	AUClast/D	AUClast
		mg/kg/day			(h)	(ng/mL)	(h*ng/mL)	(h*ng/mL)/(mg/kg)	RAUC
RP101075	0	0.2	M	2A	NA	NA	NA	NA	NA
			F	2A	NA	NA	NA	NA	NA
		0.7	M	3A	8	0.763	NA	NA	NA
			F	3A	8	0.454	NA	NA	NA
		2	M	4A	8	1.87	30.1	15.1	NA
			F	4A	8	1.31	20.9	10.5	NA
RP101075	185	0.2	M	2A	4	0.317	1.38	6.89	NA
			F	2A	2	0.411	NA	NA	NA
		0.7	M	3A	8	1.88	33.1	47.3	NA
			F	3A	8	1.78	32.8	46.8	NA
		2	M	4A	8	7.49	141	70.5	4.68
			F	4A	8	5.54	98.4	49.2	4.71

NA = Not applicable

Text Table 14  
Toxicokinetic Parameters for RP101124 in Rats

Analyte	Study Day	Dose	Sex	Group	Tmax	Cmax	AUClast	AUClast/D	AUClast
		mg/kg/day			(h)	(ng/mL)	(h <sup>+</sup> ng/mL)	(h <sup>+</sup> ng/mL)/(mg/kg)	RAUC
RP101124	0	0.2	M	2A	8	1.65	21.2	106	NA
			F	2A	8	1.98	34.2	171	NA
		0.7	M	3A	8	4.34	63.1	90.1	NA
			F	3A	8	7.71	123	176	NA
		2	M	4A	8	11.6	181	90.5	NA
			F	4A	24	16.2	307	153	NA
RP101124	185	0.2	M	2A	8	7.40	104	518	4.89
			F	2A	8	6.34	120	601	3.52
		0.7	M	3A	8	23.7	328	468	5.20
			F	3A	8	24.8	393	561	3.18
		2	M	4A	2	29.9	570	285	3.15
			F	4A	8	49.6	1050	523	3.41

NA = Not applicable

Text Table 15  
Toxicokinetic Parameters for RP101442 in Rats

Analyte	Study Day	Dose	Sex	Group	Tmax	Cmax	AUClast	AUClast/D	AUClast
		mg/kg/day			(h)	(ng/mL)	(h <sup>+</sup> ng/mL)	(h <sup>+</sup> ng/mL)/(mg/kg)	RAUC
RP101442	0	0.2	M	2A	NA	NA	NA	NA	NA
			F	2A	NA	NA	NA	NA	NA
		0.7	M	3A	24	0.921	NA	NA	NA
			F	3A	24	1.12	NA	NA	NA
		2	M	4A	24	3.74	54.6	27.3	NA
			F	4A	24	2.58	35.8	17.9	NA
RP101442	185	0.2	M	2A	2	1.69	28.1	141	NA
			F	2A	0	0.968	18.2	91.0	NA
		0.7	M	3A	4	6.1	111	159	NA
			F	3A	8	4.32	97.5	139	NA
		2	M	4A	2	23.7	526	263	9.63
			F	4A	0	13.5	260	130	7.26

NA = Not applicable

Text Table 16  
Toxicokinetic Parameters for RP101988 in Rats

Analyte	Study Day	Dose mg/kg/day	Sex	Group	Tmax	Cmax	AUClast	AUClast/D	AUClast
					(h)	(ng/mL)	(h*ng/mL)	(h*ng/mL)/(mg/kg)	RAUC
RP101988	0	0.2	M	2A	4	1.34	6.77	33.8	NA
			F	2A	4	1.57	8.45	42.2	NA
		0.7	M	3A	4	4.12	23.9	34.1	NA
			F	3A	4	5.82	63.5	90.7	NA
		2	M	4A	4	16.5	171	85.6	NA
			F	4A	4	19.5	196	98.1	NA
RP101988	185	0.2	M	2A	4	5.73	56.5	282	8.34
			F	2A	4	6.25	50.1	250	5.93
		0.7	M	3A	4	19.7	206	294	8.60
			F	3A	2	16	186	265	2.92
		2	M	4A	4	53.0	759	380	4.44
			F	4A	2	59.8	580	290	2.96

NA = Not applicable

## 9 Reproductive and Developmental Toxicology

### 9.1 Fertility and Early Embryonic Development

**Study title: RPC1063 Fertility toxicity study by the oral route (gavage) in the rat (Segment I)**

Study no.:	AB07244
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 29, 2011
GLP compliance:	Yes, OECD
QA statement:	Yes
Drug, lot #, and % purity:	RPC1063, AJ506FP-11-001, 99.5%

#### Key Study Findings

- **Fertility was not affected in male and female rats at doses up to 30 mg/kg RPC1063.**

#### Methods

Doses:	0, 0.2, 2, 30 mg/kg/day
Frequency of dosing:	Males: once daily 14 days before mating and throughout mating Females: once daily 14 days before mating until gestation day (GD) 7
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) carboxymethylcellulose
Species/Strain:	Sprague-Dawley rat CrI:OFA(SD)
Number/Sex/Group:	20
Deviation from study protocol:	Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: Formulations ranged from -15% to 6% of the nominal concentration.

Mortality & Clinical Signs: There were no unscheduled deaths. Hypersalivation occurred immediately after dosing at the HD.

Body Weight & Food Consumption: Absolute BW was decreased in MDM (10%) and HDM (14%), relative to control. Absolute weight was decreased by 5% in HDF, relative to controls, throughout mating and gestation. Food consumption was decreased in MDM (up to 11%) and HDM (up to 28%). Food consumption was decreased in HDF (11%) during the gestation period.

Mating performance, fertility, and reproductive organ weight: There was no effect on pre-coital interval, the copulation index, the fertility index, sperm motility, or sperm count. Absolute weight of reproductive tissues were not affected.

Necropsy and Caesarean Analysis: There was no effect on the number of corpora lutea, implantation site, pre-implantation loss, or post-implantation loss.

## 9.2 Embryonic Fetal Development

### Rat

Study AB03214: RPC1063: Dose range-finding study by the oral (gavage) route in the pregnant rat." Pregnant Sprague-Dawley rats (n=6/group) were given a daily oral dose of 0, 0.2, 2, or 40 mg/kg RPC1063 in 0.5% carboxymethylcellulose beginning on gestation day (GD) 6 and ending on GD 17. Fetal assessment was performed on GD 20. There were no early deaths or clinical signs. Post-implantation loss was 100% in the HDF; LD and MD pregnancy rates and implantation losses were similar to control. There were no fetal malformations observed at the LD or MD.

#### **Study title: RPC1063: Embryo toxicity study by the oral (gavage) route in the rat (Segment II)**

Study no.:	AB03215
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/2/2011
GLP compliance:	Yes, OECD GLP
QA statement:	Yes
Drug, lot #, and % purity:	RPC1063, AJ506FP-11-001, 99.5%

#### **Key Study Findings**

- **The fetal NOAEL was 0.2 mg/kg. At higher doses, incomplete skeletal ossification was evident. At the HD, anasarca and bilateral malpositioned testes were observed.**
- **The number of viable fetuses was decreased and the number of post-implantation losses was increased at the HD.**
- **A dose-dependent decrease in white blood cells was evident at all doses.**

#### Methods

Doses:	0, 0.2, 1, 5 mg/kg
Frequency of dosing:	Once daily beginning on GD 6 and ending on GD 17; euthanized on GD 20.
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% CMC
Species/Strain:	Female Sprague-Dawley rat CrI:OFA (SD)
Number/Sex/Group:	Main: 25/group; TK: 6/group
Deviation from study protocol:	Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: Formulations were within -13 to +4% of the nominal concentrations.

Mortality & Clinical Signs: There were no unscheduled deaths or RPC1063-related clinical signs.

Body Weight & Food Consumption: Absolute BW was decreased by 12% at the HD, relative to control. Food consumption was 10% lower at the HD.

**Hematology:** WBC, lymphocyte, large unstained cells, basophil, and eosinophil counts were decreased in a dose-dependent manner at all dose levels on GD 18 (sponsor's table, below).

	Historical control data range <sup>(a)</sup>	Group 1 Control	Group 2 0.2 mg/kg/day	Group 3 1 mg/kg/day	Group 4 5 mg/kg/day
Total white blood cell (G/L)	3.73-8.85	8.545	6.522*	4.660**	4.665**
Lymphocytes (G/L)	2.86-7.40	4.960	3.227**	1.840**	1.498**
Eosinophils (G/L)	0.06-0.24	0.120	0.102	0.078*	0.083*
Basophils (G/L)	0.00-0.03	0.020	0.013	0.010*	0.008*
Neutrophils (G/L)	0.49-1.16	2.988	2.740	2.367	2.668
Monocytes (G/L)	0.10-0.36	0.335	0.357	0.302	0.328
Large unstained cells (G/L)	0.02-0.08	0.123	0.087*	0.065*	0.078*

(a): Historical control data for non pregnant Sprague-Dawley rats, 14 to 23 weeks of age.

\*: 5 % significance level.

\*\*: 1 % significance level.

**Necropsy:** There were no RPC-1063-related macroscopic findings in the dams.

**Cesarean Section Data:** At the HD, the number of viable fetuses was markedly decreased (23% of control) and post-implantation loss was markedly increased (15-fold). Average absolute weight of live fetuses was decreased by 12% at the HD.

**Offspring:** Anasarca, a malformation, occurred in three fetuses from two separate litters at the HD (sponsor's table, below). Anasarca was not observed in the controls, LD, or MD, and the incidence of 4.1% at the HD exceeded the historical control data (0.04%). Bilateral malpositioned testis occurred in two fetuses from two different HD litters. Cleft palate was observed in one HD fetus. The neck cysts observed in the one LD fetus were not observed at any other dose level and were considered to be unrelated to drug.

Summary of malformations – Individual descriptions:

Group number	Female number	Fetus number	Malformation(s) <sup>#</sup>
1	/	/	No abnormality observed
2	33	6	Cyst: neck; right side
3	/	/	No abnormality observed
4	76	8	Cleft palate
	83	7 and 9	Anasarca
	91	8	Testis: malpositioned; bilateral
	92	11	Anasarca
			Testis: malpositioned; bilateral

<sup>#</sup>: Including external, visceral and skeletal examinations./: not applicable.

## Fetal incidences of selected skeletal changes (% of fetuses affected):

Finding with % of affected fetuses	Historical control data 2008-2010	Group 1 Control	Group 2 0.2 mg/kg/day	Group 3 1 mg/kg/day	Group 4 5 mg/kg/day
Number of fetuses	1238	162	151	153	42
<b>Incomplete ossification</b>					
<b>Paws:</b>					
Metacarpal (2 <sup>nd</sup> or 5 <sup>th</sup> digit)	12.9	9.3	6.6	15.0	59.5
Metatarsal	2.3	0	0.7	0.7	7.1
<b>Sternebra:</b>					
1 <sup>st</sup> / 3 <sup>rd</sup>	4.8	1.9	3.3	5.9	35.7
2 <sup>nd</sup> / 4 <sup>th</sup>	6.5	2.5	4.6	7.2	40.5
6 <sup>th</sup>	7.0	0.6	4.0	8.5	23.8
<b>Vertebrae:</b>					
Thoracic (9-13 <sup>th</sup> centrum)	7.2	8.6	5.3	5.9	28.6
Thoracic (1-4 <sup>th</sup> centrum)	3.4	1.9	2.0	5.2	28.6
<b>Skull bones:</b>					
Interparietal	12.8	13.6	17.2	24.2	28.6
Parietal	4.0	3.1	2.0	3.3	14.3
<b>Mandibular:</b>					
Presphenoid	0.1	0.6	0	0.7	9.5
<b>Sternebra:</b>					
6 <sup>th</sup>	1.1	0.6	2.0	1.3	9.5
<b>Vertebra:</b>					
Caudal centrum	0.0	0	0	0.7	9.5
<b>Other findings</b>					
<b>Bipartite ossification:</b>					
Sternebra	0.5	0	0.7	0	16.7

The incidence of incomplete ossification was increased in the fetal skull, paws, mandible, vertebrae, and sternebra at the HD compared to concurrent and historical controls (sponsor's table, above). The incidence of incomplete ossification was also increased at the MD, relative to concurrent and historical control, but not in as many skeletal regions (metacarpal, sternebra, and interparietal skull bone) as at the HD.

Toxicokinetics: TK parameters for RPC1063 and two metabolites, RP-101075 and RP-101442, are provided in the sponsor's table, below. CC112273, CC1084037, and RP101124, the major human metabolites, were not quantified.

Occasion	Compound	Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-12h</sub> (ng.h/mL)	AUC <sub>0-24h</sub> (ng.h/mL)
G6	RPC1063	0.2	3.67	4	32.1	43.6
		1	17.4	4	144	202
		5	109	2	951	1306
	RP-101075	0.2	NA	NA	NA	NA
		1	NA	NA	NA	NA
		5	4.12	8	37.8	84.5
	RP-101442	0.2	NA	NA	NA	NA
		1	1.74	24	2.47	20.3
		5	12.5	24	34.5	152
	Total agonist	0.2	3.67	4	32.1	43.6
		1	17.4	4	147	223
		5	112	2	1024	1544
G17	RPC1063	0.2	4.75	2	42.3	54.1
		1	24.4	2	209	284
		5	169	2	1420	1903
	RP-101075	0.2	NA	NA	NA	NA
		1	1.18	12	9.67	16.7
		5	8.31	8	90.9	169
	RP-101442	0.2	1.13	2	6.67	13.0
		1	5.08	12	54.2	109
		5	48.2	4	541	1065
	Total agonist	0.2	5.88	2	51.8	73.3
		1	30.3	4	274	412
		5	218	2	2052	3137

### Rabbit

Study AB03216: "RPC1063 Dose range-finding study by the oral (gavage) route in the pregnant rabbit" Pregnant New Zealand White rabbits (n=6/group) were given a daily oral dose of 0, 0.25, 2.5, or 50 mg/kg RPC1063 in 0.5% CMC, on GDs 6-19; caesarean section occurred on GD 29. There were no deaths, clinical signs, or macroscopic findings in does. Four HDF were sacrificed prior to the planned terminal sacrifice because of spontaneous abortion; the two remaining pregnant HD females had no viable fetuses at the time of assessment. At the MD, one female had no viable fetuses at the time of the planned sacrifice. There were no test article-related findings at the LD.

**Study title: RPC1063: Embryo toxicity study by the oral (gavage) route in the rabbit (Segment II)**

Study no.: AB03217  
 Study report location: EDR  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: August 1, 2011  
 GLP compliance: Yes, OECD  
 QA statement: Yes  
 Drug, lot #, and % purity: RPC1063, AJ506FP-11-001, 99.5%

**Key Study Findings**

- **There was no NOAEL determined. The incidence of malpositioned caudal vertebra was increased in a dose-dependent manner at all dose levels.**
- **Spontaneous abortion and embryoletality were evident at the HD.**
- **A dose-dependent decrease in white blood cells, lymphocytes, monocytes, eosinophils and basophils occurred at all doses in the does.**
- **At > 0.2 mg/kg, malformation of blood vessels (mainly at the aortic arch), incomplete ossification (forepaw and sternebra), and misshapen/ fusion of the sternebra occurred in fetuses.**

Doses: 0, 0.2, 0.6, 2 mg/kg  
 Frequency of dosing: Once daily beginning on GD 6 to GD 19;  
 caesarean section on GD 29  
 Dose volume: 5 mL/kg  
 Route of administration: Oral gavage  
 Formulation/Vehicle: 0.5% CMC  
 Species/Strain: NZW rabbit, Crl:KBL (NZW)  
 Number/Sex/Group: 22/group  
 Deviation from study protocol: Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: Formulations were within -12 % to 4 % of the nominal concentration.

Mortality & Clinical Signs: One HDF aborted and was euthanized on GD 27. There were no RPC1063-related clinical signs.

Body Weight & Food Consumption: BW gain from GD6 to GD20 was decreased by 10% at the HD, relative to control. Food consumption was decreased by up to 5% at the HD between GDs 6 and 20.

Hematology: WBC, lymphocytes, monocytes, eosinophils, and basophils were decreased at all dose levels on GD 20 (sponsor's table, below).

	Historical control data range <sup>(a)</sup>	Group 1 Control	Group 2 0.2 mg/kg/day	Group 3 0.6 mg/kg/day	Group 4 2 mg/kg/day
Total white blood cell (G/L)	4.06 – 11.54	6.328	2.625**	1.932**	2.042**
Lymphocytes (G/L)	2.74 – 9.35	4.412	1.175**	0.588**	0.502**
Monocytes (G/L)	0.05 – 0.66	0.167	0.070*	0.034**	0.013**
Eosinophils (G/L)	0.00 – 0.40	0.088	0.045*	0.044*	0.050*
Basophils (G/L)	0.18 – 0.84	0.287	0.102**	0.100**	0.087**
Neutrophils (G/L)	0.42-2.06	1.318	1.230	1.162	1.388

(a): historical control data for non pregnant New Zealand White KBL rabbits, 09 to 16 weeks of age.

\*: 5 % significance level.

\*\* : 1 % significance level.

Necropsy: There were no RPC1063-related macroscopic findings in does.

Cesarean Section Data: One HDF aborted on G27; this female had 5 early resorptions. Postimplantation loss was increased at the HD (30.4%). Mean live litter size was also decreased at the HD (6.8/litter), relative to concurrent (9.3/litter) and historical controls (8.8/litter).

Offspring: Malformed blood vessels (mainly at the aortic arch) were observed in 2 fetuses from two different litters at the MD and HD. The innominate (brachiocephalic) artery was absent in 6 fetuses from a single litter at the HD. The incidence of these findings was greater than in the concurrent and historical controls. Increased incidence, which exceeded concurrent and historical controls, of incomplete ossification was observed in the sternebra at the MD and in forepaw and sternebra at the HD (sponsor's table, below). A dose-dependent increase in misshapen and minor fusion of the sternebra occurred at the MD and HD. The incidence of malpositioned caudal vertebra was increased in a dose-dependent manner at all dose levels.

Fetal incidences of selected skeletal changes (% of fetuses (number of litters) affected):

Finding with % of affected fetuses	Historical control data 2008-2010	Group 1 Control	Group 2 0.2 mg/kg/day	Group 3 0.6 mg/kg/day	Group 4 2 mg/kg/day
Number of fetuses	3338	189	192	199	137
Incomplete ossification of phalanx, forepaw	1.29	0.5 (1)	0.0	0.5 (1)	2.9 (2)
Unossified phalanx, forepaw	0.42	0.5 (1)	0.0	0.5 (1)	1.5 (2)
Sternebra:					
Incomplete ossification: 1 <sup>st</sup> / 3 <sup>rd</sup>	0.63	0.5 (1)	0.5 (1)	0.0	2.2 (2)
2 <sup>nd</sup> / 4 <sup>th</sup>	4.28	5.3 (7)	3.6 (6)	10.6 (11)	16.1 (7)
Minor fusion	0.78	0.0	0.0	2.0 (3)	12.4 (12**)
Misshapen	0.03	0.5 (1)	2.6 (1)	3.5 (5)	7.3 (8)
Bipartite ossification	0.99	1.1 (2)	3.6 (6)	1.0 (2)	3.6 (4)
Asymmetric	0.75	1.6 (3)	0.5 (1)	0.0	3.6 (4)
Extraossification site	0.15	0.0	0.5 (1)	0.0	0.7 (1)
Rib: cervical	0.15	0.0	0.5 (1)	0.5 (1)	0.7 (1)
Caudal vertebra malpositioned	1.05	0.0	1.6 (2)	2.0 (4)	5.1 (6)
Number of head fetuses evaluated	1759	98	101	103	74
Nasal sutural bone	0.57	0.0	0.0	0.0	1.4 (1)

\*\* : 1 % significance level.

Toxicokinetics: TK parameters for parent and RP-101075 are provided in the sponsor's table, below. CC112273, CC1084037, and RP101124, the major human metabolites, were not quantified.

Occasion	Compound	Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t (h)	AUC <sub>0-12h</sub> (ng.h/mL)	AUC <sub>0-24h</sub> (ng.h/mL)
G6	RPC1063	0.2	1.32	4	8	10.71	NA
		0.6	3.69	8	12	35.9	48.7
		2	14.6	4	24	123	161.7
	RP-101075	0.2	NA	NA	NA	NA	NA
		0.6	2.14	8	12	14.5	24.40
		2	6.87	12	24	64	128.4
	Total agonist	0.2	1.32	4	8	10.71	NA
		0.6	5.83	8	12	51.3	73.9
		2	20.5	4	24	187	290
G19	RPC1063	0.2	NA	NA	NA	NA	NA
		0.6	3.75	4	12	30.8	40.1
		2	12.7	4	12	102	130.1
	RP-101075	0.2	NA	NA	NA	NA	NA
		0.6	2.11	8	24	20.5	35.5
		2	9.89	8	24	90	146.5
	Total agonist	0.2	2.08	2	12	14.1	19.82
		0.6	5.57	4	24	51.3	75.6
		2	20.8	4	24	192	281

### 9.3 Prenatal and Postnatal Development

#### Study title: RPC1063: A study of toxic effects on pre- and postnatal development, including maternal function in rats

Study no.: 1840-012  
 Study report location: EDR  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: May 12, 2016  
 GLP compliance: Yes, US FDA GLP  
 QA statement: Yes  
 Drug, lot #, and % purity: RPC1063, AJ527S5A-15-001, 99.6%

#### Key Study Findings

- The NOAEL in the F1 generation was the MD of 0.7 mg/kg. At the HD, there was an increase in motor activity, fine movement, and total distance (26%) in the open field assessment. HDM animals were hyperreactive beginning at Week 11.

#### Methods

Doses: 0, 0.2, 0.7, 2 mg/kg  
 Frequency of dosing: Once daily from GD 6 through lactation day 20  
 Dose volume: 5 mL/kg  
 Route of administration: Oral gavage  
 Formulation/Vehicle: 0.5% CMC  
 Species/Strain: CD [CrI:CD(SD)] rat  
 Number/Sex/Group: Time-mated females: 25/group  
 Deviation from study protocol: Deviations did not impact the validity of the study.

Dosing formulations: Formulations were within -8% and 6% of the nominal concentration.

*F<sub>0</sub> Dams*

Survival: One control dam was euthanized on PND 22 after the entire litter was cannibalized.

Clinical Signs: There were no RPC1063-related clinical signs during the gestation and lactation periods.

Body Weight and Food Consumption: Absolute BW and food consumption was not affected during the gestation or lactation periods.

Necropsy observation: There were no RPC1063-related findings.

*F1 Generation*

Survival: Number of females delivering a litter, gestation length, litter size, gestation index, stillborn index, total implantation scars, sex ratio, pup viability index, or lactation index were not affected.

Clinical signs: HDM were hyperreactive to touch beginning on Week 11.

Body weight: Absolute BW was decreased in pups at the HD by 7%, relative to control, on lactation days 7 and 21.

Physical development: There were no findings in the macroscopic examinations of stillborn, culled pups, or pups assessed on PND 28. Time to eye opening, pinna detachment, vaginal opening, and preputial separation were not affected.

Neurological assessment and development: There were no effects on righting reflex, cliff aversion, air drop righting reflex, or auditory response. HDF exhibited an increase in motor activity (20%), fine movement (24%), and total distance (26%) in the open field assessment when conducted on PND 35. Passive avoidance testing, when initiated on PND 70, was not affected.

Reproduction assessment: Mean estrous cycle length was increased from 4.2 to 5.2 days at the HD. Fertility and reproductive parameters in the F1 generation (mating index, fertility index, fecundity index, copulatory interval) were not affected.

Gross examination: There were no RPC1063-related findings.

*F2 Generation*

Observations: There was no effect on the number of resorptions, viable embryos, corpora lutea, implantation site, implantation loss, viable embryos,

F0 Generation Toxicokinetics: TK parameters for parent, RP101075, RP101988, and RP101442 are provided in the sponsor's table, below. CC112273, CC1084037, and RP101124, the major human metabolites, were not quantified.

**Table 8: Summary of Mean Toxicokinetic Parameters**

Dose (mg/kg)	Day	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>Tlast</sub> /Dose (hr*kg*ng/mL/mg)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	M:P
RPC1063										
0.2	GD 6	2.60	13.0	8	8	14.4	71.8	NA <sup>a</sup>	NA	NA
0.2	LD 20	3.11	15.6	4	8	19.3	96.5	NA <sup>a</sup>	NA	NA
0.7	GD 6	10.6	15.2	4	24	142	203	142	203	NA
0.7	LD 20	13.0	18.5	4	24	142	203	142	203	NA
2.0	GD 6	40.0	20.0	4	24	438	219	438	219	NA
2.0	LD 20	38.2	19.1	2	24	431	215	431	215	NA
RP101075										
0.2	GD 6	0.00	NA	NA	NA	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.2	LD 20	0.00	NA	NA	NA	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.7	GD 6	0.512	0.732	8	8	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.7	LD 20	0.761	1.09	8	8	4.18	5.97	NA <sup>a</sup>	NA	NA
2.0	GD 6	1.42	0.708	8	24	24.4	12.2	24.4	12.2	0.0557
2.0	LD 20	2.25	1.12	8	24	38.5	19.3	38.5	19.3	0.0894
RP101442										
0.2	GD 6	0.00	NA	NA	NA	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.2	LD 20	0.169	0.843	4	4	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.7	GD 6	0.848	1.21	24	24	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
0.7	LD 20	0.950	1.36	8	24	18.2	26.0	18.2	26.0	0.128
2.0	GD 6	3.00	1.50	24	24	NA <sup>b</sup>	NA	NA <sup>b</sup>	NA	NA
2.0	LD 20	2.93	1.47	8	24	55.9	28.0	55.9	28.0	0.130
RP101988										
0.2	GD 6	1.55	7.75	8	8	8.57	42.9	NA <sup>a</sup>	NA	NA
0.2	LD 20	1.89	9.47	4	8	10.9	54.4	NA <sup>a</sup>	NA	NA
0.7	GD 6	6.17	8.81	4	8	36.0	51.4	NA <sup>a</sup>	NA	NA
0.7	LD 20	5.96	8.52	4	8	36.5	52.1	NA <sup>a</sup>	NA	NA
2.0	GD 6	20.7	10.4	4	24	278	139	278	139	0.635
2.0	LD 20	20.9	10.4	2	24	250	125	250	125	0.580

**Table 8: Summary of Mean Toxicokinetic Parameters (Continued)**

Dose (mg/kg)	Day	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>Tlast</sub> /Dose (hr*kg*ng/mL/mg)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	M:P
RP101124										
0.2	GD 6	2.36	11.8	8	24	NA	NA	33.7	169	NA
0.2	LD 20	2.85	14.3	8	24	NA	NA	52.4	262	NA
0.7	GD 6	8.00	11.4	8	24	NA	NA	115	164	0.806
0.7	LD 20	10.1	14.4	8	24	NA	NA	154	220	1.08
2.0	GD 6	20.2	10.1	8	24	NA	NA	315	157	0.718
2.0	LD 20	24.2	12.1	8	24	NA	NA	477	238	1.11
Total Agonist (RP1063, RP101075, RP101442, and RP101988)										
0.2	GD 6	4.15	20.8	8	8	22.9	115	NA <sup>a</sup>	NA	NA
0.2	LD 20	5.18	25.9	4	8	30.7	153	NA <sup>a</sup>	NA	NA
0.7	GD 6	16.8	24.0	4	24	227	324	227	324	NA
0.7	LD 20	20.2	28.9	4	24	241	344	241	344	NA
2.0	GD 6	61.8	30.9	4	24	777	388	777	388	NA
2.0	LD 20	62.3	31.1	2	24	775	388	775	388	NA

AUC<sub>Tlast</sub> = area under the plasma concentration-time curve from time 0 to the time of the final quantifiable sample; C<sub>max</sub> = maximum plasma concentration; M:P = AUC<sub>0-24hr</sub> Metabolite/AUC<sub>0-24hr</sub> RPC1063; NA = Not applicable; T<sub>max</sub> = Time of maximum observed plasma concentration.

<sup>a</sup> AUC<sub>0-24hr</sub> not reported due to %AUC<sub>extrap</sub> > 25%.

<sup>b</sup> AUC not reported due to less than three consecutive quantifiable concentrations.

## 9.4 Juvenile Animal Development

**Study RP-TX-006-1.0: "RPC1063: 14-day repeated dose study in juvenile Sprague-Dawley rats."** Sprague Dawley rats (n=6/sex/group) were dosed by oral gavage, once daily for 14 days, with 0, 0.2, 2, or 30 mg/kg RPC1063 (Lot 028) in 0.5% CMC beginning on PND 25. Lymphocyte reduction at the end of the dosing period was observed at all dose levels (sponsor's figures, below). B220 positive B-cells, CD4 positive T-cells, and CD8 positive T-cells were all decreased.

Figure 1: Lymphocyte Reduction in Male Rats Orally Administered RPC1063 for 14 Days

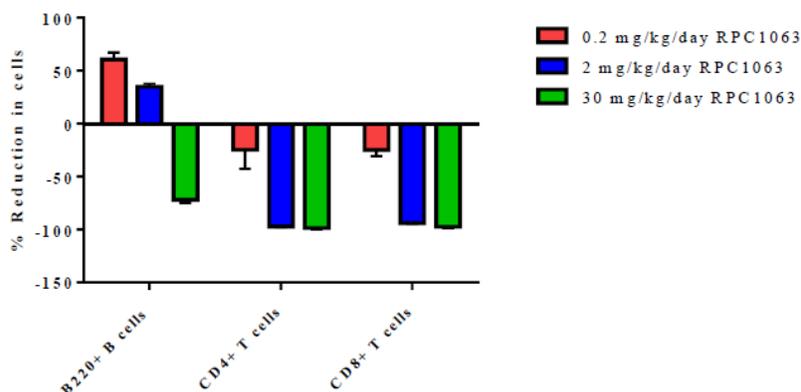
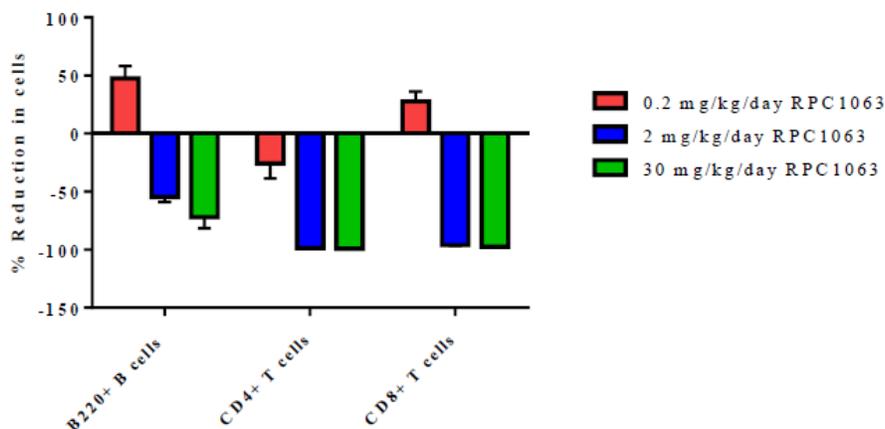


Figure 2: Lymphocyte Reduction in Female Rats Orally Administered RPC1063 for 14 Days



Relative to BW, lung weight was increased by 10 to 23% in MD and HD males and 17 to 41% in MD and HD females. Minimal to moderate alveolar histiocytosis occurred in 11/12 rats at the HD.

TK parameters for RPC1063 and its metabolites, RP101075, RP101124, RP101442, and RP101988, are provided in the sponsor's tables, below.

Table 11: Toxicokinetic Parameters in Juvenile Rats Orally Administered RPC1063 for 14 days

Dose (mg/kg) [No. doses]	Day of PK	Compound Analyzed	Gender	C <sub>max</sub> (nM)	T <sub>max</sub> (hr)	AUC <sub>0-24</sub> (nM <sup>2</sup> hr)	AUC <sub>0-∞</sub> (μM <sup>2</sup> hr)	T <sub>1/2</sub> (hr)	Vd/F (L/kg)	Clearance/F (mL/min/kg)
0.2 [14]	14	RPC1063	Male	12.3	2	113.7	123.6	6.4	24.7	72.5
		RP101075	Male	1.4	1	26.8	51.2	21.5	332.9	344.6
		RP101124	Male	45.3	8	657.4	DNS	DNS	DNS	24.7
		RP101442	Male	2.4	1	44.7	90.0	25.5	198.9	185.3
		RP101988	Male	5.7	2	50.0	50.7	3.5	47.8	159.3
		Total Agonist	Male	20.7	2	235.2	272.5	8.1	25.2	35.8
		RPC1063	Female	10.4	2	80.0	90.8	7.3	49.4	103.0
		RP101075	Female	1.5	4	22.1	53.8	30.7	443.9	418.5
		RP101124	Female	15.8	4	284.8	526.4	19.1	48.7	57.0
		RP101442	Female	1.8	1	36.2	68.0	20.9	223.6	228.8
		RP101988	Female	5.3	2	42.6	43.0	3.3	47.8	186.8
Total Agonist	Female	17.6	2	164.9	201.3	9.1	25.2	51.0		
2 [14]	14	RPC1063	Male	140.3	4	1499.1	1600.0	5.9	24.7	55.0
		RP101075	Male	14.5	4	267.0	505.5	21.1	332.9	346.4
		RP101124	Male	445.7	12	6827.3	DNS	DNS	DNS	23.8
		RP101442	Male	41.2	4	715.9	4033.2	87.9	149.1	115.7
		RP101988	Male	81.2	4	769.9	813.8	5.7	47.8	103.5
		Total Agonist	Male	277.2	4	3251.8	3981.9	9.9	25.2	25.9
		RPC1063	Female	139.7	2	1062.1	1108.8	5.7	24.7	77.6
		RP101075	Female	15.3	4	235.2	441.8	22.3	416.2	393.2

Table 11: Toxicokinetic Parameters in Juvenile Rats Orally Administered RPC1063 for 14 days (Continued)

Dose (mg/kg) [No. doses]	Day of PK	Compound Analyzed	Gender	C <sub>max</sub> (nM)	T <sub>max</sub> (hr)	AUC <sub>0-24</sub> (nM*hr)	AUC <sub>0-∞</sub> (nM*hr)	T <sub>1/2</sub> (hr)	Vd/F (L/kg)	Clearance/F (mL/min/kg)
		RP101124	Female	216	12	3919.9	DNS	DNS	DNS	41.4
		RP101442	Female	25.7	4	473.6	1316.1	38.0	198.8	174.9
		RP101988	Female	67.6	2	489.1	506.9	5.4	71.7	162.9
		Total Agonist	Female	234.3	2	2259.9	2695.2	10.1	25.2	37.2
30 [14]	14	RPC1063	Male	1863.3	4	25643.7	29520.2	8.3	24.7	48.2
		RP101075	Male	347.3	1	6051.0	16876.8	39.9	277.5	229.3
		RP101124	Male	3940.0	24	46292.7	DNS	DNS	DNS	52.6
		RP101442	Male	1633.3	4	29134.7	56838.9	23.2	49.7	42.6
		RP101988	Male	1454.0	4	15831.5	16916.1	6.4	47.8	75.5
		Total Agonist	Male	5265.0	4	76660.8	103805.6	12.9	25.2	16.5
		RPC1063	Female	1800.0	2	19748.7	22284.6	7.7	24.7	62.6
		RP101075	Female	379.3	1	6795.2	23663.4	46.6	249.7	204.2
		RP101124	Female	1940.0	24	21390.7	DNS	DNS	DNS	113.9
		RP101442	Female	1550.0	4	28335.2	64758.8	29.4	49.7	43.8
		RP101988	Female	1183.3	1	13378.3	14493.2	6.4	47.8	89.3
		Total Agonist	Female	4540.7	4	68257.3	100126.2	15.1	25.2	18.5

DNS=Data Not Sufficient to calculate

### Study Title: RPC1063: A 10-week toxicity study in juvenile rats with a 2-week recovery

Study no.: 1840-011  
 Study report location: EDR  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: June 7, 2016  
 GLP compliance: Yes, US FDA GLP  
 QA statement: Yes, signed  
 Drug, lot #, and % purity: RPC1063, Lot AJ527S5A-15-001/1052515, 99.9%

### Key Study Findings

- RPC1063-related findings consisted of known pharmacodynamic effects of the drug (i.e. decrease in circulating lymphocytes and decrease lymphocytes in spleen and thymus). There were no other RPC1063-related findings that were considered to be adverse. Therefore, the NOAEL is the HD of 10 mg/kg.
- It is notable that the learning and memory assessment consisted of passive avoidance and not a more complex task such as a Morris or Cincinnati water maze.
- Whole-body auditory startle was not assessed. Rather, the Preyer's pinna reflex was assessed using a Galton (ultrasonic) whistle.
- The major human metabolites, CC112273 and CC1084037, were not assessed in the TK samples.

### Methods

Doses: 0, 0.3, 3, 10 mg/kg/day

Frequency of dosing: Once daily for 10 weeks beginning on PND 21  
Route of administration: Oral gavage  
Dose volume: 5 mL/kg  
Formulation/Vehicle: 0.5% CMC  
Species/Strain: CD [CrI:CD(SD)] rat  
Number/Sex/Group: Main: 24/sex/group; TK: Control 12/sex/group ,  
RPC1063 27/sex/group  
Age: PND 21  
Weight: Male: 33 to 62 g; Female: 35 to 60 g  
Deviation from study protocol: Deviations did not impact the validity of the study.

Study Design: The sponsor was informed by DGIEP in a March 1, 2016, communication regarding the Initial Pediatric Study Plan (iPSP) that the design of the JAS, as described in the iPSP, "appears to be adequate." The JAS design did not contain an assessment of reproductive function, learning and memory, or whole-body auditory startle. There is no indication that DNP commented on the design of the JAS.

Dosing Formulation Analysis: Formulations were within 95% to 102% of the nominal concentration.

Mortality & Clinical Signs: All animals survived to the scheduled sacrifice. There were no RPC1063-related clinical signs during the dosing or recovery periods.

Body Weights and Food Consumption: Absolute BW was decreased by 5%, relative to control, in males at all dose levels, at the end of the dosing and recovery periods. Food consumption during the dosing and recovery periods was similar between controls and rats dosed with RPC1063.

Growth and Developmental Landmarks: Auditory response, assessed by the Preyer's pinna reflex in response to a Galton whistle, was normal in all dose groups when on PND 22. Time to sexual maturation was not affected.

Ophthalmoscopy: There were no findings when ophthalmic examination was conducted just prior to terminal and recovery necropsies.

#### Behavioral Assessment:

a) Observational Assessment: Functional Observational Battery (FOB) assessment was performed on Day 68 during treatment and Day 82 during recovery. There were no RPC1063-related findings.

b) Motor Activity: Open field activity was not affected in males on Day 35. HDF exhibited an increase in basic movement (20%), fine movement (22%), and total distance (25%).

c) Passive Avoidance: Learning and memory were assessed with the passive avoidance test which was conducted during the last week of dosing and prior to recovery necropsy. There was no effect observed.

F<sub>1</sub> Reproductive Performance: Not conducted.

Hematology and Clinical Chemistry: Lymphocyte count was decreased in a dose-dependent manner on Days 8, 30, 70, and termination (sponsor's table, below). Lymphocyte phenotyping demonstrated that the reduction in lymphocyte count was a

result of a decrease in mature T cells, helper T cells, cytotoxic T cells, and B cells at every dose level. There were no effects observed in the urinalysis, clinical chemistry, or coagulation parameters at scheduled termination or at the end of the recovery period.

**Table 8: Summary of Effects on Lymphocyte Counts (Percent Change Relative to the Control Mean)**

Group:	2/6 <sup>a</sup>		3/7 <sup>a</sup>		4/8 <sup>a</sup>	
Dose Level:	0.3 mg/kg/day		3 mg/kg/day		10 mg/kg/day	
Sex:	Male	Female	Male	Female	Male	Female
Interval						
Day 8	-56%	-48%	-59%	-62%	-66%	-50%
Day 30	-65%	-79%	-91%	-93%	-88%	-89%
Day 70	-57%	-74%	-86%	-88%	-85%	-83%
Terminal	-36%	-38%	-72%	-76%	-78%	-77%
Recovery	--	--	-28%	--	--	-22%

<sup>a</sup> Main study animals (Groups 2, 3, and 4) collected at termination and recovery; Toxicokinetic/Immunophenotyping groups (Groups 6, 7, and 8) collected on Days 8, 30, and 70.

**Bone Density and Length Assessment:** Bone length and density were not affected at the end of the dosing or recovery periods.

**Organ Weight:** Spleen (21% to 33%) and thymus (18% to 19%) weight was decreased at all dose levels.

**Gross Pathology:** There were no findings.

**Histopathology:** Adequate Battery: Yes; Peer Review: No; Signed and Dated Pathologist's Report: Yes. Lymphocytes were decreased in the spleen of MD and HD animals (sponsor's table, below). There was a decrease in cortical thymic lymphocytes and mesenteric lymph node lymphocytes at all dose levels. An increase in the lymphocytes occurred in the medulla of the thymus at all dose levels. There were no findings at the end of the recovery period. Expanded neurohistopathology was not conducted.

Dose level: mg/kg/day	0		0.3		3		10	
Sex	M	F	M	F	M	F	M	F
<b>Number Examined</b>	12	12	12	12	12	12	12	12
<b>Spleen</b>								
decreased cellularity, red pulp								
-minimal	0	0	0	0	0	0	0	1
decreased lymphocytes, marginal zone	0	0	0	0	12	9	12	12
-minimal	0	0	0	0	10	5	4	2
-mild	0	0	0	0	2	4	8	10
decreased lymphocytes, periarteriolar lymphoid sheaths								
-minimal	0	0	0	0	7	6	9	7
<b>Thymus</b>								
decreased lymphocytes, cortex	0	0	4	0	10	7	12	11
-minimal	0	0	3	0	4	2	7	5
-mild	0	0	1	0	6	5	5	6
increased lymphocytes, medulla	0	0	12	12	12	12	12	12
-minimal	0	0	7	12	0	7	0	0
-mild	0	0	5	0	12	5	12	12
<b>Lymph node, mesenteric</b>								
decreased lymphocytes, paracortex	0	0	3	3	12	10	12	12
-minimal	0	0	3	3	10	9	6	7
-mild	0	0	0	0	2	1	6	5

M-Male; F-Female

**Toxicokinetics:** TK parameters for parent and several of its metabolites, RP101075, RP101442, RP101988, RP101124. The major human metabolites, CC112273 and CC1084037, were not assessed.

**Table 10: Summary of Mean Toxicokinetic Parameters**

Dose (mg/kg/day)	Day	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg <sup>+</sup> ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr <sup>+</sup> ng/mL)	AUC <sub>Tlast</sub> /Dose (hr <sup>+</sup> kg <sup>+</sup> ng/mL/mg)	AUC <sub>0-24hr</sub> (hr <sup>+</sup> ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr <sup>+</sup> kg <sup>+</sup> ng/mL/mg)	M:P
RPC1063										
0.3	1	10.5	34.9	4	24	113	378	113	378	NA
0.3	70	5.98	19.9	2	24	58.8	196	58.8	196	NA
3	1	102	34.0	4	24	1130	376	1130	376	NA
3	70	66.4	22.1	2	24	730	243	730	243	NA
10	1	456	45.6	4	24	4070	407	4070	407	NA
10	70	254	25.4	4	24	2780	278	2780	278	NA
RP101075										
0.3	1	0.652	2.17	12	24	8.54	28.5	8.54	28.5	0.0753
0.3	70	0.263	0.877	4	12	1.85	6.15	NA	NA	NA
3	1	6.64	2.21	12	24	116	38.6	116	38.6	0.102
3	70	6.11	2.04	8	24	111	37.1	111	37.1	0.152
10	1	20.5	2.05	12	24	389	38.9	389	38.9	0.0955
10	70	23.7	2.37	4	24	426	42.6	426	42.6	0.153

RP101442										
0.3	1	0.00	NA	NA	NA	NA	NA	NA	NA	NA
0.3	70	0.970	3.23	4	24	20.1	67.1	20.1	67.1	0.342
3	1	5.33	1.78	24	24	60.9	20.3	60.9	20.3	0.0539
3	70	18.4	6.13	8	24	385	128	385	128	0.528
10	1	21.9	2.19	24	24	249	24.9	249	24.9	0.0612
10	70	83.7	8.37	4	24	1650	165	1650	165	0.594
RP101988										
0.3	1	2.23	7.42	4	24	26.0	86.7	26.0	86.7	0.229
0.3	70	3.93	13.1	4	24	39.6	132	39.6	132	0.673
3	1	23.0	7.65	4	24	271	90.2	271	90.2	0.240
3	70	59.1	19.7	4	24	711	237	711	237	0.974
10	1	92.1	9.21	4	24	1030	103	1030	103	0.253
10	70	266	26.6	4	24	2920	292	2920	292	1.05
Dose (mg/kg/day)	Day	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg <sup>+</sup> ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr <sup>+</sup> ng/mL)	AUC <sub>Tlast</sub> /Dose (hr <sup>+</sup> kg <sup>+</sup> ng/mL/mg)	AUC <sub>0-24hr</sub> (hr <sup>+</sup> ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr <sup>+</sup> kg <sup>+</sup> ng/mL/mg)	M:P
RP101124										
0.3	1	1.92	6.39	12	24	29.3	97.5	29.3	97.5	0.258
0.3	70	10.3	34.3	12	24	167	558	167	558	2.85
3	1	21.0	7.00	12	24	311	104	311	104	0.275
3	70	83.6	27.9	12	24	1420	472	1420	472	1.94
10	1	59.8	5.98	24	24	1040	104	1040	104	0.256
10	70	275	27.5	12	24	4320	432	4320	432	1.56

## 10 Special Toxicology Studies

### *Immunotoxicology*

**Study 72864:** “RPC1063: A 33-day oral gavage immunotoxicity study in Sprague-Dawley rats.” Sprague-Dawley rats (n=10/sex/group; 8 weeks old) were given a daily oral dose of 0, 0.2, 0.7, or 2 mg/kg RPC1063 (AJ513FP-13-001; 99.9%) in 0.5% CMC for 33 days. Five rats per sex were given a single daily IP injection of 6 mg/kg cyclophosphamide for 33 days. KLH was administered on Days 7 and 25 to all animals that were allocated to TDAR response assessment. WBC (up to 80%), lymphocytes (up to 90%), basophils (up to 85%), and LUC (33% to depletion) were decreased in a dose-dependent manner at all dose levels. T-cell-dependent IgG antibody response was decreased in MDM and HDM (1.4 to 4.1-fold) and females (1.9 to 3.0-fold). IgM antibody response was also decreased in all males (1.1 to 1.8-fold) and females (1.7 to 3.2-fold). The expected decrease in IgG (38- to 62-fold decrease) and IgM (7- to 14-fold) response occurred in animals dosed with the cyclophosphamide. Based on the effect at all doses, a NOAEL could not be determined.

Study 73508: “RPC1063: A 33-day oral immunotoxicity study in juvenile Sprague-Dawley rats.” Juvenile Sprague-Dawley rats (n=35/sex/group) were given a daily oral dose of 0, 0.3, 3, or 10 mg/kg RPC1063 (Lot AJ527S5A-15-001, 99.9%) beginning on PND 21 for 33 days. A separate group of juvenile rats (n=25/sex/group) were given a daily IP injection of 6 mg/kg cyclophosphamide for 33 days beginning on PND 21. The rats that were allocated to TDAR assessment (n=15/sex/group) were given subcutaneous injections of KLH on study day 7 and 25 (PND 28 and 46). After necropsy on study day 34 (PND 56), recovery animals (5/sex/group) were continued on study for an additional 14 days.

Two positive control animals were found dead on study days 16 and 24; one LDF was euthanized in extremis on study day 28. On study day 14, there was a dose-dependent decrease in WBC (up to 75%), lymphocytes (up to 85%), monocytes (up to 50%), basophils (up to 92%), and LUC (up to 91%); the magnitude of decrease at the HD was similar to the positive control. With the exception of monocytes, which were not decreased, the magnitude of decrease for WBC and white blood cell differential was similar on study day 33 to what was observed on study day 14. WBC and WBC differential was similar between controls and RPC1063-treated animals at the end of the recovery period. Anti-KLH IgG response was decreased on study day 25 at all dose levels in both males (1.9- to 6.7-fold) and females (4.4 to 21.7-fold). There was also a decrease in the secondary response to KLH on study day 33 (PND 46); anti-KLH response was decreased at all dose levels in both males (3.9- to 46.4-fold) and females (3.3- to 63.6-fold). TDAR was not assessed in recovery animals. Spleen weight was decreased at all dose levels in males (up to 35%) and in females at > 0.03 mg/kg (25%) at the end of the dosing period, but not at the end of the recovery period. Microscopy was not performed. Based on effects at all doses, a NOAEL could not be determined.

#### *Phototoxicity*

RPC1063 and two of its metabolites, RP101075 and RP101988, were not phototoxic in an in vitro 3T3 NRU phototoxicity assay (265039 and 263247).

## 11. Integrated Summary and Safety Evaluation

Ozanimod hydrochloride (RPC1063) is an extensively metabolized, small molecule sphingosine 1-phosphate (S1P) receptor agonist developed for the treatment of adults with relapsing forms of multiple sclerosis (MS). Ozanimod exhibited the greatest potency at the human S1P<sub>1</sub> and S1P<sub>5</sub> receptor subtypes. Two of the three major human metabolites of ozanimod, CC112273 and CC1084037, also exhibited agonism of the S1P<sub>1</sub> and S1P<sub>5</sub> receptors. The third major human metabolite, RP101124, is inactive at all S1P receptor subtypes.

To support marketing approval of ozanimod under the tradename ZEPOSIA, the sponsor has submitted a nonclinical study package that consists of pharmacodynamic and pharmacokinetic studies, a core safety pharmacology battery, a series of general toxicology studies including chronic dosing studies conducted in rat and monkey, a complete battery of reproductive and developmental toxicology studies conducted in rat and rabbit, carcinogenicity studies conducted in mouse and rat, and immunotoxicity studies. Although not required for approval of ZEPOSIA for use in adult MS patients, the sponsor also provided the results of a juvenile animal toxicology study conducted in rat. Given the extensive metabolism of ozanimod, the main nonclinical concern was the adequate coverage of each major human metabolite in the pivotal nonclinical studies. The lack of coverage for these metabolites was the main nonclinical reason for refusing to file the initial NDA submission on February 23, 2018. Additional data on exposure to the major human metabolites in the nonclinical studies have been provided in the current submission, and the adequacy of these data is discussed below.

Agonism of lymphocytic S1P receptors inhibits the release of T-cells and B-cells from peripheral lymphoid organs subsequently decreasing the available pool of autoreactive circulating lymphocytes available for entry into the central nervous system. The sponsor demonstrated the ability of ozanimod and its metabolites to reduce circulating CD4+, CD8+, and B220+ lymphocyte subtypes in Sprague Dawley rats. RPC1063 was also able to reduce circulating lymphocytes in C57Bl/6 mice, beagle dogs, and cynomolgus monkeys. In all species tested, the reduction in circulating lymphocytes was reversible upon cessation of treatment. Consistent with the impact of ozanimod and its metabolites on circulating lymphocytes, efficacy in the mouse (C57BL/6) experimental autoimmune encephalomyelitis model and cuprizone demyelination model were demonstrated. Efficacy in these models provides biological plausibility for the use of ozanimod to treat MS in humans. It is clear that the drug-related reduction in circulating lymphocytes is associated with decreased immune system function, as demonstrated in the immunotoxicity studies conducted with ozanimod in adult and juvenile rats; the reversibility of the effect on TDAR was not assessed.

### Off-target pharmacology of RPC1063:

Activity at several “off-target” binding sites was characterized for ozanimod and its metabolites; some of which present a concern for pharmacology-related adverse effects. Ozanimod and the major human metabolite, CC112273, were determined to be

potent hERG inhibitors in vitro (IC<sub>50</sub> of 0.2 and 0.6 μM, respectively), but QTc prolongation was not observed in monkeys dosed with ozanimod.

Monoamine oxidase B (MAO-B) was inhibited, in vitro, by the two major human metabolites of ozanimod, CC112273 (IC<sub>50</sub>= 5.7 nM) and CC1084037 (IC<sub>50</sub>= 43 to 57 nM). MAO-A was not inhibited by either metabolite. Since the inhibition of MAO-B by two of the three major human metabolites may pose the potential for drug-drug interactions in vivo, it is recommended that the finding of MAO-B inhibition be mentioned in the labeling of Zeposia; however, a final decision on appropriate labeling of this potential interaction with MAO-B is deferred to the clinical pharmacology and clinical reviewers.

#### Coverage of Ozanimod Metabolites:

Given that it was a major reason for refusing to file the initial NDA submission, evaluation and discussion of the coverage of ozanimod and the major human metabolites in the pivotal nonclinical studies will precede discussion of the ozanimod-related adverse effects in this review. The sponsor's summary Table 47, below, provides the toxicokinetic data for ozanimod, RP101124, CC112273 and CC1084037 in the pivotal chronic toxicity studies, carcinogenicity studies, and EFD studies.

**Table 47: Mean Steady-State Exposures in Pivotal Toxicology Studies**

Study Description (Study No.) Day	Species	Dose (mg/kg/day)	Mean Steady-State Exposure (AUC <sub>0-4</sub> /AUC <sub>0-24</sub> ) (ng·hr/mL)				
			Ozanimod	RP101124	CC112273 <sup>a</sup>	CC1084037 <sup>a</sup>	Total Active Drug <sup>b</sup> (Ozanimod, CC112273 and CC1084037)
			Combined Sex <sup>c</sup>	Combined Sex	Combined Sex	Combined Sex	Sum Totals
26-week Repeated Dose (71357) Day 178	Rat	0.2 (NOAEL)	49.8	67.7	2.99	0.0479	52.8
		2	683	842	41.8	2.34	727
		30	12165	15979	989.0	41.0	13200
39-week Repeated Dose (30477) Day 274	Monkey	0.1 (NOAEL)	17.8	1.70	21.2	4.83	43.8
		1	196.8	58.7	203.0	42.9	443
		15	3262	801	4100.0	947.0	8310
6-month Carcinogenicity (AE18BZ 7G8R (b) (4) Week 26	Mouse	8	8007	404.2	198.0	18.7	8220
		25	24830	1132.7	805	64.5	25700
		80	77645	3447.4	2490	206.0	80300
2-year Carcinogenicity (72515) Day 185	Rat	0.2	41.3	112.0	2.99	0.0479	44.3
		0.7	176.0	360.5	--	--	176
		2 (NOAEL)	601.0	810.0	41.8	2.34	645
Embryo-fetal Development (AB03215) Day G17	Rat (maternal)	0.2	42.3	--	2.25	--	44.6
		1 (NOAEL)	284	--	17.2	0.678	302
		5	1903	--	--	--	1900
Embryo-fetal Development (AB03217) Day G6	Rabbit (maternal)	0.2 (fetal NOAEL)	10.7	--	6.77	3.78	21.3
		0.6 (maternal NOAEL)	35.9	--	18.0	10.8	64.7
		2	123	--	--	--	123
Clinical Studies	Human	1 mg	4.776 <sup>d</sup>	3.824 <sup>d</sup>	67.097 <sup>e</sup>	13.292 <sup>f</sup>	85.165

AUC<sub>0-4</sub> = area under the plasma concentration-time curve during a dosage interval; AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; NOAEL = no-observed-adverse-effect-levels; -- = not determined.

<sup>a</sup> Nonclinical species exposure based on the analyte exposure concentration from 14-day bridging GLP-compliant PK Studies (rat [Report 1840-047 Day 14], mouse [Report 1840-040 Day 14], rabbit [Report 1840-054 Day 14] and monkey [Report 1840-043 Day 14]).

<sup>b</sup> Total active drug exposure is cumulative exposure of ozanimod+CC112273+CC1084037. These 3 contribute to 94% of total active exposure of the drug in humans (Report RPC01-1914).

<sup>c</sup> Combined Sex exposures for all studies except for EFD studies Report AB03215 and Report AB03217 where female exposures are presented

<sup>d</sup> Ozanimod and RP101124 exposure from relapsing multiple sclerosis (RMS) steady-state; Report RPC01-1001.

<sup>e</sup> CC112273 Population PK (Report A2PG-0003).

<sup>f</sup> Estimated from CC112273 AUC (population PK) and the relationship of AUC between CC112273 and CC1084037 (Report RPC01-1914).

Using these exposure data, exposure margins were calculated by the sponsor, relative to systemic exposure in humans dosed with 1 mg ozanimod, the maximum recommended human dose (MRHD). The clinical exposure multiples achieved in the chronic, carcinogenicity, and reproductive and developmental assessments are provided in sponsor's Table 48, below.

Table 48: Exposure Multiples from Nonclinical Safety Studies

Study Description (Study No.) Day	Species	Dose (mg/kg/day)	Mean Exposure Multiples <sup>a</sup>				Total Active Drug (Ozanimod, CC112273 and CC1084037) <sup>f</sup>
			Ozanimod	RP101124	CC112273 <sup>b</sup>	CC1084037 <sup>b</sup>	
			Combined Sex <sup>d</sup>	Combined Sex	Combined Sex	Combined Sex	Sum Totals
26-week Repeated Dose (71357) Day 178	Rat	0.2 (NOAEL)	10.4	17.7	0.0446	0.00360	0.620
		2	143	220	0.623	0.176	8.54
		30	2550	4180	14.7	3.08	155
39-week Repeated Dose (30477) Day 274	Monkey	0.1 (NOAEL)	3.73	0.445	0.316	0.363	0.515
		1	41.2	15.4	3.03	3.23	5.20
		15	683	209	61.1	71.2	97.6
6-month Carcinogenicity (AE18BZ.7G8R. (b) <sub>6</sub> ) Week 26	Mouse	8	1680	106	2.95	1.40	96.6
		25	5200	296	12.0	4.85	302
		80	16300	902	37.1	15.5	943
2-year Carcinogenicity (72515) Day 185	Rat	0.2	8.65	29.3	0.0446	0.00360	0.521
		0.7	36.9	94.3	--	--	2.07
		2 (NOAEL)	126	212	0.623	0.176	7.58
Embryo-fetal Development (AB03215) Day G17	Rat (maternal)	0.2	8.86	--	0.0335	--	0.523
		1 (NOAEL)	59.5	--	0.256	0.0510	3.54
		5	398	--	--	--	22.3
Embryo-fetal Development (AB03217) Days G6	Rabbit (maternal)	0.2 (fetal NOAEL)	2.24	--	0.101	0.284	0.250
		0.6 (maternal NOAEL)	7.52	--	0.268	0.813	0.760
		2	25.7	--	--	--	1.44

NOAEL = no-observed-adverse-effect-level; -- = not determined.

<sup>a</sup> Calculation = ratio of Animal Species Exposure (ng·hr/mL)/Human Exposure (ng·hr/mL).

<sup>b</sup> Nonclinical species exposure based on the analyte exposure concentration from 14-day bridging GLP-compliant PK Studies (rat [Report 1840-047 Day 14], mouse [Report 1840-040 Day 14], rabbit [Report 1840-054 Day 14] and monkey [Report 1840-043 Day 14]).

<sup>c</sup> Total active drug multiple is cumulative exposure of ozanimod+CC112273+CC1084037 divided by total human ozanimod+CC112273+CC1084037. These 3 contribute to 94% of total active exposure of the drug in humans (Report RPC01-1914).

<sup>d</sup> Combined Sex exposures for all studies except for EFD studies Report AB03215 and Report AB03217 where female exposures are presented.

Note: Mean Exposure Multiples are presented with 3 significant figures.

Based on the margins provided in Table 48 (above), exposure to the parent and the three major human metabolites equaled or exceeded the clinical exposure at the MRHD in the chronic studies conducted in rat and monkey. Adequate coverage for ozanimod and the three major metabolites was achieved in the 6-month carcinogenicity study conducted in mouse. In the 2-year carcinogenicity study conducted in rat, adequate exposure (> 50% exposure at the MRHD) to the parent, RP101124, and CC112273 was achieved; exposure to CC1084037 was inadequate (0.176-fold). In the EFD study conducted in rat, exposure to ozanimod at the HD of 5 mg/kg exceeded the exposure at the MRHD. Based on extrapolation of the exposure data from the 26-week study in rat, exposure to RP101124 and CC112273 at the HD of 5 mg/kg in the EFD study also exceeded the MRHD; exposure to CC1084037 was inadequate in the rat EFD study. At the HD of 2 mg/kg in the rabbit EFD study, exposure to ozanimod exceeded the exposure at the MRHD. Based on extrapolation, adequate coverage was also achieved for CC112273 and CC1084037 in the rabbit EFD study.

Table 48 (above) does not specifically address exposure to the parent and major human metabolites in the fertility and PPND studies conducted in rat. However, the HD tested

in the fertility study conducted in rat, 30 mg/kg, was the same as the HD tested in the 26-week study in rat; adequate coverage of parent and all 3 major human metabolites were achieved in the 26-week study. At the HD in the PPND study (2 mg/kg/), which was also the HD in the 2-year carcinogenicity study conducted in rat, adequate exposure to ozanimod, CC112273, and RP101124 was achieved; exposure to CC1084037 was inadequate.

TK parameters for the HD in the JAS, 10 mg/kg, are provided in the sponsor's table (below); adequate coverage for ozanimod and the three major human metabolites was achieved at the HD.

**Table 38: Plasma Exposure in Juvenile Rat Study (Day 70)**

Dose (mg/kg/day)	Mean Steady-State Exposure (AUC <sub>0-t</sub> /AUC <sub>0-24</sub> ) (ng·hr/mL)											
	Ozanimod			RP101124			CC112273 <sup>a</sup>			CC1084037 <sup>a</sup>		
	M	F	Exp. Mult. <sup>b</sup>	M	F	Exp. Mult. <sup>b</sup>	M	F	Exp. Mult. <sup>b</sup>	M	F	Exp. Mult. <sup>b</sup>
0.3	42.8	74.1	12.2x	167	165	43.4x	--	--	--	--	--	--
3	619	841	153x	1090	1750	371x	--	--	--	--	--	--
10 (NOAEL)	2380	3180	582x	3590	5060	1131x	239	178	3.10x	19.2	8.87	1.06x

AUC<sub>0-t</sub> = area under the plasma concentration-time curve during a dosage interval; AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; Exp = exposure; F = female; M = male; Mult = multiple; NOAEL = no-observed-adverse-effect-levels; -- = not determined.

<sup>a</sup> Nonclinical species exposure based on the analyte exposure concentration from 28-day bridging GLP-compliant juvenile PK Studies (rat [Report 1840-044 Day 28]).

<sup>b</sup> Exposure Multiple; Calculation = Combined Sex Animal Species Exposure/Human Exposure.

Ozanimod exposure (4.776 ng·hr/mL) and RP101124 exposure (3.824 ng·hr/mL) from relapsing multiple sclerosis (RMS) steady-state; Report RPC01-1001.

CC112273 Population PK exposure (67.097 ng·hr/mL) (Report A2PG-0003).

CC1084037 Exposure of 13.292 ng·hr/mL) Estimated from CC112273 AUC (population PK) and the relationship of AUC between CC112273 and CC1084037 (Report RPC01-1914).

Source: Report 1840-011.

Overall, while not consistently represented at adequate levels in all pivotal studies conducted with ozanimod, the parent and major human metabolites were adequately assessed in at least one species in chronic general toxicity, carcinogenicity, genotoxicity, juvenile animal, and reproductive and development studies, except in the two following cases:

- RP101124 was not studied in an in vitro chromosomal aberration study (detailed discussion in genotoxicity summary, below).
- CC1084037 was not adequately assessed in the PPND study conducted in rat. Although TK assessment was not conducted in this study, the 14-day bridging study conducted in rat demonstrates that CC1084037 exposure was 0.137-fold the exposure at the MRHD (sponsor's table, below).

**Table 35: Plasma Exposures in the Pre and Post Natal Assessment in the Rat on Lactation Day 20**

Dose (mg/kg/day)	Mean Steady-State Exposure (AUC <sub>0-4</sub> /AUC <sub>0-24</sub> ) (ng·hr/mL)							
	Ozanimod		RP101124		CC112273 <sup>a</sup>		CC1084037 <sup>a</sup>	
	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>
0.2	NA	--	52.4	13.7x	2.25	0.034x	NC	--
0.7	142	29.7x	154	40.3x	--	--	--	--
2 (NOAEL)	431	90.2x	477	125x	40.4	0.60x	1.82	0.137x

AUC<sub>0-4</sub> = area under the plasma concentration-time curve during a dosage interval; AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; F = female; NA = not applicable; NC = not calculated; NOAEL = no-observed-adverse-effect-levels; -- = not determined.

<sup>a</sup> Nonclinical species exposure based on the analyte exposure concentration from 14-day bridging GLP-compliant PK Studies (rat [Report 1840-047 Day 14]).

<sup>b</sup> Exposure Multiple: Calculation = Female Rat Exposure/Human Exposure.

Ozanimod exposure (4.776 ng·hr/mL) and RP101124 exposure (3.824 ng·hr/mL) from relapsing multiple sclerosis (RMS) steady-state; Report RPC01-1001.

CC112273 Population PK exposure (67.097 ng·hr/mL) (Report A2PG-0003).

CC1084037 Exposure of 13.292 ng·hr/mL Estimated from CC112273 AUC (population PK) and the relationship of AUC between CC112273 and CC1084037 (Report RPC01-1914).

Source: Report 1840-012.

In the toxicology written summary, the sponsor acknowledged the lack of adequate exposure to CC1084037 in the PPND study. The sponsor's rationale for not performing additional testing of CC1084037 is based on the fact that CC112273 and CC1084037 readily interconvert and that the combined levels of these metabolites should be used to assess if there was adequate coverage. This is not considered to be an adequate argument for accounting for the safety of an individual metabolite. CC1084037 is a major human metabolite that is structurally distinct from CC112273. Therefore, adequate coverage of CC1084037 should be demonstrated in the pivotal nonclinical studies. The circulating levels of CC1084037 achieved in the PPND study were inadequate (< 50% of the circulating level in humans). As such, the safety of CC1084037 was not adequately assessed in the PPND study. The sponsor did attempt to attain higher exposure to CC1084037 by directly administering a single oral dose of up to 1000 mg/kg to rats (Study RPC1063-DMPK-2975); the PK parameters from this study are provided in sponsor's Table 19, below.

**Table 19: Mean Pharmacokinetic Parameters of CC1084037 in CD-IGS Male Rats Following Single Oral Doses of CC1084037 at 10, 50, 500, or 1000 mg/kg or Ozanimod at 800 mg/kg.**

Compound Dosed	Dose mg/kg	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>last</sub> (ng·hr/mL)
CC1084037	10	1.49 ± 0.232	2.3 ± 1.5	10.3 ± 6.85
	50	3.06 ± 1.11	9.0 ± 13.0	38.8 ± 24.8
	500	5.97 ± 2.83	4.6 ± 3.1	69.2 ± 45.5
	1000	6.90 ± 1.66	6.0 ± 3.5	103 ± 65.4
Ozanimod	800	6.39 ± 2.04	10.7 ± 11.5	103 ± 47.9

AUC<sub>last</sub> = area under concentration versus time curve from time of dosing to last dose; C<sub>max</sub> = maximum concentration of drug in plasma; t<sub>max</sub> = time to maximum plasma concentration.

Source: Report RPC1063-DMPK-2975.

Based on the result of this study, it appears that it is not feasible to achieve, by direct oral administration of the metabolite, systemic exposure to CC1084037 that exceeds levels achieved by oral dosing with up to 800 mg/kg ozanimod. However, it does appear that direct dosing with CC1084037 can achieve systemic exposure that equals or

exceeds the clinical exposure at the MRHD (13.2 ng\*hr/mL), thereby suggesting that assessing the safety of the metabolite in a PPND study may be feasible. Since tolerability of repeat oral dosing of CC1084037 is unknown, a preliminary dose range-finding study would be recommended prior to initiating a pivotal PPND study conducted with CC1084037. It is recommended that the sponsor attempt to address the safety of CC1084037 in the pre- and postnatal development period as a post-marketing requirement.

To summarize, based on the available nonclinical data, the levels of ozanimod and the major human metabolites achieved in the nonclinical studies allow for an adequate assessment of their toxicity, except for assessment of the effect of CC1084037 in the PPND study and the assessment of RP101124 in an in vitro chromosomal aberration study.

#### Ozanimod-related Effects Observed in General Toxicity Studies:

Ozanimod was pharmacologically active in the nonclinical species (rat, monkey, rabbit, mouse) used to conduct the pivotal toxicology studies. Consistent with the established pharmacological activity of ozanimod, a reversible leukopenia occurred in rats, monkeys, rabbit, and mouse; a NOEL was not determined as the finding was present at the lowest doses tested (0.2 mg/kg in rat, 0.1 mg/kg in monkey, 0.2 mg/kg rabbit, 0.4 mg/kg mouse). Leukopenia was primarily due to a marked decrease in lymphocytes, but also involved a reduction in monocytes in rat and rabbit, neutrophils in monkey, and eosinophils, basophils, and large unstained cells (LUC) in rat, monkey, and rabbit.

The ozanimod-related decrease in circulating leukocytes was associated with a reversible decrease in lymphoid cellularity of the spleen and an alteration in thymic differentiation in rats and monkey. In rat and monkey, lymphoid depletion in the spleen was evident at all doses tested in the pivotal general toxicology studies. The NOEL for decreased ratio of cortex to medulla in the thymus in the monkey was the lowest dose tested in the 39-week study, 0.1 mg/kg. At all doses tested, loss of corticomedullary differentiation was observed in the thymus of rat. These splenic and thymic findings were considered to be secondary to the primary pharmacologic effect of ozanimod.

Lung was also a consistent target of ozanimod in rat and monkey. Increased lung weight and pulmonary macrophage infiltration were the most common ozanimod-related finding in the respiratory system. The NOEL for findings in the lung were the lowest dose tested in rat and monkey, 0.2 mg/kg and 0.1 mg/kg; these doses were also considered the NOAEL in the pivotal chronic general toxicity studies. Pulmonary edema was observed at the high dose in the 26-week study conducted in rat; pulmonary edema was not reported in monkey.

Exposure levels for all three major human metabolites that were associated with leukopenia, splenic lymphoid depletion, and pulmonary findings (except for RP101124 in the case of pulmonary edema) are similar to those expected to be achieved in humans at the MRHD. The clinical exposure margin to the NOEL for pulmonary edema

observed in rat (2 mg/kg) was < 1 for CC112273 and CC1084037; the clinical exposure margin to the other major human metabolite, RP101124 was 220-fold.

#### Genotoxicity of Ozanimod and Metabolites:

Since ozanimod is extensively metabolized, the sponsor conducted an in vitro bacterial reverse mutation assay and an in vitro chromosomal aberration assay on the parent, CC112273, and CC1084037; RP101124 was only assessed in a bacterial reverse mutation assay. Except for CC1084037, which was positive in the in vitro chromosomal aberration assay, in vitro genotoxicity assessment of ozanimod and its metabolites were negative. The parent was negative in an in vivo micronucleus assay conducted in rat. The circulating levels of parent and the three major human metabolite at the highest dose of 800 mg/kg in the rat in vivo micronucleus assay were markedly higher than the circulating levels at the MRHD. Because CC1084037 was positive in the in vitro chromosomal aberration assay, an in vivo micronucleus and Comet assay were conducted in mice dosed directly with CC1084037, which was negative in both assessments. Overall, except for the absence of an in vitro micronucleus assessment of RP101124, ozanimod and its metabolites were adequately assessed for genotoxicity. Although, by guidance, the sponsor should have assessed CC1084037 in an in vitro chromosomal aberration study, conducting a study prior to approval or as a post marketing requirement would not substantially add to the understanding of the risk of carcinogenicity for ozanimod and its metabolites. As described below, ozanimod and its three major metabolites were adequately assessed in a transgenic mouse carcinogenicity assay which was positive. Additional assessment of CC1084037 in an in vitro micronucleus assay is not recommended.

#### Carcinogenicity of RPC1063:

The 2-year carcinogenicity study conducted in rat was negative for drug-induced neoplasia. At the highest dose tested, exposure to ozanimod and RP101124 were 126- and 212-fold higher than exposure at the MRHD. However, the levels of CC112273 and CC1084037 achieved at the high dose tested in the 2-year carcinogenicity study conducted in rat (2 mg/kg) did not exceed clinical exposure at the MRHD (0.623- and 0.176-fold, respectively). Systemic exposure to ozanimod and the three major human metabolites in the 6-month carcinogenicity study conducted in transgenic mouse exceeded clinical exposure at the MRHD. In the mouse study, there was a drug-related increase in hemangioma and hemangiosarcoma. The combined incidence of hemangioma and hemangiosarcoma was increased in males at all dose levels and in females at doses > 8 mg/kg RPC1063.

#### Reproductive and Developmental Effects of Ozanimod:

An adequately designed battery of studies was conducted to assess the reproductive and developmental effects of ozanimod. In the pivotal fertility study conducted in rat, there were no drug-related effects observed up to the HD of 30 mg/kg. At this dose, the systemic exposure to ozanimod and the 3 major human metabolites, RP101124, CC112273, and CC1084037, exceeded the clinical exposure at the MRHD (2550-, 4180-, 14-, and 3-fold, respectively).

Embryolethality and developmental effects were observed in rat and rabbit fetuses exposed to ozanimod and its metabolites in utero. The fetal NOAEL in rat, 0.2 mg/kg, was associated with exposures to ozanimod and RP101124 that were higher than clinical exposures at the MRHD (9- and 17-fold, respectively). Clinical exposure to CC112273 and CC1084037 is expected to exceed exposure at the NOAEL in the rat EFD study. A NOAEL was not determined in the EFD study conducted in rabbit, based on the occurrence of malpositioned caudal vertebrae at all dose levels. Exposure to the parent at the lowest dose tested in the rabbit EFD study was 2-fold higher than the expected clinical exposure at the MRHD. Clinical exposure to CC112273 and CC1084037 is expected to exceed exposure at the lowest dose in the rabbit EFD study. RP101124 levels were not determined in rabbit. Overall, ozanimod-related findings in the EFD studies conducted in rat and rabbit occurred at exposures to the major human metabolites CC112273 and CC1084037 that would be expected to occur at the MRHD in humans (reviewer's table, below). Findings in rat occurred at exposures that markedly exceeded the clinical exposure to ozanimod (at least 10-fold) and RP101124 (at least 17-fold).

Reproductive & Development Summary			Clinical Margin for Metabolite (Fold)			
Finding	Species	NOEL (mg/kg)	Ozanimod	RP101124	CC112273	CC1084037
Caudal vertebrae, malposition	Rabbit	< 0.2	< 2	ND	< 0.1	< 0.3
Incomplete Ossification	Rat	0.2	10	17	0.04	0.003
	Rabbit	0.2	2	ND	0.1	0.3
Sternebra, misshapen/malposition	Rabbit	0.2	2	ND	0.1	0.3
Artery, Malformed or absent	Rabbit	0.2	2	ND	0.1	0.3
Embryo lethality	Rabbit	0.6	8	ND	0.3	0.8
	Rat	1	70	110	0.3	0.09
Anasarca	Rat	1	70	110	0.3	0.09
Testes, malposition	Rat	1	70	110	0.3	0.09
Cleft Palate	Rat	1	70	110	0.3	0.09

ND= not determined

In the pre- and postnatal development (PPND) study conducted in rat, hyperactivity (manifesting as increased motor activity in the open field assessment) and increased sensitivity to touch in the F1 generation were the only drug-related findings; the NOAEL was 0.7 mg/kg. As discussed above, CC1084037 was not adequately assessed in the PPND study, exposure was 0.137-fold the exposure at the MRHD. Exposure to ozanimod and RP101124 at the PPND NOAEL exceeded the clinical exposure at the MRHD by 30- and 40-fold, respectively. At the PPND NOAEL, CC112273 circulated at

levels less than the clinical exposure (0.6-fold) at the MRHD but was within 50% of the expected clinical exposure and therefore considered to be adequately assessed (sponsor's table, below).

**Table 35: Plasma Exposures in the Pre and Post Natal Assessment in the Rat on Lactation Day 20**

Dose (mg/kg/day)	Mean Steady-State Exposure (AUC <sub>0-4</sub> /AUC <sub>0-24</sub> ) (ng·hr/mL)							
	Ozanimod		RP101124		CC112273 <sup>a</sup>		CC1084037 <sup>a</sup>	
	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>	F	Exposure Multiple <sup>b</sup>
0.2	NA	--	52.4	13.7x	2.25	0.034x	NC	--
0.7	142	29.7x	154	40.3x	--	--	--	--
2 (NOAEL)	431	90.2x	477	125x	40.4	0.60x	1.82	0.137x

AUC<sub>0-4</sub> = area under the plasma concentration-time curve during a dosage interval; AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; F= female; NA = not applicable; NC = not calculated; NOAEL = no-observed-adverse-effect-levels; -- = not determined.

<sup>a</sup> Nonclinical species exposure based on the analyte exposure concentration from 14-day bridging GLP-compliant PK Studies (rat [Report 1840-047 Day 14]).

<sup>b</sup> Exposure Multiple; Calculation = Female Rat Exposure/Human Exposure.

Ozanimod exposure (4.776 ng·hr/mL) and RP101124 exposure (3.824 ng·hr/mL) from relapsing multiple sclerosis (RMS) steady-state; Report RPC01-1001.

CC112273 Population PK exposure (67.097 ng·hr/mL) (Report A2PG-0003).

CC1084037 Exposure of 13.292 ng·hr/mL Estimated from CC112273 AUC (population PK) and the relationship of AUC between CC112273 and CC1084037 (Report RPC01-1914).

Source: Report 1840-012.

Although not required to support the use of Zeposia in adults, the sponsor provided the final study reports for a 14-day dose range-finding and a 10-week pivotal juvenile animal study (JAS), both conducted in rat. Feedback regarding the design of the pivotal JAS was provided in a March 1, 2016, Pediatric Study Plan communication between the Division of Gastroenterology and Inborn Error Products. Neither the need to include a complex learning and memory assessment nor a reproductive function assessment was communicated to the sponsor at this time. The final pivotal study did not include an assessment of reproductive function and the learning and memory task consisted of passive avoidance which lacks the sensitivity of a more complex learning and memory assessment, such as the Morris or Cincinnati water maze. Additionally, whole-body auditory startle was not conducted in the JAS. Rather, pinna reflex in response to a Galton whistle was the extent of auditory assessment conducted in the pivotal study. The NOAEL in the pivotal JAS was the high dose of 10 mg/kg. At the NOAEL, exposure to ozanimod, RP101124, and CC112273 exceeded the expected clinical exposure at the MRHD (582-fold, 1131-fold, 3-fold, respectively); circulating levels of CC1084037 at the JAS NOAEL were equivalent to clinical exposure at the MRHD.

#### Summary and Recommendation:

The nonclinical package provided in the New Drug Application for Zeposia (ozanimod) is considered to be adequate to support approval, with one caveat. Since CC1084037 was not adequately assessed in the pre- and postnatal development study conducted in rat, it is recommended that the sponsor assess the impact of this metabolite in a pre- and postnatal development study as a postmarketing requirement.

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/s/  
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