

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**206255Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**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: 206255  
Supporting document/s: SD 1  
Applicant's letter date: 12/20/2013  
CDER stamp date: 12/20/2013  
Product: SOOLANTRA (ivermectin) Cream, 1%  
Indication: Rosacea  
Applicant: Galderma Research and Development, LLC,  
Cranbury, NJ  
Review Division: Dermatology and Dental Products  
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*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

Ivermectin is an anti-parasitic agent and has been marketed for the treatment of a number of parasite diseases (Stromectrol<sup>®</sup>, NDA 50742) and lice infestation (Sklice<sup>®</sup>, NDA 202736). The sponsor intends to develop SOOLANTRA (ivermectin) Cream, 1% for the treatment of rosacea through the 505(b)(2) regulatory pathway. The sponsor proposed to rely on published literature to support some nonclinical portions of this application.

## 1.2 Brief Discussion of Nonclinical Findings

### Pharmacology

Face mite infestation may be attributable to the onset of rosacea and the anti-parasitic activity of ivermectin suggests that it may be effective in the treatment of inflammatory lesions of rosacea. In addition, in vivo studies using different animal models showed that topical application of ivermectin has anti-inflammatory properties, which might also be attributable to its therapeutic effect on rosacea.

### Safety Pharmacology

No treatment-related effects on CNS were noted in rats at single oral doses up to 5 mg/kg ivermectin. In a second study a dose-dependent decrease in motor activity was noted at single oral doses of 7 and 20 mg/kg in rats. The NOAEL for neurological effects was identified as single oral dose of 3 mg/kg. Single oral doses of ivermectin up to 20 mg/kg had no effects on convulsive or analgesic activity. Ivermectin had no significant effects on the delayed rectifier potassium current in an in vitro hERG assay at concentrations up to 10  $\mu$ M. In a cardiovascular safety pharmacology study in conscious dogs, a single oral dose of 1.5 mg/kg ivermectin induced a slight decrease in blood pressure at 72 hr postdose. Ivermectin reduced the gastrointestinal transit in rats at a single oral dose of 20 mg/kg and dose-dependently reduced gastric emptying from 7 mg/kg. Ivermectin at single oral doses up to 20 mg/kg had no significant urinary effects.

### General Toxicology

Repeat dose toxicity studies were conducted in mice, rats, dogs, and minipigs via dermal or oral administration. No significant toxicity was noted in a 13-week dermal mouse study at topical doses up to 10 mg/kg/day (1% cream applied at 1 ml/kg/day). No significant toxicity was noted in a 13-week or a 9-month dermal minipig study at topical doses up to 20 mg/kg/day (1% cream applied at 2 ml/kg/day).

In a 27-week oral toxicity study in rats, treatment-related mortality was noted at 3 and 12 mg/kg/day. Decreased body weight gain or even weight loss was noted at 3 and 12 mg/kg/day during the first two weeks. It appeared that the 12 mg/kg/day dose induced significant toxicity during the first 2 weeks, especially in females, followed by a clear

habituation to the toxicity and partial recovery. Histopathology findings included slight white matter vacuolation in brain and cervical spinal cord, minimal mucosal hyperplasia and minimal to slight increase of lymphoid cells in the lamina propria of cecum, and minimal decreased secretion in seminal vesicles. The NOAEL was identified as 0.1 mg/kg/day in this study.

In a 39-week oral toxicity study in Beagle dogs, mydriasis and hypersalivation were observed at 1.5 mg/kg/day. A body weight loss was observed in both males and females at 1.5 mg/kg/day during the first week of dosing. No other significant toxicity was noted. The NOAEL was identified as 0.5 mg/kg/day in this study.

### **Genetic Toxicology**

A standard battery of genotoxicity studies was conducted with ivermectin. No genotoxicity was observed in the Ames test, the mouse lymphoma assay using L5178Y TK<sup>+/+</sup> mouse lymphoma cells, or an in vivo micronucleus test in rats.

### **Carcinogenicity**

Carcinogenicity studies were conducted in mice and rats. In a 2-year dermal mouse carcinogenicity study, there were no significant test article-related neoplastic findings in either sex, at topical doses up to 10 mg/kg/day ivermectin (1.0% cream). In a 2-year oral rat carcinogenicity study, there were no significant test article-related neoplastic findings in females, at oral doses up to 9 mg/kg/day ivermectin. A significant increase in the incidence of hepatocellular adenoma was noted in males at 9 mg/kg/day. There were no significant test article-related neoplastic findings in males treated with 1 or 3 mg/kg/day ivermectin. The multiples of human exposure at 3 mg/kg/day dose in male rats are ~600. The carcinogenic risk associated with the clinical use of ivermectin 1% cream is considered minimal.

### **Reproductive and Developmental Toxicology**

In a fertility study in rats, oral doses of 0.1, 1 and 9 mg/kg/day ivermectin were tested. High mortality was seen at high dose and therefore the mating performance and fertility could not be adequately assessed in this group. The pre-coital period was generally prolonged in the high dose group. There were no treatment-related effects on pregnancy rate, organ weights, sperm counts, sperm motility, or caesarean data. The NOAEL was identified as 1.0 mg/kg/day, for both general toxicity and mating performance/fertility.

In an embryofetal development study in rats, oral doses of 1.5, 4 and 12 mg/kg/day ivermectin were tested. Treatment-related mortality and body weight decrease was noted in high dose dams. A treatment-related decrease in fetal body weight was noted at high dose. An increased mean litter proportion of cleft palate was noted in the high dose group (0.9% per litter) compared to the control group (0% per litter). There were no other treatment-related findings. The NOAEL for maternal toxicity, embryofetal toxicity and teratogenicity was identified as 4 mg/kg/day.

In an embryofetal development study in rabbits, oral doses of 0.5, 1.5 and 4.5 mg/kg/day ivermectin were tested. Treatment-related mortality and body weight decrease was noted at high dose. Seven fetuses from 3 litters in the high dose group had carpal flexure (primarily bilateral). This finding is considered a malformation and significant. There were no other treatment-related findings. The NOAEL for maternal toxicity, embryofetal development and teratogenicity was identified as 1.5 mg/kg/day.

A second embryofetal development study in rabbits was conducted with oral doses of 2.5 and 3.5 mg/kg/day ivermectin. Treatment-related mortality/moribundity and body weight decrease was noted at both doses. A decrease in mean gravid uterine weight and mean fetal weight was noted at high dose. No treatment-related effects on fetal morphology were noted in this study. The NOAEL for maternal toxicity could not be identified in this study. The NOAEL for embryofetal toxicity was identified as 2.5 mg/kg/day and the NOAEL for teratogenicity was identified as 3.5 mg/kg/day.

A pre- and postnatal development study was conducted in rats (published literature). Oral doses of 1, 2 and 4 mg/kg/day ivermectin were tested. F<sub>1</sub> animals were exposed to the test article in utero and through lactation. Ivermectin was shown highly toxic during lactation. All the high dose pups exposed through lactation died during lactation days 3-8. The mortality rate in mid dose offspring was also very high (30.7%). In the offspring, a significant decrease in body weight was noted in mid dose and high dose groups. Ivermectin adversely affected the behavior development of newborn rats at all dose levels, particularly on motor development and general activity. A NOAEL for postnatal development was not identified in this study.

In a multi-generation study in SD rats (published literature), ivermectin was tested at 0.4, 1.2 and 3.6 mg/kg/day doses. A high mortality rate (53%) during the lactation period of F<sub>1a</sub> offspring in the high dose group was noted. The high dose F<sub>0</sub> animals were terminated early after weaning of the surviving F<sub>1a</sub> offspring. In the low and mid dose groups, a significant increase in mortality was noted in F<sub>1b</sub> and F<sub>2a</sub> litters. A NOAEL was not identified in this study. Subsequently the multi-generation study was repeated with lower dose levels: 0.05, 0.1, 0.2 and 0.4 mg/kg/day. No significant reproductive or developmental toxicity was noted in the second study. A NOAEL level of 0.2 mg/kg/day for neonatal toxicity was identified in the two multi-generation studies, under the study conditions.

A cross-fostering study showed that the neonatal toxicity of ivermectin in rats was mainly due to postnatal exposure (through lactation). A follow-up PK study showed that concentrations of ivermectin in milk from treated dams were 3-4 times higher than the maternal plasma level and resulted in a progressive increase in plasma levels in the offspring. In addition, the plasma-brain drug concentration ratio in offspring increased from 1 to 3 during postnatal days 1-10, which was consistent with the postnatal formation of a blood-brain barrier in rats. The results help to explain the high sensitivity of neonatal rats to ivermectin's toxicity. In other species in which the excretion of ivermectin in milk is lower and/or the blood-brain barrier is formed prenatally (such as

human), the potential for ivermectin induced neonatal toxicity through lactation may be considerably reduced.

### Special Toxicology

The 1% ivermectin cream was an irritant to rabbit skin after a 24 hour topical administration under occlusion. However, the 1% ivermectin cream was classified as a non-irritant to rabbit eyes, in an acute eye irritation study. Concentrations of ivermectin  $\leq$  0.5% in a propylene glycol vehicle did not elicit a positive response in the mouse local lymph node assay. The 1% ivermectin cream was classified as a sensitizer in guinea pigs. The 1% ivermectin cream did not appear to elicit a phototoxic response in guinea pigs.

The nonclinical safety program for ivermectin 1% cream is complete. The proposed clinical use of SOOLANTRA Cream is supported by nonclinical data.

## 1.3 Recommendations

### 1.3.1 Approvability

NDA 206255 for SOOLANTRA (ivermectin) Cream, 1% is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the SOOLANTRA Cream label. No postmarketing requirement is recommended for this NDA.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the sponsor proposed SOOLANTRA Cream label reproduced below.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

SOOLANTRA is (b) (4) indicated for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.

### 8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SOOLANTRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Note: The animal multiples of human exposure calculations in this label were based on AUC comparisons. The maximum topical human dose (MTHD) of SOOLANTRA Cream is 1 g applied once daily.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1.5, 4, and 12 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–17) to pregnant female rats. Maternal death occurred at 12 mg/kg/day (1909X MTHD). Cleft palate occurred in the fetuses from the 12 mg/kg/day (1909X MTHD) group. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 4 mg/kg/day (708X MTHD). Oral doses of 0.5, 1.5, 2.5, 3.5 and 4.5 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 7–20) to pregnant female rabbits. Maternal death occurred at doses  $\geq$  2.5 mg/kg/day (72X MTHD). Carpal flexure occurred in the fetuses from the 4.5 mg/kg/day (354X MTHD) group. Fetal weight decrease was noted at 3.5 mg/kg/day (146X MTHD). No treatment related effects on embryofetal toxicity were noted at 2.5 mg/kg/day (72X MTHD) and no treatment related effects on teratogenicity were noted at 3.5 mg/kg/day (146X MTHD).

A pre- and postnatal development study was conducted in rats. Oral doses of 1, 2 and 4 mg/kg/day ivermectin were administered to pregnant female rats during gestational days 6-20 and lactation days 2-20. Neonatal death occurred at doses  $\geq$  2 mg/kg/day. Behavior development of newborn rats was adversely affected at all doses.



### **8.3 Nursing Mothers**

Following oral administration, ivermectin is excreted in human milk in low concentrations. Excretion in human milk following topical administration has not been evaluated. In oral studies in rats, ivermectin was excreted in the milk of nursing mothers; (b) (4) and neonatal toxicity was observed in the litters. (b) (4)

The blood-brain barrier in neonatal rats may not be fully developed at birth (b) (4) Because of the potential for serious adverse reactions from SOOLANTRA in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **12.1 Mechanism of Action**

The mechanism of action of SOOLANTRA Cream in treating rosacea lesions is unknown.



### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year dermal mouse carcinogenicity study, ivermectin was administered to CD-1 mice at topical doses of 1, 3, and 10 mg/kg/day (0.1%, 0.3% and 1% ivermectin cream applied at 2 ml/kg/day). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 10 mg/kg/day (747X MTHD).

In a 2-year oral rat carcinogenicity study, ivermectin was administered to Wistar rats at gavage doses of 1, 3, and 9 mg/kg/day. A statistically significant increase in the incidence of hepatocellular adenoma was noted in males treated with 9 mg/kg/day (1766X MTHD) ivermectin. The clinical relevance of this finding is unknown. No drug-related tumors were noted in females up to the highest dose evaluated in this study of 9 mg/kg/day (1959X MTHD). No drug-related tumors were noted in males at doses  $\leq$  3 mg/kg/day (599X MTHD).

Ivermectin revealed no evidence of genotoxic potential based on the results of two in vitro genotoxicity tests (the Ames test and the L5178Y/TK<sup>+/+</sup> mouse lymphoma assay) and one in vivo genotoxicity test (rat micronucleus assay).

In a fertility study, oral doses of 0.1, 1 and 9 mg/kg/day ivermectin were administered to male and female rats. Mortality occurred at 9 mg/kg/day (1027X MTHD). The precoital period was generally prolonged at 9 mg/kg/day. No treatment related effects on fertility or mating performance were noted at doses  $\leq$  1 mg/kg/day (68X MTHD).



(b) (4)

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 70288-86-7, Component H<sub>2</sub>B<sub>1a</sub> 70161-11-4, Component H<sub>2</sub>B<sub>1b</sub> 70209-81-3

Generic Name: Ivermectin

Code Name: CD5024 (Galderma), (b) (4)

Chemical Name:

Ivermectin is a mixture of Component H<sub>2</sub>B<sub>1a</sub> and Component H<sub>2</sub>B<sub>1b</sub>

H<sub>2</sub>B<sub>1a</sub>: 5-O-demethyl-22,23-dihydroivermectin A<sub>1a</sub>

H<sub>2</sub>B<sub>1b</sub>: 5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroivermectin A<sub>1a</sub>

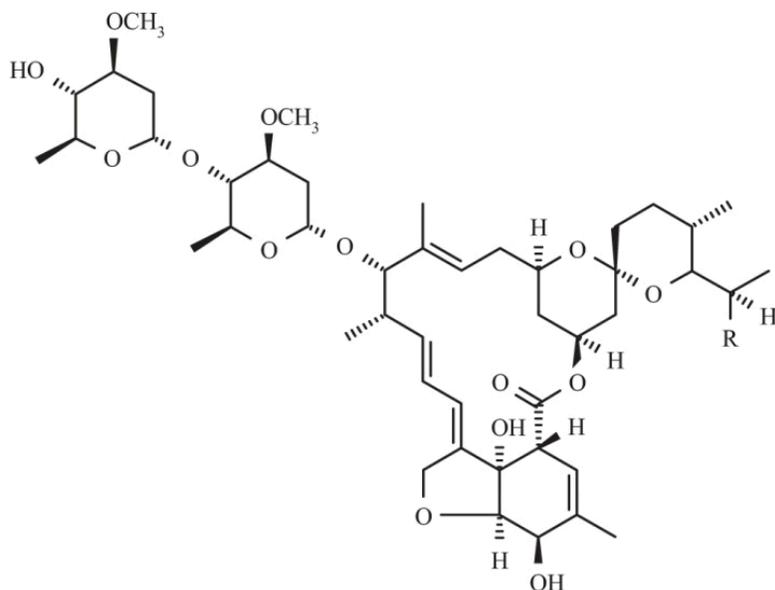
It contains no less than 95% and no more than 102% for the sum of component H<sub>2</sub>B<sub>1a</sub> plus component H<sub>2</sub>B<sub>1b</sub>, (b) (4) and the ratio (calculated by area percentage) of component H<sub>2</sub>B<sub>1a</sub> is no less than 90%.

Molecular Formula/Molecular Weight:

H<sub>2</sub>B<sub>1a</sub>: C<sub>48</sub>H<sub>74</sub>O<sub>14</sub> / 875

H<sub>2</sub>B<sub>1b</sub>: C<sub>47</sub>H<sub>72</sub>O<sub>14</sub> / 861

Structure or Biochemical Description:



Component H<sub>2</sub>B<sub>1a</sub>: R = CH<sub>2</sub>CH<sub>3</sub>

Component H<sub>2</sub>B<sub>1b</sub>: R = CH<sub>3</sub>

Pharmacologic Class: None assigned (antiparasitic and pediculicide were used previously as established pharmacologic classes for ivermectin, but they are not considered appropriate for the rosacea indication because the mechanism of action is not clear.)

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 76064 Ivermectin 1% cream, Rosacea, by Galderma Research and Development, DDDP

## 2.3 Drug Formulation

The composition of SOOLANTRA (ivermectin) Cream, 1%, is listed in the following table.

Formulation No. 575.754	% (w/w)	mg/g	Function <sup>a</sup>	Pharmacopeia Reference
<b>Active Ingredient</b>				
Ivermectin	1.0	10	Drug substance	USP
<b>Excipients</b>				
Glycerin	(b) (4)			USP
Isopropyl palmitate	(b) (4)			USP-NF
Carbomer copolymer (type B)	(b) (4)			USP-NF
Dimethicone	(b) (4)			USP-NF
Edetate disodium	(b) (4)			USP
Citric acid monohydrate	(b) (4)			USP-NF
Cetyl alcohol	(b) (4)			USP-NF
Stearyl alcohol	(b) (4)			USP-NF
Polyoxyl 20 cetostearyl ether	(b) (4)			USP-NF
Sorbitan monostearate	(b) (4)			USP-NF
Methylparaben	(b) (4)			USP-NF
Propylparaben	(b) (4)			USP-NF
Phenoxyethanol	(b) (4)			USP-NF
Propylene glycol	(b) (4)			USP
Oleyl alcohol	(b) (4)			USP-NF
Sodium hydroxide	(b) (4)			USP-NF
Purified water	(b) (4)			USP

<sup>a</sup> Function given according to USP-NF pharmacopeia in "USP and NF excipients, listed by category" except for purified water, glycerin and oleyl alcohol for which the function is based on the physicochemical characteristics

(b) (4)

(b) (4)

This to-be-marketed formulation is named "Type A" formulation and a "Type B" formulation was also used in dermal toxicology studies (refer to the following table for the list of nonclinical studies using Type A or B formulation). The only differences between the two formulations

(b) (4)

These minor differences are not considered significant regarding the toxicity potential of the two formulations.

Study Number	Study Type	Study Number	Study Type
Formulation Type A (including the final to be marketed formulation)		Formulation Type B	
RDS.03.SRE.8547	4-week repeat-dose in rat	RDS.03.SRE.4778	Single and 14 day repeat-dose PK in rat
RDS.03.SRE.12447	4-week repeat-dose in minipig	RDS.03.SRE.31024	Single dose PK in mouse
RDS.03.SRE.12437	Acute dermal irritation (rabbit)	RDS.03.SRE.31025	4-week repeat-dose PK in minipig
RDS.03.SRE.12436	Acute eye irritation (rabbit)	RDS.03.SRE.8552	4-week repeat-dose in mouse
RDS.03.SRE.12438	Sensitization Potential (Buehler test) (guinea pig)	RDS.03.SRE.12491	13-week repeat-dose in minipig
RDS.03.SRE.12439	Phototoxic and photosensitization potential (guinea pig)	RDS.03.SRE.12500	13-week repeat-dose in mouse
		RDS.03.SRE.12519	13-week repeat-dose DRF photocarcinogenicity in mice
		RDS.03.SRE.12510	9-month repeat-dose in minipig
		RDS.03.SRE.12508	104-week dermal carcinogenicity (mouse)
		RDS.03.SRE.12597	Photocarcinogenicity (mouse)

## 2.4 Comments on Novel Excipients

Per the nonclinical review dated 03/08/2008, the carbomer copolymer type B used in the drug product is associated with a potential (b) (4) impurity at a concentration less than (b) (4) %, which is considered acceptable. There are no novel excipients. All the inactive ingredients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products.

## 2.5 Comments on Impurities/Degradants of Concern

None.

## 2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with inflammatory lesions of rosacea, 18 years of age or older.

Dosing regimen: Apply a pea-size amount once daily to each of the five areas of the face (forehead, chin, nose, each cheek) avoiding the eyes and lips.

The mean clinical dose that has been tested in a maximum use clinical PK trial was 1 g SOOLANTRA Cream, 1%, applied once daily for 4 weeks to adult subjects with severe papulopustular rosacea (PPR).

## 2.7 Regulatory Background

Ivermectin 1% cream was developed under IND 76064 (opened on 10/29/2007). An End-of-Phase 2 meeting was conducted on 03/18/2008. A Pre-Phase 3 meeting was conducted on 08/10/2011. A Pre-NDA meeting was conducted on 06/12/2013. Exec

CAC meetings were conducted on 01/23/2007 (study protocols) and 06/17/2014 (study results).

### 3 Studies Submitted

#### 3.1 Studies Reviewed

##### Pharmacology studies:

1. Evaluation of the anti-inflammatory activity of CD5024 and CD0036 after single topical administration in TPA-induced ear edema model on Balb/c mice (Study# RDS.03.SRE.46099)
2. Evaluation of the anti-inflammatory activity of CD5024 and CD0036 after single topical administration in Arachidonic acid-induced ear edema model on Balb/c mice (Study# RDS.03.SRE.46100)
3. Evaluation of CD06746, CD07550 and Ivermectin (CD5024) activity in the TPA-induced TNF $\alpha$  production model (Study# RDS.03.SRE.47047)
4. Evaluation by the topical route of the immunomodulatory potential of CD5024 (Ivermectin) and CD10213 (Triamcinolone acetonide) in the dermatophagoides-induced AD-like mouse model (Study# RDS.03.SRE.48005)

##### Safety Pharmacology studies:

5. Irwin profile test in the rat after oral administration of ivermectin (Study# RDS.03.SRE.12391)
6. Assessment of synergistic/antagonistic activity of ivermectin on pentylentetrazole-induced convulsions after single oral administration in the male rat (Study# RDS.03.SRE.12492)
7. Assessment of the intrinsic convulsive activity of ivermectin after single oral administration in the male rat (Study# RDS.03.SRE.12493)
8. Assessment of the anesthetic activity of ivermectin after single oral administration in the male rat (Study# RDS.03.SRE.12494)
9. Neurobehavioural observations and automated motor activity assessment after single oral administration of ivermectin in the male rat (Study# RDS.03.SRE.12495)
10. Assessment of the analgesic activity of ivermectin after single oral administration in the male rat (Study# RDS.03.SRE.12499)
11. Evaluation of CD5024 on gastrointestinal transit test in the rat (p.o. administration) (Study# RDS.03.SRE.12576)
12. Evaluation of CD5024 on diuresis and urinary electrolyte excretion in the rat (p.o. administration) (Study# RDS.03.SRE.12578)
13. Assessment of cardiovascular risk for CD5024 in the conscious dog monitored by telemetry (p.o. administration) (Study# RDS.03.SRE.12602)
14. In vitro effects of CD5024 on hERG current ( $I_{kr}$ ) expressed in Human Embryonic Kidney (HEK) cells (Study# RDS.03.SRE.12603)

Pharmacokinetic studies:

15. Development and validation of an HPLC analytical method for determination of CD 5024 (Ivermectin) in rat plasma (Study# RDS.03.VRE.34020)
16. Development and validation of an HPLC analytical method for determination of CD 5024 (Ivermectin) in dog plasma (Study# RDS.03.VRE.34021)
17. Validation of an HPLC method for determination of ivermectin in rabbit plasma with fluorescence detection (Study# RDS.03.VRE.34101)
18. Long term stability of ivermectin in rabbit plasma (Study# RDS.03.VRE.34102)
19. Validation of an HPLC method for determination of ivermectin in mouse plasma with fluorescence detection (Study# RDS.03.VRE.34112)
20. Validation of an HPLC method for determination of ivermectin in minipig plasma with fluorescence detection (Study# RDS.03.VRE.34114)
21. Long term stability of ivermectin in mouse plasma (Study# RDS.03.VRE.34117)
22. Long term stability of ivermectin in minipig plasma (Study# RDS.03.VRE.34118)
23. Bioanalytical method for determination of ivermectin (CD5024) in rat plasma samples by HPLC with fluorescence detection-validation (Study# RDS.03.VRE.34158)
24. Transfer and complementary validation of an HPLC method for the determination of ivermectin in mouse plasma with fluorescence detection (Study# RDS.03.VRE.34187)
25. Transfer and complementary validation of an HPLC method for the determination of CD5024 (ivermectin) in dog plasma with fluorescence detection (Study# RDS.03.VRE.34188)
26. Bioanalytical method for determination of ivermectin (CD5024) in rat plasma samples by HPLC with fluorescence detection-validation (Study# RDS.03.VRE.34190)
27. Transfer and complementary validation of an HPLC method for the determination of CD5024 (ivermectin) in rabbit plasma with fluorescence detection (Study# RDS.03.VRE.34196)
28. Pharmacokinetic study of CD5024 in the Sprague Dawley rat after a single oral, topical or intravenous administration (Study# RDS.03.SRE.31004)
29. Pharmacokinetic study of CD5024 after a single oral, topical or intravenous administration in Beagle dogs (Study# RDS.03.SRE.31005)
30. Pharmacokinetic study of ivermectin after single iv, oral and dermal administration in the mouse (Study# RDS.03.SRE.31024)
31. CD5024 cream: 4 week topical pharmacokinetics study in the minipigs (Study# RDS.03.SRE.31025)
32. To compare the in vitro percutaneous absorption of ivermectin contained at 1% (w/w) in three formulations (Study# RDS.03.SRE.4742)
33. [<sup>3</sup>H]-Ivermectin: Absorption, distribution, metabolism and excretion study in Sprague-Dawley rats (Study# RDS.03.SRE.4754)
34. Ivermectin: Absorption, excretion and metabolism study in the Beagle dog (Study# RDS.03.SRE.4755)

35. [<sup>3</sup>H]-Ivermectin (CD5024): Absorption, skin distribution, excretion and metabolism study in the Gottingen minipig after single intravenous and topical administration (Study# RD.03.SRE.4766)
36. Pharmacokinetics of ivermectin cream 1% (w/w) after single or repeated dermal application in male Sprague-Dawley rat (Study# RDS.03.SRE.4778)
37. Ivermectin pharmacokinetics in the Wistar rat after a 2-week repeated oral administration (Study# RD.03.SRE.4908)
38. [<sup>3</sup>H]-Ivermectin: Interspecies comparison of in vitro plasma protein binding and plasma/blood cell partitioning in mouse, rat, rabbit, dog, minipig and human (Study# RDS.03.SRE.4756)
39. Tissue distribution of [<sup>3</sup>H]-CD5024 (ivermectin cream 1%) in Sprague Dawley rat after dermal single and repeated application (Study# RD.03.SRE.4784)
40. The placental transfer of total radioactivity following single oral administration of [<sup>3</sup>H]-CD5024 (ivermectin) to the pregnant rat (Study# RD.03.SRE.4796)
41. Reaction phenotyping: Identification of CYP enzymes involved in the metabolism of CD5024 (Study# RD.03.SRE.31037)
42. In vitro evaluation of CD5024 as an inducer of cytochrome P450 expression in cultured human hepatocytes (Study# RD.03.SRE.31038)
43. In vitro evaluation of CD5024 as an inhibitor of human cytochrome P450 enzymes (Study# RD.03.SRE.31039)
44. Production of 20 mg of two metabolites (M1 and M2) of ivermectin (Study# RD.03.SRE.31085)
45. Feasibility study for the production of M2 metabolite of ivermectin by hydroxylation of the aglycon molecule (Study# RD.03.SRE.31106)
46. Structural elucidation of an ivermectin metabolite identified in in vivo plasma sample (Study# RD.03.SRE.34169)
47. In vitro study of interspecies liver metabolism of (Tritium-labeled) Ivermectin using hepatocytes in suspension (Study# RDS.03.SRE.4739)
48. Structural identification of major ivermectin metabolites in human liver microsomes (Study# RD.03.SRE.4830)

General Toxicology studies:

49. Ivermectin: Single dose oral (gavage) limit test in mice (Study# RDS.03.SRE.8553)
50. Ivermectin: Single dose oral (gavage) limit test in the Sprague Dawley rat (Study# RDS.03.SRE.8550)
51. Ivermectin cream 0.1-0.3-1% (w/w) 4-week dermal toxicity study in CD1 mice (Study# RDS.03.SRE.8552)
52. Ivermectin - 13 week dermal dose-range finding study in the mouse (Study# RDS.03.SRE.12500)
53. Thirteen-week topical range-finding study of Ivermectin cream and Ivermectin placebo cream in hairless mice, with or without simulated sunlight (Study# RDS.03.SRE.12519)
54. Ivermectin 1% cream: 4-week dermal toxicity study in Sprague Dawley rat (Study# RDS.03.SRE.8547)

55. Ivermectin – 13 week oral (gavage) dose-range finding study in the rat (Study# RDS.03.SRE.12505)
56. A 13-week oral toxicity study in rats (Study# RDS.03.SRE.12413)
57. Ivermectin - 27-week oral (gavage) toxicity study in the rat (Study# RDS.03.SRE.12537)
58. Ivermectin – 4-week oral (gavage) dose range-finding toxicity study in Beagle dog (Study# RDS.03.SRE.12514)
59. A 13-week oral toxicity study in dogs (Study# RDS.03.SRE.12426)
60. Ivermectin - 39-week oral (gavage) toxicity study in the beagle dog (Study# RDS.03.SRE.12511)
61. Ivermectin 1% (w/w) cream preliminary 4-week dermal study in minipigs (Study# RDS.03.SRE.12447)
62. Ivermectin – 13-week dermal toxicity study in the minipig (Study# RDS.03.SRE.12491)
63. Ivermectin - 9-month dermal toxicity study in the minipig (Study# RDS.03.SRE.12510)

Genetic Toxicology studies:

64. Ivermectin-bacterial reverse mutation test (Study# RDS.03.SRE.12440)
65. In vitro mammalian cell gene mutation test in L5178Y TK+/- mouse lymphoma cells (Study# RDS.03.SRE.12441)
66. Bone marrow micronucleus test by oral route in rats (Study# RDS.03.SRE.12443)

Carcinogenicity studies:

67. CD5024 – 104-week dermal carcinogenicity study in the mouse (Study# RDS.03.SRE.12508)
68. Twelve-month topical study to determine the influence of Ivermectin Cream and Ivermectin placebo cream on photocarcinogenesis in hairless mice (Study# RDS.03.SRE.12597)
69. CD5024 – 104-week oral (gavage) carcinogenicity study in the rat (Study# RDS.03.SRE.12507)

Reproductive and developmental toxicology studies:

70. Ivermectin - Fertility toxicity study by the oral route (gavage) in the rat (Segment I) (Study# RDS.03.SRE.12504)
71. Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rabbits (Study# RDS.03.SRE.12444)
72. Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rats (Study# RDS.03.SRE.12445)
73. An oral dose study of the effects of ivermectin on embryo/fetal development in rabbits (Study# RDS.03.SRE.12460)

74. An oral dose study of the effects of ivermectin on embryo/fetal development in rats (Study# RDS.03.SRE.12461)
75. Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rats (Study# RDS.03.SRE.12490)
76. An oral dose study of the effects of CD5024 on embryo/fetal development in rabbits (Study# RDS.03.SRE.12623)
77. Ivermectin. *In: Toxicological evaluation of certain veterinary drug residues in food. Thirty-sixth (36<sup>th</sup>) Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Feb 5-14, 1990; Rome. World Health Organization (WHO), Geneva. WHO Food Additives Series, No. 27, 1991.*  
[<http://www.inchem.org/documents/jecfa/jecmono/v27je03.htm>]
78. Poul. Effects of perinatal ivermectin exposure on behavioral development of rats. *Neurotoxicol Teratol.* 1988;10: 267-72
79. Lankas et al. Effects of ivermectin on reproduction and neonatal toxicity in rats. *Food Chem Toxicol.* 1989;27:523-9

#### Special toxicology studies:

80. Acute eye irritation in rabbits (Study# RDS.03.SRE.12436)
81. Acute dermal irritation in rabbits (Study# RDS.03.SRE.12437)
82. Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications) (Study# RDS.03.SRE.12438)
83. Phototoxic and photoallergenic potential by cutaneous route in guinea pigs (Study# RDS.03.SRE.12439)
84. Assessment of contact hypersensitivity to ivermectin in the mouse (local lymph node assay) (Study# RDS.03.SRE.12498)
85. In vitro evaluation of immunomodulatory effects of CD5024 on human leukocytes, polymorphonuclear and CD34+ progenitor cells (Study# 564111R)

### **3.2 Studies Not Reviewed**

86. Photomutagenicity test with Ivermectin on induction of reverse mutations in bacteria (Study# RDS.03.SRE.12482)
87. Photomutagenicity test with Ivermectin on formation of chromosomal aberrations in cultured Chinese Hamster Ovary (CHO) cells (Study# RDS.03.SRE.12483)

*Reviewer's comment:* Photomutagenicity tests are no longer considered useful for risk assessment in human and therefore the two studies are not reviewed.

### **3.3 Previous Reviews Referenced**

- Nonclinical reviews, IND (b) (4), by Dr. Barbara Hill, dated 01/25/2007 and 03/07/2008
- Nonclinical reviews, IND (b) (4), by this reviewer, dated 10/15/2008, 12/24/2008, 03/11/2009, 04/05/2011, and 08/03/2011

## 4 Pharmacology

### 4.1 Primary Pharmacology

Ivermectin, a member of the avermectin class, causes death of parasites, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels, the avermectins have a low affinity for mammalian ligand-gated chloride channels, and ivermectin does not readily cross the blood brain barrier in humans.

The exact cause of rosacea has not been determined. One of the hypotheses is that mite infestation may be attributable to the onset of rosacea. Ivermectin may act directly through its antiparasitic activity against *Demodex folliculorum*, a species of face mite which is often present at high levels in the skin of patients with rosacea. Its antiparasitic activity against face mite suggests that ivermectin may be effective in the treatment of inflammatory lesions of rosacea.

### 4.2 Secondary Pharmacology

In vivo studies using different animal models showed that topical application of ivermectin has anti-inflammatory properties.

In a mouse model in which ear edema was induced by topical application of 0.01% 12-O-tetradecanoyl-phorbol-13-acetate (TPA), ivermectin at concentrations of 0.1, 0.3, and 1% reduced ear edema by 24, 62, and 88%, respectively (vehicle: ethanol). In another mouse model, ivermectin at concentrations of 0.1, 0.3, and 1% (vehicle: THF/methanol 1:1) reduced arachidonic acid-induced ear edema by 25, 29, and 51%, respectively. In a TPA-induced ear edema and TNF- $\alpha$  production mouse model (vehicle: THF/methanol 1:1), TNF- $\alpha$  level was measured in mouse ear at 8 hr after topical application of 0.01% TPA and/or test article. The inhibition rate of TNF- $\alpha$  production was 75, 75, and 85% for ivermectin at concentrations of 0.003, 0.03, and 0.3%, respectively.

In a mouse model of allergen-induced atopic dermatitis (AD), cutaneous inflammation was induced by repeat topical application of a protein allergen solution [extract from house dust mite, *Dermatophagoides farinae*, 12.5 mg/ml in 70% DMSO, applied to the right ear once a week for six weeks (on Days 1, 8, 15, 22, 29, and 36)]. Topical application of 20  $\mu$ l of vehicle or test article was performed on both sides of the right ear once daily from Day 19 to Day 36. On the challenge days with the allergen solution (Days 22, 29, and 36), the application was made 6 hr following the application of allergen. The induced skin inflammation was evaluated by ear thickness measurement,

histology examination, serum total IgE, eosinophil peroxidase quantification, and mast cell count.

In a first study using this model, topical ivermectin was tested at 0.1% and 0.2% (vehicle: acetone) and no increase in efficacy was seen at 0.2% compared to 0.1%. In a second study, a larger dose range of ivermectin was tested: 0.03, 0.1, 0.3, and 0.5% (same vehicle). In that study, an inverse dose response was noted, where a complete loss of anti-inflammatory activity was noted at 0.5%. In a third study, a lower dose range was evaluated (0.003, 0.01, 0.03, and 0.1%, same vehicle). In this study at 0.003%, ivermectin application significantly reduced clinical symptoms of inflammation (ear edema), as well as epidermal thickness, skin eosinophil peroxidase level, skin mast cell count, and serum IgE content. In this model, ivermectin 0.003% showed an activity similar to triamcinolone acetonide 0.01% or 0.05%. Again, an inverse dose response was noted, where concentrations of 0.01, 0.03, and 0.1% were less potent than the lowest concentration, 0.003%, in anti-inflammatory effects (the concentrations of 0.01-0.1% significantly reduced ear edema but the effects on other parameters were not significant).

### 4.3 Safety Pharmacology

#### Neurological effects

The neurological effects of ivermectin were evaluated in male SD rats. Single oral (gavage) doses of 0 (untreated), 0 (vehicle: 0.5% carboxymethylcellulose), 0.5, 1 and 5 mg/kg ivermectin were administered to male SD rats (6/group). Neurobehavioral activity was assessed using a modified Irwin's method at 0, 0.5, 1, 2, 5 and 24 hr post dose. No treatment-related effects on spontaneous activity, CNS excitability, sensory, motor, autonomic or neuromuscular function or body temperature was noted in this study. The NOAEL for neurological effects was identified as 5 mg/kg ivermectin in rats, under the conditions of this study.

Single oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7 and 20 mg/kg ivermectin were administered to male SD rats (10/group). Neurobehavioral activity was assessed by conduct of a functional observational battery and automated motor activity assessment conducted on the day prior to treatment and at 2 and 24 hr postdose. A dose dependent decrease in motor activity was noted at 2 hr postdose in mid and high dose animals. A reduction of more than 20% of the total distance moved was noted in high dose animals. No treatment-related difference in motor activity was noted at 24 hr postdose. No treatment-related effects on the functional observational battery parameters were noted in this study. The NOAEL for neurological effects (specifically motor activity) was identified as 3 mg/kg, under the conditions of this study.

The effect of ivermectin on pentylentetrazole-induced convulsive activity was evaluated in male Wistar rats. Single oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7, and 20 mg/kg ivermectin were administered to male SD rats (10/group). A positive control, single 0.75 mg/kg physostigmine (i.p.) dose, was included in this study. All animals received a single subcutaneous dose of 75 mg/kg

pentylentetrazole at 2 hr postdose. The latency of the onset of initial convulsive activity, intensity of initial convulsive activity, latency of the onset of threshold seizures and the highest intensity of observed convulsive activity was recorded immediately after administration of pentylentetrazole. Ivermectin treatment had no effects on pentylentetrazole-induced convulsive activity in this study.

The intrinsic convulsive activity potential of ivermectin was evaluated in male Wistar rats. Single oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7, and 20 mg/kg ivermectin were administered to male Wistar rats (10/group). Intrinsic convulsive activity was assessed in all animals during a 30-minute observation period at 2 hr postdose. No treatment-related effects on convulsive activity were noted in this study.

The effect of ivermectin on pentobarbital-induced anesthesia was evaluated in male Wistar rats. Single oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7, and 20 mg/kg ivermectin were administered to male Wistar rats (10/group). Antagonistic and synergistic controls, single 3 mg/kg amphetamine sulfate (i.p.) and 5 mg/kg diazepam (i.p.), respectively, were included in this study. All animals were dosed with 25 mg/kg sodium pentobarbital immediately after test article administration. The latency to and the duration of loss of righting reflex, indicative of pentobarbital-induced anesthesia, were recorded. No ivermectin treatment-related effects on pentobarbital-induced anesthesia were noted in this study.

The intrinsic analgesic activity potential of ivermectin was evaluated in male Wistar rats. Single oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7, and 20 mg/kg ivermectin were administered to male Wistar rats (10/group). A positive control, single oral dose of 10 mg/kg physostigimine, was included this study. The analgesic activity was evaluated by measuring the tail withdrawal latency after immersion of the tail in 55°C water. The latency of tail withdrawal was measured within 15 min prior to administration and 1, 2, 4 and 6 hr postdose. No ivermectin treatment-related effects on tail withdrawal were noted in this study.

### Cardiovascular effects

An in vitro hERG assay was conducted to evaluate the effects of CD5024 on the delayed rectifier potassium current ( $I_{kr}$ ) in stably transfected HEK293 cells. Ascending concentrations of 0.01, 0.1, 1, and 10  $\mu$ M CD5024 were tested. There were no significant effects on the amplitude of  $I_{kr}$  at any tested concentrations of CD5024, compared with vehicle control (DMSO). Because there was no significant inhibition, the concentration inducing 50% inhibition ( $IC_{50}$ ) could not be determined. As a positive control, terfenadine at 1  $\mu$ M markedly decreased the amplitude of  $I_{kr}$  by 86%.

The cardiovascular effects of CD5024 were evaluated in conscious Beagle dogs (3/sex) monitored by telemetry. A single oral dose of 1.5 mg/kg CD5024 was tested. Each animal received the vehicle (0.5% carboxymethylcellulose), then CD5024, with a washout period of 48 hr. Cardiovascular parameters evaluated in this study included:

mean, systolic and diastolic arterial blood pressure, heart rate and PR, QT, and QTc intervals. For vehicle control parameters were measured at 30 min predose and 24 hr postdose. For CD5024 measurements were taken at 30 min predose and 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hr postdose. There were no behavior changes or signs of morbidity. During the first 24 hr, administration of CD5024 at 1.5 mg/kg did not have significant effects on the measured parameters. From time points 48 hr to 240 hr (Day 2 to Day 10), blood pressure was overall slightly reduced with maximum effects observed at 72 hr postdose (-15%, -13% and -19% for mean, systolic and diastolic pressure, respectively). Heart rate remained steady, although a reduction was observed on Day 10 (-20%). There was no significant change in PR interval. The QT interval was slightly lengthened (+11% at 48 hr and +13% at 240 hr). However, due to the decrease of heart rate, the QTc interval calculated using the Fridericia's formula was not significantly changed (+6% at 48 hr). When using the Van Water's formula, the slight increase in QTc interval at 48 hr reached statistical significance (+6%). However, similar increase was also seen in the vehicle control group and it was not considered a significant treatment-related effect.

Overall CD5024 at 1.5 mg/kg induced a slight decrease in blood pressure in dogs, under the study conditions.

#### Gastrointestinal effects

The effects of CD5024 on gastrointestinal transit were examined in male Wistar rats following single oral doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7 and 20 mg/kg. At 60 min postdose, a suspension of charcoal was given to the rats (p.o.) and the rats were sacrificed 20 min later. The small intestine was removed and the distance covered by the charcoal (a) and the total length of the small intestine (b) were measured. The stomach content was also measured. Morphine (12 mg/kg p.o.) was used as a reference. CD5024 at single doses of 3 and 7 mg/kg had no significant effect on the intestinal transit. At 3 mg/kg, it had no effect on the gastric content. At 7 mg/kg, the gastric content was significantly higher than control (+37%). CD5024 at 20 mg/kg significantly reduced the distance covered by charcoal (-23%) and increased the gastric content (+70%), compared with the vehicle control. Morphine significantly reduced the distance covered by charcoal (-42%) and increased the gastric content (+205%) as compared with vehicle control. These results showed that CD5024 significantly reduced the gastrointestinal transit at a single oral dose of 20 mg/kg and dose-dependently reduced gastric emptying from 7 mg/kg.

#### Urinary effects

The effects of CD5024 on diuresis and urinary electrolyte excretion were examined in male Wistar rats following single oral doses of 0 (vehicle: 0.5% carboxymethylcellulose), 3, 7 and 20 mg/kg. Urine was collected over a 6 hr period postdose. Furosemide (32 mg/kg p.o.) was also tested as a reference. CD5024 at single oral doses up to 20 mg/kg had no significant effects on urinary volume, urinary pH, potassium, sodium, or creatinine excretion, compared to vehicle control. Furosemide significantly increased

the urinary volume, sodium excretion and potassium excretion and significantly decreased creatinine excretion.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

The pharmacokinetics of ivermectin was investigated after topical, oral and intravenous (IV) administration in the mouse, rat, dog, and minipig. Bioanalytical methods (solid/liquid phase extraction/derivatization followed by reverse phase HPLC with fluorescence detection) for ivermectin have been developed and validated for rat, dog, mouse, rabbit and minipig plasma samples. The limit of quantification (LOQ) was 1 ng/ml for rat and dog plasma, 0.5 ng/ml for mouse plasma, and 0.2 ng/ml for rabbit and minipig plasma. A similar HPLC with fluorescence detection were also used to measure ivermectin in an in vitro percutaneous absorption study, with a LOQ of 1 ng/ml.

#### Absorption

As predicted from ivermectin's high molecular weight and high lipophilicity ( $\log P=4.4$ ), its dermal absorption was limited. The in vitro absorption of [ $^3\text{H}$ ]-ivermectin applied as a 1% cream was evaluated using human excised skin. The total penetrated dose was 2.2%. The radioactivity mainly recovered in the stratum corneum (1.6%) and only 0.03% was recovered in the receptor fluid. Following topical application of ivermectin in the mouse, rat, dog or minipig [either the 1% cream or formulated in propylene glycol/ethanol, 60/40 (w/w)], the estimated absolute bioavailability was 4% in the mouse, 2% in the rat and 0.4% in the dog. In the minipig, after a single 6-hr topical application (0.5 g/kg 1% cream applied to 10% BSA), plasma concentrations of CD5024 were below the LOQ (0.2 ng/ml) at all sampling time points. The dermal bioavailability of ivermectin in minipigs was estimated to be 0.4% in males and 0.2% in females based on excretion data.

Following oral administration, ivermectin was absorbed rapidly with a  $t_{\max}$  of 2 h or less in the mouse and rat, and 5 h or less in the dog. The absolute bioavailability of ivermectin following single oral administration was 72% in the mouse, 25-41% in the rat and 30-41% in the dog.

An overview of PK results after single IV, oral, or topical doses in the mouse, rat, dog, and minipig or after repeat topical dose in the minipig is shown in the table below (copied from the sponsor's submission).

Species	Gender	Method of Adm.	Dose (mg/kg)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	Mean Residence Time (h)	AUC <sub>0-12h</sub> (ng.h/mL)	AUC <sub>0-24h</sub> (ng.h/mL)	t <sub>1/2</sub> (h)	Clearance (L/h/kg)	V <sub>dis</sub> (L/kg)	Bioavailability (%)	Study Report
Mouse	Male	IV	2	2384	0.08	9.87	8458	8708	9.1	0.23	2.3	NA	RDS.03.SRE.31024
		Oral	2	543	2	11	6234	6293	6.9	ND	ND	72	
		Topical <sup>2</sup>	12	60	6	32.9	2088	2098	21.3	ND	ND	4	
Rat	Male	IV	1	1234	0.083	29	4917	4933	27	0.2	6	NA	RDS.03.SRE.31004
		Oral	1	111	1	28	1981	2033	36	ND	ND	41	
		Topical <sup>2</sup>	20	17	216	ND	1787	ND	ND	ND	ND	2	
	Female	IV	0.5	432	0.2	16.9	2999	3026	15	0.17	3.5	NA	RDS.03.SRE.4754
		Oral	0.5	47	6	17.8	688	743	12	ND	ND	25	
		Topical <sup>2</sup>	0.5	480	0.2	20.6	2535	2607	18	0.19	5.0	NA	
Dog <sup>1</sup>	Male	IV	1	2030	0.083	41	19360	19712	38	0.05	2.2	NA	RDS.03.SRE.31005
		Oral	1	257	5	38	5207	5334	32	ND	ND	30	
		Topical <sup>2</sup>	20	16	168	ND	1458	ND	ND	ND	NA	0.4	
	Female	IV	0.5	1154	0.1	49	11764	11924	45	0.04	2.2	NA	RDS.03.SRE.4755
		Oral	0.5	183	2.0	40	4758	4904	29	0.10	4.3	41	
		Topical <sup>2</sup>	0.5	1380	0.1	71	13741	14097	61	0.04	2.6	NA	
Minipig <sup>1</sup>	Male	IV	0.5	653	0.15	ND	2432	2450	12.5	0.22	2.3	NA	RDS.03.SRE.4766
		Oral	0.5	149	2.0	54	4071	4191	48	0.12	8.0	30	
		Topical <sup>2</sup>	5	BLQ	ND	ND	ND	ND	ND	ND	ND	ND	
	Female	IV	0.5	1146	0.09	ND	3708	3727	17.6	0.15	1.7	NA	RDS.03.SRE.31025
		Oral	0.5	BLQ	ND	ND	ND	ND	ND	ND	ND	ND	
		Topical <sup>2</sup>	5	BLQ	ND	ND	ND	ND	ND	ND	ND	ND	
Minipig <sup>1</sup>	Male	Topical (28 days repeated)	5	2.98	9	ND	57.5 <sup>3</sup>	ND	ND	ND	ND	ND	RDS.03.SRE.31025
		Topical (28 days repeated)	5	3.32	2	ND	65.8 <sup>3</sup>	ND	ND	ND	ND	ND	

<sup>1</sup>: Mean value; <sup>2</sup>: Formulation: Propylene glycol/ ethanol (60/40, w/w); <sup>3</sup>: AUC<sub>0-24h</sub> values

NA: Not Applicable; ND: Not Determined; BLQ: Below lower limit of quantification (0.2 ng/mL).

## Distribution

[<sup>3</sup>H]-ivermectin showed high plasma protein binding in vitro (99.9% over the range of 5 to 500 ng/ml) in the mouse, rat, rabbit, dog, minipig and human. [<sup>3</sup>H]-ivermectin demonstrated low in vitro partitioning into red blood cells, with a blood-to-plasma ratio below 0.1 in the mouse, rat, rabbit, dog and human, and below 0.2 in the minipig. High values of volume of distribution were noted (1.7-6.0 l/kg, refer to the table above) in the mouse, rat, dog or minipig after a single IV dose, indicating extensive tissue distribution. Following a single IV administration of [<sup>3</sup>H]-ivermectin to SD rats, the highest concentrations of radioactivity were detected in the kidney, liver, lung, myocardium, and thyroid gland. In all animals, no radioactivity was detected in the brain indicating no or limited penetration of the blood brain barrier.

The tissue distribution of CD5024 was assessed in SD rats after single or repeated daily dermal application of 1% [<sup>3</sup>H]-CD5024 cream (1.2 g/kg 1% cream applied to ~13% BSA 6 hr daily, for one day or 8 days, respectively). After the single dose, the total radioactivity in plasma and blood was below the LOQ (17 ngeq/g). High radioactivity level (>1000 ngeq/g) was achieved only in three tissues/organs, including brown adipose, large intestine, and washed treated skin. The presence of high radioactivity in large intestine was probably due to oral ingestion (from licking the treated sites). CD5024 is a lipophilic compound, which explains the high radioactivity in adipose tissue. The results indicated that dermal absorption of CD5024 is slow and the residence time in skin is long (a reservoir effect). After repeated dermal application, the radioactivity was widely distributed in all organs and tissues, except for the brain, bone, scapula, pituitary gland, spinal cord and bone marrow where the concentrations were all or almost all below LOQ. The gastrointestinal tract (content and/or tissues) presented high and variable levels of radioactivity at different sacrifice times, which suggested oral

ingestion. The radioactivity in the treated skin and adipose tissue were higher than others and its decline was slow. Overall in the majority of tissues/organs radioactivity levels at 168 hr postdose declined to below LOQ. The cumulated amount of radioactivity in all removed tissues/organs was low (less than 5% of administered dose).

The placental transfer of drug-related radioactivity was investigated in rats. A single oral dose of 1 mg/kg [<sup>3</sup>H]-CD5024 was administered to pregnant SD rats on gestation Day 13 (end of organogenesis). [<sup>3</sup>H]-CD5024 was rapidly absorbed in different organs and tissues with a T<sub>max</sub> of 3 hr for the plasma, blood and liver, and 7 hr for the other tissues/organs. Maternal tissues/organs exposures were ~3 to 9 fold higher than those in the maternal plasma. Maternal liver, kidney, and mammary tissue contained the highest tissue concentration of radioactivity. The placenta exposure was ~3 times higher than the plasma exposure. The high exposure level in the mammary gland (approximately 10 times the plasma level based on AUC) is in accordance with the fact that ivermectin is known to be quantitatively transferred to milk. The lowest concentrations obtained at 96 hr were in amniotic fluid and fetuses. The exposure ratio between the tissues/organs and the maternal plasma were all higher than 1 except for the amniotic fluid and the fetus (0.11 and 0.27 respectively). A maximum of 0.011% of the administered dose was recovered in the whole fetuses and 0.24% in the whole fetal placenta (at 7 hr postdose). The transfer of CD5024 through placenta was very low.

## Metabolism

### In vitro

In vitro incubation of [<sup>3</sup>H]-ivermectin with cryopreserved hepatocytes indicated that the predominant routes of metabolism were similar in the CD1 mouse, SD rat, Beagle dog, Göttingen minipig and humans. After 2 hours of incubation, the metabolism of ivermectin exceeded 75% in the mouse and minipig. Slower metabolism was recorded in the dog, in humans, and in the rat with values of 38%, 30% and 15%, respectively. Five metabolites were detected across species. The apparent metabolic pathway was mainly phase I with no apparent glucuro- or sulfo-conjugates being observed. All major metabolites formed in vitro by human hepatocytes were also formed in vitro by the hepatocytes of at least one of the animal species included in this study. The five metabolites were further characterized in a human liver microsome study. These metabolites were tentatively identified as the following:

- Metabolite M1: 3''-O-desmethyl ivermectin
- Metabolite M2: 4a-hydroxy ivermectin
- Metabolite M3: O-desmethyl hydroxy ivermectin
- Metabolite M4: hydroxy ivermectin (isomer of M2 )
- Metabolite M5: O-desmethyl hydroxy ivermectin (isomer of M3)

The in vitro metabolism of ivermectin has been also studied using an extensive panel of recombinant cytochrome P450 enzymes. CYP3A4 was identified as the enzyme primarily responsible for the metabolism of [<sup>3</sup>H]-ivermectin to the major metabolites M1,

M2, and M3/M4. The potential for ivermectin to inhibit the activity of the main cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11) has been investigated in human liver microsomes. This study demonstrated that ivermectin caused a direct inhibition of CYP2B6 and CYP3A4/5 with an IC<sub>50</sub> value of 6.3 µM (5.5 µg/ml) and 12 µM (11 µg/ml), respectively. In addition, there was evidence of direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP4A11 by ivermectin, as 38%, 35%, 24%, 17%, and 28-32% inhibition was observed at an ivermectin concentration of 12 µM (11 µg/ml), respectively. However, the IC<sub>50</sub> value for these enzymes could not be estimated and was reported as greater than 12 µM.

In another in vitro study designed to investigate the induction effects on CYP enzymes (CYP1A2, CYP2B6, CYP2C9, and CYP3A4), ivermectin at concentrations up to 0.4 µM did not cause an increase in the CYP enzyme activities or their mRNA levels in primary human hepatocyte cultures.

#### *Discussion:*

Ivermectin showed an inhibitory effect on CYP3A4, which is also the primary enzyme of its metabolism. This elicited a concern that repeat administration of ivermectin might cause marked drug accumulation. However, TK results in chronic oral toxicology studies (a 27-week oral toxicity study in rats and a 39-week oral toxicity study in dogs) showed that the drug accumulation was not very significant, especially at higher doses. The drug accumulation noted at the chronic dermal toxicity study in minipigs might be partly due to the fact that skin has a reservoir effect for ivermectin, as mentioned in the distribution section. Overall the TK data from animal studies alleviated this concern. Moreover, the results of the in vitro CYP induction study (RDS.03.SRE.31038) demonstrated that treatment with CD5024 at concentrations up to 0.4 µM [i.e. 87 times higher than the C<sub>max</sub> (4.02 ng/ml corresponding to 4.6 nM) in rosacea subjects under maximum clinical use conditions] did not affect CYP3A4 activity in microsomes isolated from cultured hepatocytes. Therefore a clinical impact of this enzyme inhibition is unlikely to occur under clinical use conditions.

#### In vivo

The in vivo metabolism of ivermectin has been studied following IV and/or oral administration in the rat, dog and minipig. The major metabolic pathways were O-demethylation at the disaccharide moiety and oxidation at two different positions. M1 and M2 were identified as major metabolites in humans in a maximum use clinical PK trial (structures shown in the following figure). After daily topical administration of ivermectin 1% cream in subjects with rosacea (1 g/day), the relative AUC<sub>0-24h</sub> percentage of M1, M2, and M3/M4 compared to ivermectin was 12%, 12%, and 3% on Day 14, and 10%, 12%, and 4% on Day 28, respectively. The main metabolites found in humans were present in at least one toxicology species.

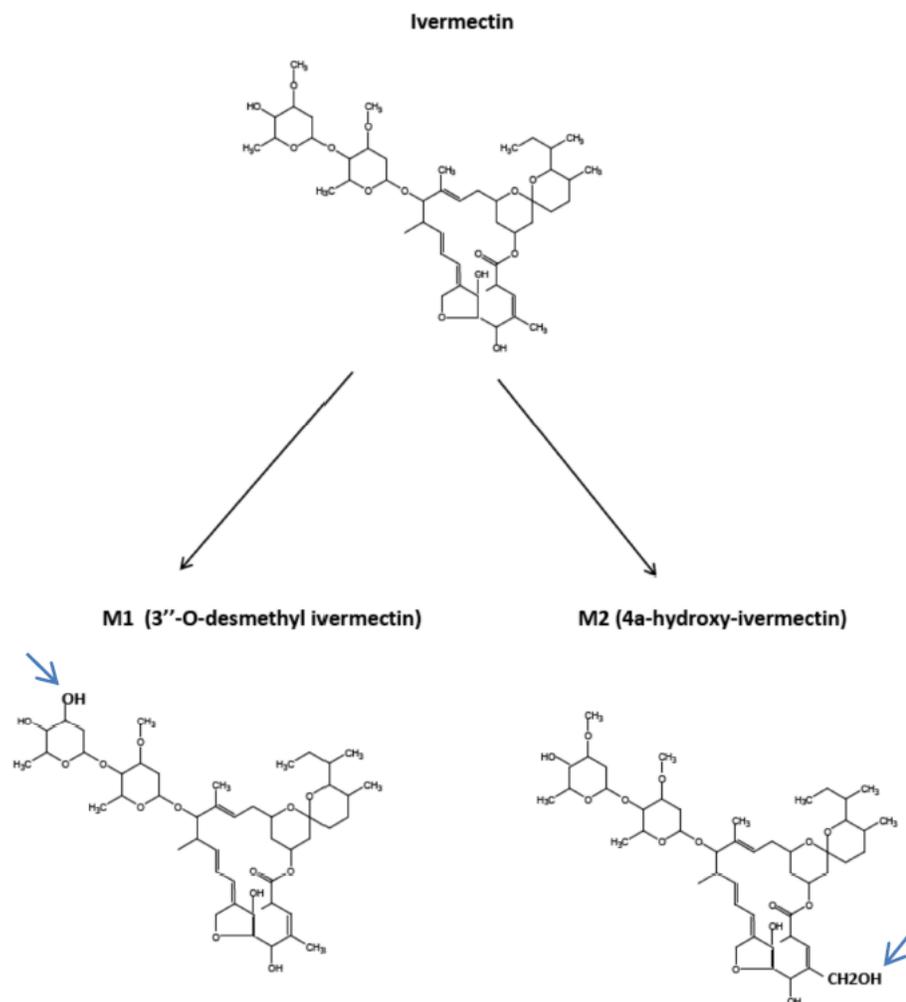


Figure 1. Main metabolic pathways of ivermectin.

In rats, the fraction of ivermectin that was metabolized was about 50% after IV or oral administration. M1 and M2 were also identified as the major metabolites in rats. The pharmacokinetics of M1 and M2 has been evaluated in a 14-day oral PK study in rats. PK parameters for M1 and M2 after repeat oral dose of 3 mg/kg/day for 14 days are shown in the table below.

Route of administration	Oral					
Dose (mg/kg/day)	3					
Compound	Ivermectin		O desmethyl metabolite (M1)		Monohydroxy metabolite (M2)	
Sex	Male	Female	Male	Female	Male	Female
T <sub>max</sub> (h)	3.00	3.00	6.00	6.00	3.00	6.00
C <sub>max</sub> (ng/mL)	708	841	296	187	43.4	48.0
T <sub>Last</sub> (h)	24.0	24.0	24.0	24.0	24.0	24.0
AUC <sub>last</sub> <sup>a</sup> (ng.h/mL)	10900	11900	5900	3360	742	752
Metabolic ratio <sup>b</sup>	NA	NA	0.551	0.286	0.0669	0.0619

NA : Not applicable

<sup>a</sup> AUC<sub>last</sub> corresponding to AUC<sub>0-24h</sub>

<sup>b</sup> Calculated from AUC<sub>last</sub> and normalized by the molecular weight

In vivo metabolism of ivermectin was assessed in the dog after single oral and IV administration of [<sup>3</sup>H]-ivermectin (0.5 mg/kg). The systemic exposure of radioactivity (AUC<sub>last</sub>, total radioactivity) was 2 fold (IV route) to 3 fold (oral route) higher than that of unchanged ivermectin (AUC<sub>last</sub>, ivermectin), suggesting that the majority of ivermectin was metabolized after IV and oral administration. The mean percentages of sample radioactivity of main metabolites in dog plasma were shown in the table below.

Metabolite <sup>a</sup>	Oral Route	Intravenous Route
O-desmethyl-ivermectin	34.99%	20.56%
Monohydroxy-ivermectin	6.29%	4.64%
O-desmethyl monohydroxy-ivermectin	17.98%	18.05%

<sup>a</sup> Identified by LC-MS/MS

In minipigs, the metabolic profile of ivermectin after a single topical application could not be determined in plasma or fecal samples due to very limited percutaneous absorption. After IV dosing, the systemic exposure of the metabolic pool was about twice that of the unchanged ivermectin. In plasma samples, the O-demethylated metabolite was the major metabolite. In fecal samples, two main metabolites were identified: the 3''-O-desmethyl-monohydroxy and the 3''-O-desmethyl ivermectin, accounting for approximately 58% and 10% of the eluted radioactivity, respectively. Unchanged ivermectin accounted for 2% to 17% of sample radioactivity.

#### Discussion:

The clinical PK data obtained from the maximum use clinical PK trial (refer to the clinical PK data section below) showed that the systemic exposure to ivermectin was similar at Days 14 and 28, indicating a steady state was reached by Day 14. Similarly, there was no significant difference between the Day 14 and Day 28 AUC<sub>0-24h</sub> values of M1 (Day 14: 5.18 ng•h/ml; Day 28: 4.25 ng•h/ml) or M2 (Day 14: 4.21 ng•h/ml; Day 28: 4.08

ng•h/ml). Hence Day 14 AUC values for M1 and M2 in human subjects could be used in the comparison with AUC values obtained from the 14-day PK study in rats. At an oral dose level of 3 mg/kg/day, the systemic exposure to M1 and M2 in rats was approximately 650 and 180 times that in human subjects under maximum clinical use conditions. In addition, per the 08/03/2011 nonclinical review under IND 76064 (by this reviewer), in a metabolite exposure comparison across species (rat, dog, minipig, and human), the systemic exposure to M1 and M2 in animals was not disproportionately lower than that in human subjects. The metabolite contribution to the overall toxicity assessment in animal test species has been established.

### Excretion

In the studied species, mouse, rat, dog and minipig, following single IV administration, ivermectin has a low plasma clearance (0.23, 0.20, 0.05, and 0.18 l/h/kg in mouse, rat, dog and minipig, respectively). The low clearance resulted in a long elimination half-life (9 hr in the mouse, 15-27 hr in the rat, 38-61 hr in the dog, and 12.5 and 17.6 hr in the male and female minipig, respectively). After topical application, the apparent terminal elimination half-life in mice was ~21 hr.

After IV administration in the rat, the majority of radioactivity was recovered within 48 hr, and the excretion balance was almost complete over 10 days (95%). Radioactivity was almost exclusively eliminated in feces (91% of the administered dose), urinary excretion being a minor route. The high proportion of the dose excreted via feces after IV administration suggested that biliary excretion is the major route of elimination. Unchanged ivermectin and O-demethylated and monohydroxylated metabolites were the main components measured in feces. In the dog and minipig, the overall elimination profile was similar. The predominance of fecal excretion across species confirms extensive biliary elimination of ivermectin and its metabolites.

After a 6-hour topical application of [<sup>3</sup>H]-ivermectin 1% cream in minipigs, the percentage of absorbed dose was 0.4% in males and 0.2% in females and confirmed a low absorption of the total radioactivity through the skin. The majority of absorbed radioactivity was excreted in the feces whereas no radioactivity was found in the urine. The majority of the fecal radioactivity was recovered within the first 72 hr of dose administration.

Ivermectin is excreted in milk in significant amounts and for extended periods of time in several species. In a published PK study in rats treated with radiolabelled ivermectin, radioactivity recovered in milk from dams was 3 to 4 times higher than that obtained from plasma samples (Food Chem Toxicol. 1989;27:523-9; refer to Section 9.3).

### Clinical PK data

Clinical PK data were used in the calculation of multiples of human exposure. In the maximum use clinical PK trial (RD.03.SRE.40064), 1 g ivermectin 1% cream was applied to the face of subjects with severe papulopustular rosacea once daily for 4 weeks. The

PK results (confirmed by the clinical pharmacology reviewer, Dr. Chinmay Shukla) are shown in the copied table below.

Parameters	Day 0 <sup>(a)</sup>	Day 7 <sup>(b)</sup>	Day 14	Day 21	Day 28
<b>Pre-dose/Cmin (ng/mL)</b>					
Mean±SD	0.37±0.21	1.17±0.88	1.26±0.53 <sup>c</sup>	1.36±0.66 <sup>c</sup>	1.36±0.63
Min to Max	[0.17 to 0.86]	[0.56 to 3.26]	[0.58 to 2.34]	[0.66 to 3.25]	[0.53 to 3.00]
<b>C<sub>max</sub> (ng/mL)</b>					
Mean±SD	0.69±0.49	NA	2.10±1.04	NA	1.74±0.77
Min to Max	[0.19 to 1.76]		[0.69 to 4.02]		[0.58 to 3.36]
<b>T<sub>max</sub> (h)</b>					
Mean±SD	9±6	NA	10±8	NA	11±4
Min to Max	[1 to 24]		[0 to 24]		[3 to 24]
<b>AUC<sub>0-24h</sub> (ng.h/mL)</b>					
Mean±SD	9.29±5.40	NA	36.14±15.56	NA	35.43±14.42
Min to Max	[3.16 to 21.28]		[13.69 to 75.16]		[12.89 to 70.08]

NA=Not applicable

<sup>a</sup> N=17; <sup>b</sup> N=13; <sup>c</sup> N=14

## 5.2 Toxicokinetics

Included in toxicology studies.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

Two single oral dose toxicity studies were conducted with ivermectin in mice and rats. The results showed that the oral LD<sub>50</sub> for ivermectin was higher than 40 mg/kg in mice (1/10 mice was euthanized on Day 2 due to morbidity at this dose) and between 40 and 60 mg/kg in female rats. Clinical signs related to CNS toxicity (reduced motor activity, piloerection, half closed eyes) were noted in both studies.

### 6.2 Repeat-Dose Toxicity

1. Ivermectin cream 0.1, 0.3, and 1% (w/w) 4-week dermal toxicity study in CD1 mice (Study# RDS.03.SRE.8552)

Topical doses of ivermectin 0 (vehicle), 2, 6 and 20 mg/kg/day [0.1%, 0.3%, and 1% ivermectin cream applied to ~10% BSA (unoccluded) at a dose volume of 2 ml/kg/day] were administered to CD-1 mice (5/sex/dose for main study) once daily for 4 weeks. Treatment-related mortality and clinical signs were noted in this study. One low dose male was sacrificed moribund on Day 13, one mid dose male was sacrificed moribund on Day 12 and two high dose males were sacrificed moribund on Days 7 and 8.

Hunched posture, reduced motor activity, piloerection, slow respiration, decreased feces production, wasted condition, cold to touch and tremor were noted in animals sacrificed moribund. No treatment-related effects on dermal irritation, body weights, food consumption, clinical pathology, gross pathology, organ weights, or histopathology (only performed for skin and gross lesions) were noted in this study. A NOAEL could not be identified in this study.

2. Ivermectin - 13 week dermal dose-range finding study in the mouse (Study# RDS.03.SRE.12500)

This study was conducted as a dose range-finding study for a subsequent 2-year dermal mouse carcinogenicity study. Topical doses of ivermectin 0 (water), 0 (vehicle), 1, 3 and 10 mg/kg/day [0.1%, 0.3%, and 1% ivermectin cream applied (unoccluded) at a dose volume of 1 ml/kg/day; 1% is the maximum feasible concentration in this formulation] were administered to CD-1 mice (12/sex/dose for main study, 18/sex/dose for TK animals) for 13 weeks. No treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 10 mg/kg/day, 1% cream applied at 1 ml/kg/day (Day 87 AUC<sub>0-24hr</sub> values: 32493 ng·hr/ml in males and 27408 ng·hr/ml in females), the highest dose tested in this study. Topical doses of 0 (untreated control), 0 (vehicle control), 1, 3 and 10 mg/kg/day ivermectin (0.1%, 0.3%, and 1% ivermectin cream applied at a dose volume of 1 ml/kg/day) were recommended for the 2-year dermal mouse carcinogenicity study.

TK results:

Dose (mg/kg/day)	Concentration (%)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
		Males	Females	Males	Females	Males	Females
Day 1							
1	0.1	143	167	6	2.5	2229	1873
3	0.3	413	352	10	10	5619	5110
10	1	743	1167	24	10	13345	14807
Day 87							
1	0.1	237	163	6	6	3459	2183
3	0.3	1006	441	10	10	14392	5583
10	1	2183	1584	10	10	32493	27408

3. Thirteen-week topical range-finding study of Ivermectin cream and Ivermectin placebo cream in hairless mice, with or without simulated sunlight (Study# RDS.03.SRE.12519)

This study was conducted as a dose range-finding study for a subsequent 1-year photocarcinogenicity study in hairless mice. Topical doses of ivermectin 0 (untreated), 0 (vehicle), 25, 50, 75, 150, 250, and 500 µg/day (0.1%, 0.3%, and 1% ivermectin cream applied at a dose volume of 25 or 50 µl/day) were administered to Crl:SKH1-*hr*

albino hairless mice (6/sex/dose) with or without UVR, once daily, 5 days per week, for 13 weeks. Test articles were applied at one hour before UV exposure on Monday, Wednesday and Friday, and at one hour after UV exposure on Tuesday and Thursday, for each week. The UV source was a 6.5 kw xenon long arc burner, which delivered a UVR dose of 600 Robertson-Berger Units (RBU) per week (120 RBU per treatment).

One male and two females in the group of high dose without UVR and one male and two females in the group of high dose with UVR were sacrificed moribund in the first week. Tremors, decreased motor activity, bradypnea, hunched posture, and dehydration were noted in these mice. Necropsy of these mice revealed that all tissues appeared normal macroscopically. Based on this mortality, test article administration at high dose (50 µl/day 1.0% cream) was stopped in the second week. Repeat topical administration of vehicle, with or without UVR, elicited skin reactions indicative of a mild irritation including erythema, flaking, wrinkling and thickening. Treatment with ivermectin cream elicited similar skin reactions, indicating the mild irritation was probably a vehicle effect.

A single skin tumor ( $\leq 1$  mm in planar diameter) was observed in one male treated with 25 µl/day 0.3% cream (without UVR), one male treated with 50 µl/day 0.3% cream (with UVR), one female treated with 25 µl/day 1.0% cream (without UVR) and one female treated with 50 µl/day 0.1% cream (with UVR). The occurrences were not dose-dependent and the result was not conclusive. The nature of these skin tumors is unknown because histology was not examined.

*Reviewer's comment:* Per the ICH M3(R2) guidance document, we no longer recommend conduct of photocarcinogenicity studies for topical drug products. However, the recommendation for conduct of a photocarcinogenicity study with this drug product was made prior to implementation of the ICH M3(R2) guidance document so the dose range-finding study and subsequent photocarcinogenicity study are reviewed in this document.

4. Ivermectin 1% cream: 4-week dermal toxicity study in Sprague Dawley rat (Study# RDS.03.SRE.8547)

Topical doses of ivermectin 0 (vehicle) and 20 mg/kg/day (1% ivermectin cream applied to ~10% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered to SD rats (10/sex/dose) for 4 weeks. No treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 20 mg/kg/day, 1% cream applied at 2 ml/kg/day (Day 28 AUC<sub>0-24hr</sub> values: 18370 ng·hr/ml in males and 33566 ng·hr/ml in females), under the study conditions.

TK results:

Dose (mg/kg/day)	Concentration (%)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
		Males	Females	Males	Females	Males	Females
Day 1							
20	1	141	390	24	8	2645	7057
Day 28							
20	1	970	1706	8	8	18370	33566

5. A 13-week oral toxicity study in rats (Study# RDS.03.SRE.12413)

Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.3, 1.0 and 3.0 mg/kg/day were administered to Wistar rats (10/sex/dose for main study, 6/sex/dose for TK animals) for 13 weeks. No treatment-related effects on mortality, clinical signs, body weight, food consumption, functional observational battery, locomotor activity, ophthalmology, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 3.0 mg/kg/day (Day 28 AUC<sub>0-24hr</sub> values: 7786 ng·hr/ml and 7470 ng·hr/ml in males and females, respectively), the highest dose tested in this study.

TK results:

Dose (mg/kg/day)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
0.1	8.3	4.9	3	5	97.1	68.0
0.3	28.9	20.2	5	3	496	285
1.0	159	83.4	3	5	2041	1122
3.0	417	367	5	3	4770	4803
Day 88						
0.1	11.0	8.8	5	5	167	134
0.3	45	31	5	3	580	497
1.0	240	140	3	5	2949	2107
3.0	558	508	5	3	7786	7470

6. Ivermectin – 13 week oral (gavage) dose-range finding study in the rat (Study# RDS.03.SRE.12505)

In order to determine the MTD and help dose selection for a subsequent oral carcinogenicity study, a second 13-week oral rat toxicity study was conducted. Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3, 9 and 12 mg/kg/day were administered to Wistar rats (10/sex/dose for main study, 6/sex/dose for TK animals) for 13 weeks. The animals used in this study were younger than the animals used in the first 13-week study (5 weeks of age vs. 8 weeks of age). Treatment related mortality was noted in the mid-high and high dose groups during the first two weeks of treatment. Two mid-high dose females (one main and one TK animal), four

high dose males (2 main and 2 TK animals) and seven high dose females (4 main and 3 TK animals) were sacrificed moribund due to severe clinical signs, body weight loss and decreased food consumption. Treatment related effects on clinical chemistry parameters (increased glucose, cholesterol and ALP levels, decreased triglyceride levels) were noted in the mid-high and high dose groups compared to the control group at the end of the treatment period.

A dose-dependent decrease in seminal vesicle weight was noted in mid-low, mid-high and high dose males (-19-30%) compared to control males. Increased liver weights (+8-15%) were noted in mid-high and high dose animals compared to control animals. Histopathological findings included: a slight decrease of seminal vesicle secretion noted in one mid-low dose male, two mid-high dose males and two high dose males; a minimal decrease of prostate secretion noted in one mid-low dose male, three mid-high dose males and one high dose male; and minimal to slight apoptosis in the thymus noted in one mid-low dose male, 5 mid-high dose animals (4 males, 1 female) and 6 high dose animals (3 males, 3 females).

The NOAEL was identified as the low dose, 1 mg/kg/day (Day 91 AUC<sub>0-24h</sub> values: 1629 ng·hr/ml in males and 1431 ng·hr/ml in females), under the conditions of this study. Based on the results of this study, oral doses of 0 (vehicle), 1, 3 and 9 mg/kg/day ivermectin were recommended for the 2-year carcinogenicity study based on MTD.

TK results:

Dose (mg/kg/day)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
1	81.6	91.5	9	3	1417	1337
3	488	497	5	3	6863	7286
9	1833	1633	5	5	20752	30649
12	1703	2066	9	5	26737	43115
Day 91						
1	128	112	5	3	1629	1431
3	695	805	5	3	8876	10296
9	2758	2062	5	5	42647	30649
12	2642	2689	5	5	42658	43115

7. Ivermectin - 27-week oral (gavage) toxicity study in the rat (Study# RDS.03.SRE.12537)

Initially oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3 and 12 mg/kg/day were administered to Wistar rats (20/sex/dose) for 27 weeks. The high dose, 12 mg/kg/day, was reached by dose titration (6 mg/kg/day on first three days, 9 mg/kg/day on the next 4 days, 12 mg/kg/day thereafter). Because of severe clinical signs observed at high dose, two additional groups [Control 2 (vehicle) and low dose 2 (0.1 mg/kg/day)] were added starting Day 49.

Mortality was noted at 3 mg/kg/day (1 male) and 12 mg/kg/day (3 males and 12 females). High dose animals had marked clinical signs, first noted after the second or third administration at the final high dose and were noted for up to 5 and 9 days for males and females, respectively, which included subdued behavior, thin appearance, piloerection, red stained, rough and soiled fur, abnormal chewing and hypersalivation, and tremor. Decreased body weight gain or even weight loss was noted at 3 and 12 mg/kg/day during the first two weeks. Thereafter weight gains were generally similar to controls and the overall weight gain of high dose males and females during Days 0-188 was 6% and 10% lower than control. On Day 86 a decrease in lymphocyte count was noted in females treated with 3 or 12 mg/kg/day. Histopathology findings included slight white matter vacuolation in brain and cervical spinal cord (only in early decedent females at 12 mg/kg/day, but not in early decedent males or in scheduled sacrifice), minimal mucosal hyperplasia and minimal to slight increase of lymphoid cells in the lamina propria of cecum (in mid-high and high dose males and in mid-low, mid-high, and high dose females), minimal decreased secretion in seminal vesicles (in mid-low, mid-high, and high dose males and in one low dose male).

It appeared that the high dose induced significant toxicity during the first 2 weeks, especially in females, followed by a clear habituation to the toxicity and partial recovery. At the dose of 0.1 mg/kg/day, the only noteworthy effect was minimal decreased secretion in seminal vesicles seen in 1/20 male. At the dose of 1 mg/kg/day, the notable effects were minimal decreased secretion in seminal vesicles seen in 2/20 males and minor microscopic findings in cecum seen only in females. The low dose, 0.1 mg/kg/day, is considered the NOAEL in this study (Week 27 AUC<sub>0-24h</sub> values: 173 ng·h/ml in males and 204 ng·h/ml in females).

TK results:

	Dose mg/kg/day	Sex	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>(0-24h)</sub> (ng.h/mL)	AUC <sub>(0-24h)</sub> Dose (h.kg/L)
Day 0	0.1	Male	6.8	3	80.8776	0.81
		Female	6.7	5	95.2767	0.95
Week 13	0.1	Male	22.98	3	308.813	3.09
		Female	26.51	5	313.011	3.13
	1	Male	264.52	5	2811.68	2.81
		Female	204.91	5	2964.03	2.96
	3	Male	1125.52	5	12017.3	4.01
		Female	1121.41	3	12671.3	4.22
	12	Male	3271.74	3	48560.4	4.05
		Female				
Week 27	0.1	Male	14.14	3	173.017	1.73
		Female	14.5	5	204.023	2.04
	1	Male	292	5	3886.35	3.89
		Female	308.81	5	4280.01	4.28
	3	Male	1067.87	5	13939.8	4.65
		Female	936.91	3	14434.8	4.81
	12	Male	3606.25	3	55151.7	4.60
		Female				

8. Ivermectin – 4-week oral (gavage) dose range-finding toxicity study in Beagle dog (Study# RDS.03.SRE.12514)

Initially (Phase 1) oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 3 and 9 mg/kg/day were administered to Beagle dogs (2/sex/dose). Dosing of Phase 1 was stopped after 2 days in high dose animals and after 9 days for the rest due to mortality. Subsequently in Phase 2 oral (gavage) doses of 0 (vehicle), 1.5 and 2.5 mg/kg/day were administered (2 dogs/sex/dose) once daily for 28 days. In Phase 1 all high dose animals were euthanized moribund on Day 2. One low dose female was euthanized moribund on Day 6. In Phase 2 one high dose male and one high dose female were sacrificed moribund on Day 8. Treatment related clinical signs included lying down, tremors, subdued appearance, hypersensitivity, closed eyes, slow breathing, unsteady gait, dilated pupils and hypersalivation. Body weight loss and decreased food consumption was noted in all treatment groups. No treatment-related effects on ECG, clinical pathology, or gross pathology were noted. Histological examination was not performed. A NOAEL was not identified in this study.

TK results:

Dose (mg/kg/day)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
1.5	572	458	3	3	6012	5516
2.5	869	902	3	3	10431	10010
Week 4						
1.5	843	1555	2	3	10844	25095
2.5	700	2049	3	3	27898	11147

9. A 13-week oral toxicity study in dogs (Study# RDS.03.SRE.12426)

Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.25, 0.5 and 1.5 mg/kg/day were administered to Beagle dogs (4/sex/dose) for 13 weeks. No treatment-related effects on mortality, food consumption, ophthalmology, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. A higher incidence of excessive salivation was noted in high dose animals. Decreased body weight was noted in high dose animals (males: -11%; females: -4%) compared to control animals. The NOAEL was identified as 0.5 mg/kg/day (Day 90 AUC<sub>0-24hr</sub> values: 5629 ng·hr/ml in males and 4166 ng·hr/ml in females), under the study conditions.

TK results:

Dose (mg/kg/day)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
0.1	39	27	3.5	3	471	361
0.25	96	102	3	3	1128	1152
0.5	195	209	2.5	3	2282	2494
1.5	906	635	3	3	11376	8037
Day 90						
0.1	45	45	3	2	749	749
0.25	183	146	3	3	2801	2322
0.5	365	282	3	3	5629	4166
1.5	1579	1029	3	4.5	23547	19385

10. Ivermectin - 39-week oral (gavage) toxicity study in the beagle dog (Study# RDS.03.SRE.12511)

Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.5, and 1.5 mg/kg/day were administered to Beagle dogs (4/sex/dose) for 39 weeks. No treatment-related effects on mortality, hematology, urinalysis, ECG, gross pathology, or histopathology examination were noted in this study. Dilated pupils were noted in high dose animals from the first or the second week of administration. The mydriasis was

observed until the end of study but was generally reversible between daily treatments. Hypersalivation was also noted in high dose animals. A body weight loss was observed in both high dose males and females during the first week of dosing. In a high dose female, a marked increase in AST (22 fold) and ALT (50 fold) levels was noted on Day 89, but then the increased levels gradually returned to normal range a few weeks later. Without histological findings in the liver, the isolated changes in a single animal were considered incidental.

The NOAEL was identified as 0.5 mg/kg/day (Week 39 AUC<sub>0-24hr</sub> values: 4154 ng·hr/ml in males and 7000 ng·hr/ml in females), under the study conditions.

TK results:

Gender/ Ivermectin dose (mg/kg/day)	AUC <sub>0-24h</sub> (ng.h.mL <sup>-1</sup> )			Cmax (ng.mL <sup>-1</sup> )			Tmax (h)	
	Day 0	Week 39	Week 39/D0 Ratio	Day 0	Week 39	Week 39/D0 Ratio	Day 0	Week 39
Males (n=4)								
0.1	195	402	2.1	18.40	26.97	1.5	3.0	3.0
0.5	1848	4154	2.2	175.03	286.43	1.6	3.0	3.0
1.5	5635	16293	2.9	489.44	1085.41	2.2	3.0	3.0
Females (n=4)								
0.1	201	762	3.8	18.35	51.98	2.8	3.0	3.0
0.5	2055	7000	3.4	181.49	476.69	2.6	3.0	3.5
1.5	5936	19363	3.3	509.67	1348.94	2.6	3.0	3.5

11. Ivermectin 1% (w/w) cream preliminary 4-week dermal study in minipigs (Study# RDS.03.SRE.12447)

Topical doses of ivermectin 0 (vehicle) and 5 mg/kg/day (1% ivermectin cream applied to ~10% BSA, occluded, at a dose volume of 0.5 ml/kg/day) were administered to Gottingen minipigs (4/sex/dose) for 4 weeks. No treatment-related effects on mortality, clinical signs, dermal irritation, body weight, food consumption, ophthalmology, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 5 mg/kg/day, 1% cream applied at 0.5 ml/kg/day (Day 28 AUC<sub>0-24hr</sub> values: 38.1 ng·hr/ml in males and 46.1 ng·hr/ml in females), under the study conditions.

TK results:

Dose (mg/kg/day)	Concentration (%)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
		Males	Females	Males	Females	Males	Females
Day 1							
5	1	NC	NC	NC	NC	NC	NC
Day 28							
5	1	1.69	2.10	0.5	12.8	38.1	46.1

NC = not calculated

12. Ivermectin – 13-week dermal toxicity study in the minipig (Study# RDS.03.SRE.12491)

Topical doses of ivermectin 0 (vehicle), 2, 6 and 20 mg/kg/day (0.1, 0.3 and 1% ivermectin cream applied to ~10% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered to Gottingen minipigs (5/sex/group) for 13 weeks. No treatment-related effects on mortality, clinical signs, dermal irritation, body weight, food consumption, ophthalmology, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 20 mg/kg/day, 1% cream applied at 2 ml/kg/day (Day 91 AUC<sub>0-24hr</sub> values: 95.4 ng·hr/ml in males and 161.9 ng·hr/ml in females), the highest dose tested in this study.

TK results:

Dose (mg/kg/day)	Concentration (%)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hours)		AUC <sub>0-24 hr</sub> (ng·hr/ml)	
		Males	Females	Males	Females	Males	Females
Day 1							
2	0.1	0.1	0.0	24.0	NC	1.2	0.0
6	0.3	1.8	0.6	20.5	22.0	29.7	7.6
20	1	4.4	3.8	17.2	4.0	63.7	56.7
Day 91							
2	0.1	0.8	2.2	7.4	10.0	15.6	34.9
6	0.3	4.0	4.6	6.2	9.8	77.7	77.6
20	1	5.1	8.1	6.8	4.8	95.4	161.9

13. Ivermectin - 9-month dermal toxicity study in the minipig (Study# RDS.03.SRE.12510)

Topical doses of ivermectin 0 (vehicle), 2, 6 and 20 mg/kg/day (0.1, 0.3 and 1% ivermectin cream applied to ~20% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered to Gottingen minipigs (4/sex/group) for 9 months. A high dose male was euthanized moribund due to sudden severe clinical signs noted on Day 83: dark red staining on flanks, presence of blood in pen (urinary origin), liquid feces, weakness, and reduced activity. Laboratory tests mainly showed a marked anemia, an elevated urea level, and a marked decrease in platelet count. Histopathological examination

showed hemorrhagic syndrome involving multiple organs. The diagnosis was thrombocytopenic purpura syndrome, which was known in Göttingen minipigs. Because there were no similar findings in other animals in this study, this early death was not considered treatment-related. No treatment-related effects on mortality, clinical signs, dermal irritation, body weight, ophthalmology, blood pressure, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 20 mg/kg/day, 1% cream applied at 2 ml/kg/day (Week 39 AUC<sub>0-24hr</sub> values: 66.5 ng·hr/ml in males and 139.5 ng·hr/ml in females), the highest dose tested in this study.

TK results (based on Amendment 1 of the study report):

Dose (mg/kg/day)	Concentration (%)	C <sub>max</sub> (ng/ml)		T <sub>max</sub> (hr)		AUC <sub>0-24hr</sub> (ng·hr/ml)	
		Male	Female	Male	Female	Male	Female
Day 0							
2	0.1	0.10	0.06	24	24	NA	NA
6	0.3	0.58	0.41	24	24	NA	NA
20	1.0	0.98	1.11	24	24	12.79	15.85
Week 39							
2	0.1	0.77	1.20	7.5	18	10.92	20.94
6	0.3	4.23	3.39	4.5	2.3	59.55	61.64
20	1.0	6.59	6.97	0*	12	66.48*	139.46

\*n=3 for high dose males

NA: not applicable, due to low number of evaluable concentrations

## 7 Genetic Toxicology

### 1. Ivermectin-bacterial reverse mutation test (Study# RDS.03.SRE.12440)

Ivermectin was tested in the bacterial reverse mutation assay using strains of *S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 and *E. coli* WP2uvrA in the presence or absence of S9. In the dose finding study (10-5000 µg/plate), A moderate to marked precipitate was noted at doses ≥1000 µg/plate. In the definitive assay, doses of 62.5, 125, 250, 500 and 1000 µg/plate ± S9 were evaluated in each of the tester strains.

This assay was adequately conducted and ivermectin was negative for mutagenicity under the conditions of this study.

### 2. In vitro mammalian cell gene mutation test in L5178Y TK<sup>+/-</sup> mouse lymphoma cells (Study# RDS.03.SRE.12441)

Ivermectin was tested in the mouse lymphoma assay using L5178Y TK<sup>+/-</sup> mouse lymphoma cells in the absence or presence of S9. In a preliminary range-finding test, doses of 10, 100, 500, 1000, 2500, and 5000 µg/ml were tested (3 hr incubation with or without S9, 24 hr incubation without S9). Severe toxicity was noted at doses ≥ 100

µg/ml. In the definitive study, doses of 1.25, 2.5, 5, 10, 20, 30, 40, and 75 µg/ml were tested with a 3-hr incubation period, with or without S9, and doses of 0.94, 1.88, 3.75, 7.5, 15, 20 and 25 µg/ml were tested with a 24-hr incubation period, without S9. Adequate doses were tested in this study, indicated by cytotoxicity.

This assay was adequately conducted and ivermectin was negative for genotoxicity under the conditions of this study.

3. Bone marrow micronucleus test by oral route in rats (Study# RDS.03.SRE.12443)

Ivermectin was tested in a rat micronucleus assay to evaluate the potential of the test article to induce micronucleated erythrocytes in bone marrow of SD rats. Oral (gavage) doses of 0 (vehicle: 0.5% hydroxypropyl cellulose), 5, 10, and 20 mg/kg/day ivermectin were administered to SD rats (5/sex/dose) once daily for 2 days. Animals were sacrificed at 24 hr after the last dose. In a preliminary dose range-finding study, oral (gavage) doses of 20, 27, and 50 mg/kg/day ivermectin were administered to rats (3/sex/dose) once daily for two days. At 50 mg/kg/day, 1 male was found dead after the first dose and sedation and coma were noted in the surviving animals. All rats were found dead 27.5 hours after the first treatment (no second treatment was administered to this group). At 27 mg/kg/day, 1 female was found dead following the second treatment. The surviving animals showed piloerection, hypoactivity, dyspnea, ocular secretion and rhinorrhea. No mortality was noted at 20 mg/kg/day. Clinical signs noted at this dose included piloerection, hypoactivity, dyspnea, sedation and rhinorrhea. The dose of 20 mg/kg/day was selected as the high dose for the definitive study, which is considered appropriate.

No mortality was noted in this study. Clinical signs of toxicity noted in high dose animals included piloerection, rhinorrhea, ocular secretion and sedation. The count of micronucleated polychromatic erythrocytes (MPE) and the ratio of polychromatic erythrocytes to normal chromatic erythrocytes (PE/NE) were calculated in each group and served as indication of clastogenicity and cytotoxicity, respectively. There were no significant differences in the count of MPE or PE/NE ratio in any dose group compared with vehicle control. Ivermectin was negative for clastogenicity under the study conditions.

Plasma levels of ivermectin were measured at different time points (at 1, 3, and 6 hours after the second dose) for high dose animals (shown in the table below).

Sampling time (hours)	Ivermectin plasma level (ng/ml)	
	Males	Females
1	1280	2092
3	2105	2462
6	3621	3079

## 8 Carcinogenicity

Study #1: A 2-year dermal mouse carcinogenicity study

### Background:

An Executive Carcinogenicity Assessment Committee (Exec CAC) meeting was conducted on 01/23/2007 and the proposed doses received Exec CAC concurrence (meeting minutes dated 01/25/2007). The study was initiated on 03/27/2007. On 12/25/2008 the sponsor submitted a request for early termination of the dermal mouse carcinogenicity study due to increased mortality noted at Week 89. The decrease in survival was similar in all groups and was not considered test article-related. The sponsor's request for early termination was considered inappropriate and the following comments were relayed to the sponsor on 12/24/2008:

1. *The study should continue without further modification for the present.*
2. *Dosing of any remaining treatment group (within a gender) should stop if the number of animals in that group should decline to 20, but treatment of other groups should continue. A given treatment group (within a gender) should be terminated and subjected to necropsy per the protocol if the number of surviving animals in that group declines to 15. If the study has reached at least 100 weeks of treatment by the time a given treatment group declines to 15, then all groups of that gender may be sacrificed at that time (but treatment of the other gender would continue). If no group declines to 15 animals, then the study should continue until the scheduled terminal sacrifice. You should notify the Executive Carcinogenicity Assessment Committee (through the Division) prior to termination of any group.*

On 03/04/2009 the sponsor notified the Division that all male groups at Week 100 would be sacrificed as the number of surviving animals in the main study has achieved 15 in one male group (low dose). Treatment of female groups of the main study would be continued to the end of the study since the number of surviving animals is superior to 20 in all groups (refer to nonclinical memo dated 03/11/2009). Low dose males were necropsied during Week 100. All other male groups were necropsied during Week 101. All females were necropsied during Weeks 105 and 106.

**Study title:** CD5024 – 104-week dermal carcinogenicity study in the mouse

Study no.: AA35168, Sponsor Ref# RDS.03.SRE.12508  
 Study report location: SD 1, NDA 206255 (eCTD)  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 03/27/2007  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: CD5024 vehicle gel, lot# 575.754P/03818/1004  
 and 575.754P/056199  
 CD5024 0.1% cream, lot# 575.757/03786/1004  
 and 575.757/03786/2000  
 CD5024 0.3% cream, lot# 575.767/03814/1004  
 and 575.767/03814/2000  
 CD5024 1.0% cream, lot# 575.754/03750/1004  
 and 575.754/056256  
 CAC concurrence: Yes

**Key Study Findings**

There were no significant differences in the survival rate among different groups in either gender. No treatment-related clinical signs or local skin reaction at the application site were noted in the study. Throughout the study, the mean body weight was slightly lower in the high dose male group, compared to the two control groups.

A complete list of tissues was examined histopathologically. No significant test article-related neoplastic findings were noted in this study. Non-neoplastic histopathological findings were noted in treated skin and lymphoid organs. Epidermal hyperplasia, amyloidosis, inflammation, ulceration and pustule formation were at higher incidences in the vehicle control group than in the water control group. These findings were overall comparable among the three dose groups and the vehicle control group, indicating vehicle effects. However, an increase in the incidence of epidermal hyperplasia and amyloidosis at high dose suggested that an exacerbation of the vehicle-related effects by CD5024-treatment was likely. The incidence of lymphoid hyperplasia (all lymphoid tissue combined) was slightly higher in the vehicle control group than the water control group. When the dose groups were compared to the vehicle control group, the incidence of lymphoid hyperplasia was only higher in mandibular lymph nodes in high dose group. Lymphoid hyperplasia was likely a vehicle effect, but a relationship to CD5024-treatment could not be ruled out.

CD5024 cream was not carcinogenic when administered topically to mice at concentrations up to 1% once daily for 2 years. Week 52 AUC<sub>0-24</sub> values were 48519 and 26461 ng·hr/ml in high dose males and females, respectively.

**Adequacy of Carcinogenicity Study**

This carcinogenicity study was adequately conducted.

## Appropriateness of Test Models

The test model was appropriate for this study.

## Evaluation of Tumor Findings

There were no biologically significant test article-related neoplastic findings, under the study conditions.

*Note:* The evaluation of this dermal carcinogenicity study received CAC concurrence during the Exec CAC meeting on 06/17/2014 (refer to Appendix I for the CAC meeting minutes).

## Methods

Doses:	0 (water control), 0 (vehicle control), 1, 3 and 10 mg/kg/day (0.1%, 0.3%, and 1.0% cream)
Frequency of dosing:	Once daily for up to 104 weeks
Dose volume:	1 ml/kg, applied to at least 10% BSA
Route of administration:	Dermal, unoccluded. Once a week the dosing sites were washed with lukewarm tap water and dried with absorbent paper ~6 hr after the daily application. No collar was used to prevent oral ingestion.
Formulation/Vehicle:	Type B formulation (refer to Section 2.3)
Basis of dose selection:	MTD (refer to the CAC meeting minutes dated 01/25/2007 under IND 76064)
Species/Strain:	Swiss CD1 mouse [CrI:CD1 (ICR)]
Number/Sex/Group:	60 for main study animals
Age:	5 weeks
Animal housing:	The animals were individually housed in stainless steel mesh cages.
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK animals (6/sex/group for two control groups, 18/sex/group for three dose groups)
Deviation from study protocol:	None remarkable

## Observations and Results

### Mortality

Cumulative survival rate at the end of study:

For males: 38%, 28%, 25%, 33%, and 33%, for water control, vehicle control, low dose, mid dose, and high dose groups, respectively

For females: 33%, 33%, 28%, 33%, and 43%, for water control, vehicle control, low dose, mid dose, and high dose groups, respectively

There were no significant differences in the survival rate among different groups in either gender. No statistical significance was achieved in either the dose response analysis or pairwise comparisons (refer to the statistical review, by Dr. Mohammad Rahman).

### **Clinical Signs**

Animals were observed daily. A detailed clinical examination (including dermal irritation at the application sites) was performed once every 4 weeks until Week 25 and once weekly thereafter. No treatment-related clinical signs or local skin reaction at the application site were noted in the study.

### **Body Weights**

Body weight was measured weekly for the first 17 weeks and every 4 weeks thereafter. Throughout the study, the mean body weight was slightly lower in the high dose male group, compared to the two control groups (~ -7% at terminal sacrifice).

### **Feed Consumption**

Food consumption was measured weekly for the first 16 weeks and every 4 weeks thereafter. No significant treatment-related effects were noted.

### **Gross Pathology**

No significant test article-related macroscopic observations were noted in either sex.

### **Organ Weights**

The following organs were weighed at scheduled necropsy for all terminal sacrificed animals: adrenal glands, liver, prostate, seminal vesicles and thymus. The weight of seminal vesicles and prostate was lower in treated males than vehicle control (seminal vesicles: -17%, -21%, and -27% in absolute weight for low, mid, and high dose animals; prostate: -19%, -25%, and -27% in absolute weight for low, mid, and high dose animals). However, it was unlikely a treatment-related finding because the mean organ weight of seminal vesicles and prostate in water control males was also lower than vehicle control (-15% and -23%, respectively) and there were no correlated histopathological findings.

### **Histopathology**

Peer Review: Yes.

All tissues listed below were examined for main study animals in the water control group, vehicle control group, and high dose group, and for animals found dead or sacrificed moribund during the study. Histology was examined for all tumors in all groups. In addition, histopathological examination was performed for all gross lesions

from animals in all groups, except those for which the diagnosis is judged unnecessary for the outcome of the study by the pathologist.

Adrenal glands, aorta, bone (femur and sternum) and articulation, bone marrow, brain, bronchi, epididymides, eyes, gastrointestinal tract [esophagus, stomach (fundus and pylorus), duodenum, jejunum, ileum, cecum, colon, and rectum], gall bladder, Harderian gland, heart, kidneys, larynx, liver, lungs, lymph nodes (mandibular, mesenteric, submaxillary, and those adjacent to any subcutaneous masses), mammary gland, nasal and ethmoidal mucosa, optic nerves, ovaries, oviducts, pancreas, Peyer's patch, pituitary, preputial/clitoris glands, prostate, salivary glands (mandibular, parotid, and sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin (treated and untreated), spinal cord, spleen, testes, thymus, thyroid and parathyroid glands, tongue, trachea, ureters, urinary bladder, uterus with cervix, vagina, Zymbal's glands, and all gross lesions.

#### Neoplastic:

The tumor incidence data were analyzed by the statistical reviewer, Dr. Rahman. A pairwise comparison test was conducted for water control group vs. vehicle control group. Pairwise comparison tests were also conducted for each dose group, compared with each control group separately. In addition, a dose response relation test (trend analysis) was conducted with the three dose groups and with each control group separately. As recommended by this reviewer, in addition to the analysis of each individual tumor types seen in this study, the following combinations of tumors noted in this study were also analyzed:

For male mice:

- combine hemangioma and hemangiosarcoma seen in all organs
- Harderian gland: combine adenoma and adenocarcinoma
- liver: combine hepatocellular adenoma and carcinoma
- lung: combine alveolar/bronchiolar adenoma and carcinoma
- skin: combine squamous cell papilloma and carcinoma, in both treated area and untreated area
- thymus: combine benign and malignant thymoma
- thyroid gland: combine C-cell adenoma and carcinoma; combine follicular cell adenoma and carcinoma

For female mice:

- combine hemangioma and hemangiosarcoma seen in all organs
- bone: combine osteoma and osteosarcoma
- liver: combine hepatocellular adenoma and carcinoma
- lung: combine alveolar/bronchiolar adenoma and carcinoma
- ovary: combine adenoma and adenocarcinoma; combine cystadenoma and cystadenocarcinoma
- skin: combine squamous cell papilloma, in both treated area and untreated area

- uterus: combine adenoma and adenocarcinoma; combine leiomyoma and leiomyosarcoma

The CDER Exec CAC criteria for considering a common tumor as treatment related are if both the trend and pairwise comparison analysis have a p-value less than 0.01.

The following table (copied from Dr. Rahman’s review and addendum, with adjustment) displays the tumor incidence results that had at least one test that achieved a nominal  $p \leq 0.05$  level of significance.

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**Tumor Types with P-Values  $\leq 0.05$  for Dose Response Relationship and/or Pairwise Comparisons in Mice**

<u>Comparisons of Treated Groups with Control</u>										
Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Male										
<b>(Using vehicle control group)</b>										
	KIDNEYS	Adenoma, solid	0	0	0	3	0.0150*			0.1201
<b>(Using water control group)</b>										
	KIDNEYS	Adenoma, solid	1	0	0	3	0.0452	1.0000	1.0000	0.2636
	LIVER	Hepatocellular adenoma,	9	14	18	10	0.5575	0.1218	0.0324	0.3846
		Hepatocellular carcinoma,	2	4	7	8	0.0363	0.2819	0.0783	0.0375
		Hepatocullular Ade+Carci,	10	15	23	15	0.2529	0.1400	0.0085*	0.1400
Female										
<b>(using placebo control group)</b>										
	LIVER	Hepatocellular adenoma,	0	0	0	3	0.0168*			0.1296
	SKIN (Tre+Untre)	Squamous cell papilloma,	0	0	0	3	0.0168*			0.1296
<b>(Using water control group)</b>										
	LIVER	Hepatocellular adenoma,	0	0	0	3	0.0175*			0.1397
	SKIN (Tre+Untre)	Squamous cell papi+carci,	0	0	0	3	0.0175*			0.1397
<u>Pairwise Comparisons of Water and Vehicle Control Groups</u>										
	Sex	Organ Name	Tumor Name	Water Control		Vehicle Control		P_Value		
				N=60	N=60	N=60	N=60			
	Female	WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	5			0.0333*		

\*Statistically significant

In the pairwise comparison of the two control groups, the incidence of “hemangioma + hemangiosarcoma” (whole body) in the vehicle control group had a p value  $< 0.05$  ( $p = 0.03$ ). This tumor combination is considered common tumors based on spontaneous tumor incidence rates in CD-1 mice and therefore this tumor finding is not considered significant ( $p > 0.01$ ). In addition, this tumor finding was unlikely induced by vehicle because pairwise comparisons between dose groups and water control group did not show such finding.

When evaluating the tumor incidences in dose groups, a significance level of  $\alpha = 0.01$  should be used in the trend analysis of common tumors, such as hepatocellular adenoma. In addition, usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend analysis and

pairwise comparison test. According to such criteria, none of the tumor findings listed in the table above is considered to be biologically significant.

Overall, there were no significant test article-related neoplastic findings in either sex.

#### Non Neoplastic:

Histopathological findings were noted in treated skin and lymphoid organs.

In the skin from treated area, epidermal hyperplasia, amyloidosis, inflammation, ulceration and pustule formation were seen at higher incidences in the vehicle control group than in the water control group, as shown in the table below (placebo in the study report referred to vehicle):

#### Findings in treated skin:

Group Treatment (mg/kg/day)	1 (water)		2 (placebo)	
	0		0	
Sex	M	F	M	F
No. of animals examined	60	60	60	60
- Epidermal hyperplasia	7	10	46	50
- Amyloidosis	1	-	8	10
- Inflammation	4	2	12	5
- Ulceration	2	2	11	2
- Pustule formation	3	1	11	6

The incidences of such findings were much lower in untreated skin (head skin) (see the table below).

#### Findings in untreated skin:

Group Treatment (mg/kg/day)	1 (water)		2 (placebo)		3		4		5	
	0		0		1		3		10	
Sex	M	F	M	F	M	F	M	F	M	F
No. of animals examined	60	60	60	60	45	43	40	40	60	60
- Epidermal hyperplasia	4	4	5	3	1	7	5	1	7	9
- Amyloidosis	2	-	-	1	1	3	1	1	-	2
- Inflammation	2	3	3	2	2	2	2	-	2	-
- Ulceration	-	-	-	2	-	-	-	-	2	-
- Pustule formation	1	1	1	2	-	2	2	-	1	-

These findings were overall comparable among the three dose groups and the vehicle control group, indicating vehicle effects (see the table below). However, an increase in the incidence of epidermal hyperplasia and amyloidosis at high dose suggested that an exacerbation of the vehicle-related effects by CD5024-treatment was likely.

## Findings in treated skin:

Group Treatment (mg/kg/day)	2 (placebo)		3		4		5	
	0		1		3		10	
Sex	M	F	M	F	M	F	M	F
No. of animals examined	60	60	46	46	40	43	60	60
- Epidermal hyperplasia	46	50	42	43	39	41	51	60
- Amyloidosis	8	10	14	14	9	19	18	23
- Inflammation	12	5	10	6	9	6	9	1
- Ulceration	11	2	8	4	6	4	7	1
- Pustule formation	11	6	8	6	9	5	8	2

Lymphoid hyperplasia was seen in the Peyer's patches, thymus, spleen, and lymph nodes. The incidence of lymphoid hyperplasia (all lymphoid tissue combined) was slightly higher in the vehicle control group than the water control group, mainly due to a higher incidence of lymphoid hyperplasia in spleen. When the dose groups were compared to the vehicle control group, the incidence of lymphoid hyperplasia was only higher in mandibular lymph nodes in high dose group. Lymphoid hyperplasia was likely a vehicle effect, but a relationship to CD5024-treatment could not be ruled out.

**Toxicokinetics**

TK parameters were measured in TK animals in Week 52. TK results are shown in the copied table below.

Gender/ CD5024 dose (mg/kg/day)	AUC <sub>0-24</sub> (ng.h.mL <sup>-1</sup> )	AUC <sub>0-24</sub> /dose	C <sub>max</sub> (ng.mL <sup>-1</sup> )	C <sub>max</sub> / dose	T <sub>max</sub> (h)
Males					
1	5996	5996	456.50	456.50	6
3	11456	3819	708.11	236.04	10
10	48519	4852	3171.51	317.15	6
Females					
1	3058	3058	256.88	256.88	0.75
3	8354	2785	679.93	226.64	6
10	26461	2646	2060.24	206.02	10

The systemic exposure to ivermectin was higher in males than in females and increased roughly dose proportionally in the dose range of 1-10 mg/kg/day.

**Dosing Solution Analysis**

Dosing formulations were directly supplied by the sponsor and no solution analysis was performed in this study.

Study #2: A 2-year oral rat carcinogenicity study

**Study title:** CD5024 – 104-week oral (gavage) carcinogenicity study in the rat  
**Study no.:** AA35169, Sponsor Ref# RDS.03.SRE.12507  
**Study report location:** SD 1, NDA 206255 (eCTD)  
**Conducting laboratory and location:** (b) (4)  
**Date of study initiation:** 04/20/2007  
**GLP compliance:** Yes  
**QA statement:** Yes  
**Drug, lot #, and % purity:** CD5024 (ivermectin); lot # RM000547N1536  
(H<sub>2</sub>B<sub>1a</sub> + H<sub>2</sub>B<sub>1b</sub> content: 89.5%), 08.00564  
(90.8%) and 08.00856 (90.2%)  
**CAC concurrence:** Yes

### Key Study Findings

There were no significant differences in the cumulative survival rate among different groups in females. The cumulative survival rate was lower in high dose males. Ten high dose females had treatment-related clinical signs during the first two weeks of treatment. Six out of these 10 females were euthanized moribund on Days 6 and 7. The mean body weights of high dose animals were lower in the first few weeks and then gradually recovered to control level. It appeared that the high dose induced significant toxicity during the first few weeks, especially in females, followed by a habituation to the toxicity and recovery. Macroscopically, a higher incidence of hepatic masses and raised areas was noted in high dose males. An increase in liver weight was noted in mid dose and high dose animals.

A complete list of tissues was examined histopathologically. Non-neoplastic histopathological findings included an increase in the incidence of retinal atrophy in all dose groups, an increase in the incidence of glandular stomach erosion/ulceration in high dose animals, a dose-related increase in the incidence of periportal to diffuse vacuolation noted at mid dose and high dose, a higher incidence of peliosis hepatis in high dose females, and a higher incidence of alveolar histiocytosis in high dose animals. As a neoplastic finding, an increase in the incidence of hepatocellular adenoma was noted in high dose males and it is considered biologically significant.

Overall, a positive tumor finding (hepatocellular adenoma in high dose males) was noted in this carcinogenicity study. Week 52 AUC<sub>0-24</sub> values were 62567 and 69406 ng·hr/ml in high dose males and females, respectively.

### Adequacy of Carcinogenicity Study

This carcinogenicity study was adequately conducted.

## Appropriateness of Test Models

The test model was appropriate for this study.

## Evaluation of Tumor Findings

There were no biologically significant test article-related neoplastic findings in females. A statistically significant increase in the incidence of hepatocellular adenoma was noted in high dose males and this neoplastic finding is considered biologically significant.

*Note:* The evaluation of this oral carcinogenicity study received CAC concurrence during the Exec CAC meeting on 06/17/2014 (refer to Appendix I for the CAC meeting minutes).

## Methods

Doses:	0 (vehicle control), 1, 3 and 9 mg/kg/day
Frequency of dosing:	Once daily for up to 104 weeks
Dose volume:	2.5 ml/kg (dose concentrations: 0.4, 1.2, and 3.6 mg/ml)
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% carboxymethylcellulose in water for injection
Basis of dose selection:	MTD (refer to CAC meeting minutes dated 01/25/2007 under IND 76064)
Species/Strain:	Wistar rats [CrI: WI (Han)]
Number/Sex/Group:	72 for main study animals
Age:	5 weeks
Animal housing:	The animals were housed in groups of 3 of the same sex and dose group in stainless steel mesh cages.
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK animals (6/sex/group for vehicle control group, 9/sex/group for three dose groups)
Deviation from study protocol:	None remarkable

## Observations and Results

### Mortality

Cumulative survival rate at the end of study (104 weeks):

For males: 68%, 82%, 61%, and 44%, for vehicle control, low dose, mid dose, and high dose groups, respectively

For females: 65%, 65%, 65%, and 67%, for vehicle control, low dose, mid dose, and high dose groups, respectively

There were no significant differences in the cumulative survival rate among different groups in females. Mortality rate was higher in high dose males compared to other male groups (both trend analysis and pairwise comparison were statistically significant for the high dose male group. Refer to the statistical review, by Dr. Rahman).

### **Clinical Signs**

Animals were observed daily. A detailed clinical examination was performed once every 4 weeks until Week 25 and once weekly thereafter. Ten high dose females had treatment-related clinical signs during the first two weeks of treatment. These signs included subdued behavior (with prostration), thin appearance and piloerection, red stained, rough fur, hypersalivation, hunched gait, intermittent tremors, and decreased activity. Six out of these 10 females were euthanized moribund on Days 6 and 7.

### **Body Weights**

Body weight was measured weekly for the first 16 weeks and every 4 weeks thereafter. During the first 4 weeks, a decrease in body weight gain (-19%) was noted in high dose females. The mean body weight of high dose females at Week 4 was lower than control (-8%). The difference between the control group and high dose female group remained constant (-4 to -6 %) until Week 28. The mean body weight of high dose males was also slightly lower than control during the first 20 weeks (-3 to -5%). The mean body weight was similar to the control group during Weeks 28-52 for high dose females and during Weeks 20-84 for high dose males. The mean body weight of high dose males and females was slightly lower (-2 to -4% for males and -2 to -7% for females) up to the end of study. Mean body weights for low dose and mid dose animals were similar or slightly higher than control (2-7%) during the study.

*Reviewer's comment:* The mortality and clinical sign findings and body weight changes were consistent with the results of the chronic oral toxicity study in rats that high dose induced significant toxicity during the first few weeks, especially in females, followed by a habituation to the toxicity and recovery.

### **Feed Consumption**

Food consumption was measured weekly for the first 16 weeks and every 4 weeks thereafter. High dose males and females had lower feed consumption than control during the first week of treatment (-14% in males and -16% in females). Then food consumption was slightly higher during Weeks 2-23 in high dose males and during Weeks 6-40 in high dose females. Food consumption was generally similar to control during the rest of treatment period for high dose animals. Food consumption was generally similar or slightly higher in low dose and mid dose animals, compared to control.

### **Gross Pathology**

A higher incidence of hepatic masses and raised areas in the liver was noted in high dose males. There was a slight increase in the incidence of pale areas in the lung in all

treated male groups when compared with control males. These pale areas often correlated microscopically with alveolar histiocytosis.

### Organ Weights

The following organs were weighed at scheduled necropsy for all terminal sacrificed animals: adrenal glands, liver, prostate, seminal vesicles and thymus.

An increase in liver weight was noted in mid dose and high dose animals (see the copied table below). This finding was probably related to increased incidences of hepatocellular adenoma and/or increased incidences of periportal to diffuse vacuolation.

Group	Males				Females			
	1	2	3	4	1	2	3	4
Treatment (mg/kg/day)	0	1	3	9	0	1	3	9
Number of values	49	56	39	31	47	46	46	48
Absolute liver weight	18.82	19.32	20.99*	21.62**	14.39	14.73	16.73*	16.74*
% difference from control group	-	+2.7	+11.6	+14.9	-	+2.3	+16.2	+16.3
Relative liver weight	3.34	2.93	3.09	3.50**	3.65	3.34	3.90*	4.45**
% difference from control group	-	-12.3	-7.7	+4.7	-	-8.5	+6.6	+21.8

Statistically significant levels: \*:  $p \leq 0.05$ , \*\*:  $p \leq 0.01$  ; -: Observation not recorded in group.

An increase in absolute adrenal weight was noted in dose groups, mainly in the mid dose and high dose groups (+16%–+30% in males and +8%–58% in females). However, no correlated histopathological findings were noted.

### Histopathology

Peer Review: Yes.

All tissues listed below were examined for main study animals in the vehicle control group and high dose group, and for animals found dead or sacrificed moribund during the study. In addition, for low dose and mid dose animals, histology was examined for (1) all macroscopic findings, (2) liver in males, and (3) spleen, thymus, bone marrow (sternum), lymph nodes (mandibular and mesenteric), pancreas and eyes from males and females.

Adrenal glands, aorta, bone (femur and sternum) and articulation, bone marrow, brain, bronchi, epididymides, eyes, gastrointestinal tract [esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum], Harderian gland, heart, kidneys, larynx, liver, lungs, lymph nodes (mandibular, mesenteric, and those adjacent to any subcutaneous masses), mammary gland, nasal and ethmoidal mucosa, optic nerves, ovaries, oviducts, pancreas, Peyer's patch, pituitary, preputial/clitoris glands, prostate,

salivary glands (mandibular, parotid, and sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, testes, thymus, thyroid and parathyroid glands, tongue, trachea, ureters, urinary bladder, uterus with cervix, vagina, Zymbal's glands, and all gross lesions and masses.

Neoplastic:

The tumor incidence data were analyzed by the statistical reviewer, Dr. Rahman. Pairwise comparison tests were conducted for each dose group, compared with vehicle control. In addition, a dose response relation test (trend analysis) was conducted with the three dose groups and the vehicle control group. As recommended by this reviewer, in addition to the analysis of each individual tumor types seen in this study, the following combinations of tumors noted in this study were also analyzed:

For male rats:

- combine hemangioma and hemangiosarcoma seen in all organs
- adrenal: combine cortical adenoma and carcinoma; combine benign and malignant pheochromocytoma
- kidney: combine lipoma and liposarcoma
- pancreas: combine islet cell adenoma and carcinoma
- pituitary gland: combine adenoma and carcinoma
- skin: combine fibroma and fibrosarcoma; combine lipoma and liposarcoma; combine sebaceous cell adenoma and carcinoma
- thymus: combine benign and malignant thymoma
- thyroid gland: combine C-cell adenoma and carcinoma; combine follicular cell adenoma and carcinoma

For female rats:

- combine hemangioma and hemangiosarcoma seen in all organs
- adrenal: combine cortical adenoma and carcinoma
- mammary gland: combine adenoma and adenocarcinoma
- ovary: combine benign and malignant granulosa-theca cell tumors
- pancreas: combine islet cell adenoma and carcinoma
- pituitary gland: combine adenoma and carcinoma
- skin: combine lipoma and liposarcoma; combine squamous cell papilloma and carcinoma
- thymus: combine benign and malignant thymoma
- thyroid gland: combine follicular cell adenoma and carcinoma
- tongue: combine squamous cell papilloma and carcinoma
- uterus with cervix: combine stromal polyp and stromal cell sarcoma

The CDER Exec CAC criteria for considering a common tumor as treatment related are if both the trend and pairwise comparison analysis have a p-value less than 0.01.

The following table (copied from Dr. Rahman's review and addendum, with adjustment) displays the tumor incidence results that had at least one test that achieved a nominal  $p \leq 0.05$  level of significance.

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**Tumor Types with P-Values  $\leq 0.05$  for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Control in Rats**

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P-Value			
			N=72	N=72	N=72	N=72	Dose Resp	C vs. L	C vs. M	C vs. H
fff										
Male	ADRENAL MEDULLA	Malignant pheochromocytoma,	0	0	0	2	0.0493			0.2188
	LIVER	Hepatocellular adenoma,	0	1	2	9	<0.001*	0.5231	0.2439	<0.001*
	MESENT. LYMPH N	Hemangioma,	4	1	2	6	0.0423	0.9774	0.8926	0.2872
	PANCREAS, ENDOC	Islet cell adenoma,	2	3	4	7	0.0163	0.5439	0.3321	0.0531
	PITUITARY GLAND	Adenoma of pars distalis,	20	10	13	21	0.0498	0.9944	0.9418	0.3747
	SYSTEMIC NEOPLA	Malignant lymphoma,	0	2	6	2	0.2380	0.2755	0.0145*	0.2188
Female	PANCREAS, ENDOC	Islet cell carcinoma,	2	1	0	5	0.0246	0.8869	1.0000	0.2056
	WHOLE_BODY	Hemangioma+Hemangiosarcoma,	0	6	1	2	0.5591	0.0160*	0.5082	0.2395

\*Statistically significant

When evaluating the tumor incidences in dose groups, for common tumors the significance level of  $\alpha = 0.01$  should be used in the trend analysis and pairwise comparison. The finding of "hemangioma + hemangiosarcoma" (whole body) in the low dose female group is therefore not considered statistically significant. In addition, usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend analysis and pairwise comparison test. According to such criteria, the only tumor finding considered to be biologically significant is hepatocellular adenoma noted in high dose males (incidences of 0, 1, 2, and 9 in vehicle control, low, mid, and high dose males, respectively;  $p < 0.001$  in both trend analysis and pairwise comparison between high dose and vehicle control groups).

*Reviewer's comments:*

Hepatocellular adenoma is a common tumor seen in Wistar rats. In a published review in which neoplastic data from control Wistar rats between 1980 and 1990 were analyzed (*Fundam Appl Toxicol 1994 22:65-72*), the spontaneous incidence rate of hepatic adenoma was 1.02% in males (in a range of 0-2.5%). In a subsequent review in which neoplastic data from control Wistar rats between 1990 and 1995 were analyzed (*Toxicol Sci 1998 45:1-8*), the spontaneous incidence rate of hepatocellular adenoma was 2.8% in males (in a range of 0-5%). In this study the incidence rates of hepatocellular adenoma were 0, 1.3, 2.8, and 12.5% in the control, low, mid, and high dose males. The increase in the incidence of hepatocellular adenoma in high dose males is considered biologically significant.

Non Neoplastic:

Treatment-related histopathological findings were noted in the eye, stomach, liver, and lung.

A significant increase in the incidence of retinal atrophy was noted in all dose groups when compared with control (incidences of 11, 24, 20, and 29 in males and 11, 17, 21, and 30 in females for vehicle control, low, mid, and high dose groups, respectively). An increase in the incidence of glandular stomach erosion/ulceration was noted in high dose males and females. In the liver, a dose-related increase in the incidence of periportal to diffuse vacuolation was observed at mid dose and high dose (incidences of 3, 4, 8, and 14 in males and 6, 13, 22, and 27 in females for vehicle control, low, mid, and high dose groups, respectively). Peliosis hepatitis was observed at a higher incidence in high dose females. Higher incidences of alveolar histiocytosis were noted in the lung in high dose males and females.

### Toxicokinetics

TK parameters were measured in TK animals in Week 52. TK results are shown in the copied table below.

Dose (mg/kg/day)		CD5024 Results		
		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC* <sub>(0-last)</sub> (ng.h/mL)
1	M	371.18	5	5241.02
	F	389.32	5	4335.89
3	M	1415.13	3	21225.60
	F	2028.41	5	24779.90
9	M	3760.47	5	62567.60
	F	3841.88	3	69406.70

\*AUC<sub>(0-last)</sub> = AUC<sub>0-24hr</sub>

No gender effects were noted in the TK results. The systemic exposure to ivermectin increased more than dose proportionally in the dose range of 1-9 mg/kg/day.

### Dosing Solution Analysis

Dosing formulations were analyzed for stability. The test item in the vehicle was shown to be stable for 24 hr at room temperature, for at least 14 days at ~ 4°C and for 1 month at ~ -20°C. The homogeneity of dosing formulations was verified pretest and during Weeks 2, 51 and 103. The actual concentrations were within ±15% of the nominal concentrations of 0.4, 1.2, and 3.6 mg/ml (deviations between -13.1% to +0.2%).

#### Discussion:

A positive neoplastic finding (hepatocellular adenoma) was noted in high dose males in this oral rat carcinogenicity study. The systemic exposure levels of ivermectin recorded in the two carcinogenicity studies (at Week 52) are compared to that obtained in the maximum use clinical PK trial (shown in the table below). The multiples of human

exposure at 3 mg/kg/day dose in male rats, where no significant treatment-related neoplastic findings were noted, are ~600. The multiples of human exposure at 9 mg/kg/day dose in female rats, where no significant treatment-related neoplastic findings were noted, are ~2000. In addition, very high systemic exposure levels (up to 1369-fold in males and 747-fold in females compared to human exposure) were achieved in the 2-year dermal mouse carcinogenicity study with no significant treatment-related neoplastic findings. Overall the carcinogenic risk associated with the clinical use of ivermectin 1% cream is considered minimal.

2-year Oral Rat Carcinogenicity Study				2-year Dermal Mouse Carcinogenicity Study			
Dose (mg/kg/day)		AUC <sub>0-24hr</sub> (ng•hr/ml)	Multiples of Human Exposure*	Dose (mg/kg/day)		AUC <sub>0-24hr</sub> (ng•hr/ml)	Multiples of Human Exposure*
Male	1	5241	148	Male	1	5996	169
	3	21226	599		3	11456	323
	9	62568	1766		10	48519	1369
Female	1	4336	122	Female	1	3058	86
	3	24780	699		3	8354	236
	9	69407	1959		10	26461	747

\*Comparing to Day 28 AUC<sub>0-24hr</sub> (35.43 ng•hr/ml) obtained under maximum clinical use conditions (1 g ivermectin 1% cream, applied to face once daily for 4 weeks, 0.17 mg/kg/day ivermectin for a 60 kg subject)

### Study #3: A 12-month photocarcinogenicity study in hairless mice

Study Title: Twelve-month topical study to determine the influence of Ivermectin Cream and Ivermectin Placebo Cream on photocarcinogenesis in hairless mice (Study# OMT00010, Sponsor Ref# RDS.03.SRE.12597)

Topical doses of 25 µl/mouse 0 (Placebo Cream, referred to vehicle), 0.1%, 0.3%, and 1.0% ivermectin cream were administered to albino hairless mice (Crl:SKH1-*hr*, 36/sex/group), once daily, five days per week, for 40 weeks. The vehicle was Type B formulation (refer to Section 2.3). Test articles were applied at one hour before UV exposure on Monday, Wednesday and Friday, and at one hour after UV exposure on Tuesday and Thursday, for each week. The UV source was a 6.5 kw xenon long arc burner, which delivered a UVR dose of 600 Robertson-Berger Units (RBU) per week (120 RBU per treatment) for the treated groups. This study also included two untreated control groups, with one group receiving a lower UVR dose (600 RBU/week, same as the treated groups) and the other group receiving a higher UVR dose (1200 RBU/week). After the completion of 40 weeks of formulation administration and UV exposure, mice were maintained for up to an additional 12 weeks, for a total of 52 weeks.

The dose selection was based on the result of a dose range-finding study (described above in Section 6.2). The selected doses are considered acceptable. The selected concentrations of ivermectin cream were the same as tested in the 2-year dermal rat carcinogenicity study for females.

The UV radiation dose is also considered acceptable. The lower UVR control level was 600 RBU per week. Accumulated historic data indicate that this level produces an appropriate tumor median latent period for comparison with other groups. The higher control level was 1200 RBU per week; a significant decrease in median tumor latent period is produced by this dose level. The test level of UVR (600 RBU per week) was selected to permit detection of enhanced photocarcinogenesis within the response range of the test system and in the presence of a test article that is neither protective nor phototoxic.

Mortality, clinical observations, body weights, skin reaction observations and skin tumor development were assessed over the 52-week evaluation period. Skin tumor development was evaluated in terms of prevalence, median tumor onset, statistical group comparisons and yield. The tumor potency factor (TPF), a measure of stimulus rate for a photocarcinogenicity study, was calculated, based on the unbiased median week to tumor for each group (tumors  $\geq 1$  mm).

There were no significant test article-related effects on survival. There were no gender differences in survival. As expected, after week 28, survival declined precipitously in the untreated control group with high UVR exposure, primarily because mice were sacrificed in moribund condition due to individual tumor burden criteria. The remaining mice in that group were sacrificed in week 36 after having achieved group tumor burden sacrifice criteria. Skin reactions occurred in both male and female mice and included erythema, edema, flaking, thickening, wrinkling, residue, white raised areas and erythemic raised areas. The incidence and frequency of skin reactions were higher in the vehicle control group, compared to the untreated control group with lower UV exposure. In addition, compared to the vehicle control group, a dose-related increase in the incidence and frequency of skin reactions were noted in the mid dose and high dose groups. The results indicated that the vehicle with UV exposure elicited skin irritation and ivermectin cream exacerbated the skin irritation. No significant treatment-related clinical observations, excluding the skin reaction observations, were noted. No significant treatment-related effects on body weights were noted.

As anticipated, the mice in the UVR calibration groups (untreated controls with UVR) developed skin tumors, and tumors developed earlier in the high UVR exposure group. The median tumor onset was 40 and 25 weeks (sex combined) in the untreated control groups with low and high UVR, respectively. The study results also showed that in general, skin tumors occurred earlier in the vehicle control group, indicating enhanced photocarcinogenesis. In addition, an exacerbation of such enhancement (shortening of tumor onset time) was noted in test article-treated groups at all dose levels. The following table showed the median tumor onset in all groups.

**Unbiased Median Week to Tumor for Tumors  $\geq 1$  mm<sup>a</sup>**

Dosage Group	1	2	3	4	5	6
Formulation/ Concentration	IVERMECTIN PLACEBO CREAM	IVERMECTIN 0.1% CREAM	IVERMECTIN 0.3% CREAM	IVERMECTIN 1.0% CREAM	Untreated	Untreated
UVR Exposure (RBU/week)	600	600	600	600	600	1200
Sexes Combined Median (Weeks)	28.00	26.00	25.00	23.50	40.00	25.00
Males Median (Weeks)	26.00	25.50	23.00	22.00	42.00	23.00
Females Median (Weeks)	30.00	27.00	27.00	28.00	39.00	25.00

a. The number of mice on which each median was calculated was 72 (sexes combined) or 36 (males or females, separately).

The TPF values suggested the similar results, that the vehicle induced an enhancement of photocarcinogenesis (sex combined TPF 1.69 vs. 1.00 in untreated control with low UVR), and ivermectin cream induced an exacerbation of such enhancement (sex combined TPF: 1.89, 2.00, 2.19 in low dose, mid dose, and high dose groups). A dose response in tumor onset and TPF was noted in males but not in females. There was good concordance between the induction of skin irritation and the enhancement of photocarcinogenesis.

**Estimated Tumor Potency Factors  
( $\geq 1$  mm Tumor Size)**

Dosage Group	1	2	3	4	5	6
Formulation/ Concentration	IVERMECTIN PLACEBO CREAM	IVERMECTIN 0.1% CREAM	IVERMECTIN 0.3% CREAM	IVERMECTIN 1.0% CREAM	Untreated	Untreated
UVR Exposure (RBU/week)	600	600	600	600	600	1200
Sexes Combined	1.69	1.89	2.00	2.19	1.00	2.00
Males	1.74	1.78	2.00	2.10	1.00	2.00
Females	1.51	1.77	1.77	1.68	1.00	2.00

**Adequacy of Carcinogenicity Study**

The photocarcinogenicity study was adequately conducted.

**Appropriateness of Test Models**

The test model was appropriate for this study.

**Evaluation of Tumor Findings**

Only skin tumors were evaluated in this study, which was the primary objective of the study. Treatment with vehicle exhibited an enhancement of photocarcinogenesis in both males and females, as compared to the untreated group with low UV exposure. Topical treatment with ivermectin cream elicited further enhancement of UV-induced photocarcinogenesis, in both males and females, at all dose levels, as compared to the vehicle control group.

*Reviewer's comment:* Per the ICH M3(R2) guidance document, we no longer recommend conduct of photocarcinogenicity studies for topical drug products, as the current photocarcinogenicity testing in hairless rodents is not considered useful for the evaluation of human risk. Therefore, the study results are not recommended to be included in the ivermectin cream drug label.

## 9 Reproductive and Developmental Toxicology

### 9.1 Fertility and Early Embryonic Development

Study #1: Ivermectin - Fertility toxicity study by the oral route (gavage) in the rat (Study# RDS.03.SRE.12504)

Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 1 and 9 mg/kg/day were administered to SD rats (20-30/sex/dose). Males were treated 28 days before mating, during mating and until the day before necropsy. Females were treated 14 days before mating, throughout mating and until Day 7 of gestation (inclusive). In total, 7/30 high dose males and 18/30 high dose females were terminated in a moribund condition. All of the decedent males and 10 females were terminated between Days 5 and 9 of treatment. Six females were terminated during pairing and two females were sacrificed on Gestation Day 3. The majority of these decedents had a marked body weight loss over the days preceding death and showed subdued behavior, a thin appearance and red staining on the head and fore limbs. Necropsy of the decedent animals did not reveal the cause of death. There was no mortality at the lower dose levels.

The mating performance and fertility of the high dose group could not be adequately assessed due to the mortality. The precoital period was generally prolonged in the high dose group (5.3 days on average), compared with the control group (2.9 days on average). Twenty high dose females survived to pairing, of which 8 died during cohabitation. Eleven out of 12 of the surviving pairs of high dose rats mated and 10 females became pregnant. All pairs in the other groups copulated and no significant effects on precoital period were noted. There were 4 non-pregnant females in the mid dose group and none in the low dose and control groups. This higher incidence of non-pregnant females in the mid dose group was considered incidental, in view of the lack of a similar effect amongst the surviving high dose rats and the absence of any effects on other reproductive parameters. In addition, the pregnancy rate in the mid dose group was within the limits in the recent historical control data of this testing laboratory.

At the scheduled sacrifice, necropsy examination did not reveal any significant lesions in any group. The testis and epididymis weights of males and ovary weights of females were not adversely affected by treatment. The testicular sperm counts of the males were similar in all groups. Sperm motility was not significantly affected by treatment. There were no significant treatment-related effects on caesarean data (numbers of corpora lutea, pre-implantation loss, post-implantation loss, and live embryos).

The mid dose, 1.0 mg/kg/day was identified as the NOAEL in this study, for both general toxicity and mating performance/fertility in both males and females, at which the AUC<sub>0-24h</sub> values were 2414 ng·h/ml for males on treatment Day 27 and 2887 ng·h/ml for females on treatment Day 13, respectively (see the table below).

CD5024 Dose (mg/kg/day)	CD5024 Results							
	C <sub>max</sub> (ng/mL)		T <sub>max</sub> (h)		AUC <sub>(0-24h)</sub> (ng.h/mL)		AUC <sub>(0-24h)</sub> /Dose (kg.h/L)	
	F Day 13	M Day 27	F Day 13	M Day 27	F Day 13	M Day 27	F Day 13	M Day 27
0.10	9.35	9.18	3	3	155.51	130.95	1.56	1.31
1.0	186.48	190.18	5	5	2887.32	2413.80	2.89	2.41
9.0	2103.37	2288.29	3	3	40606.70	36379.10	4.51	4.04

## 9.2 Embryonic Fetal Development

Study #2: Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rats (Study# RDS.03.SRE.12445)

Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 2.5, 5 and 10 mg/kg/day ivermectin were administered to pregnant SD rats (6/dose) during gestational Days 6 – 17. All maternal animals were sacrificed on gestation Day 20. A laparohysterectomy was performed on each animal on gestation Day 20. The uteri, placenta and ovaries were examined for the total number of fetuses, early and late resorptions, total implantations and corpora lutea. Gravid uterine weights were obtained. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

No treatment-related effects on mortality, clinical signs, body or gravid uterine weight, food consumption or maternal macroscopic visceral findings were noted in this study. No treatment-related effects on intrauterine growth, fetal survival, or fetal external malformations or developmental variations were noted in this study. In summary, no maternal or embryofetal toxicity was noted at 10 mg/kg/day, the highest dose evaluated in this study.

Study #3: Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rats (Study# RDS.03.SRE.12490)

Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 10, 15 and 25 mg/kg/day ivermectin were administered to pregnant SD rats (6/dose) during gestational Days 6 – 17. All maternal animals were sacrificed on gestation Day 20. A laparohysterectomy was performed on each animal on gestation Day 20. The uteri, placenta and ovaries were examined for the total number of fetuses, early and late

resorptions, total implantations and corpora lutea. Gravid uterine weights were obtained. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

All females in the high dose group and 3/6 females in the mid dose groups were euthanized moribund within the first week of treatment. Prior to euthanasia, body weight losses and severely decreased food consumption were noted in these females. Clinical findings noted for euthanized females included red material around the nose and mouth, hypoactivity and abnormal posture. These same treatment-related clinical findings were noted in surviving mid dose females. Decreased mean maternal body weight gain (low dose: -5%; mid dose: -13%) with a corresponding decreased food consumption were noted in low and mid dose animals compared to control animals during gestation Days 8 - 20.

No treatment-related effects on gravid uterine weight or maternal macroscopic visceral findings were noted in this study. No treatment-related effects on intrauterine growth, fetal survival, or fetal external malformations or developmental variations were noted in this study. The NOAEL was identified as 10 mg/kg/day, under the conditions of this study. Based on the results of this study, oral doses of 1.5, 4 and 12 mg/kg/day ivermectin were selected for the definitive embryofetal development study in rats.

Study #4: An oral dose study of the effects of ivermectin on embryo/fetal development in rats (Study# RDS.03.SRE.12461)

Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1.5, 4 and 12 mg/kg/day ivermectin were administered to pregnant SD rats (25/group) during gestational Days 6 – 17. All maternal animals were sacrificed on gestation Day 20. Toxicity parameters evaluated in this study included mortality, clinical signs, maternal body weights and food consumption. The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination. Half of the fetuses were examined for soft tissue abnormalities and half of the fetuses were examined for skeletal abnormalities.

Treatment-related mortality was noted in high dose dams (3/25). A treatment-related decrease in mean body weight was noted in high dose animals (-5% to -13%), with an associated decrease in food consumption, compared to control animals during gestation Days 6 – 17. Treatment-related clinical signs noted in high dose animals included red material around the nose, forelimbs and urogenital areas and decreased defecation. No treatment-related maternal toxicity were noted in low or mid dose dams. The NOAEL for maternal toxicity was 4 mg/kg/day, at which the AUC<sub>0-24h</sub> values were 25099 ng-h/ml on gestation day 17.

A treatment-related decrease in fetal body weight was noted in the high dose group (-8%) compared to the control group. The number of fetuses (liters) available for

morphological evaluation were 392 (25), 406 (25), 386 (24) and 345 (22) in control, low, mid and high dose groups, respectively. No treatment-related effects on the number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss or viable fetuses were noted. No treatment-related effects on gravid uterine weights or fetal sex ratio were noted. An increased mean litter proportion of cleft palate was noted in the high dose group (0.9% per litter) compared to the control group (0% per litter). No treatment-related fetal toxicity or teratogenicity were noted in low or mid dose groups. The NOAEL for both embryofetal toxicity and teratogenicity was 4 mg/kg/day, at which the AUC<sub>0-72h</sub> values were 25099 ng·h/ml on gestation day 17.

TK results:

<b><u>TOXICOKINETIC RESULTS</u></b>				
Ivermectine Oral Dosage	Ivermectine Results			
	AUC* (ng·h/mL)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	Half-life (h)
<u>Gestation Day 6</u>				
1.5 mg/kg/day	5254	267	3.0	10
4 mg/kg/day	16354	929	3.0	10
12 mg/kg/day	41784	1975	3.0	12
<u>Gestation Day 17</u>				
1.5 mg/kg/day	7829	523	3.0	27
4 mg/kg/day	25099	1991	3.0	28
12 mg/kg/day	67625	4675	5.0	31

\*AUC<sub>0-∞</sub> for GD 6 and AUC<sub>0-24</sub> for GD 17.

**Study #5:** Oral dose range-finding study for effects of ivermectin on embryo-fetal development in rabbits (Study# RDS.03.SRE.12444)

Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1.5, 3 and 6 mg/kg/day ivermectin were administered to pregnant New Zealand White Rabbits (6/dose) during gestational days 7 – 20. All maternal animals were sacrificed on gestation day 29. Toxicity parameters evaluated in this study included mortality, clinical signs, maternal body weight and food consumption. The uteri, placenta and ovaries were examined for the total number of fetuses, early and late resorptions, total implantations and corpora lutea. Gravid uterine weights were obtained. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

One high dose female was euthanized in extremis on gestation day 13. Decreased defecation was noted in low, mid and high dose animals. Significant decreased maternal body weight (-10% on gestation day 20) and maternal body weight gain (high dose: -65 g for gestation day 7 – 21; control animals: +334 g for gestation day 7 – 21)

was noted in high dose animals compared to control animals. Decreased maternal body weight gain was noted from gestational day 7 – 21 in low and mid dose animals (low dose: -9%; mid dose: -28%) compared to control animals. Mean food consumption was decreased in high and mid dose groups. No treatment-related effects on gravid uterine weight or maternal macroscopic findings were noted in this study.

Decreased fetal weight was noted in the high dose group (-9.4%) compared to the control group. No other treatment-related effects on intrauterine growth, fetal survival, or fetal external malformations or developmental variations were noted in this study. Based on the results of this study, oral doses of 0.5, 1.5 and 4.5 mg/kg/day ivermectin were selected for the definitive embryofetal development study in rabbits.

Study #6: An oral dose study of the effects of ivermectin on embryo/fetal development in rabbits (Study# RDS.03.SRE.12460)

Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 0.5, 1.5 and 4.5 mg/kg/day ivermectin were administered to pregnant New Zealand White rabbits (22/group) during gestational days 7 – 20. All maternal animals were sacrificed on gestation day 29. Toxicity parameters evaluated in this study included mortality, clinical signs, maternal body weight and food consumption. The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

Treatment-related mortality was noted at high dose (1/22). One high dose female aborted on gestation day 23. Treatment-related effects on clinical signs noted in high dose animals included decreased defecation, small feces and clear or green material around the mouth and/or nose. Significant decreased maternal body weight (-11% on gestation day 20) and maternal body weight gain (high dose: -101 g for gestation days 7 – 21; control animals: +353 g for gestation days 7 – 21) was noted in high dose animals compared to control animals. A corresponding decrease in food consumption was noted in high dose animals. No significant treatment-related maternal toxicity was noted at low dose or mid dose. The NOAEL for maternal toxicity was 1.5 mg/kg/day ivermectin ( $AUC_{0-24hr} = 2766 \text{ ng}\cdot\text{hr}/\text{ml}$  on gestation day 20).

No treatment-related effects on maternal macroscopic parameters were noted in this study. The number of fetuses (litters) available for morphological evaluation were 184 (20), 177 (22), 191 (20) and 170 (20) in control, low, mid and high dose groups, respectively. No treatment-related effects on the mean number of corpora lutea, uterine implantations, resorptions, pre-/post-implantation loss or viable fetuses per dam were noted. No treatment-related effect on gravid uterine weights was noted in this study. No treatment-related effect on fetal body weight or fetal sex ratio was noted in this study.

The number of viable fetuses (litters) with noted malformations were 1 (1), 0 (0), 3 (2) and 12 (7) in control, low, mid and high dose groups, respectively. Seven fetuses from 3 litters in the high dose group had carpal flexure (primarily bilateral) with 1 litter having 5 out of 12 fetuses affected. The study report indicates that there were no alterations in ossification or structural development of the appendicular skeleton to correlate with these findings. The mean litter proportion of carpal flexure (4.2% per litter) in this group was above the maximum mean value in the (b)(4) (test laboratory) historical control data (0.8% per litter). The study report indicated that although classified historically as a malformation, no underlying skeletal alterations could be identified for the carpal flexure findings observed in the high dose group. The testing laboratory stated that these findings would likely resolve during early postnatal development and have no long-term or life threatening consequences. However, in the absence of data from an actual study to demonstrate the reversal of the carpal flexure finding, it is difficult to verify whether this would be true or not. Therefore, the increased litter proportion of carpal flexure in the high dose group is considered a malformation and significant. No other treatment-related malformations (external, visceral or skeletal) were noted in this study.

The NOAEL for both embryofetal development and teratogenicity was 1.5 mg/kg/day ivermectin ( $AUC_{0-24hr} = 2766 \text{ ng}\cdot\text{hr}/\text{ml}$  on gestation day 20).

TK results:

Dose (mg/kg/day)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hours)	AUC <sub>0-24 hr</sub> (ng·hr/ml)	t <sub>1/2</sub> (hr)
Day 7				
0.5	13.1	4.0	747	NC
1.5	348	4.0	15985	NC
4.5	220	5.0	9126	NC
Day 20				
0.5	26.7	2.5	403	49
1.5	145	1.8	2766	43
4.5	681	9.3	12556	43

NC: not calculated.

*Reviewer's comments:* Without actual data that clearly demonstrate the reversal of the carpal flexure finding noted at 4.5 mg/kg/day dose in this study, it is considered a malformation and significant. The sponsor subsequently conducted a second definitive embryofetal development study in rabbits with lower doses, which is reviewed below.

#### Study #7

**Study title:** An oral dose study of the effects of CD5024 on embryo/fetal development in rabbits

Study no.: (b) (4) 502009 (Sponsor Ref# RDS.03.SRE.12623)  
 Study report location: eCTD, SDN 1  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 05/22/2008  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: CD5024, lot# RM000547N1536, 89.5%

### Key Study Findings

Treatment-related mortality/moribundity was noted at both doses (1/22 at low dose and 2/22 at high dose). Decreased defecation was noted at both doses beginning as early as gestation day 8. Rales were observed in 3 high dose females during gestation days 9-19. Dose-related body weight loss and/or decrease in body weight gain were noted at both doses.

No significant treatment-related maternal macroscopic findings were noted during necropsy. No treatment-related effects on the mean number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss and viable fetuses per dam were noted. A decrease in mean gravid uterine weight (-13.5%) and mean fetal weight (-11.9%) was noted at high dose. No treatment-related effects on fetal morphology were noted in this study.

The NOAEL for maternal toxicity could not be identified in this study because mortality/moribundity was seen at both dose levels. The NOAEL for embryofetal toxicity was considered to be 2.5 mg/kg/day ivermectin, based on fetal weight decrease noted at 3.5 mg/kg/day. The NOAEL for teratogenicity was considered to be the high dose, 3.5 mg/kg/day. AUC<sub>0-24</sub> values at gestation day 20 were 2545 and 5159 ng·hr/ml at 2.5 and 3.5 mg/kg/day, respectively.

### Methods

Doses: 0 (vehicle), 2.5 and 3.5 mg/kg/day  
 Frequency of dosing: Once daily  
 Dose volume: 5 ml/kg  
 Route of administration: Oral (gavage)  
 Formulation/Vehicle: 0.5% carboxymethylcellulose  
 Species/Strain: female New Zealand White rabbits  
 Number/Sex/Group: 22 females/group  
 Satellite groups: TK animals: 4/group  
 Study design: Oral (gavage) doses were administered daily from gestation days 7 – 20. All maternal animals were sacrificed on gestation day 29.  
 Deviation from study protocol: None remarkable

## Observations and Results

### Mortality

One low dose female was euthanized in extremis on gestation day 19 and 2 high dose females were found dead on gestation day 29 following an extended period (11-14 days) of minimal food consumption and body weight loss. All of these females had decreased defecation for at least 1 week prior to death or euthanasia. Although a cause of death could not be determined for these females at necropsy, the mortality and moribundity noted at low and high doses were considered to be treatment-related.

### Clinical Signs

For the surviving females, a test article-related increase in the incidences of decreased defecation was noted at both doses beginning as early as gestation day 8. Rales were observed on 2 to 4 occasions in 3 high dose females during gestation days 9-19. There were no other test article-related clinical findings noted at the daily examinations or 1 hr following dose administration.

### Body Weight

Dose-related body weight loss and/or decrease in body weight gain were noted at both doses. On gestation day 20 (the end of treatment), the mean body weight were 4.4% and 10.1% lower in the low dose and high dose groups, respectively, compared to the control group.

### Food Consumption

Mean maternal food consumption, evaluated as g/animal/day and g/kg/day, was reduced in both dose groups throughout the treatment period.

### Macropathology

No significant treatment-related macroscopic findings were noted during necropsy.

### Toxicokinetics

Blood samples (approximately 3.5 ml each) for toxicokinetics were collected on gestation days 7 and 20 at predose and 1, 3, 5, 9 and 24 hr postdose. Blood samples were also collected on gestation day 20 at 72, 120, 168 and 192 hr postdose. The TK results are shown in the copied table below. Drug accumulation was noted after repeat dosing.

CD 5024 Results (n=4)									
Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)		T <sub>max</sub> (h)		AUC <sub>(0-24h)</sub> (ng.h/mL)			AUC <sub>(0-24h)</sub> /Dose (mg.h/mL)	
	Day 7	Day 20	Day 7	Day 20	Day 7	Day 20	AI	Day 7	Day 20
2.5	72.06 +24.94	155.60 +146	3.50 +1.00	3.00 +0.00	930 +238	2545 +2284	3.17 +3.43	372 +95	1018 +914
3.5	125 +42.10	310 +184	3.00 +0.00	2.33 +1.15	1521 +480	5159 +3175	3.37 +2.15	435 +137	1474 +907

AI: accumulation index.

### Dosing Solution Analysis

The mean concentrations of CD5024 in test formulations and the homogeneity analysis results were within the applied limits ( $\pm 15\%$  of nominal).

### Necropsy

#### Cesarean Section Data:

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea.

No treatment-related effects on the mean number of corpora lutea, uterine implantations, resorptions, pre-/post-implantation loss or viable fetuses per dam were noted. A decrease in mean gravid uterine weight (-13.5%) was noted at high dose, compared to control animals. This was likely due to the lower mean fetal weight noted in this group.

#### Offspring:

The numbers of fetuses (litters) available for morphological evaluation were 207(21), 194(20) and 187(20) in the control, low dose and high dose groups, respectively. All fetuses were weighed, sexed and examined for external, visceral and skeletal malformations and developmental variations.

Mean fetal weight in the high dose group was 11.9% lower than the control group value. No test article-related effects on fetal weight or gravid uterine weight were noted in the low dose group. No test article-related effects on intrauterine survival were noted in the low dose or high dose groups. Malformations were observed in 5(3), 0(0) and 4(4) fetuses (litters) in the control, mid dose and high dose groups, respectively. No treatment-related effects on fetal morphology were noted in this study.

### 9.3 Prenatal and Postnatal Development

The sponsor intends to rely on published literature to provide prenatal and postnatal development toxicity information to support this NDA. Under this section the sponsor provided two literature references shown below:

- Ivermectin. In: Toxicological evaluation of certain veterinary drug residues in food. Thirty-sixth (36<sup>th</sup>) Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Feb 5-14, 1990; Rome. World Health Organization (WHO), Geneva. WHO Food Additives Series, No. 27, 1991.
- Poul. Effects of perinatal ivermectin exposure on behavioral development of rats. Neurotoxicol Teratol. 1988;10: 267-72

Only brief summary information was contained in the JECFA report, which does not allow an in-depth review. The reproductive toxicity information of ivermectin in rats summarized in the JECFA report is shown in the following table (copied from the sponsor's submission):

Dosing periods/ type of study	Oral Dose levels (mg/kg/day)	Major findings
Dosing 15 days before mating until 20 days post-partum	0.4, 0.8, 1.6	Higher mortality in pups of dams treated by 1.6 mg/kg/day. Slightly higher average pup weights from the 0.4 mg/kg/day dams, development slightly accelerated.
3 generations	0.4, 1.2, 3.6	F <sub>0</sub> : increased average length of gestation and decreased maternal weight gains at 3.6 mg/kg/day; F <sub>1a</sub> : 92% pup mortality rate during lactation at 3.6 mg/kg/day F <sub>1b</sub> : increased pup mortality at 0.4 and 1.2 mg/kg/day F <sub>2a</sub> : increased pup mortality at 0.4 and 1.2 mg/kg/day In all instances, delays in development were associated with pup mortality. Study terminated before completion due to high toxicity
3 generations Continuous dosing throughout the production of two litters in each of 3 generations	2	Increased pup mortality. Study terminated before completion due to high toxicity
3 generations Dosing for the entire life-span	0.05, 0.1, 0.2, 0.4	Decreased mean body weights among F <sub>1b</sub> females in the 0.4 mg/kg/day group and among F <sub>2b</sub> males in the 0.2 and 0.4 mg/kg/day groups during the post-weaning period. F <sub>0</sub> : mother and father – F <sub>1</sub> : first generation pups (F <sub>1a</sub> : pups from first litter; F <sub>1b</sub> : pups from second litter). F <sub>2</sub> : second generation pups (F <sub>2a</sub> : pups from first litter; F <sub>2b</sub> : pups from second litter). No treatment related mortality or physical signs of toxicity among parents or offspring in any dose group throughout the production of two litters in each of the F <sub>0</sub> , F <sub>1b</sub> and F <sub>2b</sub> generations.

F<sub>0</sub>: mother and father – F<sub>1</sub>: first generation pups (F<sub>1a</sub>: pups from first litter; F<sub>1b</sub>: pups from second litter)

F<sub>2</sub>: second generation pups (F<sub>2a</sub>: pups from first litter; F<sub>2b</sub>: pups from second litter)

The second literature reference provided detailed information for the evaluation of pre- and postnatal development in rats. This literature reference is reviewed below.

**Study #8**

Study title: Effects of perinatal ivermectin exposure on behavioral development of rats

Study no.: N/A  
Study report location: eCTD, SDN 1 (Neurotoxicol Teratol. 1988;10: 267-72)  
Conducting laboratory and location: Jean-Michel Poul, Laboratory National des Medicaments Veterinaires, Javene, France  
Date of study initiation: Unknown  
GLP compliance: Unknown  
QA statement: N/A  
Drug, lot #, and % purity: Ivermectin, obtained from Merck, lot# and purity unknown

**Key Study Findings**

Seven out of 13 high dose dams were not treated during lactation because ivermectin was shown highly toxic during lactation (all the high dose pups died during lactation days 3-8 when exposed to ivermectin through lactation). The mortality rate in mid dose offspring was also significantly high (30.7%). No significant differences were noted in the length of gestation, number of pups per litter or sex ratio. In the offspring, a significant decrease in body weight was noted in mid dose and high dose groups. Ivermectin adversely affected the behavior development of newborn rats at all dose levels, particularly on motor development and general activity. A NOAEL for postnatal development was not identified in this study.

**Methods**

Doses: 0 (vehicle), 1, 2, and 4 mg/kg/day  
Frequency of dosing: Once daily  
Dose volume: 1 ml/kg  
Route of administration: Oral (gavage)  
Formulation/Vehicle: Peanut oil  
Species/Strain: Sprague-Dawley rats  
Number/Sex/Group: 11-13 females/group  
Satellite groups: None  
Study design: Females were treated during gestation days 6-20 and lactation days 2-20. F<sub>1</sub> animals were exposed to the test article in utero and through lactation.  
Deviation from study protocol: In the high dose group, all pups in the first 6/13 litters treated during gestation and lactation died early. Subsequently high dose was administered only during gestation days 6-20 in the remaining 7/13 females.

**Observations and Results**

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

No significant effects on body weight or food consumption were noted. No significant differences were noted in the length of gestation, number of pups per litter or sex ratio in the different groups.

## **F<sub>1</sub> Generation**

### Mortality

All the F<sub>1</sub> pups (6 litters) treated with high dose ivermectin during gestation and lactation died between postnatal days 3 and 8. The mortality rate (before weaning) of pups (7 litters) treated with high dose ivermectin only during gestation was 22.2%. The mortality rate of offspring in the control, low dose, and mid dose groups was 0, 1.2%, and 30.7%, respectively.

### Body Weight

In the offspring, a significant decrease in body weight was noted in mid dose and high dose group (on lactation day 21, -18% in the mid dose group and -11% in the remaining litters in the high dose group)

### Prewaning Behavioral Development

The evaluated behavioral parameters included: pinna detachment, incisor eruption, eye opening, cliff avoidance, surface righting reflex, locomotion, negative geotaxis reflex, swimming ontogeny, rotorod performance and open field activity.

Delayed eye opening was noted at mid dose. A delay of the appearance of cliff avoidance reflex was seen in all dose groups. A delay of the acquisition of surface righting reflex was seen at mid dose. An inhibition of locomotion was noted in all dose groups, compared to the control group. An inhibition of negative geotaxis reflex was noted in the mid dose group. Swimming development was delayed in all three aspects (direction, angle and paddling) at mid dose. Temporary delays were also seen in low dose the high dose groups. No significant effects on rotorod performance at postnatal day 19 were noted. Prewaning open field activity was assessed at postnatal day 20. None of the dose groups were statistically different from controls, perhaps due to a high level of variability, although the mid dose group seemed to be less active than control.

## **Toxicokinetics**

Not evaluated.

*Reviewer's comments:* From the summary information in the JECFA report and the study results of the pre- and postnatal development study, it appeared that ivermectin was highly toxic to neonatal rats. To obtain more information on ivermectin's toxicity on

postnatal development, the following literature reference from Merck was cursorily reviewed, although it was not provided under this section.

Study #9: Effects of ivermectin on reproduction and neonatal toxicity in rat (Food Chem Toxicol. 1989;27:523-9), by Lankas et al., Department of safety assessment, Merck

This publication contains detailed summaries of two multi-generation studies, a cross-fostering study and a PK study in SD rats.

The effects of ivermectin (MK-0933) on reproduction and neonatal toxicity of several generations of rats were evaluated. The study design was to dose  $F_0$ ,  $F_{1b}$  and  $F_{2b}$  weanling male and female rats for 70 days and then throughout the production of two litters in each of three successive generations. At the start of the study, each group contained 20 females and 10 males. During the mating period, each male rat was housed with up to two females of the same dose group for a maximum of 24 days, and upon observation of sperm in the daily vaginal lavage (day 0 of gestation), the females were removed and housed individually.  $F_0$  and  $F_{1b}$  male rats remained in individual cages until the next mating period or until necropsy. On day 17 of gestation, mated  $F_0$  female rats were removed and placed in individual litter boxes to allow for normal delivery and rearing of offspring. Following weaning and necropsy of the  $F_{1a}$  offspring, the  $F_0$  females were individually housed for up to 3 weeks until the next mating period. After 70 days of ivermectin administration, the  $F_{1b}$  offspring were mated as described above for production of  $F_{2a}$  and  $F_{2b}$  litters. This process was repeated for production of  $F_{3a}$  and  $F_{3b}$  litters.

In the initial multi-generation study in rats, ivermectin was administered orally at dose levels of 0 (vehicle: sesame oil), 0.4, 1.2 or 3.6 mg/kg/day. There was no treatment-related mortality, physical signs of toxicity or adverse effects on body weight gains in  $F_0$  animals. There were no effects on the time to mating or pregnancy rate at any dose level. There were no adverse effects on the number of live  $F_{1a}$  offspring/litter on postnatal day 1. However, there was a high mortality rate (53%) during the lactation period of  $F_{1a}$  offspring in the 3.6 mg/kg/day dose group (the majority of the offspring died between postnatal days 5 and 10). No statistical significance was achieved in comparing survival of the  $F_{1a}$  offspring in the 0.4 or 1.2 mg/kg/day dose groups to control; however, the mortality rate at 1.2 mg/kg/day seemed to be higher (12.7% vs 6.7% in control at postnatal day 21). Due to the high mortality of  $F_1$  animals at high dose, the  $F_0$  male and female rats in this dose group were terminated after weaning of the surviving  $F_{1a}$  offspring. A significant increase in  $F_{1b}$  pup mortality was noted between postnatal days 2 and 7 in the 0.4 and 1.2 mg/kg/day dose groups (9.9% and 7.0%, respectively, vs. 1.6% in control). Lower body weights and retardation of auditory startle reflex were also noted in  $F_{1b}$  offspring in the 0.4 and 1.2 mg/kg/day dose groups. In the  $F_{2a}$  generation, the number of live pups/litter and the average live pup weight/litter on postnatal day 1 were unaffected by administration of ivermectin at 0.4 and 1.2 mg/kg/day. There were significant increases in pup mortality between postnatal days 2 and 7 in the 0.4 and 1.2 mg/kg/day dose groups. The average live pup weight/litter in

both groups was also decreased compared to control. The mortality and body weight results of F<sub>1a</sub>, F<sub>1b</sub> and F<sub>2a</sub> animals are shown in the copied table below.

**Table 1. Effect of ivermectin on neonatal mortality and body weights in the F<sub>1a</sub>, F<sub>1b</sub> and F<sub>2a</sub> generations of rats**

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Due to increased mortality in F<sub>1b</sub> and F<sub>2a</sub> litters treated at 0.4 or 1.2 mg/kg/day doses, no NOAEL for neonatal toxicity was identified in this study.

Subsequently the multi-generation study was repeated with lower dose levels: 0 (vehicle: sesame oil), 0.05, 0.1, 0.2 and 0.4 mg/kg/day. In this study, no treatment-related mortality, body weight change, or physical signs of toxicity among parents or offspring were noted in any dose group throughout the production of two litters in each of the F<sub>0</sub>, F<sub>1b</sub> and F<sub>2b</sub> generations. However, the mortality rate of the F<sub>3a</sub> offspring at 0.4 mg/kg/day seemed to be higher than other groups, although no statistical significance was achieved (refer to the copied table below).

**Table 2. Effect of ivermectin on neonatal mortality and body weight in the F<sub>3a</sub> generation of rats**

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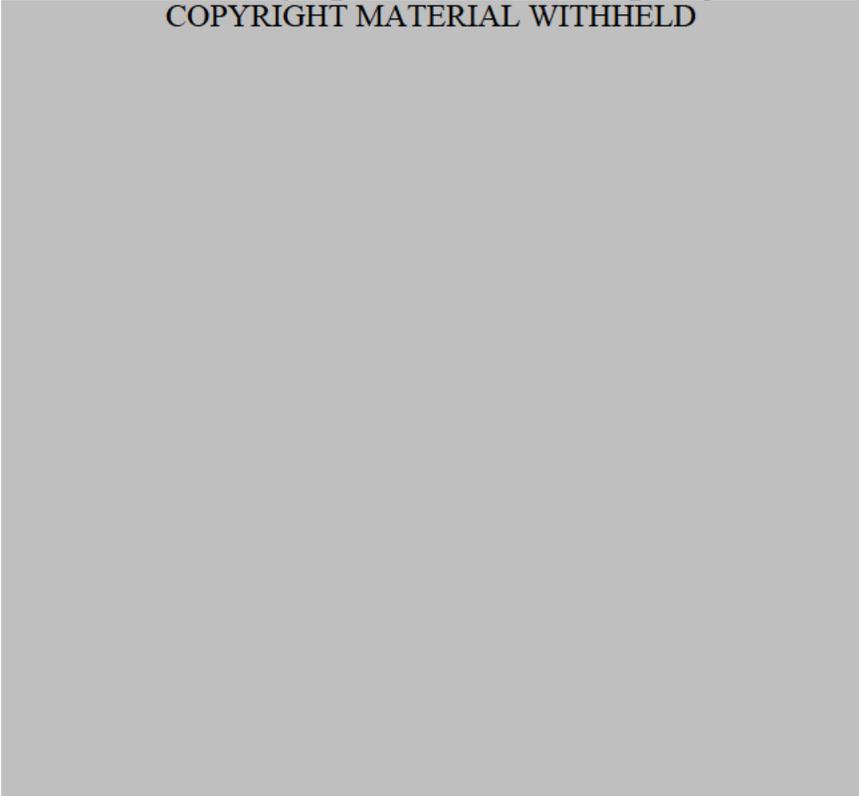
The differences in response found in the 0.4 mg/kg/day group in the two multi-generation studies were probably due to biological variation and/or the relatively steep dose-response curve for neonatal toxicity.

A cross-fostering study was conducted to determine whether the neonatal toxicity was the result of prenatal, postnatal or a combination of pre- and postnatal exposure to ivermectin. Oral doses of 0 (vehicle: sesame oil) and 2.5 mg/kg/day ivermectin were administered to female SD rats (40/group) for 61 days. These F<sub>0</sub> females were mated with untreated males of the same strain, and ivermectin administration was continued throughout mating, gestation and lactation of F<sub>1</sub> pups until postnatal day 20. On postnatal day 1, the litter size among treated and control F<sub>0</sub> dams was standardized to 4 male and four female F<sub>1</sub> pups each, and all litters were cross-fostered to F<sub>0</sub> dams, generating four groups: control F<sub>0</sub> x control F<sub>1</sub> (Group 1), control F<sub>0</sub> x treated F<sub>1</sub> (Group 2), treated F<sub>0</sub> x treated F<sub>1</sub> (Group 3) and treated F<sub>0</sub> x control F<sub>1</sub> (Group 4). Postnatal survival, growth and development of offspring in all groups were evaluated until weaning on postnatal day 25.

The results of this study showed an increase in mortality and a decrease in body weight for offspring of Groups 3 and 4, compared to control. In contrast, the survival, growth and development of pups from treated dams that were cross-fostered to control dams (Group 2) were comparable with those of pups that were fostered within the control group (Group 1). The mortality and body weight results of the 4 groups of neonatal rats are shown in the copied table below.

Table 3. Effect of ivermectin on neonatal mortality and body weights in the offspring from the cross-fostering study\*

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The results of this cross-fostering study indicated that the neonatal toxicity of ivermectin in rats was mainly due to postnatal exposure (through lactation), while in utero exposure to ivermectin did not significantly affect the mortality or body weight gain when compared to control, under the study conditions.

To determine the reason for the high sensitivity of neonatal rats to ivermectin, a PK study was conducted to measure concentrations of ivermectin and/or its metabolites in milk and in tissues from adult and neonatal rats. Six female SD rats were administered with tritiated ivermectin at a dose level of 2.5 mg/kg/day (0.2 mCi/mg) for 61 days, then throughout mating and gestation and until postpartum day 9. This group was referred to as “chronic” treatment group. An additional group of six female rats, referred to as the “subacute” treatment group, was received radiolabelled ivermectin only from post-partum days 1 to 9 at the same dose.

Plasma levels among females in the chronic treatment group were approximately three to four times higher on post-partum day 1 than on day 60 of ivermectin administration prior to mating and gestation. Plasma values in this group diminished gradually on post-partum days 4 and 6 until they reached a level on post-partum day 10 that was comparable to that maintained throughout most of the 61-day pre-mating administration of ivermectin. As expected, the average maternal plasma concentration in the subacute treatment group on post-partum day 1 was substantially lower than that of the chronic

treatment group. On post-partum day 10, however, the plasma levels in the subacute group were equal to or slightly higher than those of the chronic group.

Concentrations of total radioactivity in milk from dams in the chronic and subacute treatment groups were consistently 3-4 times higher than those obtained from plasma samples withdrawn on comparable post-partum days. Plasma radioactivity levels in offspring from dams in the chronic treatment group were very low on post-partum day 1. These levels increased rapidly until, on post-partum days 6 and 10, the concentration of [<sup>3</sup>H]ivermectin in the plasma of offspring was approximately 2-3 times greater than that found in the lactating dam. Radioactivity was not detected in the plasma of offspring in the subacute treatment group on post-partum day 1. On post-partum days 4 and 6, radioactivity was present in the plasma of offspring from the subacute treatment group at approximately half the levels of those obtained in offspring from the chronic treatment group. By post-partum day 10, the plasma levels in the subacute treatment group were comparable with those in offspring from the chronic treatment group.

Residues of ivermectin in the liver, brain and carcass of offspring in the chronic and subacute treatment groups were approximately two to three times higher than those found in these same tissues of the dams from the same treatment group. The plasma-brain ratio of radiolabelled ivermectin and/or its metabolites in offspring from dams in both the chronic and subacute treatment groups was approximately 1.0 on post-partum days 1 and 4, but increased to 2-3 on post-partum days 6 and 10.

*Discussion:*

Neonatal toxicity in rats, characterized by decreased body weight gain and pup mortality during lactation, was noted in offspring at ivermectin dose levels as low as 0.4 mg/kg/day. A NOAEL level of 0.2 mg/kg/day for neonatal toxicity was identified in the two multi-generation studies, under the study conditions. The results of the cross-fostering study indicated that the neonatal toxicity in rats were mainly due to postnatal exposure to ivermectin through lactation. Per the author of this publication, since ivermectin is a highly lipophilic compound, it accumulates in fat tissue, and the increase in plasma levels in dams at parturition and in subsequent milk concentrations might possibly due to increased utilization of depot fat in rats. The relatively high concentrations of ivermectin in milk from treated dams (3-4 times higher than the maternal plasma level) resulted in a progressive increase in plasma levels in the offspring. In addition, the plasma-brain drug concentration ratio in offspring increased from 1 on post-partum days 1 and 4 to 2-3 on post-partum days 6 and 10. These data were consistent with the postnatal formation of a blood-brain barrier in rats.

Ivermectin induced high neonatal toxicity in rats. However, this toxicity profile may be species specific. In other species in which the excretion of ivermectin in milk is lower and/or the blood-brain barrier is formed prenatally (such as human), the potential for ivermectin induced neonatal toxicity through lactation may be considerably reduced.

## 10 Special Toxicology Studies

### Study #1: Acute dermal irritation in rabbits (Study# RDS.03.SRE.12437)

A single topical application of 1% ivermectin cream (0.5 ml/application site) was applied to clipped, intact or abraded treatment sites (6 cm<sup>2</sup>), on New Zealand White rabbit (3 males) dorsal skin under occlusion for 24 hours. Dermal reactions were evaluated at 24 and 72 hours and 5, 6, 7 and 8 days following removal of occlusive bandage.

Moderate erythema was noted on the intact and abraded treatment sites at 24 and 72 hours with very slight erythema noted on days 6 – 8. Mild to moderate edema was noted on intact and abraded treatment sites at 24 and 72 hours with very slight edema noted on day 8. The 1% ivermectin cream was an irritant to intact and abraded rabbit skin after a 24 hour topical administration under occlusion.

### Study #2: Acute eye irritation in rabbits (Study# RDS.03.SRE.12436)

Test article (0.1 ml 1% ivermectin cream) was instilled in the conjunctival sac of the left eye of New Zealand White rabbits (3 males). The right eye remained untreated and served as a control. The eyes were not rinsed after test article administration. Each animal was examined for corneal irritation, opacity, mineralization, iritis, and conjunctival redness swelling and discharge at 1, 24, 48 and 72 hours and 4 and 5 days postdose.

Very slight conjunctival reactions (including very slight chemosis and very slight redness of the conjunctiva) were noted in all animals at 1 and 24 hours postdose. Complete recovery was noted by day 4 postdose. The 1% ivermectin cream was classified as a non-irritant to rabbit eyes, under the conditions of this study.

### Study #3: Assessment of contact hypersensitivity to ivermectin in the mouse (local lymph node assay) (Study# RDS.03.SRE.12498)

Test article [25 µl vehicle (propylene glycol), 0.25%, 0.5%, 1% and 2.5% ivermectin] was applied daily over the entire dorsal surface of each mouse ear (CBA/Ca mice; 4 females/dose) for 3 days. The proliferative response of the auricular lymph node (incorporation of [<sup>3</sup>H]methyl thymidine) was assessed 5 days following the initial application.

Significant toxicity (mortality, clinical signs and body weight loss) was noted in the groups treated with 1% and 2.5% ivermectin. No treatment-related toxicity was noted at the 0.25% and 0.5% ivermectin concentrations. The calculated stimulation index (SI) values were 1.0, 0.5 and 0.7 for vehicle, 0.25% and 0.5% ivermectin, respectively. No interpretable SI values could be calculated for the groups treated with 1% and 2.5%, due to significant systemic toxicity including mortality. The SI values for concentrations ≤0.5% ivermectin were less than 3, indicating a positive response was not elicited at these concentrations of ivermectin.

Study #4: Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications)  
(Study# RDS.03.SRE.12438)

Hartley Guinea pigs (10/sex in the treated group and 5/sex in the control group) were evaluated for skin sensitization. During a 3-week induction period, dermal induction was elicited by topical administration of 0.2 ml of 1% ivermectin cream spread over a filter paper (8 cm<sup>2</sup>) which was applied to a shaved area on the anterior left flank of the animal 3 times per week for 3 weeks (days 1, 3, 5, 8, 10, 12, 15, 17 and 19). The pad was held in place for 6 hours with an adhesive occlusive plaster. The application site was moved from the left to the right flank from day 12 in response to the marked skin reactions. A dry filter paper was applied under the same experimental conditions to the animals of the control group. On day 29 (first dermal challenge), 0.1 ml of 1% ivermectin cream was applied topically (Finn chamber) to the posterior right flank of all animals. The treatment sites remained under occlusion for 6 hours. On day 51 (second dermal challenge), 0.1 ml of 0.5% ivermectin cream was applied topically (Finn chamber) to the median left flank of all animals. The treatment sites remained under occlusion for 6 hours. Cutaneous reactions were evaluated at the treated sites 24 hours after each application in the induction phase, before the second challenge application and 24, 48 and 72 hours after removal of the dressing for each challenge application. A concurrent mercaptobenzothiazole positive control was included in this assay and yielded the appropriate positive response for this assay.

No treatment-related mortality or clinical signs were noted in this study. During the induction phase, discrete to intense skin reactions (erythema, dryness of the skin, edema and crusts) were noted in all animals of the test article-treated group. Erythema was noted after the second challenge dose in test article-treated animals. The 1% ivermectin cream was classified as a sensitizer in guinea pigs, under the conditions of this study.

Study #5: Phototoxic and photoallergenic potential by cutaneous route in guinea pigs  
(Study# RDS.03.SRE.12439)

This study was designed to assess photoirritation and photoallergy of topical administration of 1% ivermectin cream in hairless guinea pigs. An irradiation dose of UVA (365 nm, 9 J/cm<sup>2</sup>) and UVB (312 nm, 0.1 J/cm<sup>2</sup>) was used in this study. The photoallergy part of this study is not documented in this review as animal photoallergy study results are no longer considered useful for the evaluation of human risk. It would be preferable if a solar simulated lamp had been used as the irradiation source. However, since both UVA and UVB exposure was achieved in this study, the study design appears acceptable.

In phototoxicity testing, Group 1 (5 males) received no test article treatment, Group 2 (5 males) and Group 3 (10 males) received 0.1 ml of test article applied to a 9 cm<sup>2</sup> treatment area on the interscapular region. After approximately 30 minutes after treatment, the animals in Groups 1 and 3 received UVA/UVB irradiation for 30 minutes.

No UVA/UVB irradiation was administered to Group 2. Cutaneous reactions were scored at 1, 4 and 24 hours postdose and/or irradiation.

Mild erythema was noted at treated sites with or without UVA/UVB irradiation. No increase in dermal irritation was noted with UVA/UVB irradiation. Treatment with the 1% ivermectin cream did not appear to elicit a phototoxic response in hairless guinea pigs.

Study #6: : In vitro evaluation of immunomodulatory effects of CD5024 on human leukocytes, polymorphonuclear and CD34+ progenitor cells (Study# 56411R)

This study was conducted to evaluate the in vitro effects of CD5024 on human cells identified as possible target cells, including whole blood, peripheral blood mononuclear cells (PBMC), polymorphonuclear neutrophils (PMN) and CD34+ progenitor cells. A number of in vitro assays were conducted. The sponsor stated that in a clinical maximum use PK trial (Study# RD.03.SPR.40064), after a 4-week once daily repeated topical application of CD5024 1% cream, the highest  $C_{max}$  value of CD5024 was 2.06 ng/ml, equivalent to a concentration of 2.4 nM. In a Phase 2b trial (Study# RD.03.SPR.40027), the highest plasma concentration achieved after 12-week dosing was 6.127 ng/ml (7.0 nM). The sponsor stated that 10 nM is considered the maximal achievable plasma concentration under clinical use conditions. Phenoxyethanol, an inactive ingredient in the clinical formulation, was also tested (alone or in combination with CD5024). Moxifloxacin, an antibiotic, was tested as a reference compound.

The following assays were performed:

1. Cytotoxicity assay on PBMC and PMN

CD5024 was tested at 10 concentrations ranging from 1.5 nM to 30  $\mu$ M; phenoxyethanol was tested at 10 concentrations ranging from 9.7 nM to 191  $\mu$ M; the "CD5024 + phenoxyethanol" (ratio 1:1 w/w) combinations with the same respective concentrations were also tested; moxifloxacin was tested at 5 concentrations ranging from 120 nM to 10  $\mu$ M in the first set of experiments and 8 concentrations ranging from 1.1  $\mu$ M to 2.5 mM in the second set of experiments.

2. PBMC proliferation assay for the evaluation of immunomodulatory

(immunostimulatory and immunosuppressive) effects of CD5024 on white blood cells  
In order to evaluate immunosuppressive effects, cells were treated with medium, 0.05% DMSO, CD5024 (10 nM, 500 nM, and 5  $\mu$ M), phenoxyethanol (60 nM, 3.2  $\mu$ M and 32  $\mu$ M), the "CD5024 + phenoxyethanol" (ratio 1:1 w/w) combinations, or moxifloxacin (10  $\mu$ M), and concomitantly stimulated with 1) a mixture of 3 antigens (PPD, tetanus toxoid and diphtheria toxoid) that mimics the immune response induced by recall antigen after vaccination (proliferation of lymphocytes that need antigen presenting cells such as monocytes and dendritic cells), 2) Interleukin-2, a cytokine that allows the basal proliferation (survival) of lymphocytes, or 3) phytohemagglutinin-P (PHA), a potent mitogen that induce the T lymphocyte proliferation independently. Cyclosporine A was

used as a reference immunosuppressive compound. Cell proliferation was measured by [<sup>3</sup>H]-methyl-thymidine incorporation after 2 or 4 days of culture.

### 3. Cytokine release assay by PBMC for the evaluation of pro- or anti-inflammatory effects of CD5024 on PBMC

For the assessment of pro-inflammatory effects of CD5024, PBMC were treated for 24 hr with the same treatment procedure previously described for the PBMC proliferation assay. For the assessment of anti-inflammatory effects of CD5024, PBMC were concomitantly stimulated with LPS. Levels of interleukin (IL)-6, TNF-alpha, and RANTES (a chemokine known to recruit leukocytes into inflammatory sites) were measured in cell culture supernatants.

### 4. Slow release of IL-8 by PMN

PMN were prepared with cytochalasin B (Cyt B) treatment. Cyt B blocks cytoskeleton movements, and allows the bioavailability of receptors (and particular fMLP-receptor) at the cell surface. Five minutes after Cyt B treatment, PMN were treated with medium, 0.05% DMSO, CD5024 (10 nM, 500 nM, and 5 µM), phenoxyethanol (60 nM, 3.2 µM and 32 µM), the "CD5024 + phenoxyethanol" (ratio 1:1 w/w) combinations, or moxifloxacin (10 µM). In parallel, in order to evaluate inhibitory effects of CD5024 on IL-8 synthesis, cells were concomitantly stimulated with fMLP and treated with test articles (fMLP is a chemotactic tri-peptide which mimics the biological activity of bacterially-derived peptides). After 18-20 hr, cell supernatants were harvested and IL-8 was measured.

### 5. Rapid release of IL-8, LTB<sub>4</sub>, and elastase by PMN

This assay was performed to evaluate the effects of CD5024 on PMN degranulation. The concentrations of test articles were the same as in the slow release assay. Human elastase, IL-8, and LTB<sub>4</sub> were measured after cells were treated for 20 min. In parallel, in order to evaluate inhibitory effects of CD5024 on PMN degranulation, cells were concomitantly stimulated with fMLP and treated with test articles.

### 6. Produce of ROS by PMN

The ROS production was evaluated by measuring the reduction of ferricytochrome C by reading the absorbance spectrum at 550 nm vs. 540 nm. PMN were treated with Cyt B and ferricytochrome-C, at 5 min before the treatment with the test articles: medium alone, 0.05% DMSO, CD5024 (10 nM, 500 nM, and 5 µM), phenoxyethanol (60 nM, 3.2 µM and 32 µM), the "CD5024 + phenoxyethanol" (ratio 1:1 w/w) combinations, or moxifloxacin (10 µM). In parallel, in order to evaluate inhibitory effects of CD5024 on ROS production, cells were stimulated with fMLP at 15 min after the treatment with test articles.

### 7. Cell surface expression of CD11a, CD11b and CD18 on PMN

The concentrations of test articles were the same as in the prior assay. PMN were treated with Cyt B at 4 min prior to the treatment with test compounds. In parallel, in order to evaluate effects of CD5024 combined with fMLP, cells were treated with fMLP at 15 min after the treatment with test compounds. Fluorochrome-conjugated

monoclonal antibodies were used to detect CD11a, CD11b, and CD18 (expression level measured by fluorescence intensity).

8. Human CD34+ progenitor assay for the evaluation of effects of CD5024 on hematopoietic progenitors

Isolated CD34+ cells (from 2 umbilical blood donors) were treated for 2 days with medium, 0.05% DMSO, CD5024 (500 nM), phenoxyethanol (3.2  $\mu$ M), CD5024 + phenoxyethanol" (ratio 1:1 w/w) combination, or moxifloxacin (10  $\mu$ M). Only one concentration was tested for each test article because CD34+ cells are rare. After treatment, cells were maintained for 14 days and granulocyte-erythrocyte-macrophage-megakaryocyte colony-forming units (CFU-GEMM), granulocyte-macrophage colony-forming units (CFU-GM), granulocyte colony-forming units (CFU-G), macrophage colony-forming units (CFU-M) and erythrocyte burst-forming units (BFU-E) were scored under microscope.

9. Histamine release assay for the evaluation of an immune allergic response by direct effects of CD5024 on basophils

Fresh human venous blood was stimulated with the basophil activation buffer and simultaneously treated for 60 min with: medium alone, 0.05% DMSO, CD5024 (10 nM, 500 nM, and 5  $\mu$ M), phenoxyethanol (60 nM, 3.2  $\mu$ M and 32  $\mu$ M), the "CD5024 + phenoxyethanol" (ratio 1:1 w/w) combinations, or moxifloxacin (10  $\mu$ M). A23187 calcium ionophore was used as a positive control of histamine release. Histamine was quantified using an enzyme immunoassay.

## Results

1. Cytotoxic effects on PBMC and PMN

CD5024 was not cytotoxic for PBMC or PMN at concentrations up to 10  $\mu$ M. However, cytotoxicity of CD5024 was almost 100% (2-3% surviving cells) at 30  $\mu$ M. Phenoxyethanol exhibited no cytotoxicity on PBMC or PMN at concentrations up to 191  $\mu$ M. The combination of these 2 compounds did not show higher cytotoxicity than CD5024 alone.

2. Effects on lymphocyte proliferation

In the absence of an antigen stimulation, none of the test compounds stimulated lymphocyte proliferation. However, an inhibition of spontaneous proliferation was noted for CD5024 at 5  $\mu$ M, alone or in combination with phenoxyethanol (42% inhibition alone, 36% inhibition in combination). The reference compound cyclosporine A showed a 68% inhibition at 1  $\mu$ g/ml (830 nM). Antigen-induced lymphocyte proliferation was inhibited by cyclosporine A (79%) and CD5024 at 5  $\mu$ M (~80%), alone or with phenoxyethanol. IL-2 induced lymphocyte proliferation was inhibited by cyclosporine A (90%) and CD5024 at 5  $\mu$ M (57%). PHA-induced lymphocyte proliferation was inhibited by cyclosporine A (95%), but not inhibited by CD5024, alone or in combination with phenoxyethanol.

3. Cytokine release

In the absence of stimulation, none of the test compounds stimulated the release of TNF-alpha, IL-6, or RANTES by PBMC. None of the test compounds modulated the LPS-induced synthesis of TNF-alpha, IL-6 or RANTES by PBMC.

#### 4. Effects on slow release (production of IL-8) by PMN

In the absence of fMLP stimulation, CD5024 at 5  $\mu$ M and phenoxyethanol at 3.2  $\mu$ M showed higher IL-8 production (59% and 145%, respectively, compared to control). FMLP induced high levels of IL-8 (4366 pg/ml); while none of the test compounds inhibited the fMLP-induced release. On the contrary, CD5024 at 5  $\mu$ M, alone or in combination with phenoxyethanol, increased the IL-8 level (8896 and 8076 pg/ml, alone and with phenoxyethanol, respectively).

#### 5. Effects on PMN degranulation

In the absence of fMLP stimulation, none of the test compounds stimulated the release of elastase or IL-8. CD5024 and phenoxyethanol did not stimulate the release of LTB<sub>4</sub>, while moxifloxacin caused a ~4 fold increase of LTB<sub>4</sub> level in one blood donor. FMLP induced significant high levels of elastase, IL-8, and LTB<sub>4</sub>; while none of the test compounds showed significant modulation of the fMLP-induced release.

#### 6. Effects on ROS production in PMN

For unstimulated PMN, no tested compounds induced ROS production. In response to fMLP stimulation, PMN produced significant ROS production; while CD5024 at 5  $\mu$ M alone or with phenoxyethanol reduced the fMLP-induced ROS production by 51% and 59%, respectively.

#### 7. CD11a, CD11b and CD18 expression at the cell surface of PMN

The expression of the 3 markers CD 11a, CD 11b and CD18 at the cell surface of PMN was not increased by fMLP. CD5024 at 5  $\mu$ M alone or mixed with phenoxyethanol decreased the expression of CD11b (68% and 65%, respectively) and CD18 (76% and 75%, respectively).

#### 8. Effects on hematopoietic progenitor cells

CFU-GEMM cells and CFU-GM cells were not included in the analysis due to very low number. For all other progenitors, no significant modulations were noted for CD5024, alone or in combination with phenoxyethanol. Moxifloxacin at 10  $\mu$ M inhibited CFU-E formation by 31%.

#### 9. Effects on histamine release

A23187 induced significant histamine release from basophils. No significant modulation of histamine release was observed with CD5Q24, phenoxyethanol, or moxifloxacin.

#### *Reviewer's comments:*

The Phase 3 clinical trial (Study# RD.03.SPR.40051) was halted on 01/16/2009 due to a significant adverse effect: a decline in the neutrophil cell count (NCC) among 63% of subjects (158 out of 251) at Week 10 compared with baseline. The sponsor conducted a series of in vitro assays using human blood cells in order to identify possible biological

mechanisms which may be involved in CD5024-associated neutropenia noted in the Phase 3 clinical trial.

CD5024 was not cytotoxic for PBMC or PMN at concentrations up to 10  $\mu\text{M}$ . CD5024 at 5  $\mu\text{M}$  showed an inhibitory effect on lymphocyte proliferation. CD5024 at 5  $\mu\text{M}$  reduced the fMLP-induced ROS production in PMN. CD5024 at 5  $\mu\text{M}$  decreased the expression of cell surface markers CD11b and CD18 on PMN. Overall the in vitro assays did not show a specific toxicity of CD5024 towards neutrophils. Some effects of CD5024 on PMN were noted only at high concentration, 5  $\mu\text{M}$ , which is ~500 fold of the maximal achievable plasma concentration under clinical use conditions. However, these in vitro studies have limited value in predicting biological outcomes in vivo, and do not provide a convincingly meaningful basis for the safety assessment of the potential of CD5024 to induce neutropenia in human.

## 11 Integrated Summary and Safety Evaluation

Ivermectin is an anti-parasitic agent and has been marketed for the treatment of a number of parasite diseases (Stromectrol<sup>®</sup>, NDA 50742) and lice infestation (Sklice<sup>®</sup>, NDA 202736). The sponsor intends to develop ivermectin 1% cream for the treatment of rosacea through the 505(b)(2) regulatory pathway. As the mechanism of action for ivermectin in the treatment of rosacea lesions is not clear, a pharmacologic class designation is not recommended for ivermectin. The sponsor proposed to rely on published literature to provide pre- and postnatal developmental toxicity information of ivermectin. No bridging study is needed for such use, from a pharmacology/toxicology perspective.

Ivermectin causes death of parasites primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. Ivermectin may also interact with other ligand-gated chloride channels, such as GABA channel. The selectivity of ivermectin is attributable to the fact that some mammals do not have glutamate-gated chloride channels, that ivermectin have a low affinity for mammalian ligand-gated chloride channels, and that ivermectin does not readily cross the blood brain barrier in humans. Face mite infestation may be attributable to the onset of rosacea and the anti-parasitic activity of ivermectin suggests that it may be effective in the treatment of inflammatory lesions of rosacea. In addition, in vivo studies using different animal models showed that topical application of ivermectin has anti-inflammatory properties, which might also be attributable to its therapeutic effect on rosacea.

In safety pharmacology studies, no treatment-related effects on spontaneous activity, CNS excitability, sensory, motor, autonomic or neuromuscular function or body temperature was noted in rats at single oral doses up to 5 mg/kg ivermectin. In a second study a dose-dependent decrease in motor activity was noted at single oral doses of 7 and 20 mg/kg in rats. The NOAEL for neurological effects was identified as single oral dose of 3 mg/kg. Single oral doses of ivermectin up to 20 mg/kg had no

effects on intrinsic convulsive activity or pentylenetetrazole-induced convulsive activity in rats. Single oral doses of ivermectin up to 20 mg/kg had no effects on intrinsic analgesic activity or pentobarbital-induced anesthesia.

Ivermectin had no significant effects on the delayed rectifier potassium current in an in vitro hERG assay at concentrations up to 10  $\mu$ M. In a cardiovascular safety pharmacology study in conscious dogs, a single oral dose of 1.5 mg/kg ivermectin was administered. During the first 24 hr, no significant effects on cardiovascular parameters were noted. A slight decrease in blood pressure (-15%, -13% and -19% for mean, systolic and diastolic pressure) was observed at 72 hr postdose. There was no significant change in PR interval. The QT interval was slightly lengthened (+11%) at 48 hr and (+13%) 240 hr. However, due to the decrease of heart rate, the QTc interval was not significantly changed.

Ivermectin reduced the gastrointestinal transit in rats at a single oral dose of 20 mg/kg and dose-dependently reduced gastric emptying from 7 mg/kg. Ivermectin at single oral doses up to 20 mg/kg had no significant effects on urinary volume, urinary pH, potassium, sodium, or creatinine excretion in rats.

Ivermectin's dermal absorption was limited. The total penetrated dose of [ $^3$ H]-ivermectin when applied as a 1% cream to human excised skin was 2.2%. Following topical application of ivermectin in the mouse, rat, dog or minipig [either the 1% cream or formulated in propylene glycol/ethanol, 60/40 (w/w)], the estimated absolute bioavailability was 4% in the mouse, 2% in the rat and 0.4% in the dog. In the minipig, after a single 6-hr topical application (0.5 g/kg 1% cream applied to 10% BSA), plasma concentrations of ivermectin were below the LOQ at all sampling time points. The dermal bioavailability of ivermectin in minipigs was estimated to be 0.4% in males and 0.2% in females based on excretion data. The main metabolites found in humans were present in at least one toxicology species. In a metabolite exposure comparison across species (rat, dog, minipig, and human), the systemic exposure to main metabolites of ivermectin in animals was not disproportionately lower than that in human subjects. The metabolite contribution to the overall toxicity assessment in animal test species has been established.

In single dose toxicity studies in mice and rats, clinical signs related to CNS toxicity (reduced motor activity, piloerection, half closed eyes) were noted and an oral LD<sub>50</sub> for ivermectin was higher than 40 mg/kg in mice and between 40 and 60 mg/kg in female rats.

Repeat dose toxicity studies were conducted in mice, rats, dogs, and minipigs. In a 13-week dermal toxicity study in CD-1 mice, topical doses of ivermectin 0 (water), 0 (vehicle), 1, 3 and 10 mg/kg/day [0.1%, 0.3%, and 1% ivermectin cream applied (unoccluded) at a dose volume of 1 ml/kg/day, 1% being the maximum feasible concentration in this formulation] were administered for 13 weeks. No significant toxicity was noted in this study. The NOAEL was identified as 10 mg/kg/day (1% ivermectin).

In a 4-week dermal toxicity study in SD rats, topical doses of ivermectin 0 (vehicle) and 20 mg/kg/day (1% ivermectin cream applied to ~10% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered for 4 weeks. No significant toxicity was noted in this study. The NOAEL was identified as 20 mg/kg/day (1% cream).

In a 13-week oral toxicity study in Wistar rats, oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.3, 1.0 and 3.0 mg/kg/day were administered for 13 weeks. No significant toxicity was noted in this study. The NOAEL was identified as 3.0 mg/kg/day.

In order to determine the MTD and help dose selection for a subsequent oral carcinogenicity study, a second 13-week oral rat toxicity study was conducted. Oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3, 9 and 12 mg/kg/day were administered to Wistar rats for 13 weeks. The animals used in this study were younger than the animals used in the first 13-week study (5 weeks of age vs. 8 weeks of age). Treatment-related mortality was noted in the mid-high and high dose groups (mainly in females) during the first two weeks of treatment. A dose-dependent decrease in seminal vesicle weight was noted in mid-low, mid-high and high dose males. Increased liver weights were noted in mid-high and high dose animals. Histopathological findings included: a slight decrease of seminal vesicle secretion noted in one mid-low dose male, two mid-high dose males and two high dose males; a minimal decrease of prostate secretion noted in one mid-low dose male, three mid-high dose males and one high dose male; and minimal to slight apoptosis in the thymus noted in one mid-low dose male, 5 mid-high dose animals (4 males, 1 female) and 6 high dose animals (3 males, 3 females). The NOAEL was identified as the low dose, 1 mg/kg/day, under the conditions of this study.

In a chronic oral toxicity study in rats, initially oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3 and 12 mg/kg/day were administered to Wistar rats for 27 weeks. Because of severe clinical signs observed at high dose, two additional groups (another vehicle control group and 0.1 mg/kg/day dose group) were added starting Day 49. Mortality was noted at 3 mg/kg/day (1 male) and 12 mg/kg/day (3 males and 12 females). High dose animals had marked clinical signs, including subdued behavior, thin appearance, piloerection, red stained, rough and soiled fur, abnormal chewing and hypersalivation, and tremor. Decreased body weight gain or even weight loss was noted at 3 and 12 mg/kg/day during the first two weeks. Thereafter weight gains were generally similar to controls and the overall weight gain of high dose males and females during Days 0-188 was 6% and 10% lower than control. Histopathology findings included slight white matter vacuolation in brain and cervical spinal cord (only in early decedent high dose females, but not in early decedent males or in scheduled sacrifice), minimal mucosal hyperplasia and minimal to slight increase of lymphoid cells in the lamina propria of cecum (in mid-high and high dose males and in mid-low, mid-high, and high dose females), and minimal decreased secretion in seminal vesicles (in mid-low, mid-high, and high dose males and in one low dose male). It appeared that the high dose induced significant toxicity during the first 2 weeks, especially in females, followed by a clear habituation to the toxicity and partial recovery.

At the dose of 0.1 mg/kg/day, the only noteworthy effect was minimal decreased secretion in seminal vesicles seen in 1/20 male. At the dose of 1 mg/kg/day, the notable effects were minimal decreased secretion in seminal vesicles seen in 2/20 males and minor microscopic findings in cecum seen only in females. The low dose, 0.1 mg/kg/day, is considered the NOAEL in this study.

In a 13-week oral toxicity study in Beagle dogs, oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.25, 0.5 and 1.5 mg/kg/day were administered for 13 weeks. A higher incidence of excessive salivation was noted in high dose animals. Decreased body weight was noted in high dose animals (males: -11%; females: -4%) compared to control animals. No other significant treatment-related effects were noted in this study. The NOAEL was identified as 0.5 mg/kg/day.

In a chronic oral toxicity study in Beagle dogs, oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 0.5, and 1.5 mg/kg/day were administered for 39 weeks. No treatment-related effects on mortality, hematology, urinalysis, ECG, gross pathology, or histopathology examination were noted in this study. Dilated pupils were noted in high dose animals from the first or the second week of administration. The mydriasis was observed until the end of study but was generally reversible between daily treatments. Hypersalivation was also noted in high dose animals. A body weight loss was observed in both high dose males and females during the first week of dosing. The NOAEL was identified as 0.5 mg/kg/day.

In a 13-week dermal toxicity study in Gottingen minipigs, topical doses of ivermectin 0 (vehicle), 2, 6 and 20 mg/kg/day (0.1, 0.3 and 1% ivermectin cream applied to ~10% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered for 13 weeks. No treatment-related effects on mortality, clinical signs, dermal irritation, body weight, food consumption, ophthalmology, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 20 mg/kg/day, (1% cream).

In a chronic dermal toxicity study in Gottingen minipigs, topical doses of ivermectin 0 (vehicle), 2, 6 and 20 mg/kg/day (0.1, 0.3 and 1% ivermectin cream applied to ~20% BSA, occluded, at a dose volume of 2 ml/kg/day) were administered for 9 months. No treatment-related effects on mortality, clinical signs, dermal irritation, body weight, ophthalmology, blood pressure, ECG, clinical pathology, gross pathology, organs weights or histopathology were noted in this study. The NOAEL was identified as 20 mg/kg/day (1% cream).

A standard battery of genotoxicity studies was conducted with ivermectin. No genotoxicity was observed in the Ames test, the mouse lymphoma assay using L5178Y TK<sup>+/+</sup> mouse lymphoma cells, or an in vivo micronucleus test in rats.

Carcinogenicity studies were conducted in mice and rats. In a 2-year dermal mouse carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 1, 3 and 10 mg/kg/day ivermectin (0.1%, 0.3%, and 1.0% cream, unoccluded, applied to 10% BSA

at 1 mg/kg) were administered to CD-1 mouse for 2 years. Low dose males were necropsied during Week 100 due to declining survival. All other male groups were necropsied during Week 101. All females were necropsied during Weeks 105 and 106. There were no significant differences in the cumulative survival rate among different groups in either gender. Throughout the study, the mean body weight was slightly lower in the high dose male group, compared to the two control groups. Non-neoplastic histopathological findings were noted in treated skin and lymphoid organs, including epidermal hyperplasia, amyloidosis, inflammation, ulceration and pustule formation in skin and lymphoid hyperplasia in lymphoid organs. These effects were likely vehicle-related, but a relationship to test article treatment could not be ruled out. There were no significant test article-related neoplastic findings in either sex according to the statistical criteria used by the Executive CAC.

In a 2-year oral rat carcinogenicity study, oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3 and 9 mg/kg/day ivermectin were administered to Wistar rats. There were no significant differences in the cumulative survival rate among different groups in females. Mortality rate was higher in high dose males compared to other male groups. Ten high dose females had treatment-related clinical signs during the first two weeks of treatment. Six out of these 10 females were euthanized moribund on Days 6 and 7. The mean body weights of high dose animals were lower in the first few weeks and then gradually recovered to control level. It appeared that the high dose induced significant toxicity during the first few weeks, especially in females, followed by a habituation to the toxicity and recovery. Macroscopically, a higher incidence of hepatic masses and raised areas was noted in high dose males. An increase in liver weight was noted in mid dose and high dose animals. In liver, a dose-related increase in the incidence of periportal to diffuse vacuolation was noted at mid dose and high dose. There were no statistically significant test article-related neoplastic findings in females. A statistically significant increase in the incidence of hepatocellular adenoma was noted in high dose males. There were no statistically significant test article-related neoplastic findings in low dose or mid dose males.

The multiples of human exposure at 3 mg/kg/day dose in male rats, where no significant treatment-related neoplastic findings were noted, are ~600. The multiples of human exposure at 9 mg/kg/day dose in female rats, where no significant treatment-related neoplastic findings were noted, are ~2000. In addition, very high systemic exposure levels (up to 1369-fold in males and 747-fold in females compared to human exposure) were achieved in the 2-year dermal mouse carcinogenicity study with no treatment-related neoplastic findings. Overall the carcinogenic risk associated with the clinical use of ivermectin 1% cream is considered minimal.

In a 12-month photocarcinogenicity study in hairless mice, topical doses of 25 µl/mouse 0 (vehicle), 0.1%, 0.3%, and 1.0% ivermectin cream were administered once daily, five days per week, for 40 weeks. Two untreated control groups were also included, with one group receiving a lower UVR dose (600 RBU/week, same as the treated groups) and the other group receiving a higher UVR dose (1200 RBU/week). After the completion of 40 weeks of formulation administration and UV exposure, mice were

maintained for up to an additional 12 weeks, for a total of 52 weeks. There were no significant test article-related effects on survival. Skin reactions occurred in both male and female mice and included erythema, edema, flaking, thickening, wrinkling, residue, white raised areas and erythemic raised areas. The vehicle with UV exposure elicited skin irritation and ivermectin cream exacerbated the skin irritation. Treatment with vehicle exhibited an enhancement of photocarcinogenesis in both males and females, as compared to the untreated group with low UV exposure. Topical treatment with ivermectin cream elicited further enhancement of UV-induced photocarcinogenesis, in both males and females, at all dose levels, as compared to the vehicle control group. However, per the ICH M3(R2) guidance document we no longer recommend conduct of photocarcinogenicity studies for topical drug products, as the current photocarcinogenicity testing in hairless rodents is not considered useful for the evaluation of human risk. Therefore, the study results are not recommended to be included in the ivermectin cream drug label.

Reproductive and developmental toxicity studies were conducted in rats and rabbits. In a fertility study in rats, oral (gavage) doses of ivermectin 0 (vehicle: 0.5% carboxymethylcellulose), 0.1, 1 and 9 mg/kg/day were administered to SD rats. Males were treated 28 days before mating, during mating and until the day before necropsy. Females were treated 14 days before mating, throughout mating and until Day 7 of gestation. In total, 7/30 high dose males and 18/30 high dose females were terminated in a moribund condition. Necropsy of the decedent animals did not reveal the cause of death. There was no mortality at the lower dose levels. The mating performance and fertility of the high dose group could not be adequately assessed due to the mortality. The precoital period was generally prolonged in the high dose group (5.3 days on average), compared with the control group (2.9 days on average). There were no treatment-related effects on pregnancy rate. At the scheduled sacrifice, necropsy examination did not reveal any significant lesions in any group. There were no treatment-related effects on organ weight of testis, epididymis, or ovary. There were no treatment-related effects on sperm counts, sperm motility, or caesarean data. The mid dose, 1.0 mg/kg/day was identified as the NOAEL in this study, for both general toxicity and mating performance/fertility, in both males and females.

In an embryofetal development study in rats, oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1.5, 4 and 12 mg/kg/day ivermectin were administered to pregnant SD rats during gestational Days 6 – 17. Treatment-related mortality was noted in high dose dams (3/25). A treatment-related decrease in body weight was noted in high dose animals. Treatment-related clinical signs noted in high dose animals included red material around the nose, forelimbs and urogenital areas and decreased defecation. No treatment-related maternal toxicity was noted in low or mid dose dams. A treatment-related decrease in fetal body weight was noted in the high dose group. No treatment-related effects on the number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss or viable fetuses were noted. No treatment-related effects on gravid uterine weights or fetal sex ratio were noted. An increased mean litter proportion of cleft palate was noted in the high dose group (0.9% per litter) compared to the control group (0% per litter). No treatment-related fetal toxicity or

teratogenicity was noted in low or mid dose groups. The NOAEL for maternal toxicity was identified as 4 mg/kg/day. The NOAEL for embryofetal toxicity and teratogenicity was also identified as 4 mg/kg/day.

In an embryofetal development study in rabbits, oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 0.5, 1.5 and 4.5 mg/kg/day ivermectin were administered to pregnant New Zealand White rabbits during gestational days 7 – 20. Treatment-related mortality was noted at high dose (1/22). One high dose female aborted on gestation day 23. Treatment-related clinical signs noted in high dose animals included decreased defecation, small feces and clear or green material around the mouth and/or nose. Significant decreased maternal body weight and maternal body weight gain were noted in high dose animals. No significant treatment-related maternal toxicity was noted at low dose or mid dose. No treatment-related effects on the mean number of corpora lutea, uterine implantations, resorptions, pre-/post-implantation loss or viable fetuses per dam were noted. No treatment-related effect on gravid uterine weights was noted in this study. No treatment-related effect on fetal body weight or fetal sex ratio was noted in this study. The number of viable fetuses (litters) with noted malformations were 1 (1), 0 (0), 3 (2) and 12 (7) in control, low, mid and high dose groups, respectively. Seven fetuses from 3 litters in the high dose group had carpal flexure (primarily bilateral) with 1 litter having 5 out of 12 fetuses affected. The mean litter proportion of carpal flexure (4.2% per litter) in this group was above the maximum mean value in the testing laboratory historical control data (0.8% per litter). Although there was no underlying skeletal alterations identified for the carpal flexure finding observed in the high dose group, without actual data that clearly demonstrate the reversal of the carpal flexure finding, it is considered a malformation and significant. No other treatment-related malformations were noted in this study. The NOAEL for maternal toxicity was identified as 1.5 mg/kg/day. The NOAEL for embryofetal development and teratogenicity was also identified as 1.5 mg/kg/day, under the study conditions.

A second embryofetal development study in rabbits was conducted. Oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 2.5 and 3.5 mg/kg/day ivermectin were administered to pregnant New Zealand White rabbits during gestational days 7 – 20. Treatment-related mortality/moribundity was noted at both doses (1/22 at low dose and 2/22 at high dose). Decreased defecation was noted at both doses. Rales were observed in 3 high dose females. Dose-related body weight loss and/or decrease in body weight gain were noted at both doses. No significant treatment-related maternal macroscopic findings were noted during necropsy. No treatment-related effects on the mean number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss and viable fetuses per dam were noted. A decrease in mean gravid uterine weight and mean fetal weight was noted at high dose. No treatment-related effects on fetal morphology were noted in this study. The NOAEL for maternal toxicity could not be identified in this study because mortality/moribundity was seen at both dose levels. The NOAEL for embryofetal toxicity was considered to be 2.5 mg/kg/day ivermectin, based on fetal weight decrease noted at 3.5 mg/kg/day. The NOAEL for teratogenicity was considered to be the high dose, 3.5 mg/kg/day.

A pre- and postnatal development study was conducted in rats (published literature). Oral (gavage) doses of 0 (vehicle: peanut oil), 1, 2 and 4 mg/kg/day ivermectin were administered to female SD rats during gestational days 6-20 and lactation days 2-20. F<sub>1</sub> animals were exposed to the test article in utero and through lactation. Seven out of 13 high dose dams were not treated during lactation because ivermectin was shown highly toxic during lactation (all the high dose pups died during lactation days 3-8). The mortality rate in mid dose offspring was also significantly high (30.7%). No significant differences were noted in the length of gestation, number of pups per litter or sex ratio. In the offspring, a significant decrease in body weight was noted in mid dose and high dose groups. Ivermectin adversely affected the behavior development of newborn rats at all dose levels, particularly on motor development and general activity. A NOAEL for postnatal development was not identified in this study.

In a multi-generation study in SD rats, ivermectin was administered orally at dose levels of 0 (vehicle: sesame oil), 0.4, 1.2 or 3.6 mg/kg/day. The study design was to dose F<sub>0</sub>, F<sub>1b</sub> and F<sub>2b</sub> weanling male and female rats for 70 days and then throughout the production of two litters in each of three successive generations. There was no treatment-related mortality, physical signs of toxicity or adverse effects on body weight gains in F<sub>0</sub> animals. There were no effects on the time to mating or pregnancy rate at any dose level. There was a high mortality rate (53%) during the lactation period of F<sub>1a</sub> offspring in the 3.6 mg/kg/day dose group (the majority of the offspring died between postnatal days 5 and 10). Due to the high mortality of F<sub>1</sub> animals at high dose, the F<sub>0</sub> male and female rats in this dose group were terminated after weaning of the surviving F<sub>1a</sub> offspring. A significant increase in F<sub>1b</sub> pup mortality was noted between postnatal days 2 and 7 in the 0.4 and 1.2 mg/kg/day dose groups. Lower body weights and retardation of auditory startle reflex were also noted in F<sub>1b</sub> offspring in the 0.4 and 1.2 mg/kg/day dose groups. In the F<sub>2a</sub> generation, there were significant increases in pup mortality between postnatal days 2 and 7 in the 0.4 and 1.2 mg/kg/day dose groups. Due to increased mortality in F<sub>1b</sub> and F<sub>2a</sub> litters treated at 0.4 or 1.2 mg/kg/day, no NOAEL for neonatal toxicity was identified in this study.

Subsequently the multi-generation study was repeated with lower dose levels: 0 (vehicle: sesame oil), 0.05, 0.1, 0.2 and 0.4 mg/kg/day. In this study, no treatment-related mortality, body weight change, or physical signs of toxicity among parents or offspring were noted in any dose group throughout the production of two litters in each of the F<sub>0</sub>, F<sub>1b</sub> and F<sub>2b</sub> generations. However, the mortality rate of the F<sub>3a</sub> offspring at 0.4 mg/kg/day seemed to be higher than other groups, although no statistical significance was achieved. The differences in response found in the 0.4 mg/kg/day group in the two multi-generation studies were probably due to biological variation and/or the relatively steep dose-response curve for neonatal toxicity. A NOAEL level of 0.2 mg/kg/day for neonatal toxicity was identified in the two multi-generation studies, under the study conditions.

A cross-fostering study was conducted to determine whether the neonatal toxicity was the result of prenatal, postnatal or a combination of pre- and postnatal exposure to ivermectin. Oral doses of 0 (vehicle: sesame oil) and 2.5 mg/kg/day ivermectin were

administered to female SD rats for 61 days. These F<sub>0</sub> females were mated with untreated males of the same strain, and ivermectin administration was continued throughout mating, gestation and lactation of F<sub>1</sub> pups until postnatal day 20. On postnatal day 1, all litters were cross-fostered to F<sub>0</sub> dams, generating four groups: control F<sub>0</sub> x control F<sub>1</sub> (Group 1), control F<sub>0</sub> x treated F<sub>1</sub> (Group 2), treated F<sub>0</sub> x treated F<sub>1</sub> (Group 3) and treated F<sub>0</sub> x control F<sub>1</sub> (Group 4). Postnatal survival, growth and development of offspring in all groups were evaluated until weaning on postnatal day 25. An increase in mortality and a decrease in body weight were noted in the offspring of Groups 3 and 4, compared to control. In contrast, the survival, growth and development of pups from treated dams that were cross-fostered to control dams (Group 2) were comparable to Group 1. The study results indicated that the neonatal toxicity of ivermectin in rats was mainly due to postnatal exposure (through lactation), while in utero exposure to ivermectin did not significantly affect the mortality or body weight gain when compared to control, under the study conditions.

To determine the reason for the high sensitivity of neonatal rats to ivermectin, a PK study was conducted to measure concentrations of ivermectin and/or its metabolites in milk and in tissues from adult and neonatal rats. The study results showed that concentrations of ivermectin in milk from treated dams were 3-4 times higher than the maternal plasma level and resulted in a progressive increase in plasma levels in the offspring. In addition, the plasma-brain drug concentration ratio in offspring increased from 1 on post-partum days 1 and 4 to 2-3 on post-partum days 6 and 10. These data were consistent with the postnatal formation of a blood-brain barrier in rats. The study results help to explain the high sensitivity of neonatal rats to ivermectin's toxicity. It might also indicate that the toxicity profile of ivermectin in neonatal rats may be species specific. In other species in which the excretion of ivermectin in milk is lower and/or the blood-brain barrier is formed prenatally (such as human), the potential for ivermectin induced neonatal toxicity through lactation may be considerably reduced.

The 1% ivermectin cream was an irritant to intact and abraded rabbit skin after a 24 hour topical administration under occlusion. However, the 1% ivermectin cream was classified as a non-irritant to rabbit eyes, in an acute eye irritation study. Concentrations of ivermectin  $\leq$  0.5% in a propylene glycol vehicle did not elicit a positive response in the mouse local lymph node assay. Concentrations of ivermectin  $>$  0.5% in propylene glycol could not be assessed in the mouse local lymph node assay due to mortality. The 1% ivermectin cream was classified as a sensitizer in guinea pigs. The 1% ivermectin cream did not appear to elicit a phototoxic response in guinea pigs.

The multiples of human exposure based on AUC comparisons between the NOAELs identified in the animal toxicology studies and the maximum clinical dose are shown in the following table.

Study	Species	Toxicity	NOAEL (mg/kg/day)	AUC <sub>0-24h</sub> * (ng•hr/ml)	Multiples of Human Exposure**
13-week dermal	mouse	none	10 (1% cream)	27408	774
4-week dermal	rat	none	20 (1% cream)	18370	518
13-week oral	rat	none	3	7470	211
13-week oral	rat	mortality, seminal vesicle, thymus	1	1431	40
27-week oral	rat	mortality, body weight, seminal vesicle, cecum	0.1	173	5
13-week oral	dog	body weight, salivation	0.5	4166	118
39-week oral	dog	mydriasis, body weight, salivation	0.5	4154	117
13-week dermal	minipig	none	20 (1% cream)	95	3
9-month dermal	minipig	none	20 (1% cream)	66	2
2-year dermal carcinogenicity	mouse	no tumor findings in males or females	M: 10 (1% cream)	M: 48519	1369
			F: 10 (1% cream)	F: 26461	747
2-year oral carcinogenicity	rat	no tumor findings in females, hepatocellular adenoma in males	M: 3	M: 21226	599
			F: 9	F: 69407	1959
fertility study	rat	mortality, prolonged precoital period	M: 1	M: 2414	68
			F: 1	F: 2887	81
oral embryofetal development	rat	mortality, maternal and fetal body weight, cleft palate	maternal, embryofetal, and teratogenicity: 4	25099	708
oral embryofetal development	rabbit	mortality, maternal body weight, carpal flexure	maternal, embryofetal, and teratogenicity: 1.5	2766	78
oral embryofetal development	rabbit	mortality, maternal and fetal body weight	maternal: none	n/a	n/a
			embryofetal: 2.5	2545	72
			teratogenicity: 3.5	5159	146
pre- and postnatal development	rat	mortality, fetal body weight, motor development	none	n/a	n/a
multi-generation	rat	mortality, fetal body weight	0.2	not measured	n/a

\*For single value: the lower AUC value between two sexes was used

\*\*Comparing to Day 28 AUC<sub>0-24hr</sub> (35.43 ng•hr/ml) obtained under maximum clinical use conditions (1 g ivermectin 1% cream, applied to face once daily for 4 weeks, 0.17 mg/kg/day ivermectin for a 60 kg subject)

The nonclinical safety program for ivermectin 1% cream is complete. The proposed clinical use of SOOLANTRA Cream is supported by nonclinical data. This NDA is approvable from a pharmacology/toxicology perspective. No postmarketing requirement is recommended for this NDA.

## 12 Appendix/Attachments

Appendix I: Executive CAC meeting minutes

### Executive CAC

**Date of Meeting:** June 17, 2014

**Committee:** Abigail Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Timothy McGovern, Ph.D., OND IO, Alternate Member  
Barbara Hill, Ph.D., DDDP, Supervisor  
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

**Author of Draft:** Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA #:** 206255

**Drug Name:** SOOLANTRA (ivermectin) Cream, 1%

**Sponsor:** Galderma Research and Development, Cranbury, NJ

### Background:

Ivermectin is an anti-parasitic agent. The sponsor intends to develop SOOLANTRA (ivermectin) Cream, 1% for the treatment of rosacea. On 12/18/2006 the sponsor submitted two carcinogenicity study protocols (a 2-year dermal mouse carcinogenicity study and a 2-year oral rat carcinogenicity study) to IND 76064. An Exec CAC meeting was conducted on 01/23/2007 and the Committee's recommendations were relayed to the sponsor on 01/25/2007. Subsequently the sponsor conducted the two carcinogenicity studies per CAC's recommendations and the final study reports were submitted to NDA 206255 on 12/20/2013.

### Dermal Mouse Carcinogenicity Study:

In a 2-year dermal mouse carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 1, 3 and 10 mg/kg/day ivermectin (0.1%, 0.3%, and 1.0% cream applied at 1 ml/kg) were administered to CD-1 mice. The vehicle contains (b) (4), carbomer copolymer type B (b) (4), dimethicone (b) (4), edetate disodium (b) (4), citric acid monohydrate (b) (4), cetyl alcohol (b) (4), stearyl alcohol

(b) (4) %, polyoxyl 20 cetostearyl ether (b) (4), sorbitan monostearate (b) (4), methyl paraben (b) (4), propyl paraben (b) (4), phenoxyethanol (b) (4), propylene glycol (b) (4), oleyl alcohol (b) (4), sodium hydroxide (b) (4) and purified water (b) (4).

Low dose males were necropsied during Week 100 due to declining survival. All other male groups were necropsied during Week 101. All females were necropsied during Weeks 105 and 106. There were no significant differences in the cumulative survival rate among different groups in either gender. Throughout the study, the mean body weight was slightly lower in the high dose male group, compared to the two control groups.

For histopathological examination, a complete list of tissues was examined for water control, vehicle control, and high dose groups. Histology was examined for all tumors in all groups. Non-neoplastic histopathological findings were noted in treated skin and lymphoid organs, including epidermal hyperplasia, amyloidosis, inflammation, ulceration and pustule formation in skin and lymphoid hyperplasia in lymphoid organs. These effects were likely vehicle-related, but a relationship to test article treatment could not be ruled out. There were no significant test article-related neoplastic findings in either sex according to the statistical criteria used by the Executive CAC.

#### **Oral Rat Carcinogenicity Study:**

In a 2-year oral rat carcinogenicity study, oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3 and 9 mg/kg/day ivermectin were administered to Wistar rats.

There were no significant differences in the cumulative survival rate among different groups in females. Mortality rate was higher in high dose males compared to other male groups. Ten high dose females had treatment-related clinical signs during the first two weeks of treatment. Six out of these 10 females were euthanized moribund on Days 6 and 7. The mean body weights of high dose animals were lower in the first few weeks and then gradually recovered to control level. It appeared that the high dose induced significant toxicity during the first few weeks, especially in females, followed by a habituation to the toxicity and recovery. Macroscopically, a higher incidence of hepatic masses and raised areas was noted in high dose males. An increase in liver weight was noted in mid dose and high dose animals.

For histopathological examination, a complete list of tissues was examined for vehicle control and high dose groups. In low dose and mid dose animals, histology was examined for 1) all macroscopic findings, 2) liver in males and 3) spleen, thymus, bone marrow (sternum), lymph nodes (mandibular and mesenteric), pancreas and eyes in males and females. In liver, a dose-related increase in the incidence of periportal to diffuse vacuolation was noted at mid dose and high dose. There were no statistically significant test article-related neoplastic findings in females. A statistically significant increase in the incidence of hepatocellular adenoma was noted in high dose males. There were no statistically significant test article-related neoplastic findings in low dose

or mid dose males. The multiples of human exposure for the mid dose and high dose in male rats were 599 and 1766, respectively, when the AUC values obtained in mid dose and high dose males in this study were compared to a mean human AUC value obtained in a maximum clinical use PK trial.

**Executive CAC Recommendations and Conclusions:**

- 1) Dermal mouse carcinogenicity study:
  - The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
  - The Committee concluded that there were no drug-related neoplasms in the study.
  
- 2) Oral rat carcinogenicity study:
  - The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
  - The Committee concluded that hepatocellular adenomas in high dose male livers were drug-related and there were no drug-related neoplasms in female rats.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, DDDP  
/B. Hill, Supervisor, DDDP  
/J. Wang, P/T reviewer, DDDP  
/P. Philips, Project Manager, DDDP  
/A. Seifried, OND IO

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JIANYONG WANG  
08/04/2014

BARBARA A HILL  
08/04/2014

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 206255

**Applicant:** Galderma Research and  
Development, Inc., Cranbury, NJ

**Stamp Date:**  
12/20/2013

**Drug Name:** SOOLANTRA  
(ivermectin) Cream, 1%

**NDA Type:** 505(b)(2)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Pivotal studies include chronic oral toxicity studies in rats and dogs, a chronic dermal toxicity study in minipigs, a 2-year dermal mouse carcinogenicity study, a 2-year oral rat carcinogenicity study, a fertility study in rats, and embryofetal developmental studies in rats and rabbits. The sponsor submitted literature to provide pre- and post-natal developmental toxicity information, which makes this NDA a 505(b)(2) submission.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The labeling for Sections 8.1, 8.3, and 13.1 needs to be modified.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			It is not applicable to this NDA.
11	Has the applicant addressed any abuse potential issues in the submission?			It is not applicable to this NDA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This NDA is not to support a Rx to OTC switch.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES**

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

N/A.

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

None at this time.

Jianyong Wang 01/28/2014  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Barbara Hill see sign-off date  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JIANYONG WANG  
02/03/2014

BARBARA A HILL  
02/03/2014