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*APPLICATION NUMBER:*

**206255Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

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NDA #: 206255  
Submission Date: December 20, 2013  
Brand Name: Soolantra  
Generic Name: Ivermectin cream, 1%  
Dosage Form: Cream  
Dosage Strength: 1%  
Reviewer: Chinmay Shukla, Ph.D.  
Team Leader: Doanh Tran, Ph.D.  
OCP Division: Division of Clinical Pharmacology - 3  
OND Division: Division of Dermatology and Dental Products  
Sponsor: Galderma Research and Development Inc.  
Relevant IND(s): 076,064  
Submission Type: New-submission  
Indication: Topical treatment of inflammatory lesions of rosacea in adults

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### **1. Executive Summary**

Ivermectin (CD5024) belongs to avermectin class of compounds which mostly includes broad-spectrum anti-parasitic agent. The Applicant has developed a 1% Cream formulation for once daily topical treatment of inflammatory rosacea in adult subjects.

The Applicant has followed 505(b)(2) regulatory pathway and would like to rely on published literature to describe the peri- and post-natal developmental toxicity of ivermectin. Apart from this, the Applicant has not cross referenced any other data.

The active ingredient, ivermectin, is currently approved in the US as a single oral dose (NDA 050742, Stromectol<sup>®</sup>, Approved on 11/22/1996, Applicant - Merck Sharp Dohme), with indications for use in strongyloidiasis of the intestinal tract and onchocerciasis in

adults and in children with a minimum weight of 15 kg. Ivermectin is also approved as a lotion indicated for the topical treatment of head lice infestations in subjects 6 months of age and older (NDA 202736, Sklice<sup>®</sup>, Approved on 02/07/2012, Applicant - Sanofi Pasteur Inc.).

The Applicant has conducted 14 clinical trials and these included three local tolerance trials, an oral thorough QTc (TQT) trial, two pharmacokinetic (PK) trials – one in healthy subjects and other one in subject with rosacea under maximal use conditions, one proof of concept trial and one dose ranging trial. The Phase 3 program included two identical pivotal trials consisting of a 12-week, double-blind, vehicle-controlled design aimed to assess efficacy and safety followed by a 40-week long term active-controlled safety extension part. In parallel, a multicenter, investigator-blind, Phase 3 clinical trial was conducted in Europe, comparing Ivermectin 1% Cream applied once daily (QD) versus Metronidazole 0.75% Cream applied twice daily (BID) for 16 weeks (Part A) followed by an extension period of 36 weeks (Part B) aimed to assess relapse. Part B of this trial was ongoing when this NDA was submitted and hence the Applicant has not submitted the results for Part B in this submission.

### **1.1 Recommendation**

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

### **1.2 Post-Marketing Commitments**

None

### **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

Pharmacokinetics: The applicant conducted PK assessment under maximal use conditions (Trial RD.03.SRE.40064) and assessed plasma concentrations of ivermectin and its major metabolites - M1, M2, M3/M4 via serial blood sampling on Day 0, 14 and 28. Adult male and female subjects (n = 15) with severe papulopustular rosacea (PPR) were enrolled in this trial. Systemic ivermectin concentrations were quantifiable in all the subjects after the first dose and steady state was reached by Day 14. The mean  $\pm$  SD values of  $C_{max}$ ,  $AUC_{0-24}$  and  $T_{max}$  on Day 14 were  $2.10 \pm 1.04$  ng/mL,  $36.14 \pm 15.56$  ng\*h/mL and  $10 \pm 8$  h, respectively. Following the last topical application on Day 28, the mean  $\pm$  SD value for apparent  $t_{1/2}$  was  $155 \pm 40$  hours and the prolonged value of  $t_{1/2}$  indicates that ivermectin was slowly cleared from the plasma after the treatment was stopped. The Applicant was unable to validate the bioanalytical method for metabolites due to lack to standards and due to this, relative quantification of metabolites was carried out using the calibration curve of the parent. Though this is not an ideal approach, this was considered as reasonable in this case due to large margin of safety based on animal toxicity data and lack of any systemic side effects in the clinical trials. The relative quantification approach showed that the metabolite levels were also at steady state by Day 14.

Dose finding: The drug development program included a dose finding trial (RD.03.SRE.40027) which evaluated dose-response relationship of 0.1%, 0.3 % and 1% cream applied once daily, and 1% cream applied twice daily. Also included were metronidazole 0.75% cream (active control) and vehicle cream arms. The results showed 1% QD dose had the best response with no further improvement by increasing the frequency of application to BID. The 1% cream, once daily, was chosen for development based on the superior dose response compared to other regimens as evaluated by the primary efficacy endpoint which is the % change at week 12 from baseline in inflammatory lesion counts.

In vitro metabolism and cytochrome P450 inhibition/induction: Ivermectin is a substrate of CYP3A4 but concomitant drugs that are inhibitors of CYP3A4 are not expected to increase ivermectin levels in a clinically meaningful way because steady state plasma levels under maximal use conditions had at least a 66 fold margin of safety based on the animal toxicity data and the treatment emergent adverse events (TEAEs) observed in the two Phase 3 trials were mostly local skin reactions. In vitro metabolism studies indicated that CYP3A4 was involved in the production of metabolites M1, M2 and M3/M4. In-vitro drug interaction studies indicated that at therapeutic concentrations, ivermectin is not expected to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11; or induce CYP1A2, CYP2B6, CYP2C9, or CYP3A4.

QTc interval prolongation assessment: The Applicant assessed QT prolongation (RD.06.SRE.18120) using a single oral dose of 6 mg of ivermectin (Stromectol<sup>®</sup>) and the results indicated that ivermectin did not produce any significant QT prolongation. The mean  $C_{max}$  following oral administration was  $13.86 \pm 7.22$  ng/mL and based on cross trial comparison, this was approximately 7 fold higher than the  $C_{max}$  of ivermectin at steady state under maximal use conditions following once daily topical application of the 1% Cream. Therefore once daily topical application of ivermectin 1% Cream in subjects with rosacea is not expected to produce any QT prolongation.

Exposure-response relationship for neutropenia: The applicant conducted an assessment of neutropenia trial (RD.03.SRE.40106) to evaluate exposure-response with respect to neutropenia. The results of this trial indicated that there was no exposure-relationship between ivermectin systemic concentrations and decrease in neutrophil counts. This finding was further confirmed in the two Phase 3 trials (RD.06.SRE.18170 and RD.06.SRE.18171) and based on the observed data; the incidence of neutropenia does not appear to be treatment related.

Pediatric assessment: According to the Applicant, the occurrence of rosacea in children is a rare. Due to low prevalence of the disease in children, the Applicant has applied for full waiver of pediatric studies in subjects below 18 years of age as studies would be highly impractical to conduct due to lack of subjects. The Pediatric Review Committee (PeRC) agreed with the Applicant's request for a full waiver of pediatric assessment at a meeting held on July 2, 2014.

**Clinical Pharmacology Briefing:** An optional intra-division level briefing was conducted on September 24, 2014 with the following in attendance: Hae-Young Ahn, E. Dennis Bashaw, Jane Liedtka, Jill Lindstrom, Doanh Tran and Chinmay Shukla.

## **2. Question Based Review**

### **2.1 Regulatory pathway**

#### ***2.1.1 What regulatory pathway has the Applicant followed?***

The Applicant has followed 505(b)(2) regulatory pathway and would like to rely on published literature to describe the peri- and post-natal developmental toxicity of ivermectin. Apart from this, the Applicant has not cross referenced any other data.

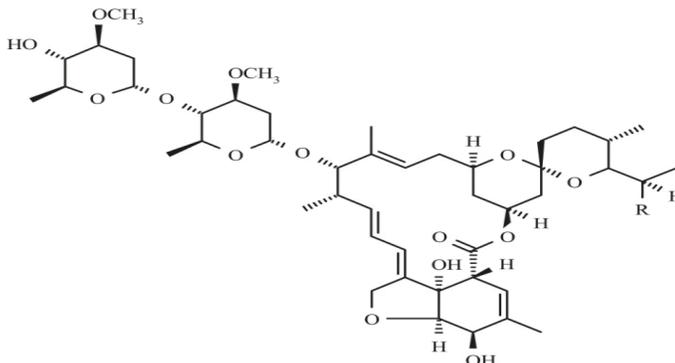
**Reviewer comments:** *The Applicant has not conducted any relative bioavailability (BA) trial to compare the BA of their formulation to the ones used in the publish literature they plan to reference. This reviewer contacted the Pharmacology-Toxicology reviewer Dr. Jianyong Wang regarding this issue and according to Dr. Wang a relative BA trial is not needed.*

### **2.2 General Attributes of the Drug**

#### ***2.2.1 What are the highlights of the chemistry and the formulation?***

**Drug substance and Formulation:** Ivermectin contains not less than 90% of H<sub>2</sub>B<sub>1a</sub> (major component). The molecular formula of H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub> is C<sub>48</sub>H<sub>74</sub>O<sub>14</sub> and C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>, respectively and the molecular weight of H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub> is 875 and 861, respectively. The chemical structure of ivermectin is shown in Figure 1.

***Figure 1: Structure of ivermectin***



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>

**Formulation:** Ivermectin 1% Cream is a white to pale yellow homogeneous cream containing 1% w/w (10 mg/g) of ivermectin as the drug substance. The composition of the to-be-marketed formulation is shown in Table 1. The Sponsor changed the

manufacturing process; however the overall composition of the formulation remained the same. The proposed commercial formulation manufactured by the new process was not used in any of the clinical trials and the formulation manufactured by the old process was used in Phase 3 clinical trials and maximal use PK trial. The Summary of formulations used in each clinical trial is in Appendix 1.

**Table 1: Qualitative and quantitative composition of to-be-marketed formulation of Ivermectin Cream, 1%**

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				USP-NF
Carbomer copolymer (type B)				USP-NF
Dimethicone (b) (4)				USP-NF
Edetate disodium				USP
Citric acid monohydrate				USP-NF
Cetyl alcohol				USP-NF
Stearyl alcohol				USP-NF
Polyoxyl 20 cetostearyl ether				USP-NF
Sorbitan monostearate				USP-NF
Methylparaben				USP-NF
Propylparaben				USP-NF
Phenoxyethanol				USP-NF
Propylene glycol				USP
Oleyl alcohol				USP-NF
Sodium hydroxide (b) (4)				USP-NF
(b) (4)				
Purified water				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)

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

**Mechanism of action:** The exact mechanism of action of ivermectin in the treatment of inflammatory lesions of rosacea is not known.

**Therapeutic indication:** Topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.

**2.2.3 What is the proposed route of administration and dosage?**

**Proposed route of administration:** Topical.

Proposed dosage: Apply a pea-size amount once daily to each of the five areas of the face: forehead, chin, nose, each cheek. Spread as a thin layer across the entire face, avoiding the eyes and lips.

## 2.3 General Clinical Pharmacology

### 2.3.1 What were the clinical trials conducted to support this NDA?

Out of the 14 clinical trials, the applicant has assessed PK in 9 trials. Table 2 shows a list of all clinical trials conducted to support this application.

**Table 2: List of all clinical trials conducted to support this NDA**

<b>Trial #</b>	<b>Purpose</b>	<b>Phase 3 formulation*</b>	<b>PK</b>
<b>PHASE 1</b>			
<i>RD.03.SRE.19055</i>	<i>Cumulative irritancy potential</i>	<i>No</i>	<i>No</i>
<i>RD.03.SRE.19081</i>	<i>Cumulative irritancy potential of different formulations</i>	<i>No</i>	<i>No</i>
<i>RD.03.SRE.40007</i>	<i>Healthy subject PK</i>	<i>No</i>	<i>Yes</i>
<i>RD.03.SRE.40023</i>	<i>Irritation and sensitization potential</i>	<i>No</i>	<i>No</i>
<i>RD.06.SRE.18120</i>	<i>TQT in healthy subjects using single oral dose of ivermectin (Stromectrol®) tablets 6 mg (2 x 3 mg)</i>	<i>Not applicable</i>	<i>Yes</i>
<b>PHASE 2</b>			
<i>RD.03.SRE.2894</i>	<i>Exploratory efficacy trial</i>	<i>No</i>	<i>No</i>
<i>RD.03.SRE.40006</i>	<i>Exploratory evaluation of safety and efficacy trial</i>	<i>Yes</i>	<i>No</i>
<i>RD.03.SRE.40027</i>	<i>Dose ranging trial</i>	<i>1% Cream was Phase 3 formulation</i>	<i>Yes</i>
<i>RD.03.SRE.40064</i>	<i>Maximal use PK trial</i>	<i>Yes</i>	<i>Yes</i>
<i>RD.03.SRE.40106</i>	<i>Assessment of potential for induction of neutropenia</i>	<i>Yes</i>	<i>Yes</i>
<b>PHASE 3</b>			
<i>RD.03.SRE.40051</i>	<i>Long term safety and efficacy trial - 52 week trial terminated at 10 weeks due to low neutrophil counts)</i>	<i>Yes</i>	<i>Yes</i>
<i>RD.06.SRE.18170</i>	<i>Safety and efficacy trial</i>	<i>Yes</i>	<i>Yes</i>
<i>RD.06.SRE.18171</i>	<i>Safety and efficacy trial</i>	<i>Yes</i>	<i>Yes</i>
<i>RD.03.SRE.40173</i>	<i>Part A: Safety and efficacy trial Part B<sup>#</sup>: Assessment of pharmacoeconomic parameters (ongoing trial to evaluate the retreatment after relapse)</i>	<i>Yes</i>	<i>Yes</i>

\* The proposed to-be-marketed formulation will be manufactured by a modified manufacturing process. The to-be-marketed formulation was not used in any of the clinical trials.

#Results of Part B not submitted in this NDA.

### 2.3.2 How was the dose selected?

The dose and dosing regimen was selected based on dose-response relationship evaluated by the primary efficacy endpoint, which is the % change in inflammatory lesion counts from baseline at week 12 (Trial RD.03.SRE.40027). The trial was conducted in adult male and female subjects with papulopustular rosacea and based on the primary efficacy results (Table 3) the Applicant selected 1% Cream to be applied once daily for further development.

**Table 3: Percentage change in inflammatory lesion count at week 12**

	CD50240 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	metronidazole 0.75% BID	vehicle QD
Total n (%)	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)
Mean ± SD	-65.5± 31.5	-67.5 ± 36.8	-70.0 ± 38.1	-69.2 ± 34.3	-59.9 ± 52.2	-46.5 ± 59.4
Median	-79.3	-76.5	-78.3	-78.9	-69.2	-60.6
Minimum/Maximum	-100/31	-100/79	-100/74	-100/41	-100/212	-100/177
p-value vs. vehicle	0.158	0.061	0.006	0.014	NA	NA

### 2.3.3 What are the design features of the maximal use PK trial?

The pivotal clinical pharmacology trial was the maximal use PK trial (RD.03.SRE.40064) which was conducted by applying 1 gram of the 1% Cream once daily for 4 weeks to the face of 15 adult male and female subjects with severe papulopustular rosacea [Investigator’s Global Assessment (IGA) scores of 4 at Baseline (see Table 4)]. All drug applications were performed in the morning by a qualified person and there was no self-drug application in this trial. PK was assessed on Days 0, 14 and 28 via serial plasma sampling by obtaining one pre-dose sample at baseline followed by post-dose samples at 1, 3, 6, 9, 12, and 24 hours. Additional pre-dose plasma samples were obtained on Days 7, 14, 21, and 28 to determine C<sub>min</sub> levels. After the final dose on Day 28, additional plasma samples were obtained for another 28 days. Systemic levels of ivermectin and its metabolites M1, M2 and M3/M4 were also assessed in this trial. By Day 14, the plasma levels of ivermectin and its metabolites were at steady state and the amount of formulation used (1 gram) appears to be within the upper range of the amount used in other clinical trials.

**Table 4: Investigator’s Global Assessment (IGA) scores**

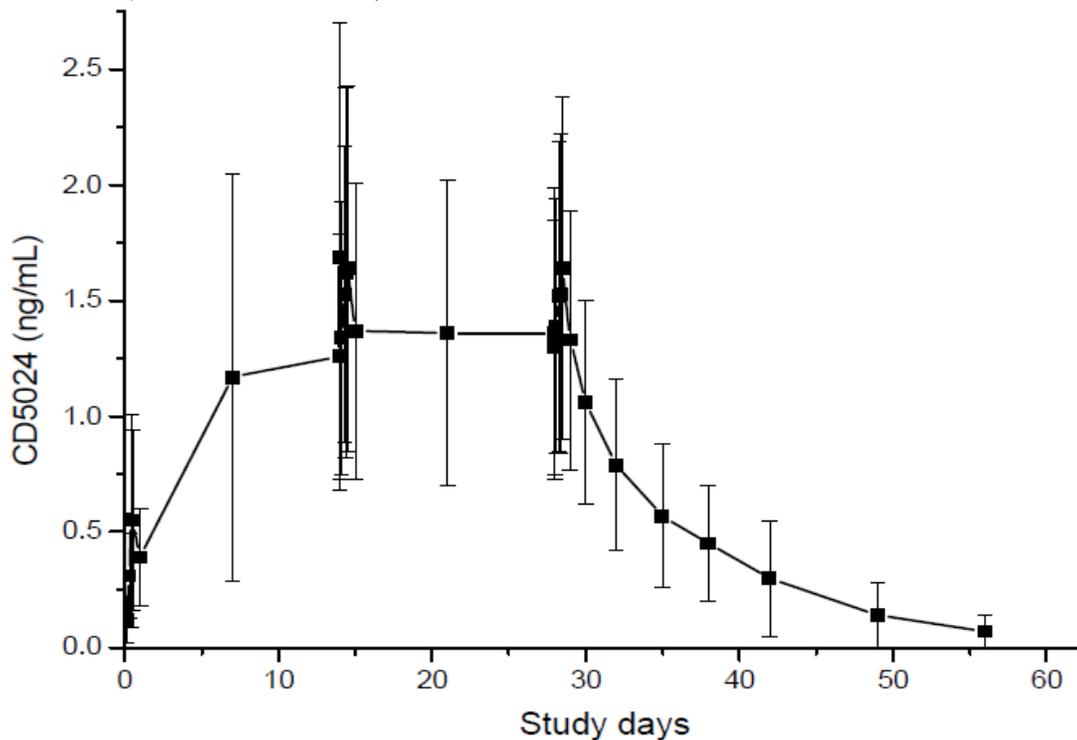
Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema or at most very mild erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

**Reviewer comments:** *In the opinion of this reviewer the maximal use PK trial was adequately designed to support labeling claims.*

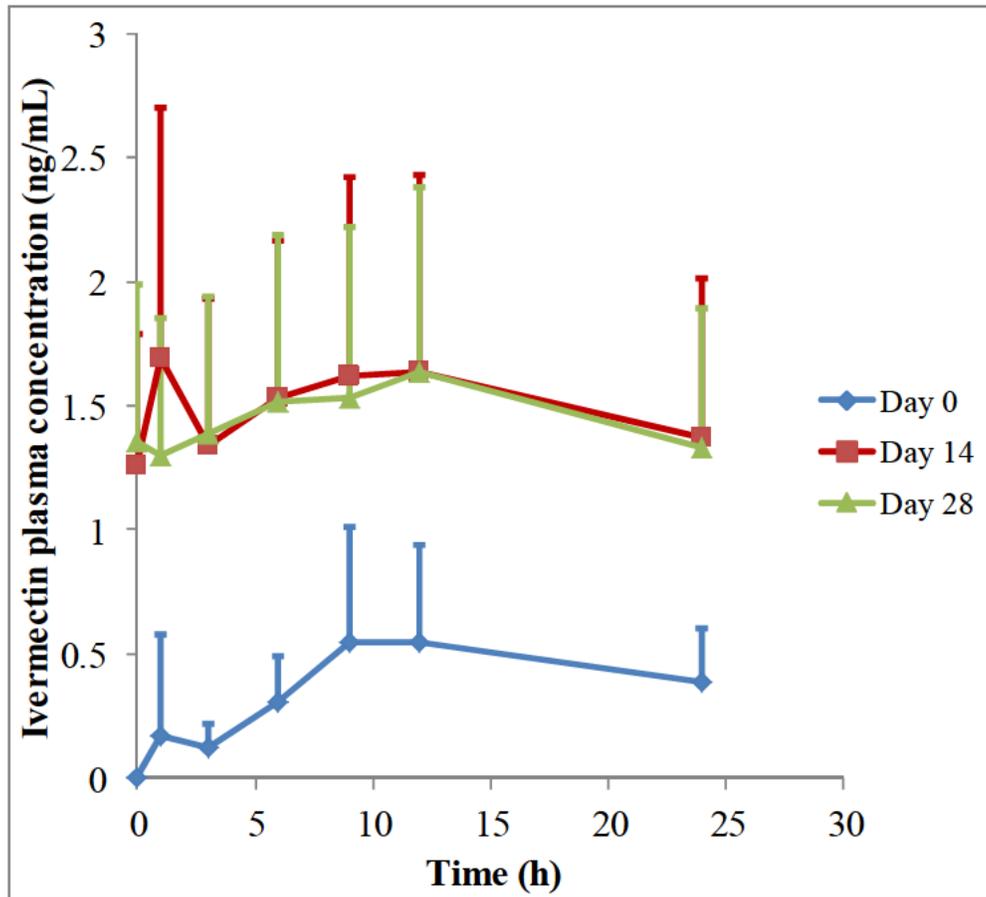
**2.3.4 What is the pharmacokinetics of ivermectin cream 1%?**

Maximal use PK trial (Trial RD.03.SRE.40064): Under maximal use conditions (Trial RD.03.SRE.40064), the PK profile for ivermectin is shown in Figure 2 and Figure 3 and the PK parameters are shown in Table 5.

**Figure 2: Plasma concentration-time curves after application of Ivermectin (CD5024) 1% Cream (Mean ± SD; N=15)**



**Figure 3: Ivermectin mean concentration versus time profile over one dosing interval on Day 0, Day 14 and Day 28**



**Table 5: PK parameters of ivermectin obtained after topical administration of Ivermectin 1% Cream in subjects with papulopustular rosacea (N=15)**

Parameters	Day 0 <sup>(a)</sup>	Day 7 <sup>(b)</sup>	Day 14	Day 21	Day 28
<b>Pre-dose/C<sub>min</sub> (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

**Reviewer comments:** Ivermectin was quantifiable in all subjects after the first dose. Steady state seems to have been reached by Day 14 based on the values of C<sub>min</sub>.

*Following topical application of Ivermectin 1% Cream QD for 28 days, the  $C_{max}$  and  $AUC_{0-24h}$  were approximately 3 fold and 4 fold higher, respectively, compared to the values observed after a single application (Day 0).*

After the last topical application of Ivermectin 1% Cream on Day 28, the mean  $\pm$  standard deviation value for apparent  $t_{1/2}$  was  $155 \pm 40$  hours ( $\sim 6.5$  days) (range of 92 to 238 hours) calculated from 14 evaluable subjects. The prolonged apparent  $t_{1/2}$  would indicate that ivermectin was slowly cleared from the plasma after treatment was stopped.

**Reviewer comments:** *A summary of PK experience from other trials is provided in Appendix 2.*

**PK of metabolites:**

Three circulating metabolites (M1, M2, and M3/M4) were also assessed in the maximal use PK trial. The applicant was unable to validate the bioanalytical method for metabolites due to lack of standard metabolite compounds and have conducted a relative quantification of metabolites based on the parent calibration curve. The results indicated that metabolite levels were at steady state by Day 14.

**Reviewer comments:** *The relative quantification of metabolites using parent calibration curve, though not an ideal approach, appears to be reasonable in this case as looking at the representative chromatograms submitted by the Applicant, the metabolite peak areas appear to be small compared to parent. Further as per the Applicant, the margin of safety for M1 and M2 is 649 and 176 fold, respectively. This reviewer contacted the Pharmacology-Toxicology reviewer Dr. Jianyong Wang who has stated that the overall toxicity of the metabolites in the animal species has been adequately established and there appears to be no significant safety concerns for the metabolites at the proposed clinical dose (for further information see Pharmacology-Toxicology review by Dr. Wang in DARRTS dated 08/04/2014). In addition to this, there were no systemic side effects observed the Phase 3 clinical trials. Due to these reasons, indirect quantification of metabolites using parent calibration curve was deemed reasonable for qualitative assessment.*

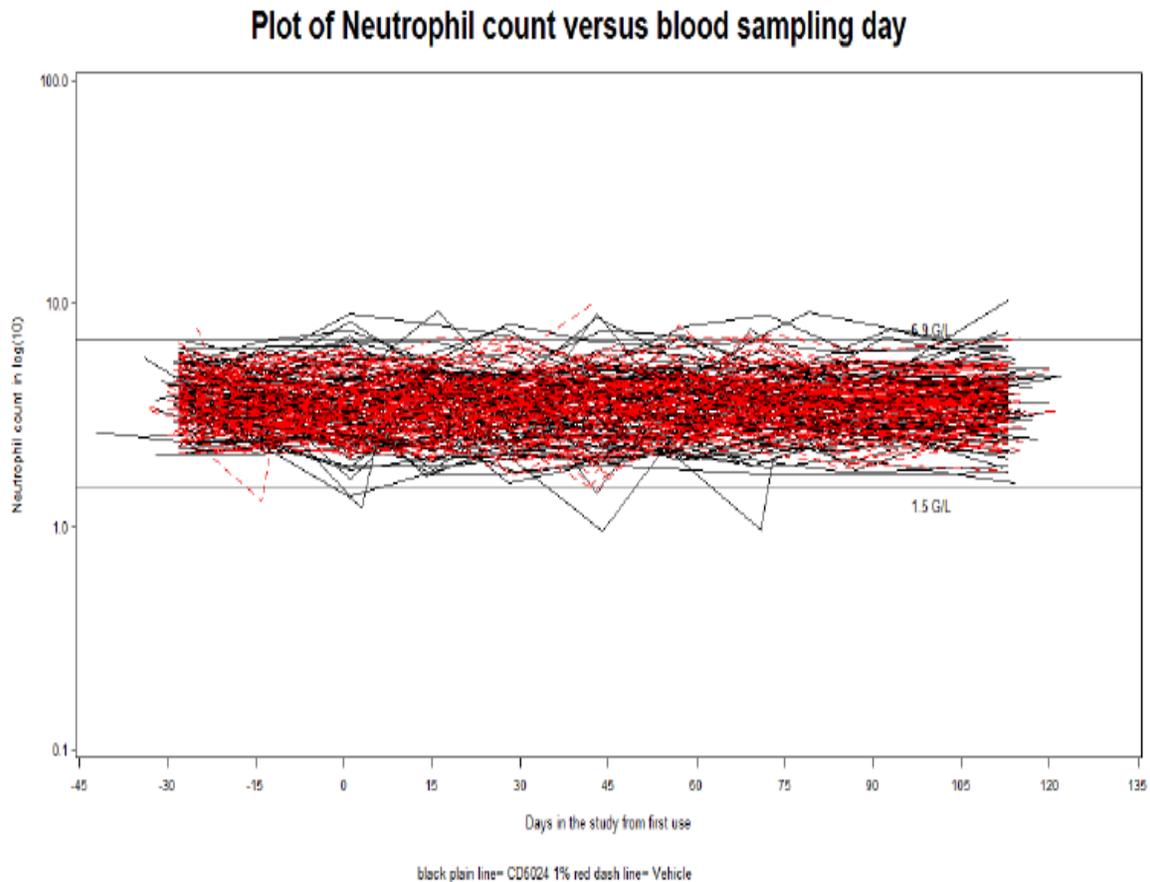
**2.3.5 What is the exposure-response with respect to neutropenia?**

The observed data for exposure-response showed no correlation between ivermectin systemic levels with the incidence of neutropenia. Also the incidence of neutropenia does not appear to be treatment related. A brief summary of the supporting information is provided below and details are shown in Appendix 2.

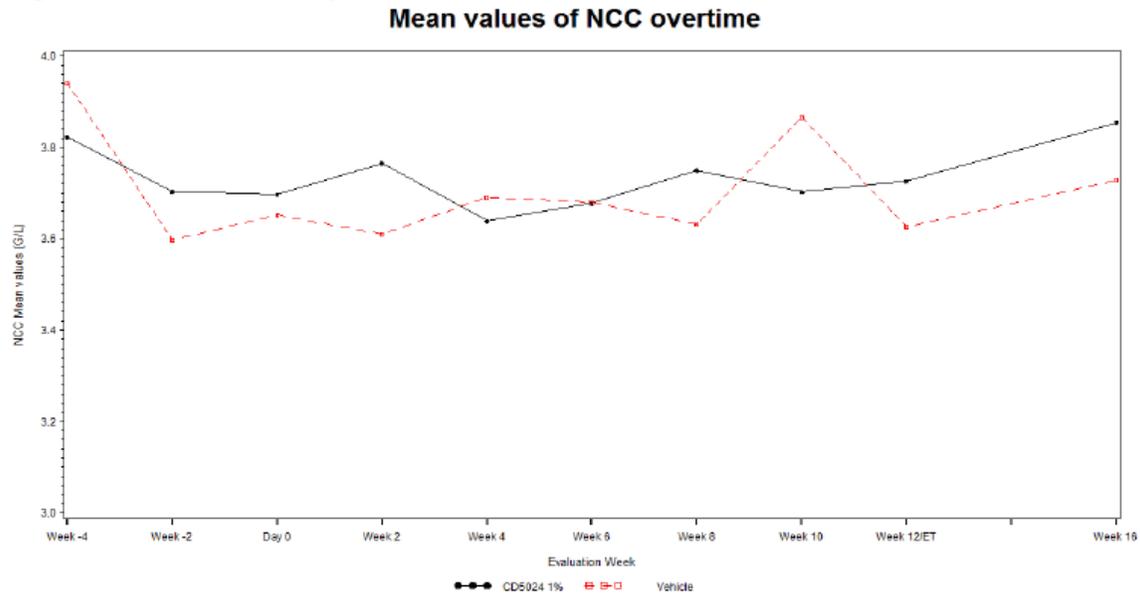
The incidence of neutropenia surfaced in a Phase 3 long term safety trial (RD.03.SRE.400051) and this 52 week trial was prematurely terminated at week 10 because of low neutrophil cell counts (NCC) (below the threshold value of 1.5 G/L) observed in 3 subjects.

This issue of neutropenia was further investigated in a dedicated Phase 2 trial (RD.03.SRE.40106). The aim of this trial was to assess the effect of Ivermectin 1% Cream QD on the induction of neutropenia (defined as NCC <1.5 G/L) in subjects with moderate to severe papulopustular rosacea with IGA score  $\geq 3$  (see Table 4 for IGA scores), compared to the Vehicle Cream. The results showed that there were 4 subjects [3 active + 1 vehicle] with single treatment emergent NCCs values below the threshold value of 1.5 G/L. The plasma concentrations of ivermectin for these 3 subjects were (0.37, 2.6 0.73 ng/mL) not the highest level (6.75 ng/mL) observed in this trial. Furthermore, on re-test the NCC levels returned back within the normal range. The NCCs for all subjects at each sampling visit are graphically depicted in Figure 4 and the mean values are shown in Figure 5. The figures show that the mean NCC values over time remained stable and similar between treatment and vehicle arms and the fact that there were only single time points where NCC values were below the threshold indicating lack of any trend.

**Figure 4: Plot of Neutrophil count versus blood sampling day for all subjects**

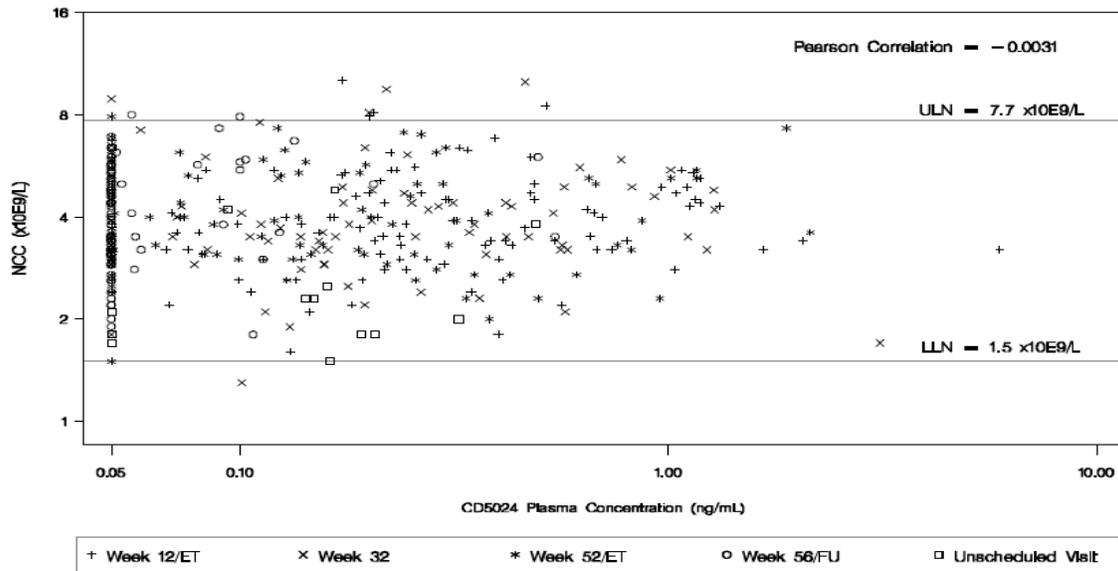


**Figure 5: Mean Values of NCC over time**



Additional monitoring for neutropenia was done in the two Phase 3 trials (RD.06.SRE.18170 and RD.06.SRE.18171). The results indicated that ivermectin plasma concentrations in subjects reporting  $NCC \leq 1.5$  G/L were within the range of exposures observed in other subjects that did not have NCC values below the threshold. Individual NCC measurements were plotted against plasma ivermectin concentration and the data suggests lack of any exposure-response (see Figure 6 and 7).

**Figure 6: Neutrophil cell counts versus ivermectin plasma concentration (ng/mL) in the Ivermectin 1% Cream (Part A and Part B) group (N=105; Study 18170)**



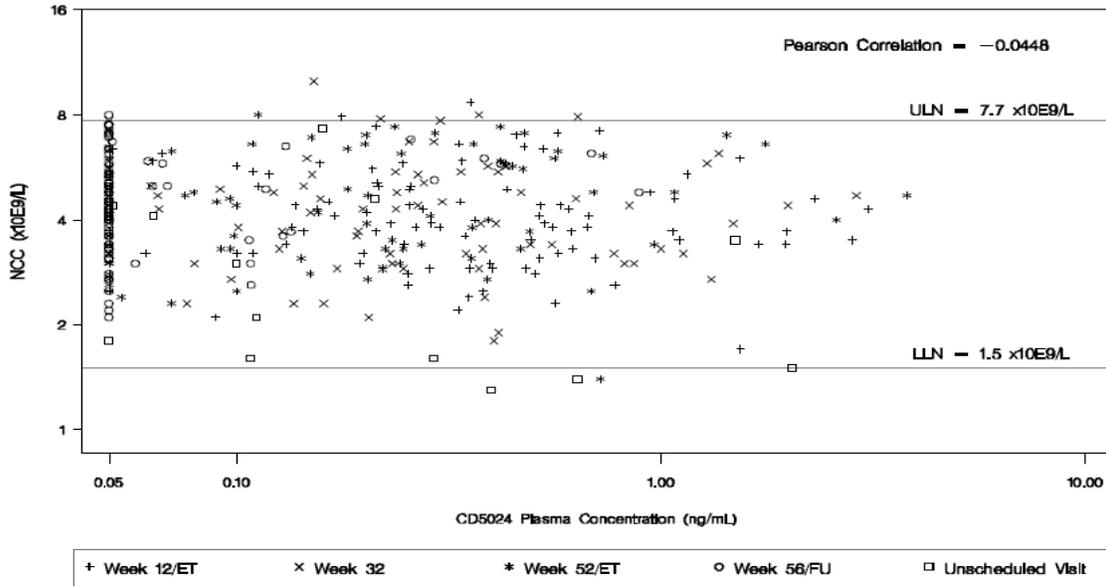
Below limit of quantification (BLQ) values of plasma concentration are imputed using the LOQ.

Pearson correlation of NCC value and CD5024 Plasma Concentration is calculated.

For NCC value, Upper limit of Normal (ULN) and Lower limit of Normal (LLN) reference lines are provided.

Case report form (CRF) visits are used. ET=Early termination. FU=Follow up.

**Figure 7: Neutrophil cell counts versus ivermectin plasma concentration (ng/mL) in the Ivermectin 1% Cream (Part A and Part B) group (N=92; Study 18171)**



Below limit of quantification (BLQ) values of plasma concentration are imputed using the LOQ.  
 Pearson correlation of NCC value and CD5024 Plasma Concentration is calculated.  
 For NCC value, Upper limit of Normal (ULN) and Lower limit of Normal (LLN) reference lines are provided.  
 Case report form (CRF) visits are used. ET=Early termination. FU=Follow up.

Overall analysis of NCC data over the one-year duration of the two Phase 3 pivotal Trials (18170 and 18171) including their long-term extension part showed that the incidence of NCCs  $\leq 1.5$  G/L was similar or lower in the ivermectin group compared to the vehicle/azelaic acid group (Note: Azelaic acid is the active treatment). After 1 year of exposure, the cumulative incidence of NCCs  $\leq 1.5$  G/L was 2.18% in the ivermectin group and 2.36% in the vehicle/azelaic acid group suggesting that the incidence of neutropenia is not treatment related.

In the ongoing Phase 3 trial (RD.03.SRE.40173), ivermectin plasma levels were measured only in subjects who were reported with NCC  $\leq 1.5$  G/L. There were 6 subjects that were reported to have treatment-emergent NCC  $< 1.5$  G/L during Part A of this trial, out of which, 3 subjects were treated with ivermectin 1% Cream QD and the other 3 subjects were treated with Metronidazole 0.75% Cream QD. As per the Applicant there were no subjects in Part B up to a cutoff date of 8 April 2013, who had NCC  $\leq 1.5$  G/L, thus no plasma samples were collected. Similar to other trials, the results from this ongoing trial so far, has also indicated lack of any exposure-response with respect to neutropenia.

Based on this data, the Applicant claims that, in general, subjects presenting NCCs below 1.5 G/L had low systemic exposures to CD5024 in comparison to the overall data. This shows the absence of a relationship between neutropenia and ivermectin plasma concentrations.

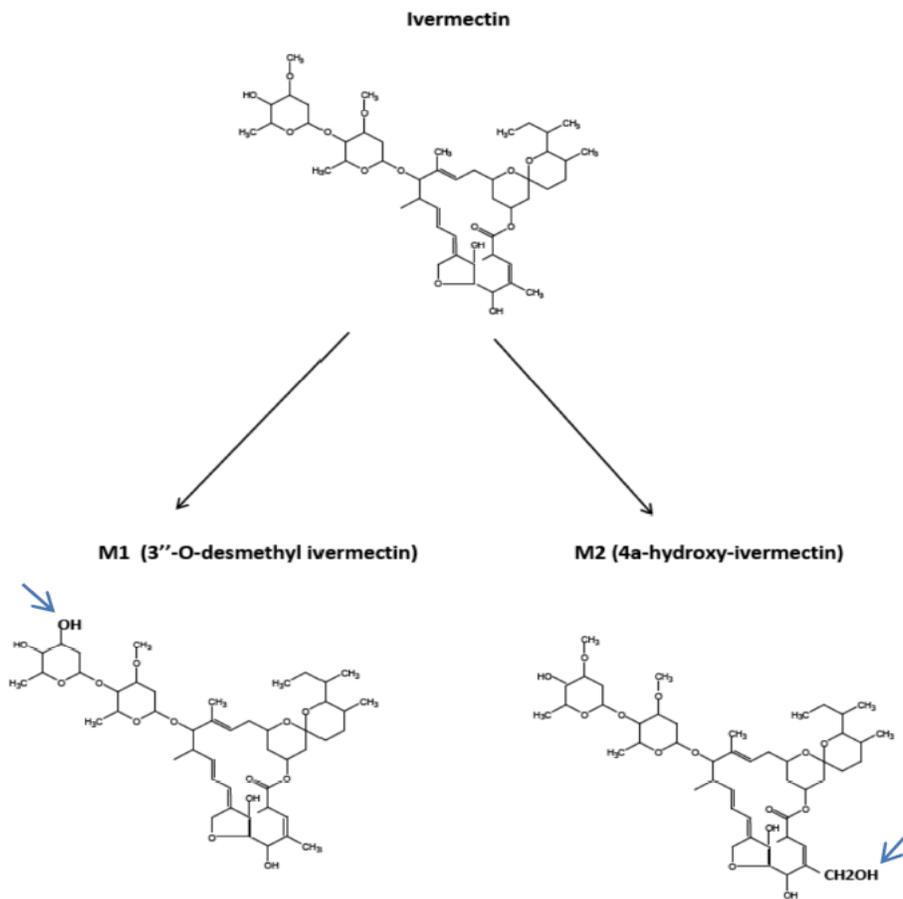
**Reviewer comments:** This reviewer concurs with the Applicant's conclusion which suggests lack of any correlation between neutropenia and ivermectin plasma concentrations based on the observed data.

### 2.3.6 What information is known about drug metabolism?

Five metabolites were tentatively identified in the in-vitro studies using human hepatocytes and liver microsomes. M1 and M2 were considered as major metabolites and Figure 8 shows the metabolic pathway. The 5 metabolites are as follows:

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

**Figure 8: Main metabolic pathway of ivermectin (H<sub>2</sub>B<sub>1a</sub>)**



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 formation of metabolites M1, M2, and M3/M4.

***Reviewer comments:*** CYP3A4 was found to be involved in the metabolism of ivermectin to produce metabolites M1, M2 and M3/M4. Hence inhibitors of CYP3A4 might lead to an increase in ivermectin systemic levels. According to the Applicant, an increase in ivermectin systemic exposure would not have any clinically meaningful effects because following once daily topical administrations under maximal use conditions, the steady state plasma levels had at least a 68 fold margin of safety based on the animal toxicity data. This reviewer checked with the Pharmacology-Toxicology reviewer Dr. Jianyong Wang who confirmed that the margin of safety was at least 66 fold (for further information see Dr. Wang's review in DARRTS).

**Exposure of metabolites:** The Applicant was unable to validate the bioanalytical method for metabolites due to lack of standard metabolite compounds and have conducted a relative quantification of metabolites based on the parent calibration curve. Due to lack of validated bioanalytical method for the metabolites, the values of the ratio of AUC metabolite and AUC parent cannot be fully relied upon. Metabolite levels for M1, M2 and M3/M4 were assessed in the maximal use PK trial (RD.03.SRE.40064) and the relative quantification showed that steady state appears to have reached by Day 14.

**Activity of the metabolites:** With the original submission, information on the pharmacological activity of metabolite M1 and M2 was not submitted. Hence an information request (IR) was sent to the applicant on 02/28/2014 after filing this NDA. The applicant responded to this IR on 03/28/2014 and indicated that they have not assessed the activity of metabolites M1 and M2, but their systemic levels have been characterized in the maximal use PK trial. The applicant has further indicated that, from a safety standpoint, based on the no observed adverse event level (NOAEL) from animal toxicity studies, there appears to be a 649 fold and a 176 fold margin of safety for M1 and M2 exposures in human plasma, respectively.

***Reviewer comments:*** The activity of the metabolites is unknown, but relative exposure of the metabolites appears to be small compared to the parent. Hence in the opinion of this reviewer, the fact that the contribution of pharmacological activity of the metabolite is unknown, would be of interest from a purely scientific standpoint and will not affect the regulatory decision in this case.

### ***2.3.7 Does application of ivermectin cream, 1% lead to QT interval prolongation?***

Based on the results of TQT trial (RD.06.SRE.18120) the Interdisciplinary Review Team for QT (IRTQT) has concluded that no significant QTc prolongation effect of ivermectin 6 mg oral dose was detected. Based on this finding, at therapeutic doses ivermectin cream 1% is not expected to prolong QTc interval (for further information see review dated 12/16/2011 by Dr. Moh Jee Ng in DARRTS under IND 76064). Following is a brief summary of the findings.

The purpose of the TQT trial was to evaluate the effect of a supra-therapeutic single oral dose of 6 mg of ivermectin (Stromectol<sup>®</sup>) administered as 2 x 3 mg over-encapsulated tablets, on ventricular repolarization in healthy subjects compared to placebo.

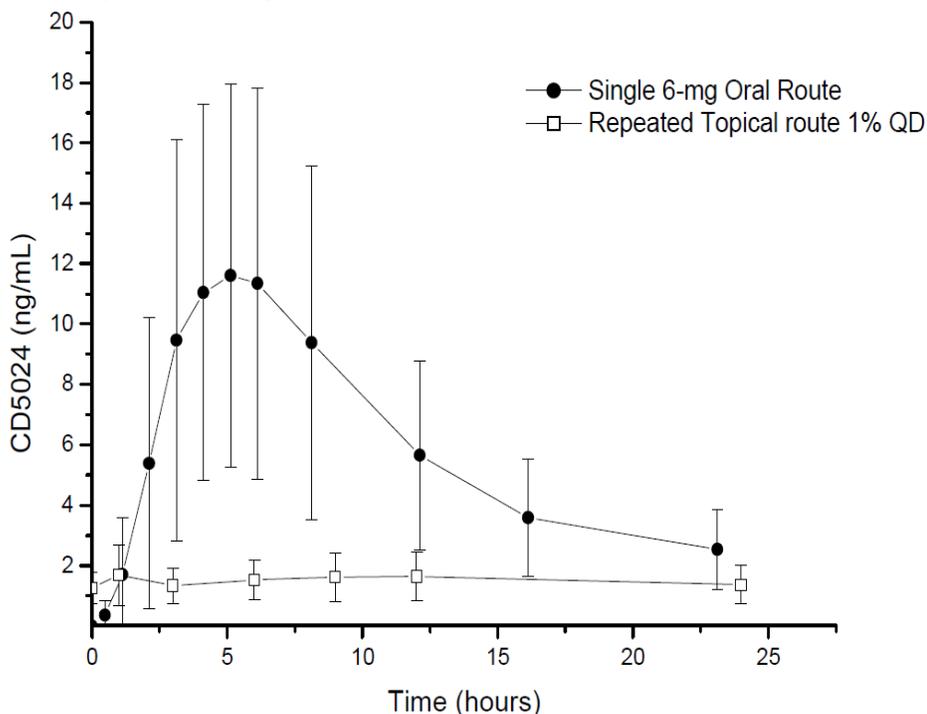
Moxifloxacin (400 mg over-encapsulated tablet) was included as the positive control to demonstrate the expected QTc response in the subjects. Serial plasma samples for PK analysis were obtained from subjects 15 minutes prior to dosing and immediately following the 10 minute window of ECG extractions post-dosing at 42 minutes, 1 hour and 12 minutes, 2 hours and 12 minutes, 3 hours and 12 minutes, 4 hours and 12 minutes, 5 hours and 12 minutes, 6 hours and 12 minutes, 8 hours and 12 minutes, 12 hours and 12 minutes, 16 hours and 12 minutes, and 23 hours 12 minutes. The PK results are shown in Table 6 below.

**Table 6: Summary of mean  $\pm$  SD PK parameters for ivermectin (Study 18120)**

<i>PK parameter</i>	<i>Ivermectin 6 mg (N = 53)</i>
$C_{max}$ (ng/mL)	13.86 $\pm$ 7.22
$T_{max}$ (hours)	4.62 $\pm$ 1.57
$AUC_{0-t}$ (ng*h/mL)	134.03 $\pm$ 65.97

Based on cross trial comparison the value of  $C_{max}$  of ivermectin following single oral dose of 6 mg was approximately 7 fold higher compared to the steady state  $C_{max}$  value (Day 14) following topical administrations of ivermectin Cream 1% under maximal use conditions (see PK data in Table 5) (Note - The bioanalytical method used to quantify the systemic levels was the same between the two trials). Figure 9 shows a plot of ivermectin plasma levels following 6 mg single oral dose and at steady state (Day 14) following topical administrations under maximal use conditions using the 1% Cream.

**Figure 9: Ivermectin plasma concentrations (Mean  $\pm$  SD) for oral (Day 0) versus topical (Day 14) route of administration (Studies 18120 and 40064)**



### 2.3.8 What is the summary of safety?

According to the Applicant, the clinical development program of topical ivermectin included 15 trials (5 trials in 453 healthy subjects and 10 trials in 3546 subjects with papulopustular rosacea), with a total of 2431 subjects exposed at least once to Ivermectin 1% Cream.

Across the two pivotal Phase 3 trials (Part A), their long-term extension (Part B), and an additional 4-week treatment free follow-up (Part C), treatment emergent adverse events (TEAEs) were reported by 68.8% subjects in the Ivermectin 1% Cream QD group, and by 68.5% subjects in the Vehicle Cream QD/Azelaic Acid 15% Gel (active control) BID group. The majority of TEAEs reported for both Phase 3 pivotal studies and their long-term extensions were considered by the Investigators to be either mild or moderate in severity and the highest number of incidences were local and included skin irritation (1.5% vs. 5.0% in the ivermectin and vehicle/azelaic acid groups, respectively), contact dermatitis (1.4% vs. 2.2%), and skin burning sensation (1.3% vs. 3.5%). Other TEAEs included nasopharyngitis (12.6% vs. 12.3% in the ivermectin and vehicle/azelaic acid groups, respectively), upper respiratory tract infection (9.3% vs. 8.4%), and sinusitis (5.6% vs. 5.2%). For a detailed review of safety, see Clinical review by Dr. Jane Liedtka in DARRTS.

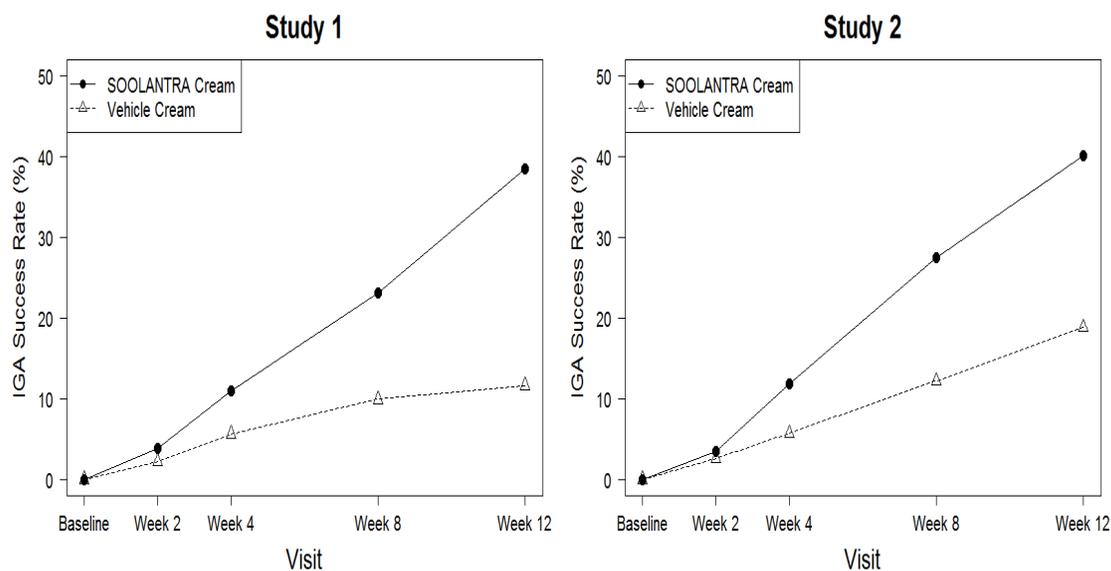
### 2.3.9 What is the summary of efficacy?

The results from the two Phase 3 clinical trials demonstrated that Ivermectin Cream, 1% applied once daily for 12 weeks was more effective than vehicle cream in terms of IGA success rate and absolute change in inflammatory lesion counts as shown in Table 7 and Figure 10. For further information, see Clinical review by Dr. Jane Liedtka and Biostatistics review by Dr. Matthew Guerra in DARRTS.

**Table 7: Summary of efficacy results from Phase 3 trials**

	Study 1		Study 2	
	SOOLANTRA Cream (N=451)	Vehicle Cream (N=232)	SOOLANTRA Cream (N=459)	Vehicle Cream (N=229)
<b>Investigator Global Assessment:</b>				
Number (%) of Subjects Clear or Almost Clear	173 (38.4%)	27 (11.6%)	184 (40.1%)	43 (18.8%)
<b>Inflammatory Lesion Counts:</b>				
Mean Absolute (%) Change from Baseline	20.5 (64.9%)	12.0 (41.6%)	22.2 (65.7%)	13.4 (43.4%)

**Figure 10: IGA success rate over time**



## 2.4 Intrinsic Factors

### 2.4.1 Effect of gender

The effect of gender on PK was not explored by the Applicant. The low systemic exposures observed in the maximal use PK trial and the at least 66 fold margin of safety based on animal toxicity data, do not warrant this investigation (*for further information on safety margin see Pharmacology-Toxicology review by Dr. Jianyong Wang*).

### 2.4.2 Pediatric subjects

According to the Applicant, the occurrence of rosacea in children is a rare. Due to low prevalence of the disease in children, the Applicant has applied for full waiver of pediatric studies in subjects below 18 years of age. The Pediatric Review Committee (PeRC) agreed with the Applicant's request for a full waiver of pediatric assessment at a meeting held on July 2, 2014.

### 2.4.3 Renal and hepatic impairment

The effect of Ivermectin 1% Cream in subjects with renal and hepatic impairment was not evaluated conducted by the Applicant. The low systemic exposures observed in clinical studies and the at least 66 fold margin of safety based on animal toxicity data, does not warrant this investigation (*for further information on safety margin see Pharmacology-Toxicology review by Dr. Jianyong Wang*).

### 2.4.4 What pregnancy and lactation use information is there in the application?

The Sponsor has not conducted any trials in pregnant and lactating women.

## 2.5 Extrinsic Factors

### 2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated in-vivo. The potential for drug-drug interaction was evaluated in-vitro (see section 5.5.2).

### 2.5.2 Drug interactions

#### Effects of other drugs on the PK of ivermectin cream:

The in vitro metabolism of ivermectin was studied using an extensive panel of recombinant cytochrome P450 enzymes. CYP3A4 was identified as the enzyme primarily responsible for the metabolism of ivermectin to produce metabolites M1, M2, and M3/M4 (M1 and M2 are considered as major metabolites).

***Reviewer comments:*** *Inhibitors of CYP3A4 leading to an increase in ivermectin systemic levels would be unlikely to have any clinically meaningful safety effects because the steady state plasma ivermectin levels had at least a 66 fold margin of safety based on the animal toxicity data and there were no apparent systemic safety concerns in the Phase 3 trials.*

#### Effect of ivermectin cream on the PK of other drugs:

The potential for ivermectin to inhibit the activity of the cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11) was investigated in-vitro 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, respectively, was observed at the highest ivermectin concentration of 12 μM (11 μg/mL). 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 the induction effects on CYP enzymes (CYP1A2, CYP2B6, CYP2C9, and CYP3A4) was investigated. Ivermectin at concentrations up to 0.4 μM (0.35 μg/mL) did not cause an increase in the CYP enzyme activities or their mRNA levels in primary human hepatocyte cultures.

***Reviewer comments:*** *The mean ± standard deviation C<sub>max</sub> at steady state in the maximal use PK trial was 2.10 ± 1.04 ng/mL (range 0.69 – 4.02 ng/mL) and the calculated R values were below the threshold of 1.1. Hence at therapeutic concentrations ivermectin is not expected to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,*

*CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11 or induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4.*

## **2.6 General Biopharmaceutics**

***2.6.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?***

The Applicant has not submitted any information on BCS classification.

***2.6.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?***

Manufacturing process change: The applicant made modification to the manufacturing process which included (b) (4)  
(b) (4) The new formulation appears to (b) (4)  
compared to the formulation manufactured by the old process, however, the overall composition of the new formulation was the same as the formulation manufactured by the old process. The applicant has not conducted in-vivo relative bioavailability trial but has conducted in-vitro release test (IVRT) to bridge the old and the new formulation. The proposed commercial formulation manufactured by the new process was not used in any of the clinical trials. The formulation manufactured by the old process was used in Phase 3 clinical trials and maximal use PK trial.

***2.6.3 What data support or do not support a waiver of in vivo BE data?***

As per SUPAC-SS guidance, the change in the manufacturing process would represent a Level 2 change and in-vitro release test (IVRT) is the recommended method for bridging between the formulations. As per Biopharmaceutics reviewer Dr. Kelly Kitchens, the IVRT results support establishment of a bridge between old and new formulation (for further information see reviewer by Dr. Kelly Kitchens dated 08/28/2014 in DARRTS). These findings support a waiver for not conducting an in-vivo BE trial.

***2.6.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

Effect of food on the BA is not evaluated for topical formulations.

## **2.7 Analytical Section**

***2.7.1 How are the active moieties identified, and measured in the clinical trials?***

High performance liquid chromatography (HPLC) with fluorescence detection was used to detect ivermectin and metabolites M1, M2 and M3/M4.

The bioanalytical method was originally developed by (b) (4). The method was later transferred to the Applicant and in this process the Applicant (b) (4). The Applicant re-validated the bioanalytical method (Report number: RDS.03.VRE.34154). All the PK plasma samples from the clinical trials were analyzed by the Applicant.

**2.7.2 Which metabolites have been selected for analysis and why?**

Metabolites M1, M2 and M3/M4 were selected for analysis as they were considered as major metabolites by the applicant.

**2.7.3 Is the bioanalytical method to quantify metabolites validated?**

The bioanalytical method for the metabolites was not validated because the Applicant could not obtain appropriate quantities of standard references for the metabolites. Because of the absence of the standard references, the extraction recovery of the metabolites from plasma could not be estimated. Relative quantification of the circulating metabolites was performed using the calibration curve for ivermectin.

According to the applicant, initially, based on results of the in vitro Study 4830, no correction factor was deemed necessary for the determination of metabolite concentrations in biological samples (using a calibration curve obtained with ivermectin). Subsequently, this indirect analytical approach for M1 and M2 (based on ivermectin calibration curves, with no additional correction factor) was applied for the quantification of the circulating metabolites in Studies 40064 and 18120.

However, in parallel within the development program, the Applicant made an attempt to (b) (4), and to confirm the structure of the major metabolites detected in plasma (Studies 31085 and 31106).

(b) (4)



**2.7.4 For all moieties measured, is free, bound, or total measured?**

Total concentrations were measured for all moieties.

**2.7.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?**

The range of the standard curve for ivermectin was 0.05 ng/mL to 10 ng/mL. The range was adequate to quantify plasma levels of ivermectin in the clinical trials as none of the plasma concentrations exceed the upper limit of 10 ng/mL. The lower limit of quantification (LLOQ) was 0.05 ng/mL.

**2.7.6 What are the accuracy and precision at LLOQ?**

Within-run accuracy %	6.2%
Between-run accuracy %	-1.1%
Within-run precision %	7.9%
Between-run precision %	14%

**2.7.7 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?**

<i>Parameter</i>	<i>Results</i>
Freeze/Thaw cycle stability	Stable for 3 cycles at - 20°C
Room temperature stability	At least 24 hours
Auto-sampler stability	At least 3 days
Refrigeration stability	At least 1 month at 4°C and at least 6 months at - 20°C
Long term stability	445 days at -70 °C protected from light
Internal standard stability	At least 1 month at 4°C and at least 6 hours at room temperature

**Reviewer comments:** *The long term stability of 445 days was adequate to cover the stability of PK samples obtained in different clinical trials. The duration of PK sample storage for each clinical trial is shown in Table 8 below.*

**Table 8: Summary of PK sample storage duration in each clinical trial**

Study Number	First Sample Collection Date	Last Sample Analysis Date	Duration of Sample Storage (Days)
40007	20 Sep 2005	13 Jan 2006	116
18120	28 Sep 2008	3 Dec 2008	67
40064	8 Sep 2008	18 Dec 2008	102
40027	25 Oct 2006	28 Sep 2007	339
40051	1 Dec 2008	22 Apr 2009	143
40106	27 Oct 2010	13 Jun 2011	110
18170	29 Feb 2012	5 Aug 2013	153
18171	19 Mar 2012	10 Sep 2013	176
40173 <sup>a</sup>	17 Sep 2012	19 April 2013	215

Note: The storage condition for all samples in all studies was -20°C.

<sup>a</sup> Only data from Part A of Study 40173 has been presented in this Section. The dates and sample storage duration presented are for Part A only and the Bioanalytical report will be completed at the end of the study.

### **2.7.8 What are the results of incurred sample reanalysis (ISR)?**

The applicant has conducted ISR for one clinical trial (18170) (see Table 23) where ISR was performed on 10% of study samples at steady state (Week 12 to Week 52) and the results indicated that at least two-thirds of the repeated samples were within the 20% threshold.

### 3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

#### 7 DRUG INTERACTIONS

**In vitro studies have shown that SOOLANTRA Cream at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.**

8.4 Pediatric Use  
Safety and effectiveness of **SOOLANTRA Cream** in pediatric patients have not been established.

#### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

(b) (4)



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

##### 12.2 Pharmacodynamics

###### Cardiac Electrophysiology

**At therapeutic doses, SOOLANTRA Cream is not expected to prolong QTc interval.**

##### 12.3 Pharmacokinetics

###### Absorption

The absorption of ivermectin from SOOLANTRA **Cream** was evaluated in a clinical trial in **15** adult **male and female** subjects with severe papulopustular rosacea **applying 1 g SOOLANTRA Cream once daily;**   
 At steady state (after 2 weeks of treatment), plasma concentrations of ivermectin peaked (**T<sub>max</sub>**) at  <sup>(b) (4)</sup>  $10 \pm 8$  hours (mean  $\pm$  standard deviation) post-dose, **the maximum concentration (C<sub>max</sub>) was**  $2.10 \pm 1.04$  ng/mL (range:

0.69 - 4.02 ng/mL) and the <sup>(b) (4)</sup> **area under the concentration versus time curve** (AUC<sub>0-24hr</sub>) was 36.14 ± 15.56 ng.hr/mL (range: 13.69-75.16 ng.hr/mL). In addition, systemic exposure assessment in longer treatment duration (Phase 3 studies) **showed** <sup>(b) (4)</sup> that there was no plasma accumulation of ivermectin over the 52-week treatment period. <sup>(b) (4)</sup>

#### Distribution

An in vitro study demonstrated that ivermectin is greater than 99% bound to plasma proteins and is bound primarily to human serum albumin. No significant binding of ivermectin to erythrocytes was observed.

#### Metabolism

In vitro studies using human hepatic microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. In vitro studies show that ivermectin **at therapeutic concentrations** does not inhibit the CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, **2E1**, 3A4 **or** 4A11, or <sup>(b) (4)</sup> (1A2, 2B6, 2C9 or 3A4). <sup>(b) (4)</sup>

#### Excretion

**The apparent terminal half-life averaged** <sup>(b) (4)</sup> **6.5** days (mean ± **standard deviation:** <sup>(b) (4)</sup> **-155± 40** hours, range 92-238 hours) in patients receiving a once daily cutaneous application of SOOLANTRA Cream <sup>(b) (4)</sup> for 28 days. <sup>(b) (4)</sup>

#### 4. INDIVIDUAL STUDY REVIEW

##### **Trial Number: RD.03.SRE.40064 (Maximal use PK trial)**

**Title:** Plasma PK study of CD5024 1% Cream in subjects with papulopustular rosacea.

**Bio-analytical Facility:** Bioanalysis Group of Galderma R & D

**Trial Objectives:** The objective of this trial was to investigate under maximal use conditions the PK profile of CD5024 1% cream applied once daily for four weeks in subjects with severe papulopustular rosacea (PPR).

**Study Drug:** CD5024Cream, 1%

**Formulation:** 575-754 (Phase 3 formulation)

**Trial Design:** This was an open-label, single-treatment group, involving 15 adult male or female subjects with severe papulopustular rosacea (PPR) [Investigator's Global Assessment (IGA) scores of 4 at Baseline]. Subjects were treated with CD5024 1% cream once daily in the morning during a 4 week period. Drug application was performed by a qualified person and there was no self-application by the subjects. A thin layer of 1 gram of the product was applied to the entire face, except the upper and lower eyelids and the lips. Blood sampling for PK assessment was performed as shown in the Table 9 below with serial samples obtained on Day 0, Day 14 and Day 28 (last day of drug application). Additional blood samples were also obtained for another 28 days after the last drug application. The subjects were monitored for 4 weeks after treatment.

**Table 9: Blood sampling schedule**

Sampling Day	D0 <sup>1</sup>	D1	D7	D14	D15	D21	D 28 <sup>2</sup>	D29	D30	D32	D35	D38	D42	D49	D56
Hours post the previous morning application	1, 3, 6, 9,12	0 <sup>3</sup>	0 <sup>3</sup>	0 <sup>3</sup> , 1, 3, 6, 9,12	0 <sup>3</sup>	0 <sup>3</sup>									
Hours after the last application							0 <sup>3</sup> , 1, 3, 6, 9,12	24 (1 day after the last application)	48 (2 day after the last application)	96 (4 day after the last application)	168 (7 days after the last application)	240 (10 days after the last application)	336 (14 days after the last application)	504 (21 days after the last application)	672 (28 days after the last application)

<sup>1</sup>First application day

<sup>2</sup>Last application day (final application = D28 morning)

<sup>3</sup>0<sup>3</sup> = Blood sample collection to be performed within the hour before the treatment application.

***Reviewer comments:*** Based on the daily mean amounts of formulation applied in different trials (Table 10), it appears that the 1 gram of the formulation used in the maximal use PK trial was within the upper range of the amount used.

**Table 10: Mean ± SD of the amount of formulation used across different clinical trials**

<b>Trial #</b>	<b>Purpose</b>	<b>Mean ± SD daily dose of ivermectin cream, 1%</b>
<b>PHASE 2</b>		
RD.03.SRE.40027	Dose range – Subjects with rosacea	<u>1% strength QD*</u> Mean = 0.7 ± 0.4 g Median = 0.68 g Range = 0.08 – 1.77 g
RD.03.SRE.40064	Maximal use PK – Subjects with rosacea	1 gram (Drug applied by the clinical staff)
RD.03.SRE.40106	Assessment of potential for induction of neutropenia – Subjects with rosacea	Mean = 0.88 ± 0.81 g Median = 0.72 g Range = 0.08 – 7.94 g
<b>PHASE 3</b>		
RD.03.SRE.40051	Long term safety and efficacy - Subjects with rosacea (52 week trial terminated at 10 weeks due to low neutrophil counts)	Mean = 0.83 ± 0.45 g Median = 0.76 g Range = 0.00 – 2.47 g
RD.06.SRE.18170	Safety and efficacy - Subjects with rosacea	<u>Part A</u> Mean = 0.65 ± 0.66 g Median = 0.56 g Range = 0.06 – 12.83 g <u>Part B</u> Mean = 0.67 ± 0.68 g Median = 0.68 g Range = 0.03 – 12.26 g
RD.06.SRE.18171	Safety and efficacy - Subjects with rosacea	<u>Part A</u> Mean = 0.64 ± 0.33 g Median = 0.57 g Range = 0.10 – 2.03 g <u>Part B</u> Mean = 0.75 ± 1.84 g Median = 0.58 g Range = 0.07 – 37.66 g

\*Other strengths and 1% BID application is not reported here

**Reviewer comments:** From the table above, in the two Phase 3 trials, the upper limit of the range of the formulation applied is very high.

- Trial RD.06.SRE.18170: The upper limit of the range in Part A was 12.83 g and in Part B was 12.26 g.
- Trial RD.06.SRE.18170: The upper limit of the range in Part B was 37.66 g.

The really large upper limit to the ranges was due to a single subject (See Table 11 below). For Trial 18170, note that the subject who had an average daily usage of 12.83 in Part A is not the same subject who had an average daily usage of 12.26 in Part B. The 3

subjects (highlighted) all had treatment duration of 1 day and they all discontinued from the trial (details are provided in Table 12).

**Table 11: Large upper limit of the amount of formulation used followed by second largest amount**

Study	Part	Treatment	Max	Second Largest
18170	A	SOOLANTRA	12.83	1.77
		Vehicle	1.89	1.79
	B	SOOLANTRA	12.26	2.05
		Azelaic Acid 15% Gel	2.96	2.87
18171	A	SOOLANTRA	2.03	1.95
		Vehicle	1.65	1.54
	B	SOOLANTRA	37.66	1.71
		Azelaic Acid 15% Gel	2.76	2.69

**Table 12: Details on subjects that used large amount of formulation**

	Average Daily Use (g)				Discontinuation Reason	Exit Comment
	Part A		Part B			
USUBJID	Amount (total/duration)	Duration (days)	Amount (total/duration)	Duration (days)		
SPR18170-8120-003	12.83	1	**	**	Subject request	Consent withdrawn as per subject's request
SPR18170-8336-016	0.42	84	12.26	1	Lost to follow-up	Subject was contacted several times. She reported having car troubles and rescheduled her visit multiple times
SPR18171-8018-004	0.66	84	37.66	1	Subject request	Subject did not return to the clinic and requested not to participate by telephone due to work related issues

**Number of subjects:** A total of 17 subjects were enrolled and 15 (9 females and 6 males) completed this trial. The 2 subjects that discontinued had abnormal laboratory results and PK profiles for these 2 subjects were obtained only at Day 0 (Baseline). Specifically the discontinued subjects were:

- **Subject 9081:** This subject had an increased fibrinogen at screening, but the test results were not back until after the first treatment. Once the investigators saw this, this subject was discontinued.

- **Subject 9026:** This subject had positive hepatitis C at screening, but the test results were not back until after the first treatment. Once the investigators saw this, this subject was discontinued.

**Reviewer comments:** The reasons for discontinuation were confirmed with the medical officer Dr. Jane Liedtka via e-mail.

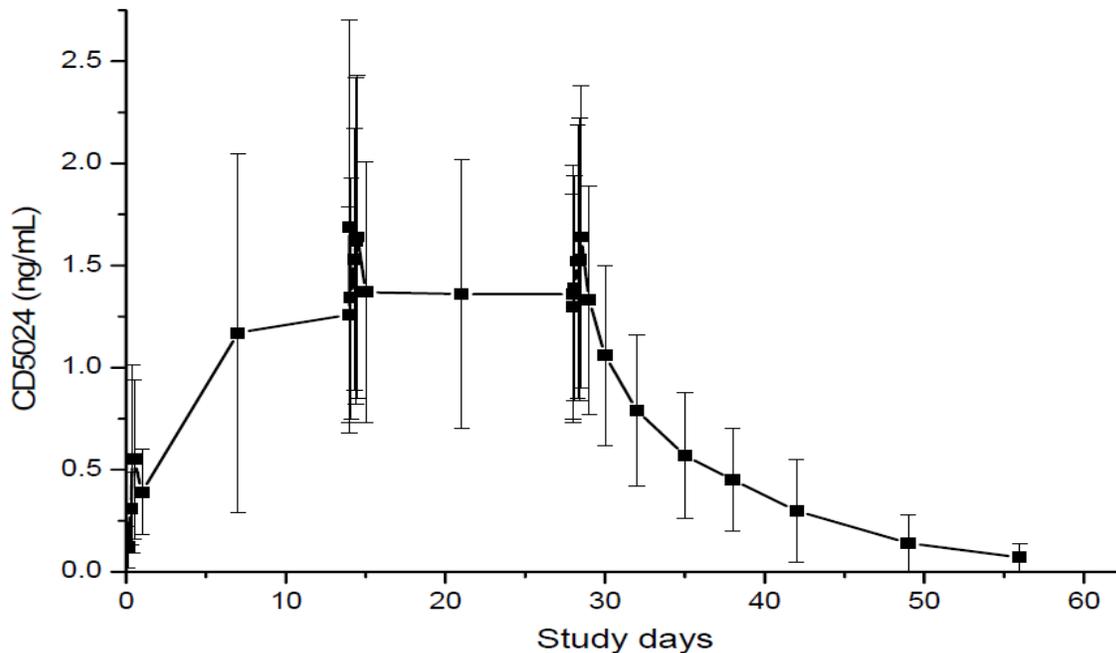
**Demographic data:** Shown in Table 13 below.

**Table 13: Demographic Data**

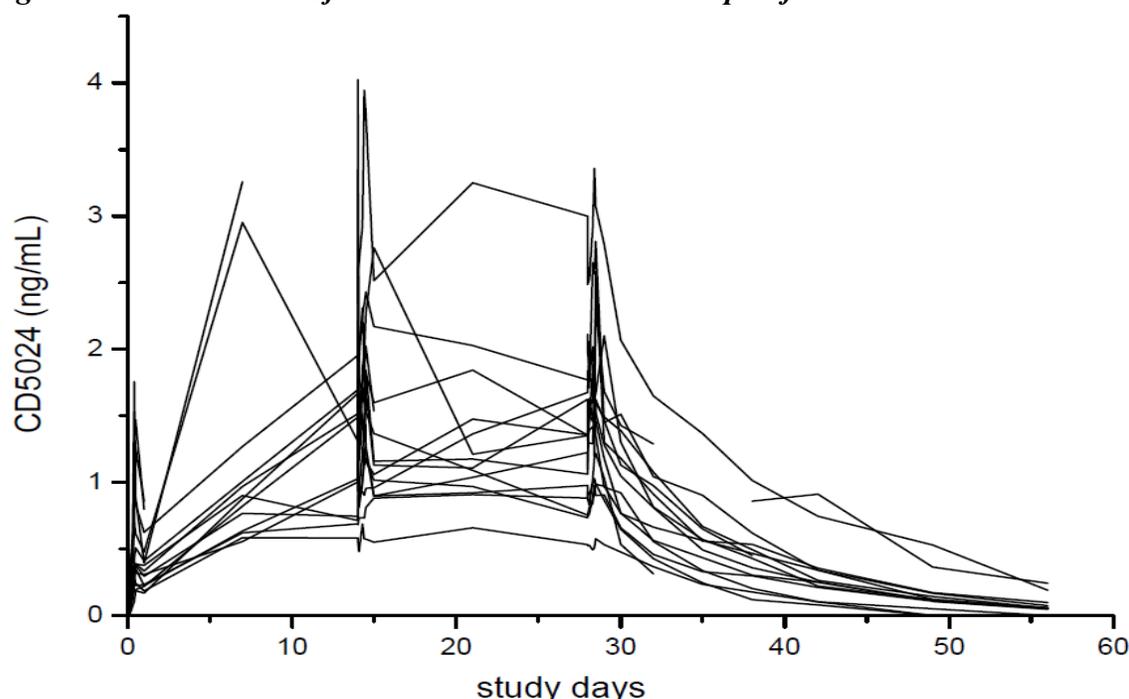
		Total
Age (in Years)	N	17
	Meant±SD	54.29±11.74
	Median	55.00
	Min~Max	35.00~74.00
Gender	N	17
	Female	11 (64.7%)
	Male	6 (35.3%)
Race	N	17
	Caucasian	17 (100.0%)

**PK results:** The overall arithmetic mean CD5024 plasma profiles over the 28-day treatment application is shown in Figure 11. Individual subject concentration versus time profiles are shown in Figure 12. The arithmetic mean ± SD and the range (Min- Max) values of  $C_{min}$ ,  $C_{max}$ , and  $AUC_{0-24h}$  on all sampling days are provided in Table 14 below.

**Figure 11: Arithmetic mean ± SD of CD5024 plasma concentrations (n=15)**



**Figure 12: Individual subject concentration versus time plot for ivermectin**



**Table 14: Pharmacokinetic parameters of ivermectin (mean ± SD)**

Parameters	Day0 <sup>a</sup>	Day7 <sup>b</sup>	Day14	Day21	Day28
Pre-dose/C <sub>min</sub> (ng/mL):					
Mean ± SD	0.37 ± 0.21(a)	1.17 ± 0.88	1.26 ± 0.53( c)	1.36 ± 0.66(c)	1.36 ± 0.63
Min-Max	[0.17 - 0.86]	[0.56 - 3.26]	[0.58 - 2.34]	[0.66 - 3.25]	[0.53 - 3.00]
C <sub>max</sub> (ng/mL):					
Mean ± SD	0.69 ± 0.49	NA	2.10 ± 1.04	NA	1.74 ± 0.77
Min-Max	[0.19 - 1.76]		[0.69 - 4.02]		[0.58 - 3.36]
T <sub>max</sub> (h):					
Mean ± SD	9 ± 6	NA	10 ± 8	NA	11 ± 4
Min-Max	[1 - 24]		[0 - 24]		[3 - 24]
AUC <sub>0-24h</sub> (ng.h/mL):					
Mean ± SD	9.29 ± 5.40	NA	36.14 ± 15.56	NA	35.43 ± 14.42
Min-Max	[3.16 - 21.28]		[13.69 - 75.16]		[12.89 - 70.08]

(a) N=17, (b) N=13, (c) N=14  
NA: not applicable

Right after the first single topical application (Day 0) of CD5024 1 % cream, quantifiable CD5024 levels were detected in the plasma of all the 17 subjects. Plasma concentrations of CD5024 peaked within 9 hours post dose (mean 0.69 ng/mL range: 0.19 -1.76 ng/mL) and then slowly decreased thereafter to 0.37 ng/mL, 24 hours post dose (C<sub>min</sub>).

After 28-days once daily topical application of CD5024 1 %cream, the systemic exposure was higher than that calculated after one single application. The arithmetic mean (± SD) pre-dose concentrations (C<sub>min</sub>) of CD5024 were 1.26 ± 0.53 ng/mL, 1.36 ± 0.66 ng/mL and 1.36 ± 0.63 ng/mL at Day 14, Day 21 and Day 28, respectively. It appears that steady state was reached by Day 14. The results in the Table 14 indicate that the mean C<sub>max</sub> and

AUC on Day 14 were approximately 3 fold and 4 fold higher than the values observed on Day 0 following single dose application.

At the end of the 28-day application period, the Applicant obtained additional blood samples for up to another 28 Days. The apparent mean terminal half-life was approximately 6.5 days (mean  $\pm$  standard deviation: 155 $\pm$  40 hours, range 92-238 hours). This prolonged apparent half-life indicates that CD5024 was slowly cleared from plasma after treatment was stopped.

**Metabolite levels:** The Applicant could not validate the bioanalytical assay for the metabolites due to lack of standards. Hence they assessed the systemic concentrations of metabolites M1, M2 and M3/M4 based on relative quantification using parent compound calibration curve. Though this is not an ideal approach, it was deemed acceptable in this case due to reasons mentioned under Section 2.3.4. Since bioanalytical method for the metabolites was not validated, the PK parameters of the metabolites cannot be relied upon. However, based on relative quantification, the metabolite levels appeared to have reached steady state by Day 14

**Brief summary of adverse events (AEs) as provided by the Applicant:** Five (29.4%) subjects out of the 17 who received treatment reported a total of six AEs (see Table 15). None of the events was reported as related, serious, severe or leading to discontinuation or to death.

**Table 15: Summary of adverse events**

		CD5024 1% cream (n=17)	
		N events	N(%) Subj*
ANY ADVERSE EVENTS		6	5 (29.4%)
CARDIAC DISORDERS		1	1 (5.9%)
	Tachycardia	1	1 (5.9%)
INFECTIONS AND INFESTATIONS		3	3 (17.6%)
	Gastroenteritis	1	1 (5.9%)
	Nasopharyngitis	1	1 (5.9%)
	Sinusitis	1	1 (5.9%)
RENAL AND URINARY DISORDERS		2	1 (5.9%)
	Chromaturia	2	1 (5.9%)

Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE  
 A subject was counted once per SOC and once per Preferred term even if more than one occurrence of an event was reported within a SOC or Preferred term.

None of the AEs led to the withdrawal of the subjects. Laboratory parameters as well as cutaneous tolerance, vital signs, physical findings, and other observations related to safety did not raise any safety concern for a cutaneous treatment over 28 days with CD5024 1% cream.

**Efficacy assessment as provided by the Applicant:** According to the Applicant, the results of the investigator global assessment (IGA) showed that after 28 days of treatment two (12.5%) subjects from the initial 17 subjects still presented with a severe rosacea whereas 14 (87.5%) subjects improved from Baseline by at least one grade. The majority of subjects (9 or 56.3%) had moderate rosacea.

## 5. APPENDIX 1: Formulation information

Table 16 provides a summary of the formulations that were used in each clinical trial (Formulation # 575-754 is the to-be-marketed formulation) and Table 17 shows the side-by-side comparison of the composition of different formulations.

**Table 16: Tabular summary of formulations used in each clinical trial (Formulation 575.754 is the Phase 3 formulation whose composition is the same as to-be-marketed formulation)**

Type of study	Formulation Number	Batch Number	Stability Study Protocol Number
<b>CLINICAL STUDIES</b>			
<b>Phase 1</b>			
RD.03.SRE.19055	575.702	575.702/2F4	RDP.06.SPR.15005 b
RD.03.SRE.40007	0575.0755	03380/0005-03381/0005	RDS.03.SPR.5498 b
RD.03.SRE.40023	0575.0755	03380/0005-03381/0005	RDS.03.SPR.5498 b
	0575.0765	03377/0001-03378/0001	
	0575.0764	03374/0001/03375/0001	
	0575.0766	03371/0005-03372/0005	
<b>Phase 2</b>			
RD.03.SRE.2894	575.702	575.702/2F4	RDP.06.SPR.15005b
RD.03.SRE.40006	575.754a	575.754/2F13	RDS.03.SPR.5489 b
RD.03.SRE.40027	575.754a	575.754/03750/1003&1004&1005	RDS.03.SPR.5502c
	575.757	575.757/03786/1002&1003&1004	
	575.767	575.767/03814/1002&1003&1004	
RD.03.SRE.40064	575.754a	056256	1.BD.05.PSP.0053
RD.03.SRE.40106	575.754a	067224-066993	1.BD.05.PSP.0053
<b>Phase 3</b>			
RD.03.SRE.40051	575.754a	056256	1.BD.05.PSP.0053
RD.06.SRE.18170	575.754a	083720	1.BD.05.PSP.0113
RD.06.SRE.18171	575.754a	083720	
RD.03.SRE.40173	575.754a	083720	
<b>NON-CLINICAL TOXICOLOGY STUDIES</b>			
<b>Repeat-dose toxicity</b>			
RD.03.SRE.8547	575.754a	575.754/2F4	RDS.03.SPR.5489 b
RD.03.SRE.12447	575.754a	575.754/2F13	
		575.754/2F14	
RD.03.SRE.12491	0575.0755	03380/0005-03381/0005	
RD.03.SRE.12519	0575.0765	03377/0001-03378/0001	
RD.03.SRE.8552	0575.0764	03374/0001-03375/0001	
RD.03.SRE.12500	0575.0755	03380/0005-03381/0005	
	0575.0765	03377/0001-03378/0001	
	0575.0764	03374/0001-03375/0001	
RD.03.SRE.12510	575.757	03786/1002-03786/1003	
	575.767	03814/1002-03814/1003	
	575.754	03750/1003-03750/1005	
<b>Local tolerance</b>			
RD.03.SRE.12439	575.754a	575.754/2F13	RDS.03.SPR.5489 b
RD.03.SRE.12436	575.754	575.754/2F2	RDP.06.SPR.15006 b
RD.03.SRE.12437	575.754	575.754/2F2	
RD.03.SRE.12438	575.754	575.754/2F2	
<b>Carcinogenicity and photocarcinogenicity</b>			
RD.03.SRE.12508	575.754a	03750/1004	RDS.03.SPR.5502 1.BD.05.PSP.0053 (for 056256)
	575.757	03786/1004	
	575.767	03814/1004	
RDS.03.SRE.12597	575.754a	056256	1.BD.05.PSP.0053
	575.757	03786/1004	RDS.03.SPR.5502c
	575.767	03814/1004	

NA= Not applicable

a Commercial formulation

b Early stability studies, thus not provided in Section 3.2.P.8.1

c Only stability data of formulation 575.754 presented in Section 3.2.P.8.1

**Table 17: Side-by-side comparison of different formulations (Formulation 575.754 is the Phase 3 formulation whose composition is the same as to-be-marketed)**

Formulation number	575.702	575.754	0575.0755	575.757	0575.0764	0575.0765	575.767
Ingredient	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Ivermectin	1.0	1.0	1.0	<u>0.1</u>	<u>0.1</u>	<u>0.3</u>	<u>0.3</u>
Glycerin	(b) (4)						
Isopropyl palmitate							
Carbomer copolymer (type B)							
(b) (4)							
Polyoxyl 20 cetostearyl ether <sup>c</sup>							
Sorbitan monostearate							
(b) (4)							
(b) (4)							
Dimethicone (b) (4)							
Edetate disodium							
Citric acid monohydrate							
Cetyl alcohol							
Stearyl alcohol							
(b) (4)							
Methylparaben							
Propylparaben							
Phenoxyethanol							
Propylene glycol							
Oleyl alcohol							
(b) (4)							
Sodium hydroxide (b) (4)							
Purified water							

## **APPENDIX 2: Summary of PK results from other trials and assessment of neutropenia**

**Trial Number: RD.03.SRE.40007 (Healthy subject PK trial):** This trial was conducted with a formulation which was slightly different from the Phase 3 formulation and the results will not be discussed in this review.

**Dose ranging trial (RD.03.SRE.40027):** The purpose of this trial was to conduct dose-ranging in subjects with PPR in order to select the dose and dosing regimen of Ivermectin Cream for subsequent Phase 2 and 3 trials. Subjects in the trial were randomized to receive the following dose and regimen of Ivermectin Cream:

- 0.1% QD
- 0.3% QD
- 1% QD (to-be-marketed formulation)
- 1% BID (to-be-marketed formulation)

Single blood samples were obtained at ~ 14 hours (near Tmax) post-dose at Week 4 (at steady state) in 183 subjects and at Week 12 (end of treatment) in 190 subjects. Table 18 shows the plasma ivermectin levels.

**Table 18: Arithmetic mean values for ivermectin plasma concentrations Trial 40027**

Applied Daily Concentration (%) - Dose Regimen	Mean±SD (ng/mL)	Min to Max (ng/mL)	N	CV (%)
<b>Week 4</b>				
0.1% QD	0.13±0.16	BLQ to 1.00	49	129
0.3% QD	0.31±0.33	BLQ to 1.55	44	109
1% QD	0.72±0.75	BLQ to 4.05	50	105
1% BID	0.82±0.54	BLQ to 2.09	40	66
<b>Week 12</b>				
0.1% QD	0.09±0.07	BLQ to 0.41	49	73
0.3% QD	0.29±0.30	BLQ to 1.49	45	100
1% QD	0.77±1.05	BLQ to 6.13	50	136
1% BID	0.88±0.70	BLQ to 2.87	46	80

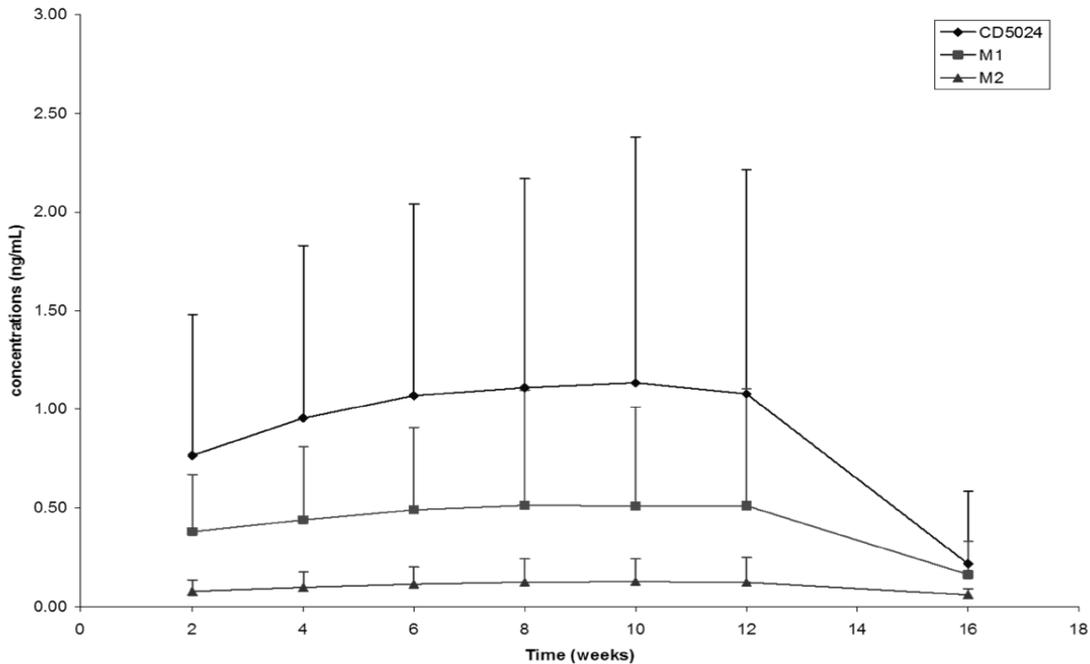
BLQ=Below the limit of quantification (< 0.05 ng/mL)

After repeated topical applications of Ivermectin 1% Cream QD in subjects with PPR, mean ± SD plasma concentrations of ivermectin were  $0.72 \pm 0.75$  ng/mL and  $0.77 \pm 1.05$  ng/mL at Week 4 and Week 12, respectively (N=50). The highest plasma concentration value was 6.13 ng/mL at Week 12. The systemic ivermectin concentrations increased with increasing concentration, but less than proportionally. According to the applicant, the mean (geometric or arithmetic) ivermectin plasma concentrations measured at Week 4 and at Week 12 were similar between each treatment group, thereby supporting the assumption that steady state had already been reached by Week 4 in subjects applying Ivermectin 1% Cream, with no evidence of plasma accumulation over the 12-week treatment period.

**Study RD.03.SRE.40106 (Phase 2 safety and efficacy study in subjects with papulopustular rosacea):** The primary objective of this Phase 2b trial was to investigate the potential effect of Ivermectin 1% Cream QD on the induction of neutropenia (defined as NCC <1.5 G/L) in subjects with PPR, compared to the Vehicle Cream. Approximately 250 subjects were screened and randomized in a 1:1 ratio in order to obtain at least 200 completers. The applicant claims that in terms of disease severity the population was similar to trial RD.03.SRE.40051 (subjects with PPR with IGA score  $\geq 3$ ).

The trough level systemic concentrations of ivermectin and ivermectin metabolites (M1 and M2) from only the Treatment arm were assessed at each visit during the treatment period (Weeks 2, 4, 6, 8, 10, and 12/Early termination), as well as at the Week 16 follow-up and at any unplanned visits that may have occurred due to individual cases of NCC values <1.5 G/L. Of the 104 subjects randomized to receive CD5024 1% Cream, plasma samples from 101 subjects (97.1%) were evaluable for PK analyses. The systemic concentrations of the parent remained stable during the treatment period (up to 12 weeks) confirming that steady state conditions were reached by 6 weeks of treatment. The limit of quantification (LOQ) for CD5024 was 0.05 ng/mL. Ivermectin systemic levels are shown in Table 19 and concentration versus time profile is shown in Figure 13.

**Figure 13: Mean plasma profile of ivermectin (mean  $\pm$  SD, N=86 to 102; Study 40106) (Note: Metabolite profiles of M1 and M2 are not considered accurate because the bioanalytical method for the metabolites was not validated)**



Non-quantifiable data were replaced by the LOQ (i.e., 0.05 ng/mL for ivermectin and M2, and 0.11 ng/mL for M1).

**Table 19: Plasma concentrations of ivermectin measured during the 12-week treatment period and at the Week 16 follow-up (Study 40106)**

Week	N	Systemic concentration (ng/mL) (Mean ±SD)	Min* to Max (ng/mL)
2	101	0.77±0.71	0.05 to 3.66
4	99	0.95±0.88	0.05 to 4.55
6	99	1.07±0.97	0.05 to 5.78
8	99	1.11±1.06	0.05 to 5.66
10	99	1.13±1.25	0.05 to 6.66
12	102	1.06±1.12	0.05 to 6.75
16 (Follow-up)	99	0.21±0.36	0.05 to 1.08

\*BLQ data were imputed to the LOQ of 0.05 ng/mL

Assessment of neutropenia: Distribution of the neutrophil counts was characterized over time by treatment and the Applicant concluded that 4 subjects (3 Active + 1 Vehicle) had single treatment-emergent NCCs below the threshold value of 1.5 G/L [Note - Normal range of neutrophil cell counts provided by the central laboratory ( (b) (4) ) was 2.1 G/L to 6.9 G/L]. The Applicant plotted individual neutrophil counts against plasma ivermectin concentration at each visit. For the 3 subjects in the active arm exhibiting treatment-emergent NCC count below 1.5 G/L, the corresponding ivermectin plasma concentrations are listed in Table 20.

**Table 20: Subjects with low NCC and corresponding ivermectin concentration in the plasma**

Subject number	Neutrophil cell counts (G/L)	CD5024 plasma concentrations (ng/mL)
5140-009	0.96	0.3674
5532-003	0.97	2.5484
5668-004	1.42	0.7325

Individual plasma profiles for each of these three subjects are provided below:

**Subject 5140-009** had an NCC at Week 6 of 0.96 G/L and a corresponding CD5024 concentration of 0.37 ng/mL (Table 21). A retest performed six days later yielded an NCC of 2.70 G/L, a value within the normal range. All subsequent NCC measurements were within the normal range.

**Table 21: NCC and CD5024 concentrations for Subject 5140-009**

Sampling date	13/10/10	26/10/10	10/11/10	24/11/10	23/12/10	29/12/10	29/12/10	05/01/11	19/01/11	03/02/11	03/03/11
Visit	Week - 4	Week - 2	Week 0	Week +2	Week +6	Retest	Retest	Week +8	Week +10	Week +12	Week +16
Local Lab assessment NCC (G/L)	-	-	-	-	-	2.70	-	-	-	-	-
Central Lab assessment NCC (G/L)	2.24	2.41	3.10	3.89	0.96	-	1.68	3.00	2.72	2.83	3.07
CD5024 plasma concentration (ng/mL)	-	-	-	0.4209	0.3674	-	NS	0.2423	0.2029	0.2264	BLQ

ND = not done; NS = not significant

**Subject 5532-003** had an NCC at Week 10 of 0.97 G/L and a corresponding CD5024 concentration of 2.55 ng/mL (Table 22). Two retest values were both within the normal range. The CD5024 plasma concentration remained stable throughout the treatment period, thus indicating that there was no definitive relationship between CD5024 plasma concentrations and NCCs for this subject.

**Table 22: NCC and CD5024 concentrations for Subject 5532-003**

Sampling date	24/11/10	08/12/10	22/12/10	05/01/11	19/01/11	02/02/11	15/02/11	02/03/11	04/03/11	07/03/11	16/03/11	13/04/11
Visit	Week - 4	Week - 2	Week 0	Week +2	Week +4	Week +6	Week +8	Week +10	Retest	Retest	Week +12	Week +14
Central Lab assessment NCC (G/L)	2.54	2.88	-	2.36	2.64	2.44	2.00	0.97	2.03	2.13	2.72	2.77
CD5024 plasma concentration (ng/mL)	-	-	-	2.5951	2.6759	3.0710	2.4317	2.5484	2.5832	2.1785	2.3162	0.4507

**Subject 5668-004** had an NCC of 1.42 G/L at Week 6 with a corresponding CD5024 concentration of 0.7325 ng/mL (Table 23). At retest, the NCC was recorded at 1.67 G/L and all subsequent measurements were within the normal range

**Table 23: NCC and CD5024 concentrations for Subject 5668-004**

Sampling Date	30/11/10	13/12/10	27/12/10	10/01/11	24/01/11	07/02/11	09/02/11	21/02/11	04/03/11	04/03/11	23/03/11	15/04/11
Visit	Week - 4	Week - 2	Week 0	Week +2	Week +4	Week +6	Retest	Week +8	Week +10	Week +10	Week +12	Week +16
Local lab assessment NCC (G/L)	-	-	-	-	-	-	-	-	3.64	-	-	-
Central lab assessment NCC (G/L)	3.45	3.50	ND	3.85	4.41	1.42	1.67	4.20	-	ND	3.26	4.00
CD5024 concentration (ng/mL)	-	-	-	0.3460	1.7924	0.7325	0.6639	0.5836	-	0.8470	0.5893	0.0534

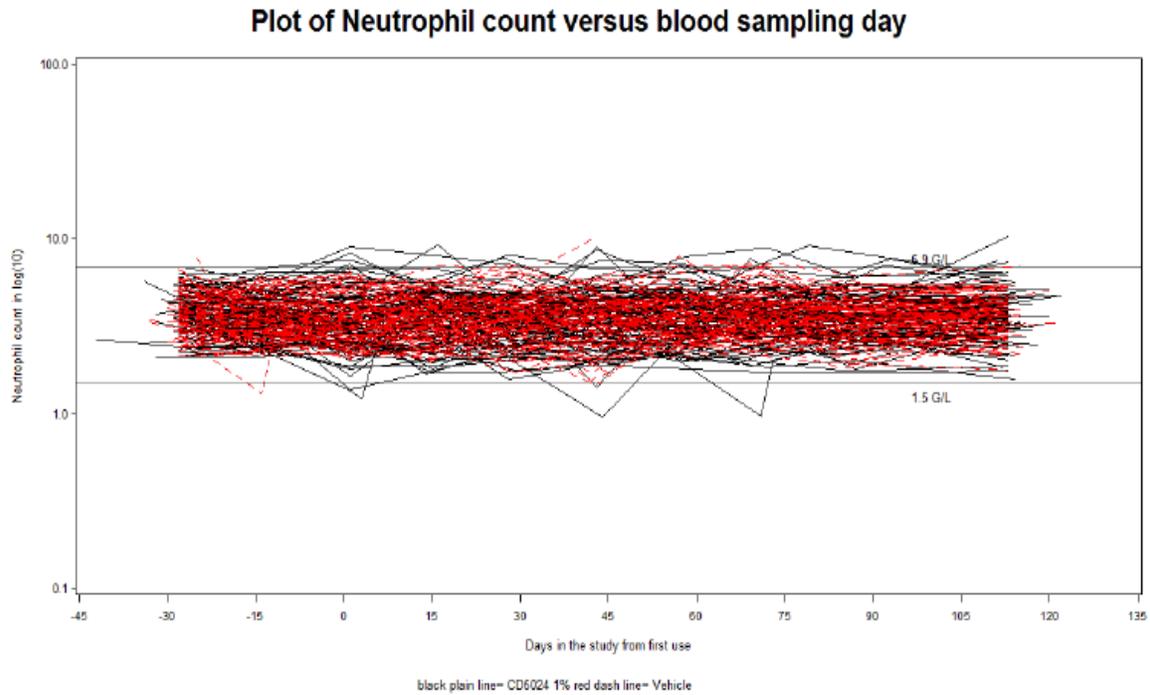
ND = Not done

The plasma concentration of ivermectin obtained at Week 10 for Subject 5532-003 was not among the highest observed in this trial. The maximum CD5024 concentration was 6.75 ng/mL, and it was observed in Subject 5140-008 at the Week 12 visit, which

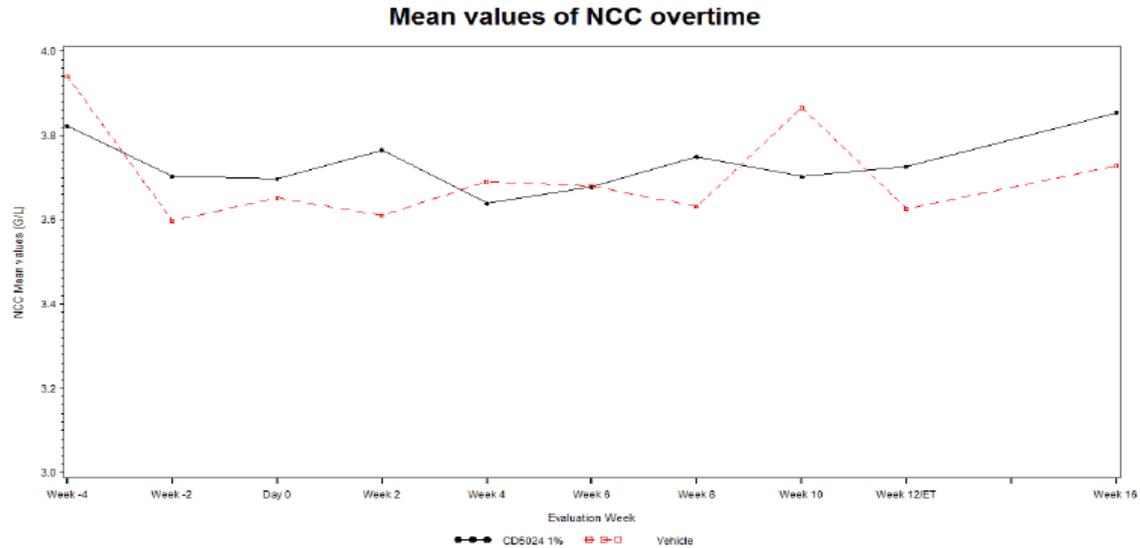
corresponded to an NCC of 2.68 G/L. Based on the data, the Applicant claims that, in general, subjects presenting NCCs below 1.5 G/L had low systemic exposures to CD5024 in comparison to the overall data. This shows the absence of a relationship between neutropenia and ivermectin plasma concentrations.

Neutrophil counts for all subjects: The neutrophil counts for all subjects at each sampling visit are graphically depicted in Figure 14. Figure 15 shows that the mean NCC values over time remained stable and similar between treatment and vehicle arms.

**Figure 14: Plot of Neutrophil count versus blood sampling day for all subjects**



**Figure 15: Mean Values of NCC over time**



Based on the findings from this trial, the Applicant concluded that there was no exposure-response relationship between ivermectin systemic concentrations and incidence of neutropenia and furthermore, the incidence of neutropenia does not appear to be drug related.

***Reviewer comments:*** *This reviewer concurs with the Applicant's conclusion which suggests lack of any correlation between neutropenia and ivermectin plasma concentrations based on the observed data.*

**Study RD.06.SRE.18170 (Phase 3 pivotal study in subjects with papulopustular rosacea):** This was a multicenter, randomized, parallel-group study conducted to demonstrate the efficacy and assess the safety of Ivermectin 1% Cream for up to 52 weeks of treatment, and for 4 weeks after treatment discontinuation (Week 56).

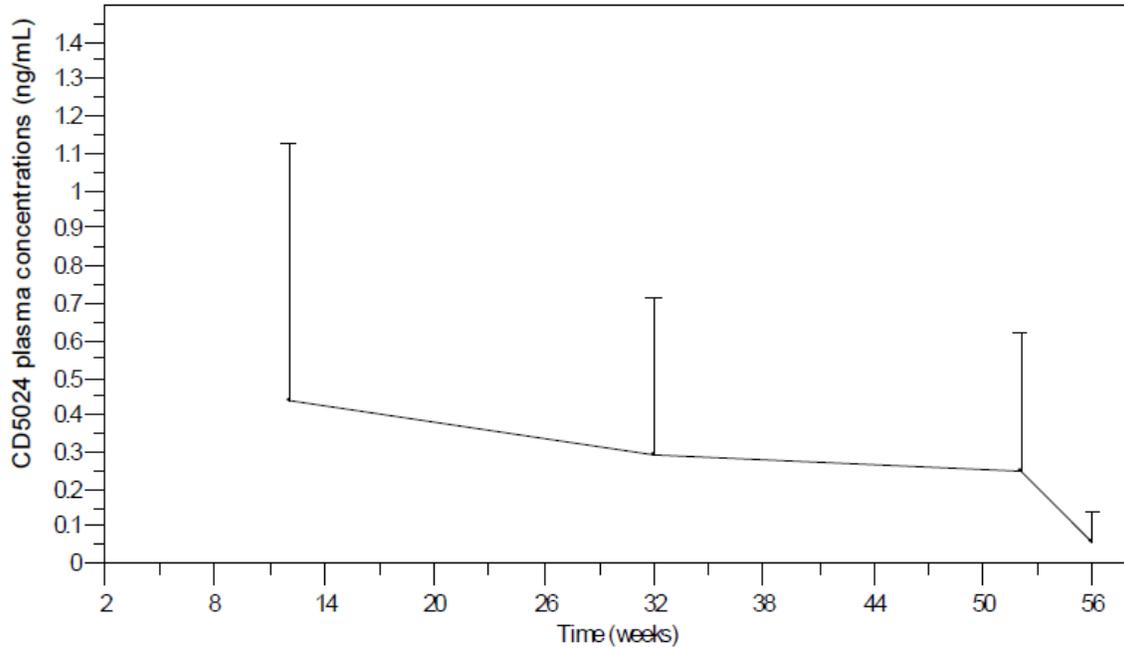
The study was divided into 3 parts as follows:

- Part A: treatment with Ivermectin 1% Cream QD or Vehicle Cream QD for 12 weeks.
- Part B: long-term extension period up to Week 52 during which subjects received Ivermectin 1% Cream QD or Azelaic Acid 15% Gel BID (active-controlled part of the study). [Note that subjects who received Ivermectin 1% Cream QD in Part A, continued with the same treatment in Part B. Subjects on Vehicle Cream QD in Part A switched to Azelaic Acid 15% Gel in Part B].
- Part C: 4-week treatment-free follow-up period to enable collection of safety data after treatment discontinuation.

Plasma samples for PK assessment were obtained from subjects at selected investigational sites at 12±2 hours after the last application at Week 12, Week 32 and Week 52. In addition, 1 plasma sample was obtained at the Week 56 (follow-up) visit. The objective of PK assessment was to confirm previous measurements of ivermectin levels from previous trials and investigate the relationship between ivermectin exposure with NCC values.

Of the 683 subjects enrolled in the study, blood samples were collected for PK purposes from 163 subjects at selected investigational sites in a blinded manner. Of these 163 subjects, 109 subjects were in the Ivermectin 1% Cream QD (Part A and Part B) group and 54 subjects were in the Vehicle Cream QD/Azelaic Acid 15% Gel BID group. Additional blood samples were taken during unscheduled visits from 17 subjects; however, the data from these subjects were not included in the evaluation of systemic exposure and steady state assessment. Mean  $C_{\text{trough}}$  values obtained from subjects receiving Ivermectin 1% Cream QD at each PK visit (i.e., at Weeks 12, 32, 52, and 56) are provided in Table 24, and the mean ivermectin plasma profile over the study duration is displayed in Figure 16.

**Figure 16: Mean plasma profile of ivermectin (mean+SD, N=105; Study 18170)**



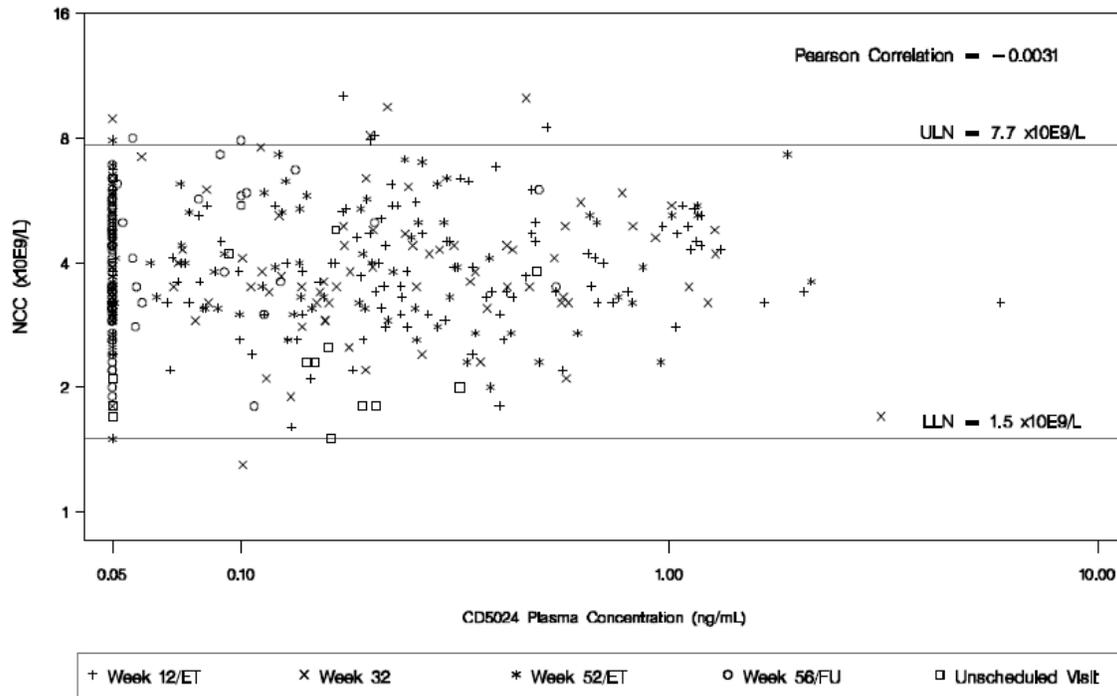
**Table 24: Plasma concentrations of ivermectin (ng/mL) measured up to Week 56 (Study 18170)**

C <sub>t</sub> (ng/mL)	Week 12	Week 32	Week 52	Week 56
Mean±SD	0.46±0.70	0.35±0.44	0.31±0.40	0.07±0.08
Min to Max	0.05 to 5.95	0.05 to 3.13	0.05 to 2.15	0.05 to 0.54
CV	154%	127%	128%	109%
N (N quantifiable)	105 (98)	77 (68)	73 (62)	76 (18)

Blood samples were also taken during unscheduled visits from subjects reporting NCC  $\leq$  1.5 G/L, in order to detect any correlation with ivermectin concentration. According to the applicant, ivermectin plasma concentrations collected in these subjects were in the normal range of exposure for subjects treated with Ivermectin 1% Cream QD (Part A and Part B).

Individual NCC measurements were plotted against plasma concentration data for the Ivermectin 1% Cream QD (Part A and Part B) group over the entire study (see Figure 17). The results showed that there was no correlation between NCC values and CD5024 plasma concentrations.

**Figure 17: Neutrophil cell counts versus ivermectin plasma concentration (ng/mL) in the Ivermectin 1% Cream (Part A and Part B) group (N=105; Study 18170)**



Below limit of quantification (BLQ) values of plasma concentration are imputed using the LOQ.

Pearson correlation of NCC value and CD5024 Plasma Concentration is calculated.

For NCC value, Upper limit of Normal (ULN) and Lower limit of Normal (LLN) reference lines are provided.

Case report form (CRF) visits are used. ET=Early termination. FU=Follow up.

**Study RD.06.SRE.18171 (Phase 3 pivotal study in subjects with papulopustular rosacea):** The design of this Phase 3 trial was identical to Trial 18170.

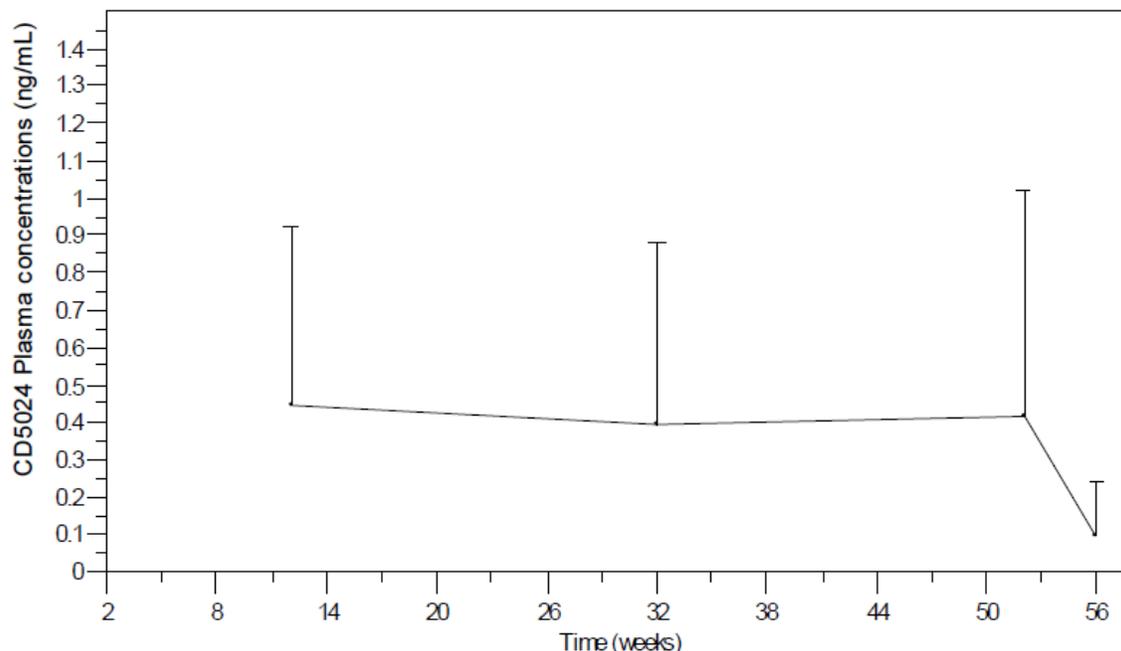
Of the 688 subjects enrolled in this trial, blood samples were collected for PK purposes from 148 subjects at selected investigational sites in a blinded manner. Of these 148 subjects, 100 subjects were in the Ivermectin 1% Cream QD (Part A and Part B) group and 48 subjects were in the Vehicle Cream QD/Azelaic Acid 15% Gel BID group. Additional blood samples were taken during unscheduled visits from 17 subjects; however, the data from these subjects were not included in the evaluation of systemic exposure and steady state assessment.

Mean  $C_{trough}$  values obtained from subjects receiving Ivermectin 1% Cream QD at each PK visit (i.e., at Weeks 12, 32, 52, and 56) are provided in Table 25, and the mean ivermectin plasma profile over the study duration is displayed in Figure 18.

**Table 25: Plasma concentrations of ivermectin (ng/mL) measured up to Week 56 (Study 18171)**

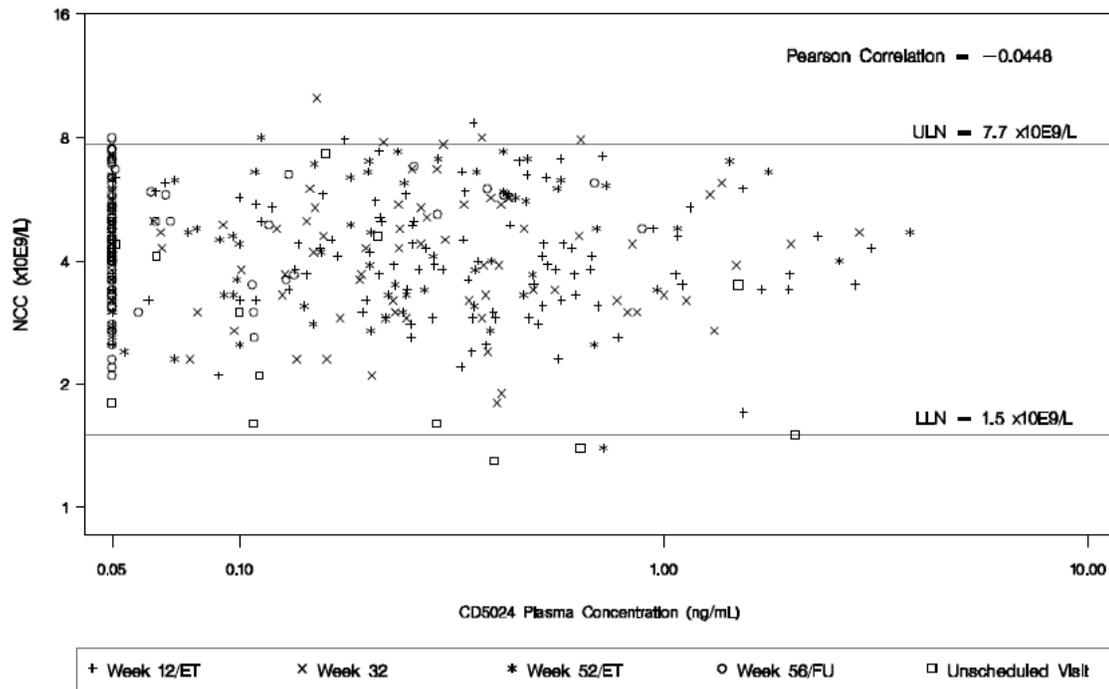
C <sub>t</sub> (ng/mL)	Week 12	Week 32	Week 52	Week 56
Mean±SD	0.43±0.49	0.40±0.49	0.41±0.61	0.10±0.14
Min to Max	0.05 to 2.81	0.05 to 2.89	0.05 to 3.80	0.05 to 0.89
CV	114%	122%	147%	146%
N (N quantifiable)	92 (81)	84 (71)	65 (54)	65 (19)

**Figure 18: Mean plasma profile of ivermectin (mean+SD, N=92; Study 18171)**



Blood samples were also taken during unscheduled visits from subjects reporting NCC  $\leq$  1.5 G/L, in order to detect any correlation with ivermectin concentration. According to the applicant, ivermectin plasma concentrations collected in those subjects were in the normal range of exposure for subjects treated with Ivermectin 1% Cream QD. Individual NCC measurements were plotted against plasma concentration data for the Ivermectin 1% Cream QD (Part A and Part B) group over the entire study (Figure 19). The results showed that there was no correlation between NCC values and ivermectin plasma concentrations.

**Figure 19: Neutrophil cell counts versus ivermectin plasma concentration (ng/mL) in the Ivermectin 1% Cream (Part A and Part B) group (N=92; Study 18171)**



Below limit of quantification (BLQ) values of plasma concentration are imputed using the LOQ.

Pearson correlation of NCC value and CD5024 Plasma Concentration is calculated.

For NCC value, Upper limit of Normal (ULN) and Lower limit of Normal (LLN) reference lines are provided.

Case report form (CRF) visits are used. ET=Early termination. FU=Follow up.

**Study RD.03.SRE.40173 (Phase 3 supportive study in subjects with papulopustular rosacea):** This was a multicenter, randomized, parallel-group Phase 3 supportive Study conducted to demonstrate the efficacy and assess the safety of Ivermectin 1% Cream QD versus Metronidazole 0.75% Cream BID for 16 weeks of treatment, followed by a 36-week extension period to evaluate relapse.

The trial was divided into 2 parts as follows:

- Part A: treatment with Ivermectin 1% Cream QD or Metronidazole 0.75% Cream BID for 16 weeks. Subjects who had an IGA score of “0” or “1” at the end of Part A were eligible for Part B.
- Part B: long-term extension period up to Week 52. (Ongoing Trial).

Ivermectin plasma levels were measured only in subjects who were reported with NCC <1.5 G/L. Blood samples were collected from 6 subjects in Part A of this study and as a part of the application there were no subjects in Part B up to a cutoff date of 8 April 2013 had NCC <1.5 G/L, thus no blood samples were collected.

Out of the 6 subjects that were reported to have treatment-emergent NCC <1.5 G/L during Part A of the study, 3 subjects were treated with Ivermectin 1% Cream QD and the other 3 subjects were treated with Metronidazole 0.75% Cream QD.

According to the applicant, none of the treatment-emergent incidences of NCC <1.5 G/L were considered related to the study drug and Ivermectin systemic levels ranged from 0.27 to 1.31 ng/mL and these levels were considered within the normal range of exposure for subjects treated with Ivermectin 1% Cream QD and were also found to be consistent with concentration ranges observed in two pivotal Phase 3 trials where ivermectin systemic concentration ranged from BLQ to 5.95 ng/mL and from BLQ to 3.8 ng/mL for trials 18170 and 18171, respectively).

**Trial RD.03.SRE.40051 (long-term safety study in subjects with papulopustular rosacea):** The objective of this trial was to determine the long-term safety and efficacy of ivermectin 1% cream in subjects with PPR over 52 weeks.

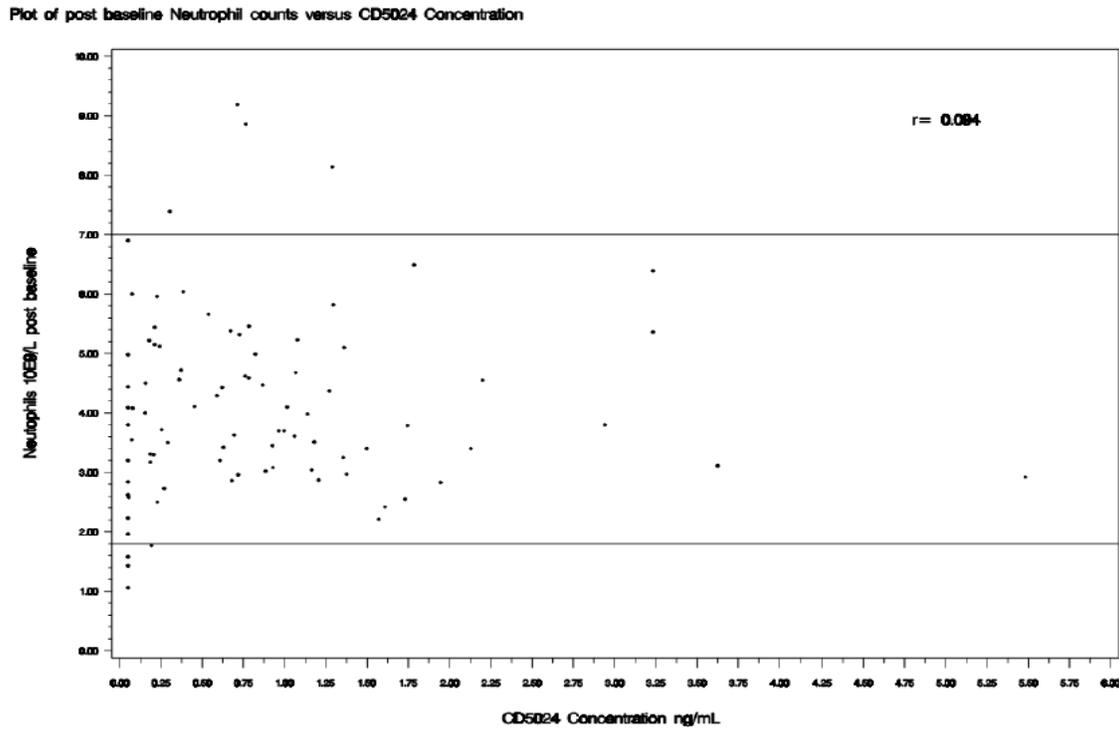
Initially, assessment of ivermectin plasma levels was planned in a sub-set of 70 of 484 subjects at Weeks 10, 28, and 52/Early Termination. However, this 52-week trial was prematurely terminated as a conservative measure due to low neutrophil cell count (NCC) values observed in 3 subjects at Week 10 and the protocol was amended to include a 4-week treatment-free follow-up period. Plasma ivermectin concentration was assessed in 79 subjects at Week 10. The mean concentration of ivermectin in plasma at Week 10 was  $0.90 \pm 0.90$  ng/mL (range BLQ to 5.48 ng/mL) and was similar to other trials performed in subjects with rosacea.

Unscheduled blood sampling for PK analysis was performed during the follow-up period for 6 subjects. Four subjects had ivermectin plasma concentrations that were BLQ, and 2 subjects had quantifiable ivermectin plasma concentrations of 0.05 ng/mL and 0.37 ng/mL. According to the applicant, the 2 subjects with quantifiable ivermectin plasma concentrations, were not the subjects who had demonstrated low NCC values.

To ensure a complete evaluation of the safety of Ivermectin 1% Cream, a post-hoc analysis was conducted to assess a potential correlation between individual ivermectin plasma concentrations and individual NCC values (Figure 20).

A total of 86 samples were analyzed and the log transformed individual ivermectin plasma concentrations were plotted against the individual neutrophil counts and no correlation was observed. From this trial, the applicant concluded that there was no relationship between ivermectin plasma concentration and low NCC value and this issue was further investigated in the Phase 2 trial RD.03.SRE.40106 (described in detail above).

**Figure 20: Ivermectin plasma concentrations versus individual neutrophil cell counts (Trial 40051, N=86)**



Overall analysis of NCC data over the one-year duration of the Phase 3 pivotal Trials 18170 and 18171 including their long-term extension: The cumulative incidence of NCC values  $\leq 1.5$  G/L at the end of each quarter of the pooled trials adjusted for drop-outs is presented in Table 26 below. The incidence of NCCs  $\leq 1.5$  G/L was similar or lower in the ivermectin group compared to the vehicle/azelaic acid group across the 4 quarters of the studies (Note: Azelaic acid is the active treatment). After 1 year of exposure, the cumulative incidence of NCCs  $\leq 1.5$  G/L was 2.18% in the ivermectin group and 2.36% in the vehicle/azelaic acid group suggesting that the incidence of neutropenia is not treatment related.

**Table 26: Cumulative Incidence of neutrophil cell count values below 1.5 G/L in Studies 18170 and 18171 at the end of each quarter, adjusted for drop-outs**

		CD5024 1%/CD5024 1%	Vehicle/Azelaic Acid
Q1	N<1.5 G/L	4 (0.46%)	3 (0.69%)
Q2	N<1.5 G/L	6 (0.70%)	5 (1.21%)
Q3	N<1.5 G/L	12 (1.49%)	6 (1.49%)
Q4	N<1.5 G/L	17 (2.18%)	9 (2.36%)

Analysis performed on the Phase 3 pivotal studies (SPR18170 and SPR18171).

Individual subject data with low neutrophil counts and follow-up information is presented in the Table 27 for the ivermectin arm and Table 28 for the azelaic acid (active control) or vehicle arm. The data presented suggests that observed low NCC levels returned to normal range at the follow-up visit for all the subjects

**Table 27: Individual subject data with low neutrophil counts and follow-up information for ivermectin arm**

Subject No	Study Period	Low NCC value	Treatment Day	Normalized (≥1.5 G/L)	IDMC Comments
<b>Study 18170</b>					
8195-026	Part B	1.3 G/L	Day 225	6 days later	It was a mild, clinically insignificant neutropenia, unlikely related to the study drug
8077-001	Part B	1.3 G/L 1.4 G/L	Day 237 Day 267 <sup>a</sup>	3 days later No retest	The subject had a mild neutropenia after chemotherapy for bladder cancer, unrelated to the study drug and probably related to cancer chemotherapy
8094-011	Part B	1.4 G/L	Day 281	28 days later	This African-American subject had borderline NCCs before treatment (1.7 G/L at Week -2 and Week -1 visits). It was a clinically insignificant neutropenia unrelated to the study drug
8340-014	Part B	1.3 G/L	Day 283	2 days later	It was a clinically insignificant mild neutropenia unrelated to the study drug
8214-027	Part B	0.6 G/L	Day 253	3 days later (5.8 G/L)	The spurious low NCC was due to a technical problem (blood sample exposed to temperature below 4°C)
8354-014	Part B	1.2 G/L	Day 285	3 days later	It was a mild neutropenia unrelated to the study drug and probably due to viral respiratory infection
8373-010	Part B	1.3 G/L 1.1 G/L 1.3 G/L <sup>b</sup> 1.2 G/L 1.4 G/L <sup>c</sup> 1.4 G/L 1.4 G/L	Day 113 Day 228 Day 232 Day 260 Day 317 Day 352 Day 373	2 days later 2 days later 2 days later 2 days later No retest No retest No retest	The subject had variable NCCs and leukocyte counts (some normal, some borderline low). Each time the subject had a mild low NCC, there was a spontaneous improvement. The IDMC concluded that the low NCCs were non clinically significant and unrelated to the study drug
<b>Study 18171</b>					
8110-026	Part B	1.4 G/L	Day 140	1 week later	It was a mild neutropenia which was clinically not significant and unrelated to the study drug
8133-016	Part B	1.1 G/L 1.0 G/L	Day 365 Day 380	- 6 days later	It was a clinically not significant mild neutropenia, and unlikely related to the study drug
8213-025	Part B	1.4 G/L 1.4 G/L	Day -7 Day 169	3 days later 2 days later	The subject had an intermittent neutropenia known since 2001. It was a mild neutropenia, clinically not significant and unrelated to the study drug
8213-028	Part A Part B	1.4 G/L <sup>d</sup> 0.7 G/L	Day 57 Day 197	5 days later 2 days later	It was a mild to moderate and probably clinically significant neutropenia, unrelated to the study drug

a. Manual control: 1.5 G/L

b. Manual control: 1.6 G/L

c. Manual control: 1.7 G/L

d. Manual control: 1.8 G/L

**Table 28: Individual subject data with low neutrophil counts and follow-up information for Vehicle/azelaic acid arm**

Subject No	Study Period	Low NCC value	Treatment Day	Normalized ( $\geq 1.5$ G/L)	IDMC Comments
<b>Study 18170</b>					
8326-001	Part B	1.4 G/L <sup>a</sup>	Day 308	10 days later	It was a clinically insignificant, mild neutropenia, unrelated to the study drug
8120-017	Part B	1.3 G/L	Day 162	2 days later	The subject had low NCCs (1.7 G/L) prior to treatment (Week -2, Week-1, Baseline). It was a mild neutropenia, clinically not significant and unrelated to the study drug
8059-009	Part B	1.3 G/L 1.2 G/L	Day 365 Day 368	3 days later	The borderline NCC values (between 1.5 and 2 G/L) observed since the Screening visit were probably due to the subject ethnicity. It was a mild neutropenia unlikely related to the study drug and clinically not significant
8195-020	Part B	1.2 G/L	Day 117	2 days later	It was a mild neutropenia, clinically not significant and unrelated to the study drug
<b>Study 18171<sup>c</sup></b>					
8010-003	Part A Part B	1.3 G/L 1.2 G/L 1.0 G/L 1.4 G/L 1.2 G/L 1.1 G/L 1.3 G/L 1.2 G/L 1.2 G/L 1.3 G/L 1.2 G/L	Day 29 Day 57 Day 113 Day 117 Day 119 Day 121 Day 131 Day 162 Day 190 Day 225 Day 316	4 days later 4 days later  3 days later  28 days later 14 days later	This subject had a borderline low NCC which varied along the whole study period (including at pretreatment test). She had a mild neutropenia at several times during the study. After each neutropenia episode, and without stopping the study drug, there was an improvement of the NCC. It was a clinically insignificant mild neutropenia, unrelated to the study drug
8143-025	Part A	1.3 G/L 1.2 G/L	Day -14 Day 28	2 days later No retest <sup>b</sup>	The subject had a mild neutropenia before the study (1.3 G/L). Neutropenia was again noted after 4 weeks of treatment. The subject was lost to follow-up. It was a mild neutropenia, clinically not significant, and unrelated to the study drug
8255-001	Part B	1.2 G/L	Day 225	1 week later	It was a non-clinically significant mild neutropenia, unrelated to the study drug

a. Manual control: 1.6 G/L

b. The subject did not return to the study site

c. Neutrophils < 1.5 G/L for Subject SPR18171-8074-003 was not taken into account because the subject was censored for Part B (see dispensation errors in Table 2).

***Reviewer comments:*** From the overall analysis, it is reasonable to conclude that incidence of neutropenia is not drug related and there is no exposure-response.

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/s/  
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CHINMAY SHUKLA  
10/03/2014

DOANH C TRAN  
10/03/2014

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 206255	<b>Reviewer:</b> Kelly M. Kitchens, Ph.D.	
<b>Submission Date:</b>	December 24, 2013		
<b>Division:</b>	Division of Dermatology and Dental Products	<b>Team Leader:</b> Tapash Ghosh, Ph.D.	
<b>Applicant:</b>	Galderma Research and Development, LLC	<b>Acting Supervisor:</b> Paul Seo, Ph.D.	
<b>Trade Name:</b>	Ivermectin 1% Cream	<b>Date Assigned:</b>	January 15, 2014
<b>Established Name:</b>	Soolantra (ivermectin) Cream, 1%	<b>Date of Review:</b>	May 15, 2014
<b>Indication:</b>	Topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older	<b>Type of Submission:</b> NDA 505(b)(2)	
<b>Formulation/strengths</b>	Cream/1%		
<b>Route of Administration</b>	Topical		
<b>Type of Review:</b>	In Vitro Release Test Method and Results		
<b><u>SUMMARY:</u></b>			
<p><b>Background:</b> The current NDA was submitted per section 505(b)(2) for Soolantra (ivermectin) Cream, 1%, for the once daily topical treatment of inflammatory lesions of rosacea. Each gram of cream contains 10 mg of ivermectin. During development, registration stability batches were made using commercial manufacturing process and packaged in the to-be-marketed container/closure system (child-resistant), whereas Phase 3 and supporting stability batches were made using clinical (Phase 3) manufacturing process and packaged in non-child-resistant container/closure system. Modifications were made to the commercial manufacturing process compared to the manufacturing process used for Phase 3 clinical batches to obtain the target (b) (4). The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. The change in manufacturing process is considered a Level 2 change per the SUPAC-SS Guidance. Therefore, the commercial manufacturing process was bridged to the clinical manufacturing process using in vitro release testing (IVRT).</p> <p><b>Submission:</b> On February 28, 2014, a “Filing Review Issues Identified” letter was sent to the Applicant, which included a request for the IVRT method development and validation reports, and IVRT raw data. On February 7, 2014, the Applicant submitted the final report from the IVRT study. On March 31, 2014 and April 23, 2014, the Applicant submitted information for the IVRT method development and validation, as well as IVRT data.</p>			

**Review:** The Biopharmaceutics review is focused on the evaluation of the IVRT method and results to bridge the clinical batch manufacturing process and the commercial batch manufacturing process.

**RECOMMENDATION:**

The Applicant has developed the following acceptable method for in vitro release testing (IVRT) of their drug product:

<b>Diffusion apparatus</b>	6 Franz cells
<b>Receptor medium</b>	Water/Ethanol (40/60)
<b>Membrane selection</b>	Polyvinylidene fluoride (Durapore HLVP) 0.45µm
<b>Sampling time points</b>	50, 100, 150, 200, 250, 300 minutes
<b>Temperature</b>	35°C
<b>Sample amount</b>	900 mg
<b>Occlusion</b>	Aluminum sheet

The clinical batch manufacturing process has been adequately bridged to the commercial batch manufacturing process using this IVRT method. The proposed IVRT acceptance criteria ( (b) (4) ) are acceptable and that will be used for product release and for stability purposes. From the Biopharmaceutics perspective, NDA 206255 for Soolantra (ivermectin) Cream, 1%, is recommended for approval.

**Signature**

Kelly M. Kitchens, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Signature**

Tapash Ghosh, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

cc. PSeo.

# BIOPHARMACEUTICS ASSESSMENT

## Drug Product:

- Ivermectin Cream, 1%, is a white to pale yellow homogeneous cream containing 1% w/w (10 mg/g) of ivermectin as the drug substance. Each gram of cream contains 10 mg of ivermectin drug substance. The composition of Ivermectin Cream is described in the following table:

**Table 1 Ivermectin 1% Cream: Qualitative and quantitative composition of Formulation 575.754**

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

\* 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)

- Ivermectin Cream was initially manufactured by (b) (4) for production of non-clinical and clinical supplies for Phase 2 clinical studies at a (b) (4) batch scale. The process was ultimately transferred to GPI, Canada with a batch scale of (b) (4) for the clinical batches of additional Phase 2 studies, Phase 3 pivotal studies, and commercialization of drug product intended for US registration. Slight modifications were implemented for the commercial manufacturing process compared to the clinical manufacturing process to ensure the target (b) (4).
- The sameness of the commercial manufacturing process and the clinical manufacturing process was evaluated using in vitro release testing (IVRT). A comparison of the Phase 3 clinical and commercial manufacturing processes is described in the following table:

**Table 8** Comparison between the pivotal clinical and commercial process

Step	Pivotal clinical manufacturing process	Commercial manufacturing process	Conclusion
(b) (4)			

**In Vitro Release Testing (IVRT) for Manufacturing Process Change:**

On February 28, 2014, the following information was requested from the Applicant in a “Filing Review Issues Identified” letter:

1. *Provide the in vitro release testing (IVRT) method development and validation reports. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:*
  - a. *Diffusion apparatus*
  - b. *Receptor medium selection*
  - c. *Membrane selection*
  - d. *Sampling time points*
  - e. *Temperature*
  
2. *The IVRT method validation report should contain (but is not limited to) the following validation components:*
  - a. *Linearity and Range*
  - b. *Accuracy/Precision and Reproducibility*
  - c. *Mass Balance & Dose Depletion*
  - d. *Sensitivity and Specificity*
  - e. *Selectivity*
  - f. *Robustness*
  - g. *Membrane Inertness*
  - h. *Receptor Solution Solubility/Stability*
  
3. *The IVRT method’s sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim*

of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

- Submit all the generated data in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm<sup>2</sup>

Time (min, hr, etc.)	Sq. rt. Time	Concentration in Cell (µg/mL)	Amount in Cell (µg)	Cumulative Amount in Cell (µg)	Cumulative Diffusion (µg/cm <sup>2</sup> )
T1					
T2					
T3					
T4					
T5					
Tn					

On February 7, 2014, the Applicant submitted an amendment to provide the final IVRT report including the raw data. In addition, the Applicant submitted method development and method validation information in response to requests #1, 2a, 2b, 2e, 2f, 2h, and 4. And on April 23, 2014, the Applicant submitted method validation information in response to requests #2c, 2d, 2g, and 3.

***IVRT Method Development:***

Parameters	Data
Source of data	Study Report for the Determination of IVRT Operating Conditions of CD5024 (Ivermectin) 1% Cream Formula 0575.754 Report no. RDS.03.SRE.26579.R00
Diffusion apparatus	6 Franz cells as described in the SUPAC-SS guidance
Receptor medium	Water/Ethanol (40/60) was selected to maintain sink conditions, and ivermectin is stable in this medium
Membrane selection	Polyvinylidene fluoride (Durapore HLVP 0.45µm) was selected because the membrane remains intact and smooth at the end of test runs
Sampling time points	50, 100, 150, 200, 250, 300 minutes were selected to allow diffusion of ivermectin through the membrane and obtain a constant release rate, and to have a 5 hour run with 6 sampling times
Temperature	35°C to meet the target temperature of 32°C (to match skin temperature)
Sample amount	900 mg was applied to allow good distribution of the formulation over the membrane
Occlusion	Aluminum sheet used (no justification for the use of occlusion)

**IVRT Method Validation:**

Parameters	Data
Source of data	Validation Report of LC Assay of CD5024 for IVRT Studies Report no. RDS.03.VRE.26313.R00
Analytes	Ivermectin
Dose depletion	Mean mass balance after (b) (4)
Membrane inertness	(b) (4) recovery with filtered solution
Sensitivity 50% and 150% LC	The method identifies higher or lower release rates with increased or decreased loading drug concentrations
Selectivity 50% and 150% LC	The method identifies drug release from higher and lower drug concentrations as inequivalent to drug release from the reference product
Specificity 50% and 150% LC	The method identifies proportional changes in drug release as a function of drug loading concentration

Validation components	Acceptance Criteria	Results
Selectivity	Blank, placebo, blank from IVRT, placebo from IVRT, preservatives : no interference at retention time of H <sub>2</sub> b <sub>1a</sub> and H <sub>2</sub> b <sub>1b</sub>	Complies
Linearity of the response	Standard solutions from 1 to 30 % of theoretical release	
	b of the 20% theoretical release concentration level < 3%	1.39%
	R <sup>2</sup> > 0.99	0.9992
Linearity of the method	Spiked samples solutions from 1 to 30 % of theoretical release	
	Day 1 : r <sup>2</sup> > 0.99	0.9998
	Day 1 : b of the 20% theoretical release concentration level < 3%	0.68%
	Day 2 : r <sup>2</sup> > 0.99	0.9994
	Day 2 : b of the 20% theoretical release concentration level < 3%	0.85%
	Day 3 : r <sup>2</sup> > 0.99	1.0000
Precision and Accuracy	95% ≤ each individual recovery ≤ 105%	Complies
	97% ≤ Mean recovery Day 1 ≤ 103 %	99%
	97% ≤ Mean recovery Day 2 ≤ 103 %	103%
	97% ≤ Mean recovery Day 3 ≤ 103 %	99%
Robustness	Stability of solutions: stable if area sample variation < 5%	65h
	Stability of solutions: stable if area standard variation < 5%	48h
LOD-LOQ	LOD in mg/L for H <sub>2</sub> b <sub>1a</sub>	0.1491
	LOQ in mg/L for H <sub>2</sub> b <sub>1a</sub>	0.4971
	LOD in mg/L for H <sub>2</sub> b <sub>1b</sub>	0.1067
	LOQ in mg/L for H <sub>2</sub> b <sub>1b</sub>	0.3558

**Table 2 Formulations used in the study**

Test articles / Formulations	Manufacturing site	Batch number	Manufacturing date	Storage
CD5024 1% cream (Prechange batch)	Galderma Production Canada Inc. 19400 Route Transcanadienne Baie d'Urfé H9X 3S4 Canada	083720 (Galderma Production Inc. codification) = 12.00059 (MES* codification)	September 8 <sup>th</sup> , 2011	Room Temperature
CD5024 1% cream (Postchange batch)	Galderma Production Canada Inc. 19400 Route Transcanadienne Baie d'Urfé H9X 3S4 Canada	100322	June 17 <sup>th</sup> , 2013	Room Temperature

\*Executive system used at the Pharmaceutical Unit within the R&D site in Sophia-Antipolis.

**Reviewer's comments on IVRT method development and validation:**

- The Applicant provided justification for their IVRT method parameters.
- The IVRT method has been adequately validated.
- The IVRT method development and validation are acceptable.

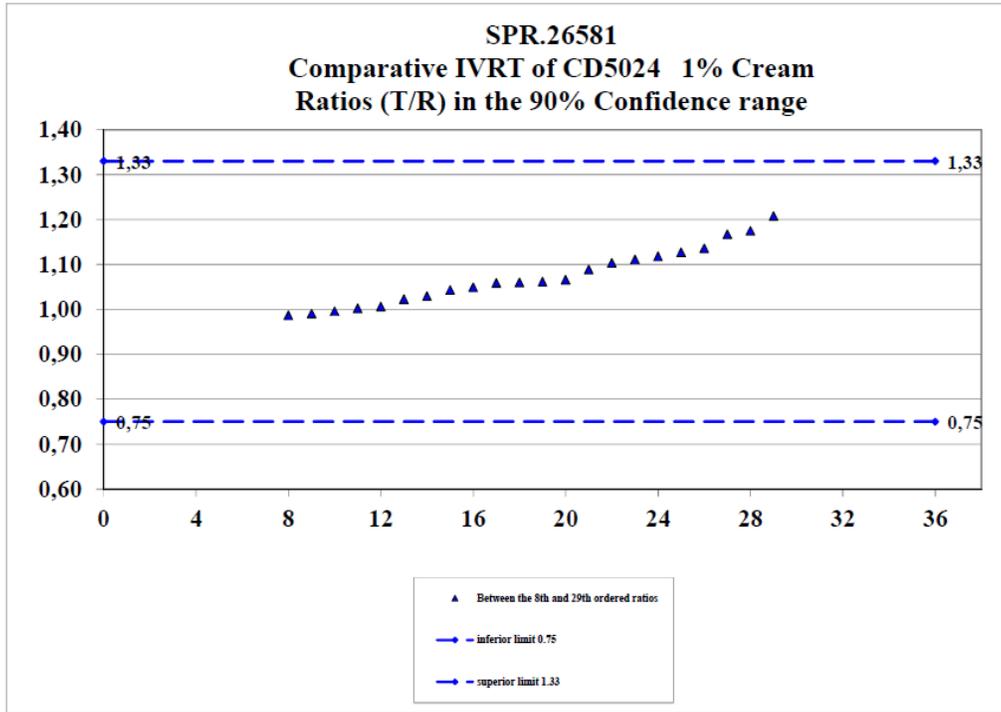
**IVRT results:**

**Batches tested:**

Description	Manufacturing Site	Bulk batch number	Packaging	Batch number	Manufacturing date	Purpose of the batch	Storage
Ivermectin 1% Cream (Prechange lot)	GPI	082160	30 g (b) (4)	083720	September 2011	Clinical batch	Room Temperature
Ivermectin 1% Cream (Postchange lot)		103650	30 g child resistant (b) (4)	100322	June 2013	Registration batch	Room Temperature

- Per the SUPAC-SS Guidance, “The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the prechange process.”
- The reference batch was near expiry and the test batch was freshly manufactured at the time of IVRT (September 9-18, 2013). Therefore, the batches tested were not of comparable age.

**Applicant's Results:**



**Reviewer's Results:**

Table 1. Reviewer-calculated slope data at first stage:

Ivermectin Release Rates ( $\mu\text{g}\cdot\text{cm}^{-2}\cdot\text{h}^{-1/2}$ )	
Pre-change batch # 083720 (R)	Post-change batch # 100322 (T)
(b) (4)	

Table 2. Reviewer-calculated individual T/R ratios at first stage:

	248.0298	445.3357	467.8284	442.2930	390.1773	418.4840
<b>471.3370</b>	1.9003	1.0584	1.0075	1.0657	1.2080	1.1263
<b>491.0951</b>	1.9800	1.1028	1.0497	1.1103	1.2586	1.1735
<b>454.9222</b>	1.8341	1.0215	0.9724	1.0286	1.1659	1.0871
<b>443.3068</b>	1.7873	0.9954	0.9476	1.0023	1.1362	1.0593
<b>414.0778</b>	1.6695	0.9298	0.8851	0.9362	1.0613	0.9895
<b>435.6943</b>	1.7566	0.9784	0.9313	0.9851	1.1167	1.0411

Table 3. Reviewer-calculated rank order of individual T/R ratios at first stage:

Rank Order	T/R Ratios
1	0.88510625
2	0.92981059
3	0.93131231
4	0.93620694
5	0.94758424
6	0.9724125
7	0.97835039
8	<b>0.98508066</b>
9	0.98947113
10	0.99544417
11	1.00229203
12	1.00749985
13	1.02152644
14	1.02855373
15	1.04112545
16	1.04973355
17	1.05838596
18	1.05931603
19	1.06125563
20	1.06566681
21	1.08707185
22	1.10275277
23	1.11033883
24	1.11665738
25	1.12629643
26	1.13616767
27	1.16593712
28	1.17351
29	<b>1.20800738</b>
30	1.25864622
31	1.66946828
32	1.75662115
33	1.78731291
34	1.83414344
35	1.90032445
36	1.97998474

**Reviewer's comments on IVRT results:**

- Although the 90% confidence intervals (8th and 29th ordered individual ratios) for Ivermectin (98.51%, 120.80%) met the acceptance criteria for IVRT, the batches tested were not of comparable age. Per the SUPAC-SS Guidance, “*The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the prechange process.*” The reference batch [REDACTED] (b) (4) at the time of IVRT (September 9-18, 2013).
- On May 6, 2014, a teleconference was held with the Applicant to discuss:
  - The presence of [REDACTED] (b) (4) in the Ivermectin Cream; and
  - In vitro drug release.
- In regards to the in vitro drug release, the FDA recommended that the Applicant propose in vitro release acceptance criteria and include the in vitro release acceptance criteria in the drug product release and stability specifications. The FDA explained that IVRT acceptance criteria are established as a quality control parameter, and would ensure that the product quality and drug release are not affected [REDACTED] (b) (4) in the drug product.
- The following Information Request (IR) comments were communicated to the Applicant on **May 29, 2014** to formally request the addition of IVRT acceptance criteria for the drug product specifications:
  1. Add an in vitro release test (IVRT) to the drug product release specification as a control for the internal structure [REDACTED] (b) (4) of the cream and potential variations in the structure from batch to batch. Your proposed IVRT acceptance criteria (range) for the drug product release specification should be based on data generated from batches manufactured using the Phase 3 manufacturing process and the commercial manufacturing process.
  2. Per the SUPAC-SS Guidance, “*The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the pre-change process.*” Therefore, the IVRT study submitted in your NDA to bridge the Phase 3 and commercial drug product manufacturing processes is deficient since the batches tested in the study are not of comparable age. [REDACTED] (b) (4). To prove the process comparability, you can do ONE of the following:
    - a. Submit data indicating that the creams produced by both manufacturing processes do not have a significant change in the drug release characteristics over the proposed expiration dating period.
    - b. Submit IVRT bridging studies using Phase 3 and commercial batches of comparable age. Both freshly made and near expired batches should be included in the bridging studies.

Alternatively, if process comparability cannot be adequately established in this review cycle, you may propose to use the Phase 3 manufacturing

process for commercial production, and propose any post-Phase 3 manufacturing process changes during the post-approval life-cycle management.

- **The Applicant responded to IR #1 on July 18, 2014.** The release specifications (Section 3.2.P.5.1) have been updated to include an in vitro release test (IVRT). Section 3.2.P.5.2 and Section 3.2.P.5.3 have been revised accordingly to describe the analytical procedure and the associated validation of the in vitro release testing which will be used by GPI (the proposed manufacturing site in Montreal, Canada) to control Ivermectin 1% Cream.
- A method transfer was necessary in order to set this IVRT release specification. The in vitro release method was first transferred from the Galderma R&D facility in Sophia-Antipolis, France (where the method was developed to generate scientific data in support of the original NDA) to Laboratoires Galderma in Alby-sur-Chéran, France to adapt it to the equipment in place at the Laboratoires Galderma facility and at the GPI facility. The adjusted method was then transferred to GPI for routine testing and where a qualification was performed to demonstrate the suitability for its intended use.
- Since no freshly made batches of drug product were originally available to set specification, the Applicant generated data from existing batches of different ages produced by both manufacturing processes at the GPI site. The study was performed at the Galderma R&D facility in Sophia-Antipolis, France. The results are presented in the following table, which show that in vitro release rates are similar for commercial and clinical batches of different ages over the proposed expiration dating period:

Table 1 Ivermectin 1% cream: release rate results obtained from study at Galderma R&D Facility

Batch number	100332	100332	100332	090842	090842	083720	083720	083720
Manufacturing site	GPI							
Manufacturing process	US Commercial	US Commercial	US Commercial	Phase 3				
Manufacturing date	12 July 2013	12 July 2013	12 July 2013	10 April 2012	10 April 2012	08 September 2011	08 September 2011	08 September 2011
Packaging size	30 g							
Stability study	1.BD.05. PSP.0141	1.BD.05. PSP.0141	1.BD.05. PSP.0141	1.BD.05. PSP.0126	1.BD.05. PSP.0126	1.BD.05. PSP.0113	1.BD.05. PSP.0113	1.BD.05. PSP.0113
Storage condition of the tested sample	5°C	25°C/60%RH	30°C/75%RH	25°C/60%RH	30°C/75%RH	25°C/60%RH	30°C/75%RH	30°C/75%RH
Age of the tested sample	Predictive of T0	12 months	12 months	26 months	26 months	34 months	34 months	34 months
Mean Release Rate ( $\mu\text{g}/\text{cm}^2/\text{h}^{1/2}$ )	382	391	366	365	358	367	370	373
RSD%	5.3	4.9	5.6	2.2	4.1	2.0	4.9	5.6

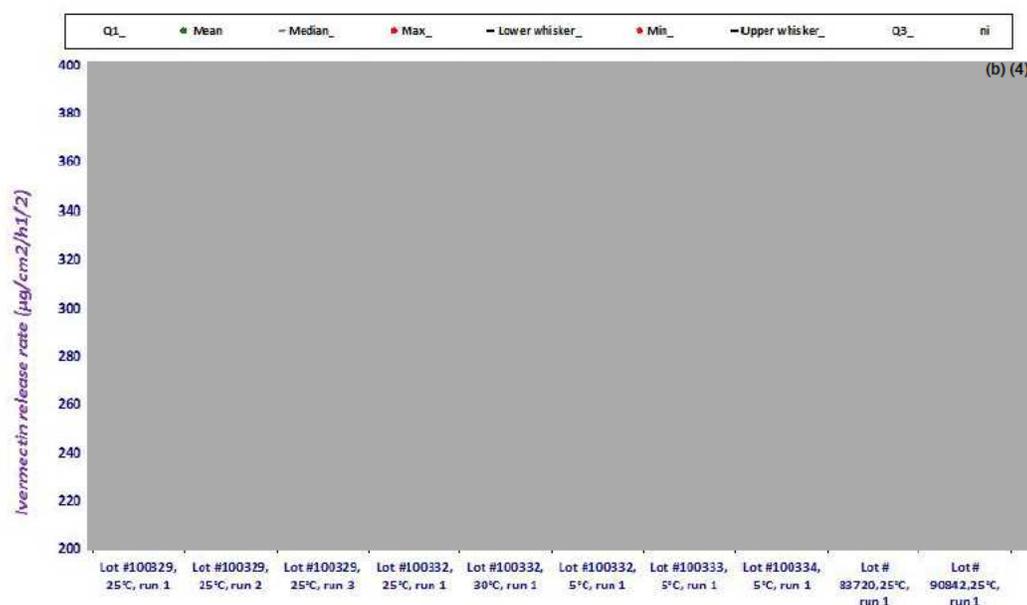
- The Applicant generated additional data from existing batches of different ages produced by both manufacturing processes at the GPI site using the analytical procedure which will be used in routine, to establish the release acceptance criteria. The study was performed at the GPI facility. The results are presented in the following table and figure, which show that the *mean* in vitro release rates are similar for commercial and clinical batches of different ages over the proposed expiration dating period:

**Table 2 Ivermectin 1% cream: release rate results obtained from study at GPI facility**

Batch number	100332			100333	100334	100329 <sup>a</sup>			083720	090842
Manufacturing site	GPI			GPI	GPI	GPI			GPI	GPI
Manufacturing process	US Commercial			US Commercial	US Commercial	US Commercial			Phase 3	Phase 3
Manufacturing date	12 July 2013			27 June 2013	17 June 2013	12 July 2013			08 September 2011	10 April 2012
Packaging size	30 g			30 g	2 g	60 g	60 g	60 g	30 g	30 g
Stability study	1.BD.05.PSP.0141			1.BD.05.PSP.0141	1.BD.05.PSP.0140	1.BD.05.PSP.0141			1.BD.05.PSP.0113	1.BD.05.PSP.0126
Storage condition of the tested sample	25°C 60%RH	5°C	30°C 75%RH	5°C	5°C	25°C/60%RH			25°C 60%RH	25°C 60%RH
Age of the tested sample	12 months	12 months (to mimic T0)	12 months	12 months (to mimic T0)	12 months (to mimic T0)	12 months	12 months	12 months	34 months	26 months
Mean Release Rate ( $\mu\text{g}/\text{cm}^2/\text{h}^{1/2}$ )	313	327	327	359	341	308	295	311	331	298
RSD%	8.6	6.2	2.7	5.2	2.6	8.3	6.4	4.6	4.6	9.3

<sup>a</sup>: Batch 100329 was tested for method qualification purposes, results are available from three independent runs

**Figure 2.- Box-and-whiskers plot of the individual runs**



- The Applicant claims that the release rate results are comparable for:
  - a same batch manufactured with the commercial process whatever the age of the finished drug product as simulated by different storage conditions (please refer to batch 100332 at 5°C, 25°C and 30°C);
  - different batches manufactured with the commercial process at release as simulated by a 12-month storage condition at 5°C (please refer to batch 100332; 100333 and 100334);
  - two different batches manufactured with the Phase 3 process (please refer to batch 083720 and 090842);
  - batches manufactured with the commercial process and the Phase 3 process (please refer to registration batch 100332 and pivotal clinical batch 083720).
- Based on the generated data, the Applicant proposes (b) (4) as the release rate specification for ivermectin in Ivermectin Cream 1%. The Applicant set the specification limits based on the overall mean (b) (4)  $\sigma_{\text{overall}}$ .

- **The Applicant responded to IR #2 on August 4, 2014.** They partially followed approach **b**, where they submitted comparable IVRT data from freshly manufactured clinical and commercial batches of comparable age, but they did not provide data on batches near expiry.

Table 13 Test substances used in the study

Description	Manufacturing Site	Manufacturing Process	Bulk batch number	Packaging	Batch number	Manufacturing date
Ivermectin 1% Cream (Prechange lot)	GPI	Phase 3	116743	30 g tube (b) (4) child-resistant)	116983	03 July 2014
Ivermectin 1% Cream (Postchange lot)		Commercial	116284	30 g tube (b) (4) child-resistant)	117154	07 July 2014

Table 14 Release rate ( $\mu\text{g}/\text{cm}^2/\text{h}^{1/2}$ )

Reference position (R) Batch manufactured with Phase 3 manufacturing process	Test position (T) Batch manufactured with commercial manufacturing process
(b) (4)	

- The Reviewer calculated the confidence intervals as 90.81% and 101.68%, which meet the IVRT acceptance criteria. Therefore, the results demonstrate sameness between the commercial batch manufacturing process and the clinical batch manufacturing process of similar age.

**Reviewer’s overall comments on the IVRT results and acceptance criteria:**

- The results from the IVRT studies demonstrate sameness between drug product manufactured with the clinical process and drug product manufactured with the commercial process regardless of the batch age.
- The proposed IVRT acceptance criteria (range) are too liberal. The following table summarizes the mean Ivermectin release rates for all the batches tested:

Ivermectin Release Rates (slopes of amount released vs. $\sqrt{\text{time}}$ ) $\mu\text{g}/\text{cm}^2/\text{hr}^{1/2}$			
Batch # (storage conditions)	Mean Release Rate (n=6)	Age (Months) at Time of Testing	Manufacturing Process
<b>From initial IVRT studies (submitted 12/30/13)</b>			
83720 (room temp.)	402	24	Clinical
100322 (room temp.)	452	3	Commercial
<b>From response to 05/29/14 IR #1 (submitted 07/18/14)</b>			
100332 (5°C)	382	12	Commercial
100332 (25°C/60% RH)	391	12	Commercial
100332 (30°C/75% RH)	366	12	Commercial

90842 (25°C/60% RH)	365	26	Clinical
83720 (25°C/60% RH)	367	34	Clinical
83720 (30°C/75% RH)	370	34	Clinical
83720 (30°C/75% RH)	373	34	Clinical
100332 (25°C/60% RH)	313	12	Commercial
100332 (5°C)	327	12	Commercial
100332 (30°C/75% RH)	327	12	Commercial
100333 (5°C)	359	12	Commercial
100334 (5°C)	341	12	Commercial
100329 (25°C/60% RH)	308	12	Commercial
100329 (25°C/60% RH)	295	12	Commercial
100329 (25°C/60% RH)	311	12	Commercial
83720 (25°C/60% RH)	331	34	Clinical
90842 (25°C/60% RH)	298	26	Clinical
<b>From response to 05/29/14 IR #2 (submitted 08/04/14)</b>			
116983 (room temp.)	379	< 1	Clinical
117154 (room temp.)	346	< 1	Commercial

- The following IR comments were communicated to the Applicant on August 12, 2014:

*Your proposed IVRT acceptance criteria (range) of [REDACTED] (b)(4) are too liberal. We acknowledge that you set your specification limits based on the individual release rates for each batch tested. However, we recommend that you set the specification limits based on mean Ivermectin release rates for each batch per the SUPAC-SS guidance. Based on the data you have submitted for all batches tested, we recommend [REDACTED] (b)(4) as an interim IVRT acceptance criteria (range) for your drug product. The recommended acceptance criteria are based on the overall mean of the mean release rates that you reported for each clinical and commercial batch tested ± the standard deviation [REDACTED] (b)(4)*

*Please acknowledge your acceptance of the recommended acceptance criteria, and commit to revising the IVRT acceptance criteria based on release data collected over 12 months.*

We request acknowledgement of the recommended IVRT acceptance criteria by COB August 13, 2014.
- The Applicant submitted the following response to this IR on August 13, 2014:**

(b) (4)

(b) (4)

(b) (4)

- Based on the submitted data for batches manufactured at the current manufacturing facility, the Applicant's proposed IVRT acceptance criteria are acceptable for batch release and stability. The Applicant will be advised to update the release specifications for their drug product to include the approved in vitro release rate acceptance criteria of (b) (4).

**Recommendation:**

The Applicant has developed an acceptable method for in vitro release testing (IVRT) of their drug product. The clinical batch manufacturing process has been adequately bridged to the commercial batch manufacturing process using this IVRT method. The proposed IVRT acceptance criteria (b) (4) are acceptable and that will be used for product release and for stability purposes. From the Biopharmaceutics perspective, NDA 206255 for Soolantra (ivermectin) Cream, 1%, is recommended for approval.

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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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KELLY M KITCHENS  
08/28/2014

TAPASH K GHOSH  
08/28/2014

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

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

	Information		Information
NDA/BLA Number	206255	Brand Name	Soolantra
OCP Division (I, II, III, IV, V)	III	Generic Name	Ivermectin
Medical Division	DDDP	Drug Class	Avermectin class of broad-spectrum antiparasitic agent
OCP Reviewer	Chinmay Shukla, Ph.D.	Indication(s)	Topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older
OCP Team Leader	Doanh Tran, Ph.D.	Dosage Form	1% Cream
Pharmacometrics Reviewer	NA	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
Date of Submission	December 20, 2013	Route of Administration	Topical
Estimated Due Date of OCP Review	August 22, 2014	Applicant	Galderma Research and Development Inc.
Medical Division Due Date	August 27, 2014	Priority Classification	Standard
PDUFA Due Date	October 20, 2014		

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

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

<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	<b>X</b>	1		Trial RD.03.SRE.40007
multiple dose:	<b>X</b>	1		Trial RD.03.SRE.40007
<b>Patients-</b>				
single dose:				
multiple dose:	<b>X</b>	1		Trial RD.03.SRE.40064 – Maximal use PK trial
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	<b>X</b>	4		In-vitro CYP enzyme profiling, induction and inhibition studies have been conducted.
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				Applicant has requested for a waiver of all pediatric assessments
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:	<b>X</b>	1		Trial RD.06.SRE.18120 (TQT)
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	<b>X</b>	2		Trial RD.03.SRE.40106 Trial RD.03.SRE.40027
Phase 3 clinical trial:	<b>X</b>	4		Trial RD.06.SRE.18170 Trial RD.06.SRE.18171 Trial RD.03.SRE.40173 Trial RD.03.SRE.40051
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				

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

<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>13</b>		

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	To-be-marketed formulation was used in the pivotal trials
2	Has the applicant provided metabolism and drug-drug interaction information?	X			In-vitro CYP enzyme profiling, induction and inhibition studies have been conducted
3	Has the Applicant submitted bioavailability data satisfying the CFR requirements?	X			Trial RD.03.SRE.40064 – Maximal use PK trial
4	Did the Applicant submit data to allow the evaluation of the validity of the analytical assay?	X			Incurred sample reanalysis is not submitted for all the trials
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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	determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Trial RD.03.SRE.40106 – Assessment of potential for neutropenia
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The Applicant has submitted a waiver for pediatric assessment.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	All reports are in English

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_  
\_\_\_ Yes \_\_\_**

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

- N.A. -

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

## Filing Memorandum

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### Clinical Pharmacology Review

**NDA:** 206255  
**Compound:** Ivermectin Cream, 1%  
**Indication:** Topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older  
**Applicant:** Galderma Research and Development  
**Date:** 01/24/2014  
**Reviewer:** Chinmay Shukla, Ph.D.  
**Related IND:** 076064

**Background:** Ivermectin belongs to avermectin class of broad-spectrum antiparasitic agent. The Applicant has developed a 1% Cream formulation for once daily topical treatment of inflammatory rosacea in adult subjects.

**Regulatory background:** The Applicant has followed 505(b)(2) regulatory pathway and would like to rely on published literature to describe the peri- and post-natal developmental toxicity of ivermectin. Apart from this, the Applicant has not indicated their plan on cross referencing any other data.

**Reviewer comments:** *The Applicant has not conducted any relative bioavailability (BA) trial to compare the BA of their formulation to the ones used in the publish literature they plan to reference. This reviewer contacted the Pharm-Tox reviewer Dr. Jianyong Wang regarding this issue and according to Dr. Wang a relative BA trial is not needed.*

**Pediatric assessment:** According to the Applicant, the occurrence of rosacea in children is a rare. Due to low prevalence of the disease in children, the Applicant has applied for full waiver of pediatric studies in subjects below 18 years of age.

**Clinical program:** The Applicant has conducted 14 clinical trials and these included 3 local tolerance trials, an oral thorough QT/QTc (TQT) trial, 2 PK trials – one in healthy subjects and other one in subject with rosacea under maximal use conditions, one proof of concept trial and one dose ranging trial. The Phase 3 program included 2 identical pivotal trials consisting of a 12-week, double-blind, vehicle-controlled part aimed to assess efficacy and safety followed by a 40-week long term active-controlled safety extension part. In parallel, a multicenter, Investigator-blind, Phase 3 clinical trial was conducted in Europe, comparing Ivermectin 1% Cream QD versus Metronidazole 0.75% Cream BID for 16 weeks (Part A) followed by an extension period of 36 weeks (Part B) aimed to assess relapse. See Appendix for a summary of the clinical trials along with information on the formulation used.

**Bioanalytical method validation and Bioanalysis reports:** Reports are submitted for review. Incurred sample reanalysis is not submitted for any of the trials. See Appendix for a summary

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

**Drug interactions:** The Applicant has evaluated the potential for drug interactions in-vitro for CYP enzymes. It appears that transporters have not been evaluated.

**Recommendation:** The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 206255 is fileable.

### **Comments to be sent to the Applicant:**

1. Submit incurred sample reanalysis reports for all clinical trials where pharmacokinetics was assessed.
2. Provide information on the activity of metabolites M1 and M2.

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

### Appendix:

*Table 1: Summary of clinical trials and formulations used*

Trial #	Purpose	To-be-marketed formulation
<b>PHASE 1</b>		
RD.03.SRE.19055	Cumulative irritancy potential – Healthy subjects	No
RD.03.SRE.19081	Cumulative irritancy potential of different formulations – Healthy subjects	No
RD.03.SRE.40007	Healthy subject PK	No
RD.03.SRE.40023	Irritation and sensitization potential - Healthy subjects	4 formulations used and none were to-be-marketed
RD.06.SRE.18120	TQT in healthy subjects using single oral dose of ivermectin (Stromectol®) tablets 6 mg (2 x 3 mg)	Not applicable
<b>PHASE 2</b>		
RD.03.SRE.2894	Exploratory efficacy study - Subjects with rosacea	No
RD.03.SRE.40006	Exploratory evaluation of safety and efficacy – Subjects with rosacea	Yes
RD.03.SRE.40027	Dose range – Subjects with rosacea	3 formulations used and one of them to-be-marketed
RD.03.SRE.40064	Maximal use PK – Subjects with rosacea	Yes
RD.03.SRE.40106	Assessment of potential for induction of neutropenia – Subjects with rosacea	Yes
<b>PHASE 3</b>		
RD.03.SRE.40051	Long term safety and efficacy - Subjects with rosacea (52 week trial terminated at 10 weeks due to low neutrophil counts)	Yes
RD.06.SRE.18170	Safety and efficacy - Subjects with rosacea	Yes
RD.06.SRE.18171	Safety and efficacy - Subjects with rosacea	Yes
RD.03.SRE.40173	Part A: Safety and efficacy – Subjects with rosacea Part B: Pharmacoeconomic parameters (ongoing trial to evaluate the retreatment after relapse) – Rosacea subjects	Yes

Manufacturing process change: The applicant made modification to the manufacturing process and this included change in the (b) (4). The overall composition of the formulation was the same. The proposed commercial formulation manufactured by the new process appeared to (b) (4) compared to the formulation manufactured by the old process. The proposed commercial formulation has not been used in any of the completed trials and it is not clear at this stage if it is

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being used in the ongoing trial RD.03.SRE.40173. The applicant has provided in-vitro release test (IVRT) to bridge the old and the new formulation and this will be reviewed by the Biopharmaceutics reviewer.

*Reviewer's comments: As per CMC reviewer, the change in the manufacturing process would represent a Level 2 change as per SUPAC-SS guidance and IVRT is the recommended method for bridging. The adequacy of bridging will be determined by Biopharmaceutics during the review of this NDA.*

Summary of trials where PK was assessed and corresponding bioanalysis information: Table 2 below provides an overview of the trials where blood levels of the drug and metabolites were assessed and corresponding bioanalytical method validation report. Also included is information whether bioanalytical method validation and bioanalysis reports are submitted or not. Table 3 provides a summary of PK sample storage duration for all trials where PK was measured. Summary of bioanalysis report is provided in Table 4.

**Table 2: Summary of analytical methods and validation reports for determination of ivermectin in human plasma**

Method Title	Testing Site	Validation Report Number	Clinical Study
Determination of Ivermectin in Human Plasma by HPLC with Fluorescence Detection	(b) (4)	RDS.03.VRE.34116 and Amendment 1	NA
Determination of Ivermectin in Human Plasma by HPLC with Fluorescence Detection	Applicant	RDS.03.VRE.34154	SRE.40007 SRE.18120 SRE.40064 SRE.40027 SRE.40051 SRE.40106 SRE.18170 SRE.18171 SRE.40173
Long-term stability of ivermectin in human plasma (up to 6 months)	(b) (4)	RDS.03.VRE.34121	SRE.40007 SRE.18120
Long-term Stability Assessment of Ivermectin in Human Plasma (up to 445 days) and Determination of Metabolite M2 <sup>a</sup> Correction Factor	Applicant	RDS.03.VRE.34303	SRE.40064 SRE.40027 SRE.40051 SRE.40106 SRE.18170 SRE.18171 SRE.40173

HPLC=High performance liquid chromatography

<sup>a</sup> The correction factor for metabolite M1 was analyzed as part of clinical Study 40106, and not as part of validation Study 34303.

**Reviewer's comment:** *The bioanalytical method was originally developed by (b) (4) (Contract Research Organization). The method was later transferred to the Applicant and in this process the Applicant (b) (4). The Applicant re-validated the bioanalytical method (Report number: RDS.03.VRE.34154).*

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**Table 3: Summary of PK sample storage duration**

Study Number	First Sample Collection Date	Last Sample Analysis Date	Duration of Sample Storage (Days)
40007	20 Sep 2005	13 Jan 2006	116
18120	28 Sep 2008	3 Dec 2008	67
40064	8 Sep 2008	18 Dec 2008	102
40027	25 Oct 2006	28 Sep 2007	339
40051	1 Dec 2008	22 Apr 2009	143
40106	27 Oct 2010	13 Jun 2011	110
18170	29 Feb 2012	5 Aug 2013	153
18171	19 Mar 2012	10 Sep 2013	176
40173 <sup>a</sup>	17 Sep 2012	19 April 2013	215

Note: The storage condition for all samples in all studies was -20°C.

<sup>a</sup> Only data from Part A of Study 40173 has been presented in this Section. The dates and sample storage duration presented are for Part A only and the Bioanalytical report will be completed at the end of the study.

**Reviewer's comments:** *From Table 2, it appears that the Applicant has established long term stability of up to 445 days. This should be adequate to support the storage stability of PK samples for all the trials listed in Table 3.*

*The Applicant has also mentioned that they could not obtain appropriate quantities of standard references for the metabolites and hence they could not design bioanalytical assay for the metabolites. Because of the absence of the standard references, the extraction recovery of the metabolites from plasma could not be estimated. Therefore, relative quantification of the circulating metabolites was performed using the calibration curve for ivermectin. The Applicant has also claimed that based on data from Study RDS.03.SRE.4830 (Structural identification of major ivermectin metabolites in human liver microsomes) no correction factor was necessary when using ivermectin calibration curves to quantify metabolite levels.*

*In the opinion of this reviewer, using calibration curve of the parent to quantify metabolites might not be a viable approach. The Applicant has provided some rationale regarding "correction factor" based on Study RDS.03.SRE.4830 and this needs to be thoroughly reviewed before making any comments. This issue will be considered during the review of this NDA. The Applicant has also not provided any information of the activity of the two major metabolites "M1" and "M2". It appears that the long term stability was not evaluated for any of the metabolites. This could be due to lack of enough quantity of the metabolites.*

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**Table 4: Summary of bioanalysis report submission**

<b>Trial#</b>	<b>Purpose</b>	<b>Bioanalysis report</b>
RD.03.SRE.40064	Maximal use PK	Submitted.
RD.03.SRE.40007	Healthy subject PK	Not submitted. Not required because old formulation used.
RD.06.SRE.18120	TQT trial	Submitted.
RD.03.SRE.40027	Dosage ranging	Submitted.
RD.03.SRE.40051	Long term safety	Submitted. (Terminated early)
RD.03.SRE.40106	Neutropenia potential	Submitted.
RD.06.SRE.18170	Phase 3 safety and efficacy	Submitted.
RD.06.SRE.18171	Phase 3 safety and efficacy	Submitted.
RD.03.SRE.40173	Part A: Safety and efficacy Part B: Relapse and retreatment	Not submitted. Study ongoing.

**Reviewer comments:** *It appears that incurred sample analysis reports are not submitted for any of the trials listed in Table 4.*

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/s/  
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02/06/2014

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02/06/2014