CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206255Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206255
Priority or Standard	Standard
Submit Date(s)	Dec 20, 2013
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Division / Office	DDDP/ODEIII
Reviewer Name(s)	Jane Liedtka, MD
Review Completion Date	Oct 15, 2014
Established Name	Ivermectin Cream 1.0%
(Proposed) Trade Name	Soolantra
Therapeutic Class	none assigned
Applicant	Galderma Research and Development, LLC
Formulation(s)	Cream 1%
Dosing Regimen	once per day
Indication(s)	treatment of inflammatory lesions of rosacea
Intended Population(s)	papulopustular rosacea

Template Version: March 6, 2009

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Reference ID: 3644887

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that NDA 206255, a 505 (b) (2) application for ivermectin 1% cream (aka Soolantra) be approved for once daily treatment of the inflammatory papules of rosacea in adults.

1.2 Risk Benefit Assessment

This clinical review has identified no significant safety or efficacy issues to impact the conclusion that sufficient evidence is provided in this application to reasonably demonstrate that the benefit of the drug product outweighs the risks when used according to the prescribing information.

Adverse reactions were generally mild and transient. In the two pivotal Phase 3 clinical trials, the most common adverse events associated with the drug product were nasopharyngitis (4.6% ivermectin 1% vs 4.8% vehicle), headache (2.5% ivermectin 1% vs 1.6 % vehicle), upper respiratory tract infection (1.6% ivermectin 1% vs 1.9% vehicle), influenza (1.2% ivermectin 1% vs 0% vehicle), sinusitis (1.2% ivermectin 1% vs 1.5% vehicle), and back pain (1.2% ivermectin 1% vs 4.8% vehicle). There were no deaths and no serious adverse events were attributed to the drug product.

Though there was an early signal for a possible effect on neutrophil cell counts (NCC) in trial 40051, extensive subsequent investigations did not reveal an association between the drug product and an effect on NCC.

Efficacy was established in two adequate and well-controlled phase 3 trials (#18170 and #18171) conducted in North America and was supported by an additional active-controlled phase 3 trial in Europe and by multiple phase 2 trials.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer has no recommendations for Postmarket Requirements or Commitments, nor were there any such recommendations from other review disciplines.

2 Introduction and Regulatory Background

2.1 Product Information

According to the CMC reviewer, the drug product is a white to pale yellow, (b) (4) cream packaged in (b) (4) laminated (b) (4) tubes with white (b) (4) caps with trade sizes of 30 g, 45 g, and 60 g, and physician sample sizes of 2 g and 5 g. The proposed formulation is provided below:

Table 1: Formulation for Ivermectin Cream 1%

Formulation No. 575.754	% (w/w)	mg/g	Function[a]	Pharmacopeia Reference
Active Ingredient				
Ivermectin	1.0	10	Drug substance	USP
Excipients				
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) (b) (4)				USP-NF
Purified water				USP

[a] 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)

Source: CMC midcycle review pg.4

See CMC Review for further details.

2.2 Table of Currently Available Treatments for Proposed Indication

Table 2: Table of Currently Available Treatments for Rosacea

Trade name	Generic name	Sponsor	NDA #	Date of approval	Indication
Metrocream	Metronidazole 0.75%	Galderma	20531	09/20/1995	inflammatory papules and pustules of rosacea
Noritate Cream 1%	Metronidazole	Valeant International Bermuda	20743	09/26/1997	inflammatory lesions and erythema of rosacea
Metrogel	Metronidazole 0.75%	Galderma	19737	11/22/1988	inflammatory papules and pustules of rosacea
Metrolotion	Metronidazole 0.75%	Galderma	20901	11/24/1998	inflammatory papules and pustules of rosacea
Finacea Gel 15%	Azealic Acid	Intendis	21470	12/24/2002	inflammatory papules and pustules of mild to moderate rosacea
Metrogel 1%	Metronidazole	Galderma	21789	06/30/2005	inflammatory lesions of rosacea
Oracea	Doxycycline monohydrate	Galderma	50805	05/26/2006	inflammatory lesions (papules and pustules) of rosacea
Mirvaso	brimonidine gel	Galderma	204708	08/23/13	persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older

Source: Clinical Reviewer's Table

2.3 Availability of Proposed Active Ingredient in the United States

NDA 050742 Stromectol (oral ivermectin) was approved by the FDA in November of 1996 for the treatment of intestinal (nondisseminated) strongyloidiasis due to the nematode parasite Strongyloides stercoralis and for the treatment of onchocerciasis due to the nematode parasite Onchocerca volvulus. The dosage for the treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 mcg of

ivermectin per kg of body weight. The dosage for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight.

The following information is from the Stromectol (oral ivermectin) label.

> Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established. The following adverse events have been reported in clinical studies: asthenia/fatigue (0.9%), abdominal pain (0.9%) anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%) dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%) pruritus (2.8%), rash (0.9%), and urticaria (0.9%), facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), tachycardia (3.5%), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, and hepatitis. Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality.
>
> The following laboratory abnormalities were seen in clinical trials (regardless of drug relationship): elevation in ALT and/or AST (2%), decrease in leukocyte count (3%) eosinophilia (3%), hemoglobin increase (1%) and elevation of bilirubin. Leukopenia and anemia were seen in one patient.

See Section 7.2.6 for discussion of ivermectin use under IND and literature review of use of oral ivermectin.

2.4 Important Safety Issues with Consideration to Related Drugs

The only other avermectin products I was able to find information on are used only in animals. These include selamectin which is used topically in dogs and cats and doramectin which is delivered via subcutaneous injection in cattle. Both are antiparasitic and insecticidal. Reported adverse events (AEs) in the labels for the animal products included vomiting, diarrhea, anorexia, lethargy, tachypnea and muscle tremors. Post approval reported AEs included urticaria, ataxia, fever, seizures and death.

A theoretical concern about medication errors that might result in the ingestion of topical products (particularly in young children) arose during development of ivermectin cream 1%. This was related to the ingestion of another product (IND 74841 brimonidine cream) for the treatment of rosacea during the investigational phase when two young children of a subject who participated in a phase 2 trial mistook the tube of brimonidine for toothpaste. The children were subsequently hospitalized. This incident heightened awareness regarding ingestion and when Sklice (ivermectin lotion 0.5%) was approved for head lice in Feb 2012 the applicant was asked to investigate the options for a child-resistant container closure system. The applicant for ivermectin cream 1% was aware of this Postmarketing Commitment (PMC) and at the Pre-NDA meeting for IND 76064

brought up the issue of whether a child-resistant container closure system should be developed. The Agency recommended this be done and details were discussed (See Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission below for details). The current submission includes a container closure system that is child resistant as well as prominent warnings on packaging (suggested by DMEPA) to keep out of reach of children.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Protocols for concurrent but separate special protocol assessments (SPAs) for two 104 week rodent carcinogenicity studies were submitted in Nov and Dec of 2006 to IND 76064.

Ivermectin Cream 1% (aka CD5024) was developed under commercial IND 76064, submitted on Oct 25, 2007. Initial studies were conducted in Europe, with Phase 3 clinical trials conducted in US and Canada.

Principal meetings are outlined in the following table:

Table 3: Principal Meeting for IND 76064

Type of Meeting	Date	Objective
EOP2 Meeting	3/18/08	To agree upon the proposed CMC, toxicology, and clinical plans to support an NDA submission for Ivermectin Cream 1% for the topical treatment of inflammatory lesions of papulopustular rosacea
Guidance	2/9/09	To clarify issues regarding the SPA response dated October 22, 2008
Pre-Phase 3	8/10/11	To discuss changes to the pivotal phase 3 studies for Ivermectin Cream 1%
Pre-NDA	6/12/13	To discuss the content and format of the NDA for Ivermectin Cream 1% for the topical treatment of inflammatory lesions of papulopustular rosacea

EOP2 Meeting - 3/18/08

An **EOP2 meeting** was held on 3/18/08. The Agency had the following comments and recommendations:

- Data from a study to determine the photo co-carcinogenic potential associated with ivermectin cream should be included with an NDA submission
- If you decide to rely on literature data to address the need for a peri- and post-natal development study, then the NDA would be a 505(b)(2) NDA submission and not a 505(b)(1) NDA submission.
- The Division considers the finding of carpal flexure noted in the oral rabbit embryofetal development study conducted with ivermectin as a malformation.

- Data from a PK study conducted under "maximal use conditions" are needed prior to initiation of Phase 3 trials, to inform about the risks for women of childbearing potential.
- Investigate the issues involving a major metabolite as being a more potent inhibitor of cytochrome P (CYP) 3A4 than the parent drug.
- Your choice of the 1% cream used QD appears to be appropriate.
- The population proposed in Phase 3 (subjects with an IGA score of 3 or 4, with 15 to 70 inflammatory lesions, and with no more than two nodules) is acceptable.
- Success (on the IGA) should be defined as those who are clear or almost clear on the IGA; this will represent a 2 grade improvement for all subjects and is inherently clinically meaningful.
- The Division recommends using absolute change in lesion count as a co-primary endpoint instead of percent change.
- As you have designed your trial, (b) (4) will not be acceptable as a claim.
- In the absence of a thorough QT/QTc study demonstrating no effect on cardiac repolarization (or a definitive PK study demonstrating no systemic exposure under maximum use conditions in diseased subjects), ECG monitoring should be performed to ensure subject safety, at a minimum at baseline, when drug concentration has reached steady state, and at end of treatment.
- Photoallergenicity should be studied in not less than 50 evaluable subjects. If there is no absorption in the UVB, UVA, or visible light spectrum, you may request a waiver for the photoallergenicity study.
- Your sample size calculation, based on your assumptions – success rates on IGA and treatment effect on absolute change in lesion counts – appears to be adequate.
- We recommend that you propose another sensitivity analysis.
- The protocol should include a specific sensitivity analysis in case the center by treatment interaction is significant; to ensure that efficacy results are not driven by extreme centers.
- We agree with your justification of not needing multiplicity adjustment.
- Your proposed method of handling small centers seems to be appropriate.

An advice letter containing pharm-tox comments was sent on 5/27/2008. An advice letter containing comments on the QTc study protocol was sent on 9/22/2008.

On 9/08/08 the applicant submitted a request for a SPA for a phase 3 pivotal trial #18116 entitled, "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study to Demonstrate the Efficacy and Safety of Ivermectin 1% Cream in

Subjects with Papulopustular Rosacea over 12 Weeks Treatment". The SPA agreement letter was sent on 10/22/2008 and included the following:

SPA Letter - 10/22/2008

AGREEMENTS

- The population to be studied with an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe) on a 5 point (0 to 4) scale, the presence of at least 15 and not more than 70 inflammatory lesions (papules and pustules) on the face, and no more than two nodules on the face is acceptable.
- The following co-primary endpoints are acceptable:
    1. Success Rate, based on IGA score, will be defined as the percentage of subjects who achieve '0 = Clear' or '1 = Almost Clear' on IGA (0 to 4 scale) at Week 12
    2. Absolute change in inflammatory lesion counts from Baseline to Week 12
- The following secondary endpoints are acceptable:
    a) Absolute change together with percent change in inflammatory lesion count
    b) Time to onset of efficacy analysis (nested analysis of co-primary endpoints for successively earlier timepoints)
- It is agreed that no claim for [redacted] (b) (4) will be possible based on the proposed study design.
- Based upon the sponsor's assumed estimates of treatment effect, sample size calculations have been verified.
- The use of the ITT population as the primary analysis population and the PP as supportive is acceptable.
- CMH stratified by analysis center to assess the percent of subjects with Week 12 IGA scores of `Clear' or `Almost Clear' is acceptable. The use of ANCOVA to test the change in inflammatory lesion counts including baseline inflammatory count as the covariate and terms for treatment and analysis center is acceptable. Efficacy will be established if both of these co-primary endpoints are significant at the two-sided α = 0:05 significant level.
- The use of LOCF as primary and the proposed sensitivities analyses using alternate imputation strategies are acceptable.
- The proposed serial gate keeping approach to control the Type I error for testing the coprimary endpoints at earlier time points if and only if both co-primary endpoints at later time points are significant at the two-sided α = 0:05 level is acceptable.

DISAGREEMENTS

- The sponsor should include additional laboratory monitoring, at Baseline and at Week 12 or Early Termination visits, consisting of liver function testing and complete blood count with differential and platelets. Although laboratory testing

was performed in Phase 2, the sample sizes involved may not allow detection of rarer events.

- In view of the fact that ivermectin is a potential human teratogen, urine pregnancy testing should be performed at the Week 3, 6, and 9 visits as well as at Baseline and at Week 12 or Early Termination visits. The urine pregnancy test should have a sensitivity of at least 25mIU/L.
- The need for contraceptive use by females of childbearing potential will be determined based on results of the Maximal Use Systemic Exposure Study to be conducted prior to Phase 3 trials.

Guidance Meeting - 2/9/09

The Agency had the following comments and recommendations at the guidance meeting held on 2/9/09 to clarify issues regarding the SPA response sent by the Agency on 10/22/08:

- Whether the percent change in inflammatory lesion count and time to onset of efficacy analysis (which are secondary endpoints) may appear in the clinical section of labeling will be a review issue.
- The multiple of human exposure for possible teratogenic effects based on the NOAEL identified in the rabbit study (i.e., 1.5 mg/kg/day; Day 20 AUC0-24 hr = 2766 ng.hr/ml) is 36 X the highest AUC0-24 hr value obtained in the Maximal Use Systemic Exposure clinical pharmacokinetic study (i.e., 75.16 ng.hr/ml). Therefore, it appears reasonably safe to allow enrollment of female subjects of childbearing potential without requiring mandatory use of contraception [in the phase 3 trials].
- No agreements were made regarding the pooling of data from European sites not under IND with data from US sites under IND.

Neutropenia Issue

The applicant's early clinical development program included a 52 week, open-label, uncontrolled long-term safety trial of once daily use of Ivermectin Cream 1%, trial RD.03.SRE.40051 (trial 40051) which began on 8/06/2008. The trial was planned to enroll 424 subjects, however the trial was stopped early (at week 10) due to abnormal laboratory findings (namely, low neutrophil counts) in 3 out of 305 subjects who were enrolled.

In these three subjects, the neutrophil count decreased below 1.5 Giga cell/L which the applicant defined as an important threshold for detecting neutropenia. The values for these three subjects were .79 G/L, 1.06 G/L, and 1.23 G/L. The absence of a control arm did not allow for a comparative assessment to see if the findings observed would be representative of the patient population enrolled.

DDDP requested that the Division of Pharmacovigilance (DPV) search the AERS database to evaluate whether there had been cases of abnormal neutrophil counts reported to the FDA associated with the use of oral ivermectin. DPV's review stated that

> Based on the limitations of spontaneous post-marketing data, we cannot make any definitive conclusions regarding the safety of this product concerning abnormal neutrophil counts. However, at this time, there does not appear to be a post-marketing safety signal for abnormal neutrophil counts with oral ivermectin.

Information Request – 5/20/10

1. In view of the neutropenia observed in the long term study please provide information about any changes to your proposed development program for this product under IND076064 and provide a summary of any additional safety monitoring to be incorporated in ongoing clinical trials.

2. Examine the studies in your development program that are completed and provide an integrated safety analysis including the data on the decline in neutrophil counts among subjects in all studies.

Statistical Review - Trial RD.03.SPR.40106 – 3/17/11

The applicant then conducted a Phase 2 trial, Trial RD.03.SPR.40106, to assess the hematological safety of once daily topical ivermectin cream 1%. The trial was performed in Europe. The trial was planned to randomize 200 subjects in a 1:1 fashion to either ivermectin cream 1% or vehicle cream. The FDA statistical review of the protocol for trial 40106 dated 3/17/11 pointed to numerous flaws in the study design as outlined below:

> Trial 40106 is likely to provide limited information on the safety of IVERMECTIN for the assessment of neutrophil counts. The following are reasons for such a determination.
>
> - The planned treatment duration of the trial is 12 weeks. With such a short term exposure to drug, this trial will not provide data on long term use of the ivermectin and its effects on neutrophil counts.
> - The trial enrollment is for 100 subjects per treatment arm. With a low incidence rate of neutrophil counts below 1.5 G/L (1% for active and an assumed incidence rate of 0.05% for the vehicle per the sponsor's protocol), the trial is not likely to observe many incidences of the safety parameter of interest. Correspondingly, the trial has power below 20% to detect a significant difference between the active and control.

The study report and the applicant's evaluation of the results were submitted to the Agency as part of the meeting package for a Type B meeting scheduled for Aug 10, 2011. The applicant's evaluation of the results included the following information:

Hematological assessments were performed every two weeks during the month prior to randomization, during the 12-week treatment period, and four weeks after the study treatment discontinuation (i.e. at Week 16).

Four (4) treatment-emergent cases of mild to moderate Neutrophil Cell Count (NCC) values below the defined threshold for neutropenia occurred during the study: 3 in the ivermectin 1% group (2.9%) and 1 in the vehicle group (0.9%). The values were 0.96 G/L, 0.97 G/L, 1.42 G/L and 1.46 G/L.

All treatment-emergent NCC values below the threshold of 1.5 GIL occurred at a single sampling timepoint for each of these 4 subjects (three at week 6 and one at week 10). All of the values returned to normal during the course of the study.

In one subject the Ivermectin Cream 1% was temporarily discontinued (as per protocol) until signs of infection (flu like symptoms) which had coincided with the decrease had resolved. The other three subjects continued treatment without interruption.

Three other subjects reported a total of 4 NCC cases ≤ 1.5G/L during the study:

- One subject, no. 5523-015 in the ivermectin 1 % cream treatment group had an NCC of 1.35 G/L before the first application of study drug, retests were performed and the subsequent retest values were 1.21G/L followed by 3.58 GIL. The subject then withdrew consent.
- Two additional subjects had NCC values once below 1.5G/L before the first application of study drug, and normal values at all post-treatment visits.

Advice Letter – 4/20/11

- Based upon the safety signal detected in Study 40051 and the limitations of the studies having been conducted to date, the proposed Phase 3 protocols should be modified to include periodic laboratory monitoring (including complete blood count with differential).
- You should propose a revised development plan that includes adequate assessment of the effect of ivermectin cream on neutrophil count. Such a study or studies should include long term exposure to ivermectin cream with an adequate control and be powered appropriately. You are encouraged to submit your proposed development plan to assess the safety of your product along with protocols for Agency review.

Pre-Phase 3 Meeting – 8/10/11

At the meeting held on 8/10/11 the following comments and recommendations were made:

  - The adequacy of the data concerning the relative bioavailability of ivermectin topical formulation in rosacea subjects (Study RD.03.SPR.40064) compared to that of the currently marketed oral immediate release tablet (Study RD.03.SPR.18120) where both parent compound and major metabolites were quantified using the same analytical method and the safety of the major metabolites will be a review issue.

- With regard to Part A of the proposed pivotal phase 3 study the population to be studied is acceptable. This population is specified as having an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe) on a 5 point scale, the presence of at least 15 and not more than 70 inflammatory lesions (papules and pustules) on the face, and no more than two nodules on the face.
- With regard to Part A of the proposed pivotal phase 3 study the following co-primary endpoints are acceptable:

  1. Success Rate, based on IGA score, will be defined as the percentage of subjects who achieve '0 = Clear' or '1 = Almost Clear' on IGA (0 to 4 scale) at Week 12
  2. Absolute change in inflammatory lesion counts from Baseline to Week 12

- With regard to Part A of the proposed pivotal phase 3 study the following secondary endpoints are acceptable:
  1. Absolute change together with percent change in inflammatory lesion count
  2. Time to onset of efficacy analysis (nested analysis of co-primary endpoints for successively earlier timepoints)
- It is agreed that no claim for (b) (4) will be possible based on the proposed study design. (SPA dated October 22, 2008)
- The Agency recommended re-randomization of subjects who continued into Part B of the proposed pivotal phase 3 study to help minimize bias, maintain blinding and ensure adequate number of subjects.
- The adequacy of the long term safety data will be a review issue.
- The sponsor agreed to modify the safety monitoring to include monthly urine pregnancy testing and active assessment for local cutaneous reactions. However, the sponsor proposed not to include lesion count assessment as a safety monitoring for Part B since disease severity will be monitored by IGA assessment. The Agency responded that the proposal was acceptable.

An advice letter stating that "a proposal to request a waiver of the clinical photo-safety assessment for ivermectin" appeared reasonable was sent on 12/21/11.

Advice letter/Information Request - 4/16/12

On 1/3/12 the Agency requested a summary of the changes made to the pivotal phase 3 study protocols. The Applicant submitted this information on 1/26/12. The Agency requested additional information and made the following comments regarding the changes in a letter sent on 4/16/12:

You have proposed a number of changes to Part A of the protocol which may conflict with the agreements reached during the SPA assessment. These include:

- You have deleted the information stating that complete blocks of treatment materials would be assigned to investigational sites. However your analysis plan calls for using the Cochran-Mantel-Haenszel (CMH) test stratified on center. It is not clear whether your randomization is still stratified by center. We recommend randomization to be stratified by center to investigate center-to-center variability and to be consistent with the analysis. You should also use block randomization with a specified block size to ensure the 2:1 treatment allocation.
- The time to onset of efficacy is listed as a secondary endpoint. By having 2 secondary endpoints, the Type I error rate for the set of secondary endpoints is no longer controlled. We recommend maintaining the original status as using a single secondary endpoint (percent change in inflammatory lesions) along with a supplementary analysis of the primary endpoints (with sequential testing) to maintain the Type I error rate.

We have the following additional comments on supportive or sensitivity analyses from Part A of the Statistical Analysis Plan (SAP) which do not impact the agreements reached during the SPA assessment

- You state in the SAP that the ranks for lesion counts will be used if the normality assumption is not met; however, you did not include the hypothesis to be tested and the significance level to be used for testing. Further, it should be noted that unless there is extra departure, which is unlikely for large trials, the preference is for analysis and interpretation of the original data.
- You state that the SAP will be finalized prior to First Subject in (FSI) and that any changes made to the SAP after finalization will be documented in the final study report. To ensure control of Type I error rate, the SAP should be finalized along with the protocol. It should be noted that revision of statistical methodology might impact control of Type I error rate and consequently impact establishing an efficacy claim.
- The proposed use of LOCF for handling missing data and the sensitivity analyses were agreed upon in the SPA letter. However, as all the proposed methods are single imputation methods, they might underestimate the dispersion in the data. We recommend including a method that uses an alternative framework for the imputation, such as multiple imputation.

We reiterate our recommendation from the pre- Phase 3 meeting (8/10/2011) that you consider randomizing subjects to either ivermectin cream 1% or azelaic acid 15% gel rather than assigning all subjects randomized to ivermectin cream 1% in Part A to continue with ivermectin cream 1% in Part B and assigning all subjects randomized to vehicle cream in Part A to begin treatment with azelaic acid in Part B.

Sponsor's Response – (SD#55) 6/14/12, (SD#58) 7/24/12

The sponsor addressed the statistical reviewer's comments in SD #55 and 58. In a review dated 10/23/12 the statistical reviewer had the following comments:

> You plan to conduct two identical Phase 3 studies to investigate the safety and efficacy of ivermectin cream 1% for the treatment of papulopustular rosacea. The following are comments regarding your amended statistical analysis plans (SAP) and responses to Agency comments submitted on June 13, 2012, and your amended Phase 3 protocols submitted on August 15, 2012:
>
> - You state that any change made to the SAP after the finalization and prior to database lock will be documented in the updated SAP and any change, such as additional analyses, decided post hoc after database lock will be documented in the final study report. It should be noted that statistical methodology used for establishing efficacy should be part of the protocol or finalized along with the protocol. Details regarding tables and exploratory analyses could be delayed.
> - In response to the Agency's previous recommendations about re-randomizing subjects in Part B, you propose to "freeze" the Week 12 IGA and lesion count data points within 5 days of entry. Instead of your proposal to freeze the data, the Agency still recommends to re-randomize subjects as this would ensure blinding and minimize bias.
> - The Agency previously commented that the impact of the expected dropouts and the handling of dropouts and safety discontinuation were not clear. For long term trials, large dropout is expected and could affect the long term safety profile. Therefore, a sensitivity analysis to investigate the impact of dropout would be helpful for a reasonable safety assessment. As a sensitivity analysis, you might consider a certain proportion (some multiple of an adverse event rate) of subjects dropped out due to adverse events and assess the safety profiles.
> - Your proposal to use block randomization with a block size of 6 (4:2 ratio) is acceptable.
> - Your proposal to have a single secondary endpoint (percent change in inflammatory lesions) and define time of efficacy onset through a supplemental analysis of the co-primary endpoints with sequential testing to control the Type I error rate is acceptable.
> - Your proposal to include a sensitivity analysis, using multiple imputation (Markov Chain Monte Carlo (MCMC) method in SAS), for the co-primary efficacy endpoints is acceptable.
> - The Independent Data Monitoring Committee (IDMC) charter appears to be acceptable; however, the charter will also need clinical judgment.

Teleconference - 11/26/12

During the teleconference, the Agency asked for the sponsor's justification for not re-randomizing subjects. The sponsor stated that all subjects have already entered Part B

and re-randomization would not be possible. The Agency expressed concerns regarding blinding and bias.

In the teleconference, the Agency stated that a sensitivity analysis to investigate the impact of dropout would be helpful for a reasonable safety assessment. As a sensitivity analysis, the sponsor might consider a certain proportion (some multiple of an adverse event rate) of subjects dropped out due to adverse events and assess the safety profiles. The sponsor stated that they are currently finalizing the safety analysis section of their SAP and that they would submit a proposal for such a sensitivity analysis in an amended SAP to the IND. The Agency responded it would be reasonable for the sponsor to amend the SAP to include such a sensitivity analysis for safety assessment. In contrast, the Agency noted that the statistical analysis plan for establishing efficacy needs to be specified at the protocol stage to ensure control of the Type I error rate. The sponsor stated that they do not plan on changing the statistical methodology for efficacy.

Investigator Misconduct Issue - 6/19/12

On 6/19/12 the Applicant notified the Agency of investigator misconduct at site 8074 in Study # 18171. Specifically, discrepancies were noted in signatures of the sub-investigator, (b) (4) with no explanation provided to the study monitor. The principal investigator, Dr. Shamban agreed to exercise greater oversight of signature verification, personally collecting signatures to ensure authenticity. Dr. Shamban's site was placed on enrollment hold and no further subjects were permitted to enter this study at this site. The 5 subjects currently participating in the study conducted under this IND were permitted to complete the trial. After conducting an audit on January 29-30, 2013, the Applicant decided to terminate the site when they found that the investigator was delinquent in following the medical monitor recommendation to terminate one subject early based on a safety concern (e.g. the delayed notification caused the subject to be exposed to 12 additional days of treatment.) The site enrolled a total of six subjects. Based on the recommendations from the OSI reviewer, no further regulatory action was initiated.

Pre-NDA Meeting – 6/12/13

- Your proposal [to "rely on literature alone to describe the peri- and postnatal developmental toxicity of ivermectin" and to not "rely on previous Agency findings of safety for a specific reference listed drug" and therefore "no comparative bioavailability data will be provided."] appears acceptable from a Pharmacology/ Toxicology perspective. Submit the full literature reference for the peri- and post-natal developmental toxicity studies with the NDA.
- At this time we are not aware of any serious safety signal that would necessitate a REMS.
- Due to the theoretical concern regarding medication errors involving the ingestion of your product, we recommend that you consider a child-resistant closure.

- The information proposed [3 months of stability data at the time of NDA submission for drug product in a child resistant container closure system, together with 36 months of stability data in the current non-child resistant container closure system] would be sufficient for NDA filing, provided that the results of an in use stability study (including package integrity and weight loss) with the child-resistant container/ closure system will also be provided in the initial submission of the NDA, and the fabrication material of the child-resistant closure is the same as the non-child-resistant closure.
- The lack of randomization and blinding can result in bias, which cannot be accounted for through alternative statistical methodology. The Agency commented during the Pre-Phase 3 meeting (8/10/2011) and reiterated in an advice letter (4/16/2012) the need for re-randomization at Week 12 to maintain blinding and minimize bias. While you "froze" the Week 12 IGA and lesion count data points within 5 days of entry and now propose to carry out various additional analyses; however, such approaches do not alleviate the concern regarding bias in efficacy assessments and reporting of adverse events.
- At the time of the NDA submission provide the following:
    a. Pooled safety data for trials with the same dose and dosing regimen.
    b. Line listings for all safety data.
    c. Subject narratives for all deaths, all serious adverse events (SAEs), all severe adverse events, all adverse events (AEs) involving neutrophil counts outside the normal range, and adverse events (AEs) resulting in discontinuation from the trials.
- In addition to subject narratives and case report forms (CRF) for severe events of special interest in certain system organ classes and narratives for events of low neutrophil count below 1.5 Giga/L, submit narrative summaries and case report forms for any:
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study
    vii. All pregnancies including outcomes
    viii. Clinically significant changes in laboratory values or vital signs
    ix. Severe AEs
- The full safety data for Part B of study 40173 (until completion) will be submitted in the 4-month safety update.
- Provide your rationale/discussion regarding why the Repeat Insult Patch Test (RIPT) with the final to-be-marketed formulation will not be needed.
- Provide your rationale/discussion regarding the acceptability of your foreign data.

2.6 Other Relevant Background Information

The applicant describes their rationale for including data from foreign clinical trials (in accordance with the ICH E6 Guideline for Good Clinical Practice) in their NDA submission to support the safety and efficacy of ivermectin 1% cream in the Clinical Overview (pg.13)

> The inclusion and exclusion criteria for all clinical studies performed by the Applicant in PPR adult subjects were similar across geographic locations. Racial, age, and gender distributions seen in subjects with PPR are generally similar across these geographical regions. Medical practices are also highly similar across these regions. The majority of subjects with PPR are Caucasian adults of European descent between 20 and 60 years of age.[1] Many North Americans presenting with PPR have Northern and Western European ancestry.[2] Therefore, the Applicant considers that the demographic and other characteristics of the study population in the Applicant's studies are representative of the target patient population in the US and in other regions.

All of the trials except for pivotal trials 18170 and 18171 were performed outside the US. The countries included were Australia (2 trials), Bulgaria (2 trials), Czech Republic (4 trials),Finland (one trial), France (5 trails), Germany (6 trials), Hungary (5 trials), Iceland (2 trials), Poland (one trial), Romania (2 trials), Russian Federation (2 trials), Slovakia (one trial), Ukraine (one trial), and the United Kingdom (one trial). After examining the demographic profiles for the trials performed in subjects with PPR that were conducted outside the US I agree with the applicant that the subjects are representative of the target patient population in the US.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On submission, the application was sufficiently complete and organized, such that necessary data could be accessed and reviewed without difficulty.

3.2 Compliance with Good Clinical Practices

According to the clinical study reports and the clinical overview, the applicant conducted all studies in the clinical development program in compliance with Good Clinical Practices as outlined in ICH E6.

[1] Oltz M, Check J. Rosacea and its ocular manifestations. Optometry. 2011 Feb; 82(2):92-103.
[2] Culp B, Scheinfeld N. Rosacea: a review. P T. 2009 Jan; 34(1):38-45.

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Department of Scientific Investigations (DSI) inspections were requested for 3 sites (displayed in the table below) with the following rationales:

Site 8196: enrollment of large # of subjects, high treatment responders for IGA, discrepancy between the findings on success rate on IGA (high response) and change in inflammatory lesions for a given site (modest response)

Site 8129: enrollment of large # of subjects, high treatment responders for both co-primary endpoints

Site 8255: enrollment of large # of subjects, high treatment responders for IGA, discrepancy between the findings on success rate on IGA (high response) and change in inflammatory lesions for a given site (vehicle responded better)

Table 4: Sites Selected for Inspection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site #8196 Holly Harris, MD The South Bend Clinic, LLP 211 N. Eddy Street South Bend, IN 46617 Tel: 574-237-9391 Fax: 574-204-6439	Study SPR18170	28 subjects randomized	Indication: inflammatory lesions of rosacea Co-primary endpoints for part A- 1. Success rate on IGA 2. Absolute Change in inflammatory lesions Secondary endpoint for Part A- percent change in inflammatory lesions
Site #8129 Fasahat Hamzavi, MD Hamzavi Dermatology 2950 Keewahdin Road Fort Gratiot, MI 48059 Tel: 810-455-1600 Fax: 810-455-1614	Study SPR18171	20 subjects randomized	Indication: inflammatory lesions of rosacea Co-primary endpoints for part A- 3. Success rate on IGA 4. Absolute Change in inflammatory lesions Secondary endpoint for Part A- percent change in inflammatory lesions
Site #8255 Lawrence Parish, MD Paddington Research 1760 Market Street, Suite 301 Philadelphia, PA 19103 Tel: 215-563-7330 Fax: 215-563-9405	Study SPR18171	22 subjects randomized	Indication: inflammatory lesions of rosacea Co-primary endpoints for part A- 5. Success rate on IGA 6. Absolute Change in inflammatory lesions Secondary endpoint for Part A- percent change in inflammatory lesions

Source: Reviewer's Table

The results of clinical inspections for sites 8196, 8129 and 8255 revealed "The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. At Dr. Parish's sites there

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were some minor protocol deviations noted including delayed collection of PK samples, and inadequate documentation of inclusion criteria for one subject but nothing that was felt to be likely to affect the data collected."

3.3 Financial Disclosures

See attached financial disclosure forms for trials 18170, 18171, 40027 and 40106 in Attachment C. According to the statistical reviewer, "the centers with financial disclosures had no effect on the results". See Attachment C for details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewer had the following issues to discuss at the midcycle meeting:

- Formulation manufacturing process change between phase 3 and marketing
- (b) (4) observed in the drug product

A teleconference was held with the applicant on May 6, 2014 to discuss the above CMC concerns. An information request letter was sent to the applicant on May 29, 2014 regarding these CMC issues. Another teleconference was held with the applicant on June 10, 2014 to discuss the applicant's plan for responding to the IR letter. The applicant proposed a three part response plan with information to be submitted on or by June 27, July 18 and Aug 4 of 2014. These submissions contained information regarding the (b) (4), IVRT and release specifications. The information was considered a major amendment and on Aug 19, 2014 the applicant was informed of a three month clock extension via advice letter. The new PDUFA date of Jan 20, 2015 was conveyed.

The biopharmaceutics reviewer gave the following summary regarding the change in the manufacturing process after reviewing all of the above mentioned submissions:

> 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).

The conclusion of the biopharmaceutics reviewer was

> 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.

With regard to the issue of the (b) (4) observed in the drug product, in Section P.5.4 the chemistry reviewer states

> The applicant concludes that both placebo batch and pivotal clinical batch exhibit the same microscopic appearance under phase contrast and polarized light. It is emphasized that examination under phase contrast shows (b) (4), and examination under polarized light shows (b) (4). The response is acceptable.

In the Executive Summary, the chemistry reviewer concludes "At this time the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product…Therefore, from the ONDQA perspective, this NDA is recommended for approval".

4.2 Clinical Microbiology

The product quality microbiology reviewer recommended approval of the application. See review in DARRTS archived on March 7, 2014.

See Section 7.2.6 for discussion of safety findings for oral ivermectin use as an antiparasitic and anti-helminth agent.

4.3 Preclinical Pharmacology/Toxicology

According to the pharmacology toxicology reviewer, the sponsor has conducted all the required nonclinical studies, except a peri- and post-natal developmental study, for which the sponsor proposed to rely on published literature. In the submitted peri- and post-natal developmental study (literature), the pharmacology toxicology reviewer states that since "no brand name of the drug (ivermectin) was mentioned; therefore a bridging study is not needed, from a pharmacology/toxicology perspective".

In addition, a statistical review of a long term rat and mouse carcinogenicity study was completed on May 7, 2014. An addendum containing some additional analyses was added on July 1, 2014. See these reviews in DARRTS for further details.

4.4 Clinical Pharmacology

The clinical pharmacology reviewer stated in his review dated Oct 3, 2014 that "this application is acceptable provided the labeling comments are adequately addressed by the Sponsor. The labeling changes below were addressed adequately by the sponsor.

4.4.1 Mechanism of Action

The applicant proposed the following statement for ivermectin cream 1% under mechanism of action in the label:

(b) (4)

The clinical pharmacology reviewer thought that this statement (b) (4) The clinical pharmacology reviewer proposed instead the following statement for the label Section 12.1 "The mechanism of action of SOOLANTRA Cream in treating rosacea lesions is unknown". I agree with the clinical pharmacology reviewer. The agreed upon labeling states that "The mechanism of action of SOOLANTRA Cream in treating rosacea lesions is unknown".

4.4.2 Pharmacodynamics

The applicant did not propose any statement for Section 12.2 of labeling. The clinical pharmacology reviewer proposed the following statement "At therapeutic doses, SOOLANTRA Cream, 1% is not expected to prolong QTc to any clinically relevant extent." The clinical recommended modifying this statement by removing the words "to any clinically relevant extent". The clinical pharmacology team agreed with this change. The agreed upon labeling states "At therapeutic doses, SOOLANTRA Cream is not expected to prolong QTc interval".

4.4.3 Pharmacokinetics

The applicant proposed the following statement for Section 12.3 of the label:

> Absorption
>
> The absorption of ivermectin from SOOLANTRA was evaluated in a clinical trial in adult subjects with severe papulopustular rosacea, (b) (4) At steady state (after 2 weeks of treatment), the highest mean (± standard deviation) plasma concentrations of ivermectin peaked within 10 ± 8 hours post-dose (Cmax: 2.10 ± 1.04 ng/mL range: 0.69 - 4.02 ng/mL) and the (b) (4) AUC0-24hr 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) (b) (4) that there was no plasma accumulation of ivermectin over the 52-week treatment period. (b) (4)
>
> 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 does not inhibit the CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 4A11 or 2E1. Ivermectin does not induce (b) (4) (1A2, 2B6, 2C9 or 3A4) (b) (4)
>
> (b) (4)

Excretion

Terminal half-life averaged (b) (4) days ((b) (4) range 92-238 hours) in patients receiving a once daily cutaneous application of SOOLANTRA for 28 days, (b) (4).

The clinical pharmacology reviewer proposed the following revisions to this section of labeling:

Absorption
The absorption of ivermectin from SOOLANTRA Cream, 1% was evaluated in a clinical trial in 15 adult male and female subjects with severe papulopustular rosacea applying 1 g SOOLANTRA Cream, 1% once daily. (b) (4) (b) (4) At steady state (after 2 weeks of treatment), the highest mean ± standard deviation) plasma concentrations of ivermectin peaked (b) (4) 10 ± 8 hours post-dose, the maximum concentration (C_{max}) was 2.10 ± 1.04 ng/mL (range: 0.69 - 4.02 ng/mL) and the area under the concentration curve (b) (4) (AUC_{0-24hr}) 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 (b) (4) that there was no plasma accumulation of ivermectin over the 52-week treatment period. (b) (4) (b) (4)

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 2E1~~. Ivermectin does not induce CYP450 enzyme expression (1A2, 2B6, 2C9 or 3A4) in cultured human hepatocytes.

(b) (4)

Excretion
The apparent t~~T~~erminal half-life averaged 6.5 days (mean ± standard deviation: 15 (b) (4) 5 ± 40 hours, range 92-238 hours) in patients receiving a once daily cutaneous application of SOOLANTRA for 28 days (b) (4) (b) (4)

The sponsor agreed to the changes recommended by the clinical pharmacology reviewer. See "agreed upon labeling" that will be attached to the approval letter for the non-track changes version.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5: Table of Trials for Efficacy, Safety and PK Data

Study #	Phase	Type	Design	Control	Popula-tion	Dose/ Duration	# of subjects
2894 Legacy 3/03-6/03	2a	Proof of Concept - early formulation	MC (9 sites OUS), R, IB, PG	vehicle + metronida-zole	PPR	Bid/ 9 wks planned, 25 days actual (mean)	60
40006 Legacy 9/04-12/04	2	safety + efficacy	MC (10 sites OUS), R,IB,PG	vehicle + metronida-zole	PPR	Bid/ 9 wks	147
40007 Legacy 9/05-12/05	1	PK - early formulation, two concentra-tions	SC, OL, Multi-regimen	none	HV	Q day +Bid/ Grp 1: 1 day Grp 2/3: 4 wks	32
40027 6/06-6/07	2	Dose-ranging-3 concentra-tions	MC (26 sites OUS), R, IB, PG	vehicle + metronida-zole	PRR	Q day +Bid/ 12 wks	296
40037 10/06-11/07	2	No Rx -fu for relapse eval	MC (25 sites OUS), E, IB	none	PPR	6 mos, Rx-free	149
40064 8/08-12/08	2	PK + Safety - max use conditions	MC (5 sites OUS), OL, Single Rx	none	PPR	Q day/ 4 wks	17
40106 9/10-5/11	2	Neutropenia evaluation	MC (24 sites OUS), DB, R, VC, PG	vehicle	PRR	Q day/12 wks	210
18170 12/11-7/13	3	Efficacy + Long term safety	MC (50 sites OUS), R, DB, PG	Pt A-vehicle Pt B-azealic acid Pt C-none	PRR	Q day/ Pt A-12wks Pt B-40wks Pt C-	Pt A-683 Pt B-622 Pt C-525

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						4wks	
18171 12/11-8/13	3	Efficacy + Long term safety	MC (50 sites OUS), R, DB, PG	Pt A-vehicle Pt B-azealic acid Pt C-none	PRR	Q day/ Pt A-12wks Pt B-40wks Pt C-4wks	Pt A-688 Pt B-636 Pt C-512
40173 Part A 4/12-4/13 Part B 4/13-ongoing	3	European safety + efficacy	MC (64 sites OUS), R, IB, PG	Pt A-vehicle Pt B-metronida-zole	PRR	Q day/ Pt A-16 wks Pt B-28 wks	Pt A-902

5.2 Review Strategy

The clinical development program for ivermectin 1% cream included 15 clinical trials. Ten of these trials were considered in the efficacy review. The pivotal trials, 18170 and 18171 were reviewed in detail for efficacy. Trials 40173, 40106, 40027, 40006 and 2894 provide supportive evidence of efficacy. Trial 40037 was a no treatment follow-up trial to the dose-ranging trial 40027 designed to evaluate relapse. Trials 40007 and 40064 provided PK information. Trial 40051 was an open label long term safety trial and was therefore not considered in the efficacy evaluation. Trials 19055, 19081 and 40023 were dermal safety trials performed in healthy volunteers and are discussed in section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations. Trial 18120 was a thorough QTc trial performed in healthy volunteers and is discussed in section 7.4.4.

In addition, literature reviews on the use of oral ivermectin (Stromectol) are discussed in Section 2.3 Availability of Proposed Active Ingredient in the United States, Section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class and 7.6.2 Human Reproduction and Pregnancy Data. These literature reviews were originally conducted for the medical review for NDA 202736 for Sklice (ivermectin lotion 0.5%) which was archived in DARRTS on Jan 13, 2012.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal trial design will be discussed here. Since Trials 18170 and 18171 were identical, only 18170 will be discussed in detail. The list of investigators will be provided for both pivotal trials 18170 and 18171 in Attachment B. Other trials are discussed as appropriate in various sections of the review. There were two protocol amendments on Jan 12, 2012 and June 29, 2012. The protocol presented below is the final protocol that

incorporates both amendments. As noted under Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, the details of the pivotal trials were the subject of a SPA.

Trial 18170

Planned Clinical Study: Protocol Number RD.06.SPR.18170

Title: A Phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of ivermectin 1 % cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of ivermectin 1% cream versus azelaic acid 15 % gel.

Objectives:

- To demonstrate the efficacy of ivermectin 1% cream applied once daily versus its vehicle during 12-week treatment in subjects with papulopustular rosacea
- To assess the long-term safety of ivermectin 1% cream applied once daily over 52 weeks

Principal Investigator(s): See Attachment B

Institutional Review Board: See submission- individual investigator 1572 forms

Drug Development Phase: 3

Study Design:

This was a multicenter, randomized, parallel-group study. Up to and including Week 12, the design was double blind, vehicle-controlled. After Week 12, the design was investigator-blinded, active-controlled.

The study was divided into 3 parts:

Part A: 12 week vehicle controlled
Part B: 40 week active (azelaic acid 15% gel) controlled
Part C: 4 week treatment free follow-up

Number of Subjects: 683 subjects were randomized in Part A, 451 to active and 232 to vehicle in trial 18170, 688 subjects were randomized in Part A, 459 to active and 229 to vehicle in trial 18171

Planned Study Period: 21 months with 58 weeks participation including 2 week screening period

Ages of Subjects for Inclusion: 18 years and older

Inclusion Criteria:

1. The subject is a male or female, 18 years of age or older.
2. The subject has papulopustular rosacea with an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe).
3. The subject has at least 15 and not more than 70 inflammatory lesions (papules and pustules) on the face
4. Females of childbearing potential (including pre-menopausal subjects) with a negative urine pregnancy test (UPT) or females of non-childbearing potential, defined as postmenopausal (absence of menstrual bleeding for one year prior to Screening visit),hysterectomy or bilateral oophorectomy
5. The subject is willing and able to comply with the requirements of the protocol. In particular, subject must adhere to the visit schedule, concomitant therapy prohibitions, and must be compliant to the treatment.
6. The subject has understood and signed an Informed Consent Form at the Screening visit prior to any investigational procedure. If applicable, the subject signs the photo consent form,
7. The subject is apprised of the Health Insurance Portability and Accountability Act (HIPAA) in the US or Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada and willing to share personal information and data as verified by signing a written authorization.

Exclusion Criteria:

1. The subject has particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other dermatoses that may be confounded with papulopustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and Acne.
2. The subject has rosacea with more than two nodules on the face at Screening or Baseline visits.
3. The subject has already been enrolled in another investigational study where ivermectin cream was tested as a topical treatment,
4. The subject has an underlying known disease, a surgical or medical condition, which in the judgment of the investigator, would put the subject at risk (e.g., uncontrolled chronic or serious diseases which would normally prevent participation in any clinical study, such as a cancer, leukemia or hematologic dyscrasia), or might confound the study assessments (e.g. other dermatological diseases), or might interfere with the subject's study participation (e.g. planned hospitalization during the study),
5. The subject has clinically significant abnormal laboratory values according to the investigator at either Screening visits (Week -2 orWeek-1),
6. The subject has a beard which would interfere with the study treatment and study assessment,

7. The subject has known allergies or sensitivities to any components of the formulation of the study products being tested (either ivermectin 1% cream or azelaic acid 15 % gel),
8. Subject is a female who is breast feeding, pregnant, or who plans to become pregnant within 13 months of the Baseline visit of the study,
9. The subject is currently enrolled in another investigational drug or device study OR participated in such a study in the month prior to Baseline or is in an exclusion period from a previous study,
10. The subject has not undergone washout periods of sufficient duration for the following treatments at Baseline:

Topical treatments on the face:	
Astringents or abrasives (scrubs, exfoliating cleansers and products containing Salicylic acid and alcohol	2 days
Benzoyl Peroxide	4 weeks
Antibiotics (e.g. metronidazole or macrolides)	4 weeks
Anti-rosacea drugs (e.g. azelaïc acid)	4 weeks
Immunomodulators	4 weeks
Corticosteroids	4 weeks
Retinoids	4 weeks
Systemic treatments:	
Antibiotics (e.g. cyclines, macrolides, metronidazole)	4 weeks
Corticosteroids	4 weeks
Oral Ivermectin	4 weeks
Other drugs used for the treatment of rosacea	4 weeks
Other on the face:	
Laser or Intense Pulsed Light (IPL) or light treatment	6 weeks
Electrocoagulation	6 weeks
Dermabrasion	6 weeks
Facial Peels	6 weeks
Any procedure on the face (such as Thermage®, etc)	6 weeks

11. The subject has been exposed to excessive UV radiation within two weeks prior Baseline visit, or the subject is planning exposure during the study (e.g. occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon),
12. Use of prohibited medications prior to the study and an unwillingness to refrain from use during the study (see exclusion criterion N°10 and section 3.3.2),
13. Subject with known history of substance abuse (drugs or alcohol) within the past 5 years.

Prohibited Therapies: No other topical treatment except moisturizers and sunscreens will be permitted on the face. All the treatments listed in exclusion criterion #12 above should not be used during the study.

Study Plan:

Part A

Subjects meeting the Inclusion/Exclusion criteria were randomized at the baseline visit. If a subject needed a wash-out for a previous medication or procedure, the subject was consented and the screening visit was performed. After completing the wash-out period and not later than two weeks after screening visit (14 days + 3 days), the subject was returned to the site for the baseline visit. In Part A, subjects were randomized in a 2:1 ratio to either ivermectin 1% cream or vehicle cream. Subjects applied ivermectin 1 % or vehicle once daily, every day at bedtime on the entire face for 12 weeks. Treatment continued irrespective of the IGA score. The subject was provided with verbal and written instructions on when and how to properly apply the study drug. Study personnel ensured the proper application of the first dose of study drug at baseline visit to demonstrate the amount of drug to use daily and the method of application. In Part A, visits occurred at screening one (week -2), screening two (week-1), baseline (week 0), weeks 2, 4, 8 and 12 (or early termination).

The subject was instructed to apply a thin film of study drug on the entire face (even if some areas do not have rosacea) once a day at night-time. Approximately one small pea size amount was applied on each of the following facial regions: right and left cheeks, forehead, chin and nose, avoiding the upper and lower eyelids and the lips.

Blinding

During Part A (Baseline to Week 12), study drugs will be packaged in the same type of tubes and no visible difference can be observed between the CD5024 1% cream and its vehicle cream. The randomization list will be maintained secured in a locked cabinet and/or an electronic file with restricted access to only the designated personnel directly responsible for labeling and handling the study drugs in Galderma or designee. The independent statistician providing analyses requested by the IDMC may keep a copy of the randomization list. During Part B of the study, the study materials (study drug and comparator product) are different in appearance, dosage form and regimen. All products should be dispensed by designated trained study personnel independent from the investigator/evaluator who will assess the subject. The study personnel dispensing the study drug will instruct the subject not to discuss the appearance of the study drug and the dose regimen with the investigator.

The DM will be assigned the Extract role in RAVE to "freeze" the Week 12 IGA and lesion count data points. These two data points will be frozen by the DM within five business days of entry by the site. Once frozen, no updates can be made by the site unless it is unfrozen by the CRA or the DM. Any updates made to previously entered data will require a reason for change. Updates will be monitored by the clinical team to ensure the integrity of the data.

Part B

Subsequently, up to Week 52,

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- Subjects initially treated with ivermectin 1% cream once daily at bedtime were continued on this treatment
- Subjects initially treated with ivermectin vehicle cream once daily at bedtime were switched to azelaic acid 15% gel twice daily, in the morning and evening.

During the 40-week investigator-blinded part of the study, the investigator stopped the treatment if the subject was considered as “Clear” (grade 0) on the IGA scale. The subject continued to attend the study visits as planned in the protocol.

The decision to restart the treatment was made by the Investigator on a visit day if the IGA score became ≥ 1 “almost clear”.

In Part B, visits occurred at weeks 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

When necessary, unscheduled visits took place because an adverse event (AE) required a specific treatment or the Neutrophil Cell Count (NCC) had been found below 1.5 G/L (units equivalent to K/uL).

14. Section 4.5 Management of NCC cases below 1.5 G/L

In cases where there is a NCC <1.5 G/L, the investigator must contact the subject immediately in order to collect information on the subject's health status (i.e. absence or presence of clinical signs of infection, such as fever)

If the subject has no clinical signs of infection, an Unscheduled Visit must occur no later than 96 hours after the first blood sample was drawn. See Section 4.5.1 below for a description of the procedures to be conducted during the Unscheduled Visits.

If the subject has any clinical signs of infection, the investigator should inform the subject of the potential risks and request that the subject return for an Unscheduled Visit no later than 48 hours after the first blood sample was drawn. If an Unscheduled visit cannot be performed at the clinic within 48 hours due to logistical reasons, the subject should be assessed by another physician as soon as possible for a clinical evaluation and a hematology retest. Note: Investigator will need to contact this physician to advise on the subject status. See Section 4.5.2 below for a description of the procedures to be conducted during these Unscheduled Visits.

In cases where there is a NCC<0.5 G/L, the investigator must follow Section 4.5.3 below and send the subject to the emergency room.

15. Section 4.5.1 Unscheduled visits when NCC 0.5 G/L ≤ NCC < 1.5G/L without clinical signs of infection

1. Continue use of study drug
2. Ask the subject whether there have been any changes to their concomitant therapies/procedures, (added, removed, or changed) since the previous visit. Document all changes on the source document and Therapy/Procedure page of the eCRF,
3. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the source document and corresponding eCRF pages,
4. Ask the subject whether there have been any changes to their smoking habits (start, stop, or change(s)) since the previous visit. Document all changes on the source document and appropriate page of the eCRF,
5. Perform the physical examination and record vital signs,
6. Record the date and time of last application for PK purpose and perform blood sampling for pharmacokinetic analysis **for randomized subjects only**,
7. Perform blood sampling for hematology, **CRP** and biochemistry. Blood samples must be shipped the day they are drawn from the subject. Review results of this blood sampling and check that there is no sign of infection.
    a. If NCC is below 0.5G/L, please refer to Section 4.5.3.
    b. If NCC below 1.5 G/L but above or equal to 0.5 G/L: the treatment is to be temporarily discontinued for this subject. Further to IDMC advice, the subject will be followed every 48-**96** hours with visits at the clinic and blood samplings for hematology and PK until normalization of the NCC. The IDMC may advise either to stop definitively or to re-start the study treatment in this subject.
    c. If NCC is above or equal to 1.5 G/L, the subject can continue the study until the planned next visit
8. Evaluate and record local cutaneous signs and symptoms (stinging/burning, dryness and itching),
9. Schedule an appointment for the next visit and, as deemed necessary, follow-up with a pre-visit phone call reminder

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16. Section 4.5.2 Unscheduled visits when NCC 0.5 G/L ≤ NCC < 1.5G/L with clinical signs of infection

1. Discontinue Study Drug temporarily in this subject,
2. Ask the subject whether there have been any changes to their concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the source document and Therapy/Procedure page of eCRF,
3. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the source document and corresponding eCRF pages,
4. Ask the subject whether there have been any changes to their smoking habits (start, stop, or change(s)) since the previous visit. Document all changes on the source document and appropriate page of the eCRF,
5. Perform the physical examination and record vital signs.
6. Record the date and time of last application for PK purpose and perform blood sampling for pharmacokinetic analysis
7. Perform blood sampling for hematology,biochemistry and antimicrobial serologies. Blood samples must be shipped the day they are drawn from the subject. Review the results of this second blood sampling.
    a. If NCC is below 0.5G/L, please refer to Section 4.5.3.
    b. If NCC is below 1.5 G/L but above or equal to 0.5 G/L: the treatment should not be restarted in this subject. The IDMC will advise on the case and will advise on the subject follow-up to be implemented as well as on the outcome decision regarding a potential code breaking, or potential permanent study discontinuation for that subject. The subject will be followed every 48-**96** hours with visits at the clinic and blood samplings for hematology and PK until normalization of the NCC.
    c. If NCC is above or equal to 1.5 G/L: ~~Perform blood sampling for hematology~~. The IDMC will advise on the potential restart of the treatment.
8. Evaluate and record local cutaneous signs and symptoms (stinging/burning, dryness and itching),
9. Schedule an appointment for the next visit and, as deemed necessary, follow-up with a pre-visit phone call reminder. If the study drug has been permanently discontinued in this subject, an "Early Termination" visit will be planned.

17. Section 4.5.3 Unscheduled visits in cases of NCC below 0.5 G/L

1. **Immediately discontinue** the Study Drug ~~(if applicable)~~ in this subject, and ask the subject to go to the emergency room for assessment (i.e. PE, vital signs, etc.) and a STAT hematology value. **Note:** Investigator to contact emergency room to advise on subject status.
    a. If NCC of < 0.5 G/L is confirmed in this second blood sample from the emergency room, the Investigator is to report the SAE as per Section 7.2.2. The

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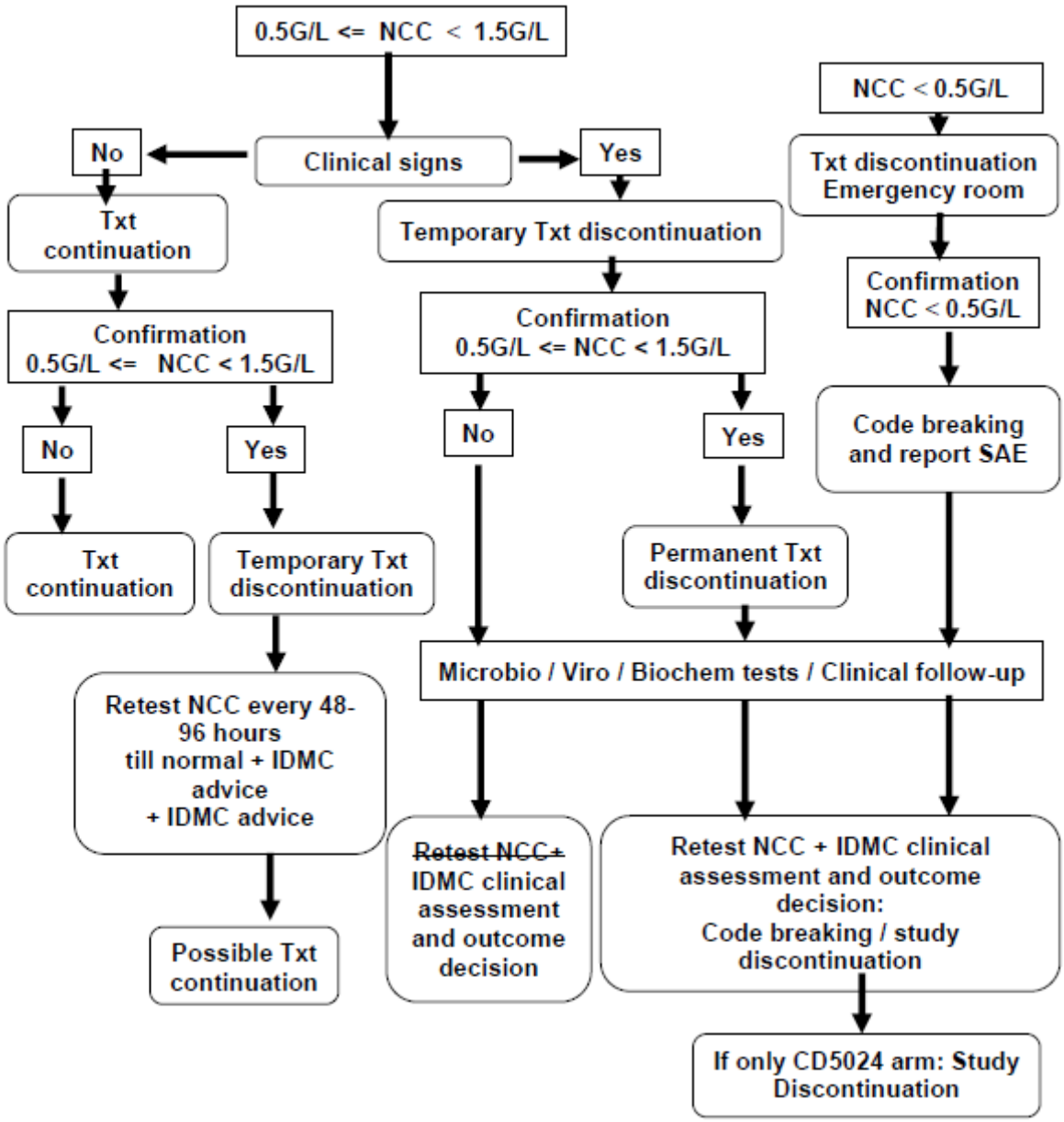
subject is permanently discontinued from study drug. The blind will be broken for this subject. The IDMC will assess this case in the context of this study.

b. If NCC of < 0.5 G/L is not confirmed in this second blood sample from the emergency room, the subject is to return to the site for an unscheduled visit.

2. Regardless of NCC emergency room value, the subject is to return to the site for an unscheduled visit as soon as possible to perform the following:
3. Ask the subject whether there have been any changes to their concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the source document and Therapy/Procedure page of eCRF,
4. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the source document and corresponding eCRF pages,
5. Ask the subject whether there have been any changes to their smoking habits (start, stop, or change(s)) since the previous visit. Document all changes on the source document and appropriate page of the eCRF,
6. Perform the physical examination and record vital signs. Record the date and time of last application for PK purposes ~~(if applicable)~~ and perform blood sampling for pharmacokinetic analysis **for randomized subjects only**. ~~Blood draw for PK is applicable only to subjects post Baseline.~~

Figure 1: Management of potential neutropenia



Part C

After 52 weeks of treatment period (Parts A and B), subjects continued in the study for 4 weeks without any treatment to enable the collection of safety data after treatment discontinuation. The “End of study” visit at week 56 was completed for each subject that completed 52 weeks of treatment.

Figure 2: Study Schematic

Figure 1 Study schematic

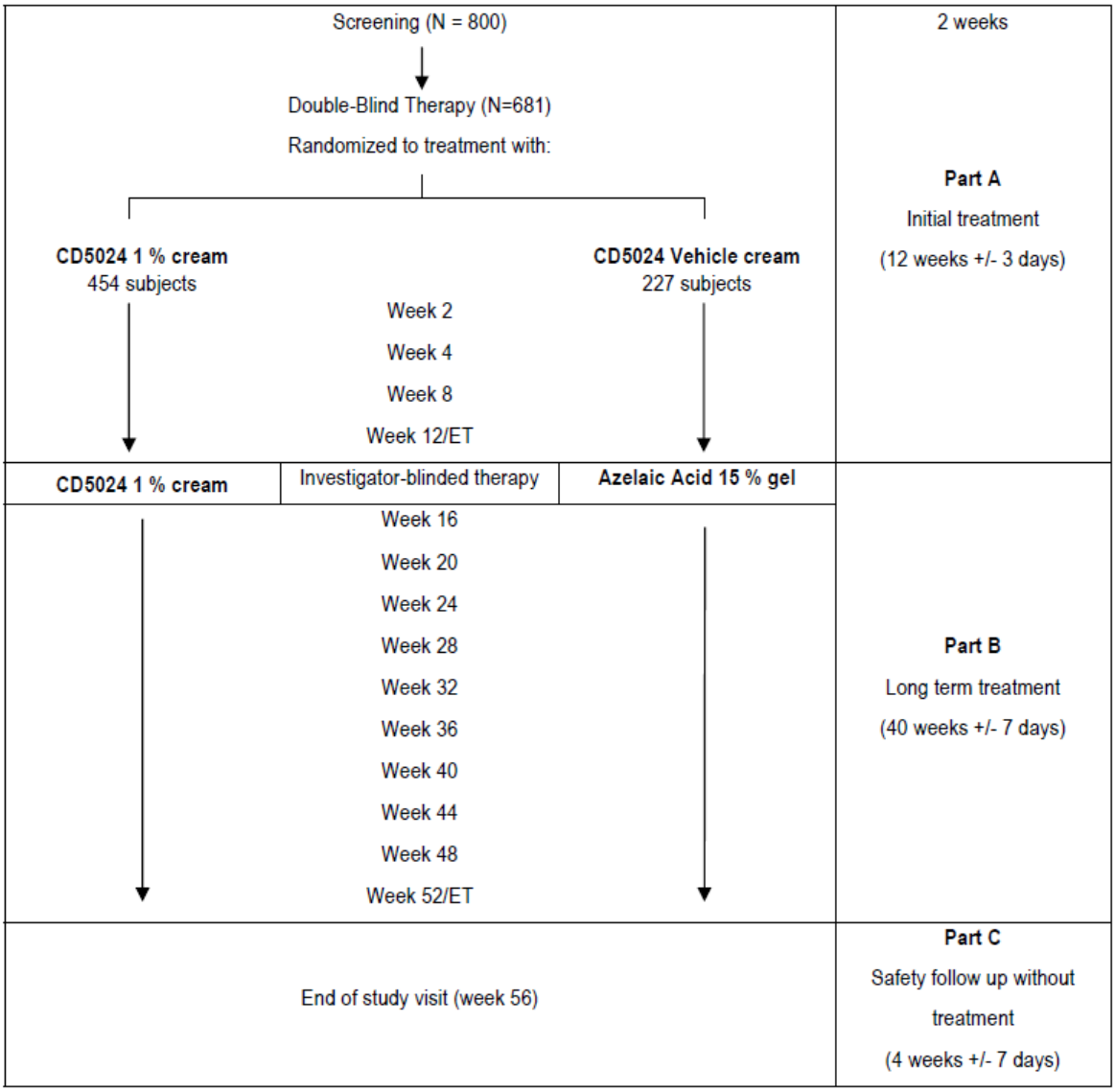


Table 6: Study Schedule

Table 2 Study flow chart/time and events schedule

Parameters	Screening (Week - 2)	Screening (Week-1)[7]	Baseline[7,8]	Week 2[7]	Week 4[7]	Week 8[7]	Week 12/ET[7,9]	Weeks 16, 20, 28, 32, 40, 44[7]	Weeks 24, 36, 48[7]	Week 52/ET[7,9]	End of study (Week 56)[7,11]	Unscheduled Visit
Informed Consent / Photography Consent / HIPAA/PIPEDA[1]	X											
Inclusion/Exclusion Criteria	X[6]		X									
Demographics/Medical History	X											
Previous Therapies / Procedures	X											
Smoking habits/change	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X				X		X[10]	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Photographs (face) at selected sites[2]			X				X					
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X		X				X		X[10]	X	X	X
Antimicrobial serologies												X[12]
CRP	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic samples at selected sites[2]							X	X (W32 only)		X	X	
Pharmacokinetic samples at all sites for randomized subjects only												X
Urinary pregnancy test[3]	X		X		X	X	X	X	X	X	X	
IGA	X		X	X	X	X	X	X	X	X		
Inflammatory Lesion count	X		X	X	X	X	X					
Erythema Assessment	X		X	X	X	X	X					
Nodule count	X		X	X	X	X	X					
Local cutaneous signs and symptoms			X	X	X	X	X	X	X	X	X	X
Quality of Life questionnaire (RosaQoL™)			X				X					
Dermatology Life Quality Index (DLQI)			X				X					
Subject's appreciation questionnaire							X					
Subject's Rosacea Improvement Assessment							X					
IWRS (Interactive Web Response System)	X		X				X					
Drug Dispensing (D) and Accountability (A)[4]			D	A	D/A	D/A	D/A	D/A	D/A	A		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies/procedures	X	X	X	X	X	X	X	X	X	X	X	X
Exit Form[5]							X			X	X	

Note:

1. Photography consent applies to selected sites; HIPAA applies to US sites only; PIPEDA applies to Canadian sites only.
2. In selected sites only
3. For females of childbearing potential only
4. Oral and Written instructions are to be provided to subject regarding dosing calendar
5. Only one Exit form should be completed per subject. It should be signed after collecting all data from the subject (including hematology and blood chemistry results), once the subject discontinues/exits the study permanently
6. For Part A there is a +/- 3 day visit window. For Part B and C, there is a +/-7 visit window.
7. Reconfirm that subject continues to meet inclusion/exclusion criteria
8. Should be conducted earlier if subject discontinues prior to week 12/52 respectively
9. Physical examination and biochemistry at Week 24 and 36 only (not at Week 48)
10. The "End of Study" visit should be completed for each subject that completed 52 weeks of treatment.
11. In case of NCC < 1.5G/L with clinical signs of infection and in all cases of NCC < 0.5 G/L

Efficacy Assessment:

Throughout the study, the IGA and lesion counts for each individual subject were performed by the same investigator/evaluator. According to the protocol, the IGA was conducted prior to performing the lesion count or evaluating erythema.

Table 7: IGA Scale

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

At each visit, the investigator/evaluator performed a count of inflammatory lesions.

Inflammatory lesions were defined as follows:

• PAPULE - A small, solid elevation less than one centimeter in diameter.
• PUSTULE - A small, circumscribed elevation of the skin, which contains yellow-white exudates

Papules and pustules were counted, separately on each of the five facial regions (forehead, chin, nose, right cheek, left cheek). Nodules were counted separately.

Nodules were defined as follows:

• NODULE - A circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth.

Erythema:

At Baseline and every following visit, the investigator/evaluator assessed the erythema on the entire face, using the following grading scale:

Table 8: Erythema Assessment

None	0	No erythema
Mild	1	Slight pinkness
Moderate	2	Definite redness, easily recognized
Severe	3	Marked erythema
Very severe	4	Fiery red

If the erythema severity was much worse on one or several parts of the face, the worst area was graded.

Subject Discontinuation from Study:

Investigators could decide to discontinue a subject from the study for safety reasons or when it was in the best interest of the subject. Any subject was free to discontinue their participation in the study at any time and for whatever reason, specified or unspecified, and without prejudice. Subjects not completing the entire study were fully evaluated, whenever possible.

All discontinuations and their causes were carefully documented by the investigator on the Exit Form, and in case of discontinuation due to an AE, on the Adverse Event Form.

Potential reasons for discontinuation, as listed on the Exit Form, were defined as follows:

Pregnancy:	**Study drug must be immediately discontinued. Complete the Pregnancy Surveillance Form.**
Lack of Efficacy:	Valid if investigator judgment only: based on therapeutic/disease-state expectations. If subject's opinion only, mark as subject request on forms. Explain in the comment section of the eCRF Exit Form.
Adverse Event:	Complete an Adverse Event Form. This category includes clinically significant worsening of the treated disease as judged by the investigator ~~and/or the IDMC~~
Subject Request:	Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the eCRF Exit Form.
Protocol Violation:	Major protocol violation, especially when subject safety is concerned. Also includes events and actions by the subject that prevent valid evaluations of the disease state. Explain the violation in the comment section of the eCRF Exit Form.
Lost to Follow-up:	Document with two phone calls and a certified letter (deliver receipt requested) without answer. Explain in the comment section of the eCRF Exit Form.
Other:	Explain the reason for discontinuation in comment section of the eCRF Exit Form. This reason should only be used if the reason for discontinuation is not better accounted for by another category.

Safety/Safety Monitoring:

1. Pregnancy testing was performed on all females of childbearing potential at Baseline and Week 12/Early Termination visits. In the case of pregnancy the subject was withdrawn from the study and the progress of the pregnancy was followed until its outcome.
2. Adverse Events were monitored at Baseline and every following visit.
3. AEs of special interest (AESI) were monitored.
   AESIs for this study were defined as:
   a) Suspected sensitization with cutaneous signs (allergic contact dermatitis)
   If a subject experienced a suspected skin sensitization (contact allergy), a procedure for follow-up was established and was specified in the protocol
   b) Suspected photosensitivity reactions
   c) Cutaneous AE related to study product leading to discontinuation
   d) Abnormal neurological signs (such as tremors, ataxia, myoclonus, nystagmus, convulsions...)
   e) All systemic AEs related to the study drug
4. Physical examination and vital signs were performed at Screening, Baseline, and Week 12/Early Termination visits.
5. Local cutaneous reactions in the form of signs and symptoms were monitored (stinging/burning, dryness, and itching) from Baseline and at every following visit. The investigator/evaluator evaluated the outcome of signs and symptoms of rosacea on a 4-point scale at each study visit:

Table 9: Local Cutaneous Signs and Symptoms

Stinging/Burning-prickling pain sensation		
None	0	No stinging/burning
Mild	1	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	2	Definite warm, tingling/stinging sensation that is somewhat
Severe	3	Hot, tingling/stinging sensation that has caused definite discomfort

Dryness - brittle and/or tight sensation		
None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness

Itching- An itching sensation		
None	0	No itching
Mild	1	Slight itching; not really bothersome
Moderate	2	Definite itching that is somewhat bothersome; without loss of sleep
Severe	3	Intense itching that has caused pronounced discomfort; night rest interrupted and excoriation of the skin from scratching may be

Laboratory assessments: Hematology and CRP were tested at screening, week-2, week-1, baseline, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 and at any unscheduled visit. Chemistries were tested at screening -2, baseline, 12, 24, 36, 48, 52, 56 and at any unscheduled visit.

Efficacy criteria:

- Primary efficacy criteria

  Co-primary efficacy endpoints:

  a. Success Rate, based on IGA score, will be defined as the percentage of subjects who achieve "Clear" (score = 0) or "Almost Clear" (score = 1) at Week 12 (ITT-LOCF).
  b. Absolute change in inflammatory lesion counts from Baseline to Week 12 (ITT-LOCF).

  Additionally, the time to onset of efficacy, nested analysis of co-primary endpoints for successively earlier time points, will be determined.

The primary analyses were the comparison between ivermectin and vehicle for these co-primary endpoints. Success rates were analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by center, using general association statistic (FREQ procedure from SAS). Absolute changes in Inflammatory lesion counts were analyzed by an analysis of covariance model including baseline inflammatory lesion count as a covariate, and treatment and center as factors. Both analyses at Week 12 (ITT-LOCF)

were required to be significant at the 0.050 level for the study to be claimed positive regarding efficacy.

Per protocol and sensitivity analyses were also performed to assess the robustness of the conclusions.

Secondary efficacy endpoints:

Percent of subjects reaching at least a 1-grade improvement on the erythema scale from Baseline to Week 12 (ITT-LOCF).

Percent Change in Inflammatory Lesion Counts was analyzed as a secondary analysis by a stratified Mann-Whitney test using the CMH procedure stratified by analysis center with the ridit transformation and the row mean score difference statistic (FREQ procedure from SAS).

6 Review of Efficacy

Efficacy Summary

The applicant has completed 15 clinical trials in the development program for ivermectin cream 1% for the treatment of the inflammatory lesions of rosacea. This included three local tolerance trials, an oral thorough QT/QTc (TQT) trial, two pharmacokinetic (PK) trials including one maximal use trial and a proof-of-concept trial. A total of 8 trials were conducted to assess the efficacy and safety of ivermectin cream in subjects with PPR: 4 Phase 2 trials and 4 Phase 3 trials. During the clinical development program, a total of 2047 subjects with inflammatory lesions of rosacea received ivermectin cream 1% once daily. Overall, a total of 1555 subjects were treated once daily for more than 12 weeks, and 519 for approximately one year.

The applicant provided substantial evidence of efficacy. The Phase 3 program included 2 identical adequate and well-controlled 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.

The co-primary endpoint in each pivotal trial was the success rate based on the IGA score defined as the percentage of subjects achieving a score of 0 or 1, and

the absolute change in inflammatory lesion counts. The primary endpoint was agreed upon with the Agency as was conveyed in the SPA agreement letter. In both trials, the applicant's product was significantly superior to vehicle in the target population. The details are discussed in Section 6.1.4.

6.1 Indication

The applicant proposes an indication for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.

6.1.1 Methods

The applicant conducted two pivotal trials (18170 and 18171) of identical design. Both were multicenter, randomized, double-blind, 12 week, vehicle-controlled, parallel-group, efficacy and safety trials which evaluated Ivermectin 1% Cream QD in subjects with rosacea. The vehicle-controlled part of the study (Part A) was followed by a 40-week safety follow-up (Part B), and a 4-week, treatment-free follow-up (Part C). The pivotal trials were conducted in the United States and Canada. The phase 1 and 2 trials were conducted in Europe.

6.1.2 Demographics

Gender, racial composition and skin phototype of the study populations reflect what is generally known about the population most often affected by rosacea, i.e. more common in women and in light-skinned Caucasians with a peak age of ≈ 50 years. The table below displays the demographic profile for trials 40027 (phase 2 dose-ranging), 40106 (phase 2 neutropenia evaluation), 18170 and 18171 (phase 3 pivotal).

Table 10: Demographic characteristics at Baseline in vehicle-controlled Studies 40027, 40106, 18170, and 18171 (ITT Population)

Variable and Descriptive Statistics	RD.03.SRE.40027		RD.06.SRE.40106		RD.06.SRE.18170 (Part A)		RD.06.SRE.18171 (Part A)	
	CD5024 1% Cream QD (N=52)	Vehicle Cream QD (N=50)	CD5024 1% Cream QD N=104)	Vehicle Cream QD (N=106)	CD5024 1% Cream QD (N=451)	Vehicle Cream QD (N=232)	CD5024 1% Cream QD (N=459)	Vehicle Cream QD (N=229)
Gender (n, %)								
Male	19 (36.5)	15 (30.0)	34 (32.7)	32 (30.2)	137 (30.4)	80 (34.5)	145 (31.6)	84 (36.7)
Female	33 (63.5)	35 (70.0)	70 (67.3)	74 (69.8)	314 (69.6)	152 (65.5)	314 (68.4)	145 (63.3)
Age (years)								
Mean	50.3	52.2	55.4	55.4	49.9	51.6	50.5	49.5
SD	14.5	14.4	12.9	12.3	12.1	11.9	12.3	12.2
Median	51.5	53.0	57.5	56.5	49.0	52.0	50.0	50.0
Min , Max	23, 78	24, 82	23, 80	25, 81	19, 88	26, 86	21, 89	18, 81
Age range, n (%)								
18-64 years	43 (82.7)	41 (82.0)	73 (70.2)	83 (78.3)	402 (89.1)	200 (86.2)	399 (86.9)	200 (87.3)
65 years and older	9 (17.3)	9 (18.0)	31 (29.8)	23 (21.7)	49 (10.9)	32 (13.8)	60 (13.1)	29 (12.7)
Race, n (%)								
Caucasian	51 (98.1)	50 (100.0)	104 (100.0)	105 (99.1)	437 (96.9)	220 (94.8)	438 (95.4)	218 (95.2)
Black	0	0	0	0	6 (1.3)	3 (1.3)	6 (1.3)	4 (1.7)
Asian	0	0	0	1 (0.9)	3 (0.7)	3 (1.3)	10 (2.2)	5 (2.2)
Other	1 (1.9)	0	0	0	5 (1.1)	6 (2.6)	5 (1.1)	2 (0.9)
Ethnicity, n (%)								
Hispanic/Latino	-	-	-	-	55 (12.2)	23 (9.9)	56 (12.2)	31 (13.5)
Not Hispanic/ Not Latino	-	-	-	-	396 (87.8)	209 (90.1)	403 (87.8)	198 (86.5)
Skin phototype, n (%)								
I	4 (7.7)	7 (14.0)	-	-	39 (8.6)	16 (6.9)	48 (10.5)	22 (9.6)
II	27 (51.9)	28 (56.0)	-	-	185 (41.0)	90 (38.8)	211 (46.0)	96 (41.9)
III	14 (26.9)	15 (30.0)	-	-	167 (37.0)	86 (37.1)	139 (30.3)	71 (31.0)
IV	7 (13.5)	0	-	-	51 (11.3)	26 (11.2)	50 (10.9)	31 (13.5)
V	0	0	-	-	8 (1.8)	11 (4.7)	11 (2.4)	7 (3.1)
VI	0	0	-	-	1 (0.2)	3 (1.3)	0	2 (0.9)

Data Source: Section 5.3.5.3, SCE Table 2.1

Source: Applicant's ISE Pg. 42.

Demographic characteristics were generally well-balanced between treatment groups for the pivotal trials 18170 and 18171. It is notable that in general the European trials (40027 and 40106) had similar demographic characteristics to the North American trials except for the fact that they had minimal representation of races other than Caucasian. This translated to minimal representation of skin types V and VI. The pivotal trials conducted in North America had some subjects with skin types V and VI, though the numbers were low. There were 1-2% non-caucasians which translated to 10-13% skin

type IV, 1.8-4.7% skin type V and 0 – 1.3% skin type VI. The applicant proposes that the demographic characteristics of the European trials are close enough to that seen in the North American trials to argue for the applicability of the foreign data obtained from these trials to subjects in the US. I agree that this is the case.

The pivotal trials were also well balanced with regard to baseline disease status, as displayed in the table below.

Table 11: Baseline disease characteristics in trials 18170, and 18171 (ITT Population)

Variable and Descriptive Statistics	RD.06.SRE.18170		RD.06.SRE.18171	
	CD5024 1% Cream QD (N=451)	Vehicle Cream QD (N=232)	CD5024 1% Cream QD (N=459)	Vehicle Cream QD (N=229)
IGA [a] score, n				
0=Clear	0	0	0	0
1=Almost Clear	0	0	0	0
2=Mild	0	0	0	0
3=Moderate	369 (81.8)	191 (82.3)	346 (75.4)	176 (76.9)
4=Severe	82 (18.2)	41 (17.7)	113 (24.6)	53 (23.1)
Inflammatory				
Mean	31.0	30.5	33.3	32.2
SD	14.3	14.4	13.6	13.9
Median	27.0	26.5	30.0	29.0
P25, P75	20, 37	20, 36	23, 41	22, 39
Min , Max	15, 70	15, 71	15, 70	14, 69

[a] In Study 40027, IGA1 scores, which included lesion counts and erythema severity, are considered in this table.

P=quartile

Data Source: Section 5.3.5.3, SCE Table 3.1.

Source: Applicant's ISE pg. 69 (modified by reviewer)

The majority 75 – 82% of subjects had moderate disease at entry in both pivotal trials with a mean of 30-33 inflammatory lesions.

6.1.3 Subject Disposition

A total of 1371 subjects were randomized and included in the ITT population in the pivotal trials 18170 and 18171. The majority of subjects completed the treatment as displayed in the table below.

Table 12: Subject disposition in the vehicle-controlled portion of trials 18170 (Part A), and 18171 (Part A) (ITT Population)

Table 4: Disposition of Subjects (ITT)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
Discontinued in Part A	37 (8.2%)	22 (9.5%)	30 (6.5%)	21 (9.2%)
Adverse Event	7 (1.6%)	4 (1.7%)	6 (1.3%)	4 (1.7%)
Lack of Efficacy	0	1 (0.4%)	1 (0.2%)	0
Subject's Request	18 (4.0%)	7 (3.0%)	9 (2.0%)	8 (3.5%)
Lost to Follow-Up	7 (1.6%)	8 (3.4%)	8 (1.7%)	8 (3.5%)
Protocol Violation	2 (0.4%)	1 (0.4%)	4 (0.9%)	0
Pregnancy	2 (0.4%)	0	1 (0.2%)	0
Other	1 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)

Source: Reviewer's Analysis

Source: Statistical Review pg.9

The most common reasons for discontinuation were withdrawal by subject (2 - 4%), lost to follow-up (1.6 - 3.5%) and adverse event (1.3 - 1.7%). The overall percent of discontinuations were similar in trial 18170 (8.2 vs 9.5%) and higher in trial 18171 in the vehicle arm (6.5 vs 9.2%). It is notable that for discontinuations due to adverse events the numbers were well balanced between active and vehicle arms with a slightly higher rate of discontinuations due to AE in the vehicle arm for trial 18171.

6.1.4 Analysis of Primary Endpoint(s)

The co-primary efficacy variables for both pivotal trials (18170 and 18171) were

- the success rate based on the IGA score defined as the percentage of subjects achieving a score of 0 or 1, and
- Absolute Change in Inflammatory Lesion Counts.

The timepoint for assessment of the primary efficacy endpoints for the pivotal trials was at week 12. All efficacy analyses for the three Phase 3 studies were performed on the ITT population, defined as all subjects who were randomized and to whom study drug was dispensed. It was further specified that both co-primary endpoints were to be statistically significant (i.e., at 0.050 level) for the studies to be considered successful. The table below, from the statistical reviewer's midcycle review shows the results.

Table 13: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Study 18170 SOOLANTRA (N=451)	Study 18170 Vehicle (N=232)	Study 18170 P-value	Study 18171 SOOLANTRA (N=459)	Study 18171 Vehicle (N=229)	Study 18171 P-value
Co-Primary:						
IGA Success[1]: n (%)	173 (38.4%)	27 (11.6%)	<0.001[2]	184 (40.1%)	43 (18.8%)	<0.001[2]
Absolute Change in Inflammatory Lesion Counts: Mean	-20.5	-12.0	<0.001[3]	-22.2	-13.4	<0.001[3]
Secondary:						
Percent change in Inflammatory Lesion Counts: Mean	-64.9%	-41.6%	<0.001[4]	-65.7%	-43.4%	<0.001[4]

Source: Reviewer's Analysis
(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear).
(2) P-value based on the CMH test stratified by analysis centers.
(3) P-value based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

Source: Statistical Reviewer's Midcycle Review, pg 1

Ivermectin cream 1% was statistically superior to vehicle for both co-primary endpoints at Week 12 in both studies. The final format for the presentation of the Co-primary efficacy results to be used in labeling is reproduced from the agreed upon label and is presented below

Table 14: Co-Primary Efficacy Results at Week 12

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

Source: Agreed upon labeling, section 14

6.1.5 Analysis of Secondary Endpoints(s)

The percent change from baseline in inflammatory lesion counts was a secondary efficacy endpoint in trials 18170 and 18171. As shown above in Table 13, ivermectin cream 1% was statistically superior to vehicle for this endpoint at Week 12 in both studies.

6.1.6 Other Endpoints

The time to onset of efficacy (earliest time point when significance was reached for both co-primary endpoints, with significance met at all subsequent time points) was evaluated by hierarchical analysis of co-primary endpoints for successively earlier time points (ITT-LOCF).

For the time to onset of efficacy, based on confirmed satisfaction of the 2 co-primary endpoints of Success Rate and Absolute Lesion Count Change, a statistically significant difference favoring Ivermectin 1% cream QD was achieved as early as Week 4 (ITT-LOCF) when compared to its vehicle and this difference was sustained until Week 12/ET. This time to onset of efficacy was confirmed in the PP population (LOCF).

6.1.7 Subpopulations

A planned exploratory analysis was conducted using the data combined from the pivotal Studies 18170 and 18171 to evaluate the relative efficacy in important subgroups based on age, gender, race, and disease severity at Baseline.

Descriptive statistics by treatment group and the differences between the treatment groups plus the 95% CIs of the differences are provided for the co-primary endpoints separately for each subcategory of each of the four subgroups (e.g., Caucasian/White or Non-Caucasian/Non-White for the subcategory of race). Age was summarized as a dichotomous variable defined as less than 65 years old and greater than or equal to 65 years old. Race was summarized as Caucasian/White or Non-Caucasian/Non-White, based on the assumption that the majority of subjects would be of the Caucasian/White race. Disease severity results are presented based on Baseline IGA scores of 3 or 4 and based on the Baseline number of inflammatory lesions.

Table 15: Success Rate at Week 12 (LOCF) by subgroups (pooled Studies 18170 and 18171) (ITT Population)

Variable	CD5024 1% Cream QD Success (n)/Total (N) (%)	Vehicle Cream QD Success (n)/Total (N) (%)	Difference in Success (95% CI)
Gender, n/N (%)			
Males	96/282 (34.0%)	28/164 (17.1%)	17.0% (8.5%, 25.4%)
Females	261/628 (41.6%)	42/297 (14.1%)	27.4% (21.6%, 33.2%)
Age Range, n/N (%)			
18-64 years	309/801 (38.6%)	54/400 (13.5%)	25.1% (20.1%, 30.0%)
65 years and older	48/109 (44.0%)	16/61 (26.2%)	17.8% (2.1%, 33.5%)
Race, n/N (%)			
Caucasians	343/875 (39.2%)	66/438 (15.1%)	24.1% (19.3%, 29.0%)
Non-Caucasians	14/35 (40.0%)	4/23 (17.4%)	22.6% (-3.4%, 48.6%)
Baseline Disease Severity, n/N (%)			
Baseline IGA = 3	299/715 (41.8%)	65/367 (17.7%)	24.1% (18.6%, 29.6%)
Baseline IGA = 4	58/195 (29.7%)	5/94 (5.3%)	24.4% (15.8%, 33.1%)

LOCF = The last observation carried forward. Baseline value was used if no post-Baseline data were available.

Success was defined as '0 = Clear' or '1 = Almost Clear' on the Investigator Global Assessment (0 to 4 scale).

95% CI for difference in success rate is based on large sample approximation with continuity correction (Fleiss 1981).

Data Source: Section 5.3.5.3, SCE Table 7.1

Source: Applicant's ISE pg 95.

The difference in success rate between active and vehicle arms was greater in female vs male subjects (27.4% vs 17%). The success rate was higher in subjects greater than 65 years (44.0% vs 38.6%) but since the over 65 arm also had a substantially higher success for the vehicle arm the difference in success favored the younger age group. Success was similar in caucasians vs non-caucasians. The success rate based on baseline disease severity favored moderate disease but since these subjects also had a higher success rate in the vehicle arm the overall difference in success was similar. The 95% CI overlap for all of these comparisons however, suggesting that none of the above stated differences are likely significant.

Table 16: Change in Inflammatory Lesion Counts at Week 12 (LOCF) by subgroups, (pooled Studies 18170 and 18171) (ITT Population)

Variable	Statistic	Baseline Inflammatory Lesion Counts		Week 12 Change in Inflammatory Lesion Counts	
		CD5024 1% Cream QD	Vehicle Cream QD	CD5024 1% Cream QD	Vehicle Cream QD
Gender					
Males	n	282	164	282	164
	Mean (SE)	33.99 (0.88)	31.06 (1.11)	-23.22 (0.94)	-13.13 (0.98)
	SD	14.80	14.22	15.86	12.58
	Median	30.0	27.0	-21.0	-13.0
	Difference (95% CI)	NA		-10.1 (-12.9, -7.2)	
Females	n	628	297	628	297
	Mean (SE)	31.34 (0.54)	31.56 (0.82)	-20.52 (0.61)	-12.50 (0.86)
	SD	13.54	14.16	15.18	14.77
	Median	27.5	28.0	-19.0	-13.0
	Difference (95% CI)	NA		-8.0 (-10.1, -5.9)	
Age Range					
18-64 years old	n	801	400	801	400
	Mean (SE)	32.45 (0.50)	32.17 (0.72)	-21.16 (0.56)	-12.61 (0.73)
	SD	14.10	14.32	15.78	14.61
	Median	28.0	28.0	-19.0	-13.0
	Difference (95% CI)	NA		-8.6 (-10.4, -6.7)	
≥65 years old	n	109	61	109	61
	Mean (SE)	30.04 (1.24)	26.26 (1.53)	-22.79 (1.20)	-13.48 (1.20)
	SD	12.99	11.96	12.57	9.37
	Median	27.0	22.0	-21.0	-15.0
	Difference (95% CI)	NA		-9.3 (-13.0, -5.7)	
Race					
Caucasian	n	875	438	875	438
	Mean (SE)	32.02 (0.47)	31.27 (0.67)	-21.33 (0.52)	-12.61 (0.66)
	SD	14.01	14.12	15.45	13.88
	Median	28.0	28.0	-19.0	-13.0
	Difference (95% CI)	NA		-8.7 (-10.4, -7.0)	

Variable	Statistic	Baseline Inflammatory Lesion Counts		Week 12 Change in Inflammatory Lesion Counts	
		CD5024 1% Cream QD	Vehicle Cream QD	CD5024 1% Cream QD	Vehicle Cream QD
Non-Caucasians	n	35	23	35	23
	Mean (SE)	35.83 (2.24)	33.48 (3.17)	-21.97 (2.57)	-15.00 (3.46)
	SD	13.23	15.18	15.21	16.61
	Median	34.0	27.0	-18.0	-16.0
	Difference (95% CI)	NA		-7.0 (-15.5, 1.5)	
Baseline Disease Severity					
IGA=3 (moderate)	n	715	367	715	367
	Mean (SE)	29.02 (0.45)	27.83 (0.60)	-19.18 (0.52)	-12.80 (0.65)
	SD	11.95	11.49	13.82	12.45
	Median	26.0	25.0	-18.0	-13.0
	Difference (95% CI)	NA		-6.4 (-8.1, -4.7)	
IGA=4 (severe)	n	195	94	195	94
	Mean (SE)	43.70 (1.07)	45.28 (1.56)	-29.34 (1.30)	-12.43 (1.96)
	SD	14.88	15.09	18.22	19.02
	Median	42.0	46.0	-29.0	-13.5
	Difference (95% CI)	NA		-16.9 (-21.5, -12.3)	

LOCF = The last observation carried forward. Baseline value was used if no post-Baseline data were available.

95% Confidence intervals are calculated using student t statistics.

Data Source: Section 5.3.5.3, SCE Table 7.2

Source: Applicant's ISE pg. 98-99

The only significant difference displayed in the above table is in the subgroup based on disease severity. The subjects with severe disease displayed a difference in change in inflammatory lesions counts vs vehicle of -16.9. This is substantially greater than shown in subjects of moderate severity which was -6.4. The confidence intervals for this comparison do not overlap.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant performed one dose-ranging trial in 296 subjects with PPR, #40027. This was a six arm, multicenter, randomized, Investigator-blind, and vehicle and active-controlled trial comparing ivermectin concentrations of 0.1% q day, 0.3% q day, and 1% q day and Bid which were tested versus its vehicle q day and versus metronidazole 0.75% cream Bid over 12 weeks. The inclusion criteria differed from the pivotal trials in that there was no requirement for a specific grade on the IGA. The main severity defining criteria for trial 40027 was a requirement for at least 15 inflammatory papules and at least mild erythema. The inflammatory papule requirement for the pivotal trials was 15-70.The efficacy endpoints for trial 40027 also differed from the pivotal trials and are presented below:

- Primary efficacy endpoint - percent change from baseline in inflammatory lesion counts at week 12
- Secondary efficacy endpoints
  - percent change in inflammatory lesion counts from baseline at interim time points
  - change from baseline at week 12 in either IGA1 or IGA2
  - success rate at week 12, defined as “clear” or “almost clear” for either IGA1 or IGA2
  - change in erythema and telangiectasia scores at week 12

I will focus on the primary efficacy endpoint, percent change from baseline in inflammatory lesion counts at week 12 and the single secondary efficacy endpoint success rate at week 12 in order to allow comparison with the results of the pivotal trials.

Table 17: Results for Success Rate and Percent Change in Inflammatory Lesions at Week 12 (LOCF, ITT) for Trial 40027

Endpoints	Ivermectin 1% Bid (N=48)	Ivermectin 1% QD (N=52)	Ivermectin 0.3% QD (N=47)	Ivermectin 0.1% QD (N=51)	Vehicle QD (N=50)	Metro 0.75%Bid (N=48)
IGA success	75% P value vs vehicle=0.021	71.2% P value vs vehicle=0.049	66% P value vs vehicle=0.161	66.7% P value vs vehicle=0.121	52%	64.6%
Percent change in Inflammatory Lesion Counts: Mean	69.2% P value vs vehicle=0.014	70% P value vs vehicle=0.006	67.5% P value vs vehicle=0.061	65.5% P value vs vehicle=0.158	46.5%	59.9%

Source: Reviewer’s Table

The above results are supportive of the efficacy of ivermectin 1% cream vs vehicle in subjects with PPR. Both ivermectin 1% QD and Bid were superior to vehicle in this population. Neither was superior to metronidazole. The percent change seen in this dose-ranging trial for ivermectin 1% was slightly higher than that seen in the pivotal trials (64.9% in 18170 and 65.7% in 18171).There was no statistically significant difference between Bid use and QD use for ivermectin 1% so based on these results the applicant opted for the QD regimen for phase 3. I agree with the applicants’ decision and that the dose-ranging trial supports the use of ivermectin 1% Q D as the regimen for the pivotal trials.

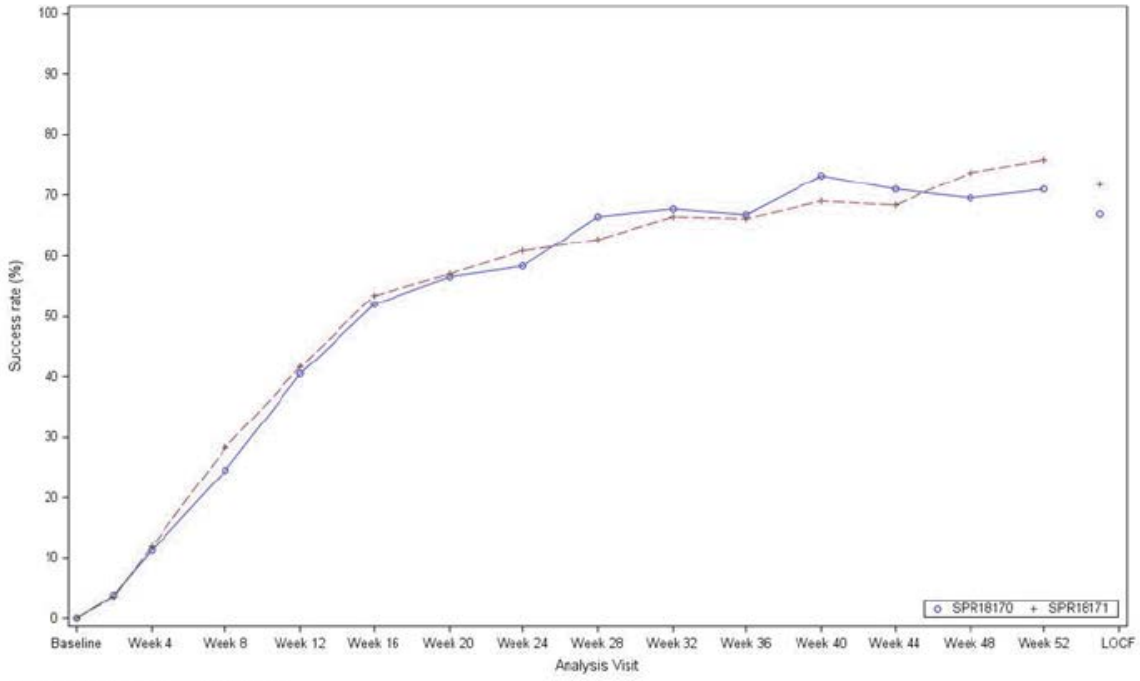
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The phase 3 trials that examined the efficacy of ivermectin 1% cream over an extended treatment regimen included Part B of the pivotal trials 18170 and 18171 (which were both 40 week active-controlled comparison vs azelaic acid).

Part B of Trials 18170 and 18171

Though Part B was destined primarily to assess safety, IGA's were performed to determine if treatment should be stopped (if subjects achieved 0= clear) or restarted (when subjects scored 1 or above). In Part B, the percentages of subjects who achieved an IGA score of 0 or 1 continued to increase up to Week 52 in both trials 18170 and 18171. This is depicted in the figure below.

Figure 3: Success Rate over time in Ivermectin randomized groups in Studies 18170 and 18171 (ITT Population)



Source: Applicant's ISE pg. 110

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6.1.10 Additional Efficacy Issues/Analyses

See statistics review for additional efficacy analyses.

7 Review of Safety

Safety Summary

The principal evaluation of safety with the final-to-be-marketed formulation occurred via the conduct of two pivotal trials, 18170 and 18171 which were conducted in North America. Supportive safety data is also available from 13 other sponsor-conducted trials. The safety information available for oral ivermectin (Stromectol) in the literature and from the approved labeling for both Stromectol and Sklice adds additional supportive data. Finally, investigations of other ivermectin formulations in clinical development have been reviewed for the safety database.

Information from the ivermectin 1% clinical development program includes 4000 subjects of whom 3547 had PPR. Of these, 1290 subjects with PPR were exposed to Ivermectin Cream 1% QD (the proposed dose for marketing) for at least 3 months, 771 subjects were exposed to Ivermectin 1% Cream QD for at least 6 months, and 250 were exposed to Ivermectin 1% Cream QD for 1 year or more.

The safety measurements were assessment of adverse events, laboratory evaluations, EKGs, assessment for local adverse events and dermal safety studies.

No deaths were seen in the ivermectin 1% cream development program. There were 111 serious adverse events (SAEs), 65 in the ivermectin arms but none were considered related by the investigators.

In the pooled safety population of “all comparative studies up to 16 weeks”, a total of 993 treatment emergent adverse events (TEAEs) were reported in 583 subjects (37.8%) in the ivermectin 1% group versus 488 TEAEs in 277 subjects (40.3%) in the vehicle group. The most common TEAEs reported in >1% of subjects in the 7 pooled studies in the ivermectin 1% group versus the vehicle group were nasopharyngitis (4.6% ivermectin 1% vs 4.8% vehicle), headache (2.5% ivermectin 1% vs 1.6 % vehicle), upper respiratory tract infection (1.6% ivermectin 1% vs 1.9% vehicle), influenza (1.2% ivermectin 1% vs 0% vehicle), sinusitis (1.2% ivermectin 1% vs 1.5% vehicle), and back pain (1.2% ivermectin 1% vs 4.8% vehicle). No signals were seen in the laboratory evaluation.

An early possible signal for decreased neutrophil counts (NCC) was seen in an open-label long term trial 40051 which was stopped early. Subsequent assessments of this issue were conducted including

- in vitro investigations into a possible effect of ivermectin 1% cream on neutrophils, including a preclinical assessment of neutrophil cell counts (NCC) across repeat-dose toxicity studies with ivermectin cream, and investigational in vitro experiments with ivermectin on neutrophils and neutrophil precursors

- an integrated safety analysis of NCC in completed trials (40051, 18120, 40027 and 40106) by the applicant
- DPV review of AERS database for signals regarding NCC for Stromectol

The phase 3 program was revised to allow for long term (over one year) assessment of NCC in the pivotal trials, initially placebo-controlled (first 16 weeks) followed by active controlled (versus azelaic acid) for a subsequent 40 weeks. None of these assessments revealed an impact on NCC by the ivermectin 1% cream.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 18: Table of Clinical Trials

Study #	Phase	Type	Design	Control	Popula-tion	Dose/ Duration	# of subjects
19055 Legacy 10/02-11/02	1	Cumulative irritancy (CI) - early formulation	SC (OUS), R, IB,	vehicle+ negative control (petrolatum)	HV	Q day/5 days per wk/ 3 wks	18
2894 Legacy 3/03-6/03	2a	Proof of Concept - early formulation	MC (9 sites OUS), R, IB, PG	vehicle + metronida-zole	PPR	Bid/ 9 wks planned, 25 days actual (mean)	60
19081 11/03-12/03	1	CI-different formulations	SC,R, IB,	vehicle+ negative control (petrolatum)	HV	Q day/5 days per wk/ 3 wks	19
40006 Legacy 9/04-12/04	2	safety + efficacy	MC (10 sites OUS), R,IB,PG	vehicle + metronida-zole	PPR	Bid/ 9 wks	147
40023 Legacy 10/05-12/05	1	RIPT – early formulation	SC,R, IB,	Vehicle + negative control (petrolatum)	HV	3 wks induction, 2 wks rest, 1 wk challenge	218
40007 Legacy	1	PK - early formulation,	SC, OL, Multi-	none	HV	Q day +Bid/	32

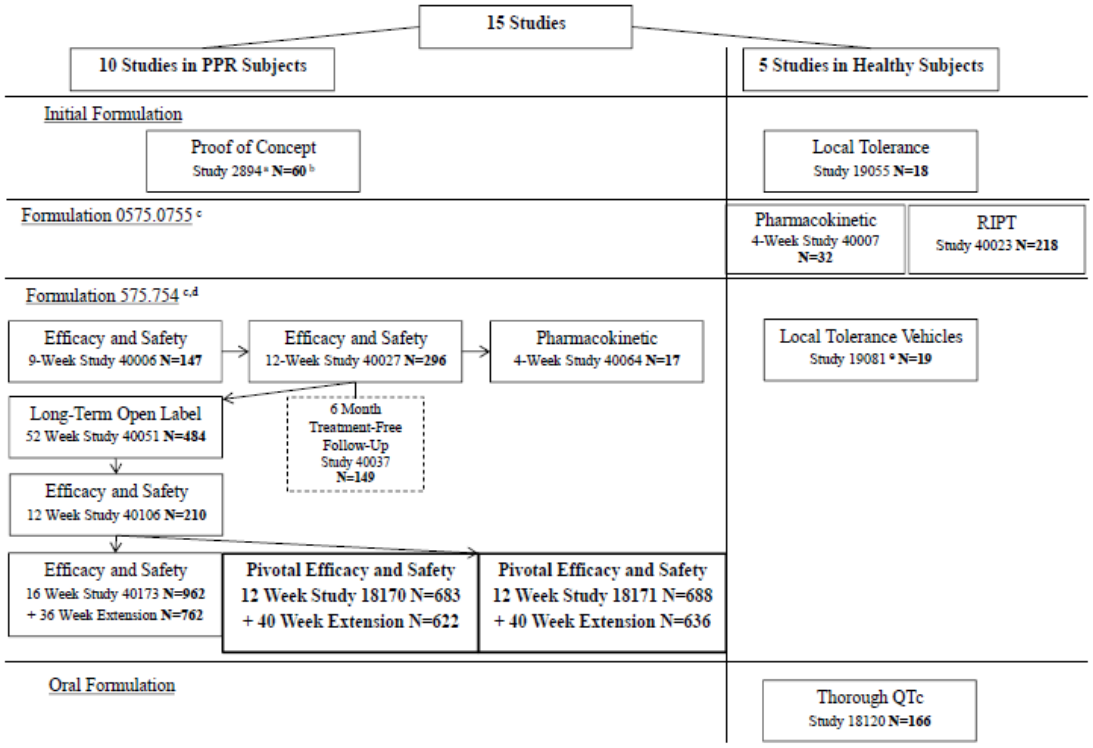
9/05-12/05		two concentra-tions	regimen			Grp 1: 1 day Grp 2/3: 4 wks	
40027 6/06-6/07	2	Dose-ranging-3 concentra-tions	MC (26 sites OUS), R, IB, PG	vehicle + metronida-zole	PRR	Q day +Bid/ 12 wks	296
40037 10/06-11/07	2	No Rx -fu for relapse eval	MC (25 sites OUS), E, IB	none	PPR	6 mos, Rx-free	149
18120 9/08-11/08	1	Thorough QTc	SC,DB, PG, single dose	oral placebo + positive control	HV	1 day	166
40064 8/08-12/08	2	PK + Safety - max use conditions	MC (5 sites OUS), OL, Single Rx	none	PPR	Q day/ 4 wks	17
40051 8/08-4/09	3	Long term safety + efficacy	MC (52 sites OUS), OL	none	PPR	Q day/52 wks planned, ≈5 mos actual	484 (Rx) 477 (fu)
40106 9/10-5/11	2	Neutropenia evaluation	MC (24 sites OUS), DB, R, VC, PG	vehicle	PRR	Q day/12 wks	210
18170 12/11-7/13	3	Efficacy + Long term safety	MC (50 sites OUS), R, DB, PG	Pt A-vehicle Pt B-azealic acid Pt C-none	PRR	Q day/ Pt A-12wks Pt B-40wks Pt C-4wks	Pt A-683 Pt B-622 Pt C-525
18171 12/11-8/13	3	Efficacy + Long term safety	MC (50 sites OUS), R, DB, PG	Pt A-vehicle Pt B-azealic acid Pt C-none	PRR	Q day/ Pt A-12wks Pt B-40wks Pt C-4wks	Pt A-688 Pt B-636 Pt C-512

40173 Part A 4/12-4/13 Part B 4/13-ongoing	3	European safety + efficacy	MC (64 sites OUS), R, IB, PG	Pt A-vehicle Pt B-metronida-zole	PRR	Q day/ Pt A-16 wks Pt B-28 wks	Pt A-902

Source: Reviewer's Table

Figure 4: Schematic of clinical studies for Ivermectin Cream

Figure 1 Schematic of clinical studies for Ivermectin Cream



N: Total number of subjects randomized/enrolled in the study
a Total paraben content is 0.24% (w/w) in Formulation 0575.0755 and 0.3% in Formulation 575.754.
b Formulation 575.754 is the To-Be-Marketed formulation.

Source: Applicant's Summary of Clinical Safety 2.7.4 Pg16

Subjects considered in the safety analyses had received at least one dose of study drug. Table #3 from the Applicant's Summary of Clinical Safety outlines which safety assessments were obtained in individual trials:

Table 19: Safety Assessments in Applicant Trials for Ivermectin 1% Cream in Subjects with Papulopustular Rosacea

Table 3 Safety assessments in Applicant studies for Ivermectin 1% Cream in subjects with papulopustular rosacea

Pooling group	Study #	Comment	AEs	Local Tolerance	Routine laboratory data		Vital Signs
					Hematology	Blood Chemistry	
Phase 3 pivotal studies	RD.06.SRE.18170 RD.06.SRE.18171	Part A only (12 weeks) Part A only (12 weeks)	Y Y	Y Y	Y Y	Y Y	Y Y
All Comparative studies up to 16 weeks	RD.06.SRE.18170 RD.06.SRE.18171 RD.06.SRE.40106 RD.03.SRE.2894 RD.03.SRE.40006 RD.03.SRE.40027 RD.03.SRE.40173	Part A only (12 weeks) Part A only (12 weeks) 12 weeks Treatment stopped before 9 weeks 9 weeks 12 weeks Part A only (16 weeks)	Y Y Y Y Y Y Y	Y Y N Y Y Y Y	Y Y Y N N Y Y	Y Y Y N N Y Y	Y Y Y N N Y Y
Long-term extension Phase 3 pivotal studies	RD.06.SRE.18170 RD.06.SRE.18171	Parts A&B&C (56 weeks)[a] Parts A&B&C (56 weeks)[a]	Y Y	Y Y	Y Y	Y Y	Y Y
Long-term Open Label studies	RD.03.SRE.40051	Treatment stopped before Week 52 (approximately around 12 weeks)	Y	Y	Y	Y	Y
Pharmacokinetic studies	RD.03.SRE.40064	4 weeks +4 weeks Follow-up	Y	Y	Y	Y	Y
Follow-up Treatment free study	RD.03.SRE.40037	6 Months treatment free	Y	N	N	N	N

a Part B is the active-controlled, 40-week extension of the pivotal studies – Part C is the following 4-week treatment-free period.
Data source: Section 5 of the Safety ISAP

Source: Applicant's Summary of Clinical Safety pg.26

Safety data from 15 clinical trials were submitted in the marketing application for Ivermectin Cream 1%. Five trials were conducted in 453 healthy subjects. Ten trials were conducted in 3547 subjects with papulopustular rosacea (PPR).

Secondary source data include literature reports and post marketing information (See Sections 7.2.6 and 7.6.2) for information regarding the safety of oral ivermectin used globally.

7.1.2 Categorization of Adverse Events

According to the applicant, the adverse events (AEs) were classified as treatment emergent adverse events (TEAEs) in the Summary of Clinical Safety (SCS) if the AE had an onset date greater than or equal to the first dose date of trial treatment, or if an event that occurred prior to randomization worsened during trial treatment. In some trials, AEs occurring the day of first use and coded within the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 system organ classes (SOCs) of "Investigations", "Blood and lymphatic system disorders", or "Hepatobiliary disorders" were not considered as TEAEs because the blood samplings and the physical

examinations were done before the time of first application. TEAEs were named “AEs” in most trials of the clinical program. The term “TEAE” was used in the Phase 3 trials 18170, 18171, and 40173.

According to the applicant, all AEs in the pooled database were coded or re-coded using MedDRA version 12.0. The MedDRA dictionaries used originally in databases of the individual studies are listed in Section 6.5.1 of the Safety ISAP. AEs were classified by MedDRA SOC and Preferred Term (PT). The adverse event categorization and the preferred terms used in the development program for Ivermectin Cream 1% appear satisfactory.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

At the Pre-NDA meeting on 6/12/13 the applicant was advised to “pool safety data for trials with the same dose and dosing regimen”. The applicant’s pre-specified pools of studies in subjects with PPR are presented in Table 1 from the Summary of Clinical Safety.

Table 20: Pooling of studies in subjects with papulopustular rosacea

Table 1 Pooling of studies in subjects with papulopustular rosacea

Pooling group	Comparators [a]	Study Number	Comment
Pivotal Phase 3 studies	Vehicle controlled	RD.06.SRE.18170 RD.06.SRE.18171	Initial 12-week treatment period (Part A) Initial 12-week treatment period (Part A)
All Comparative studies up to 16 weeks	Vehicle controlled	RD.06.SRE.18170 RD.06.SRE.18171 RD.06.SRE.40106	Initial 12-week treatment period (Part A) Initial 12-week treatment period (Part A) 12-week treatment
	Vehicle and Active controlled	RD.03.SRE.2894 RD.03.SRE.40006 RD.03.SRE.40027	Treatment was stopped before 9 weeks 9-week treatment 12-week treatment
	Active controlled	RD.03.SRE.40173	Initial 16-week treatment period (Part A)
Pharmacokinetic studies	Not Applicable	RD.03.SRE.40064	4 weeks + 4 weeks of follow-up
Long-term extension Phase 3 pivotal studies	Active controlled	RD.06.SRE.18170 RD.06.SRE.18171	40 weeks+4 weeks extension (Parts B&C) 40 weeks+4 weeks extension (Parts B&C)
Long-term open label studies	Not Applicable.	RD.03.SRE.40051	Treatment was stopped before Week 52 (approximately 12 weeks)
Follow-up Treatment-free study	Follow-up : Treatment-free	RD.03.SRE.40037	6-month treatment-free follow-up

a Active comparators are detailed in Table 2 of the Safety ISAP.

Source: Applicant’s Summary of Clinical Safety pg 24

According to the applicant, the rationale of the selected pooling strategy was to group trials by similarity of populations, length of treatment duration, and exposure. The different ivermectin groups were pooled according to dose and regimen. The vehicle groups were pooled and classified as “Vehicle”, irrespective of regimen, whereas active

comparators were kept separate. This reviewer has chosen the “all comparative studies up to 16 weeks” as the primary pooling group for in-depth analysis.

According to the applicant, the Safety Populations comprised enrolled subjects who applied the study medication(s) at least once. In the 10 trials performed in subjects with PPR, only 1 enrolled subject (in Study RD.03.SRE.2894) was excluded from the safety analysis because the subject did not apply study medication at least once.

According to the applicant, safety data from trials conducted in healthy subjects (trials 19055, 19081, 40007, 40023, and 18120) were analyzed individually, using data compiled for the respective Clinical Study Reports (CSRs). They were not pooled due to variability of trial designs (trial type, length of treatment, route of administration, formulation, and dosing regimen). No subjects were excluded from the safety analysis of trials performed in healthy subjects (trials 19055, 19081, 40007, 40023, and 18120).

The pooling strategy used in the development program for Ivermectin Cream 1% appears satisfactory.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety data from 15 clinical trials were submitted in the marketing application for Ivermectin Cream 1%. Five trials were conducted in 453 healthy subjects. Four of these trials in 287 subjects involved topical administration (2 cumulative irritancy # 19055 and 19081, 1 PK # 40007 and one repeat insult patch test # 40023) and one of the trials in 166 subjects involved oral administration (thorough QTc # 18120)]. Three of the topical trials in healthy volunteers, # 19055, 40007 and 40023 were conducted using earlier formulations of the investigational product.

Ten trials in 3547 subjects with papulopustular rosacea (PPR) were conducted. One of these trials, # 2894 was conducted using an earlier formulation of the investigational product. Eight trials were conducted using the to-be- marketed formulation and one was a treatment free (# 40037) extension of the dose-ranging trial 40027. Two pivotal phase 3 trials, #18170 and 18171 were conducted in 1371 subjects with PPR. A supportive active-controlled phase 3 trial was conducted in 962 subjects with PPR in Europe.

A total of 1290 subjects with PPR were exposed to Ivermectin 1% Cream QD for at least 3 months, 771 subjects were exposed to Ivermectin 1% Cream QD for at least 6 months, and 250 were exposed to Ivermectin 1% Cream QD for 1 year or more.

Adequacy of Clinical Exposure:

An adequate number of subjects were exposed to Ivermectin Cream at the proposed dosing regimen to assess safety for use.

Details for exposure in subjects with PPR can be found in the Tables below reproduced from the applicant's Summary of Clinical Safety:

Table 21: Number of Subjects Exposed, All Trials in Subjects with Papulopustular Rosacea

Table 6 Number of subjects exposed, all studies in subjects with papulopustular rosacea

	COMPARATIVE STUDIES[c]						OPEN-LABEL[c]	ALL STUDIES
STUDY ID	CD5024 >1%[a]	CD5024 1%	CD5024 <1%[b]	Vehicle	Azelaic Acid	Metronidazole	CD5024 1%	All
Total number of Subjects with Rosacea	116	1546	98	687	418	600	501	3546
RD.06.SPR.18170[d,e]	0 (0.0%)	452 (29.2%)	0 (0.0%)	231 (33.6%)	210 (50.2%)	0 (0.0%)	0 (0.0%)	683 (19.3%)
RD.06.SPR.18171[d,e]	0 (0.0%)	460 (29.8%)	0 (0.0%)	230 (33.5%)	208 (49.8%)	0 (0.0%)	0 (0.0%)	688 (19.4%)
RD.03.SPR.2894	19 (16.4%)	0 (0.0%)	0 (0.0%)	20 (2.9%)	0 (0.0%)	20 (3.3%)	0 (0.0%)	59 (1.7%)
RD.03.SPR.40006	49 (42.2%)	0 (0.0%)	0 (0.0%)	50 (7.3%)	0 (0.0%)	48 (8.0%)	0 (0.0%)	147 (4.1%)
RD.03.SPR.40027	48 (41.4%)	52 (3.4%)	98 (100.0%)	50 (7.3%)	0 (0.0%)	48 (8.0%)	0 (0.0%)	296 (8.3%)
RD.03.SPR.40051	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	484 (96.6%)	484 (13.6%)
RD.03.SPR.40064	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (3.4%)	17 (0.5%)
RD.06.SPR.40106	0 (0.0%)	104 (6.7%)	0 (0.0%)	106 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	210 (5.9%)
RD.03.SPR.40173	0 (0.0%)	478 (30.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	484 (80.7%)	0 (0.0%)	962 (27.1%)

a. CD5024 >1% corresponds to CD5024 1% BID
b. CD5024 <1% corresponds to CD5024 0.1% QD and 0.3% QD
c. Comparative studies are 18170, 18171, 40106, 2894, 40006, 40027, 40173 (Part A). Study 40037 is not included since this was a treatment-free study. Non comparative, open label studies are 40051 and 40064.
d. In Studies 18170 and 18171, due to study design (vehicle and azelaic acid were administered at two different periods), subjects were counted once in the 'All Studies' column
e. Medication dispensing errors occurred in 4 subjects in Studies 18170 and 18171; in the safety assessments, these subjects were analyzed according to the treatment actually received.
Data source: Module 5.3.5.3 SCS Table 1.1.

Source: Applicant's Summary of Clinical Safety pg. 39

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Table 22: Summary of Treatment Duration (Days) in Trials of Subjects with Papulopustular Rosacea

Table 8 Summary of treatment duration (days) in studies of subjects with papulopustular rosacea

		COMPARATIVE STUDIES[d,e]						OPEN-LABEL[d]
		CD5024 >1%[b]	CD5024 1%	CD5024 <1%[c]	Vehicle	Azelaic Acid	Metronidazole	CD5024 1%
Treatment duration in days[a]	N	116	1546	98	687	418	600	501
	Mean±STD	61.6±25.6	222.6±129.2	82.8±11.0	77.1±19.7	234.6±79.6	99.7±26.6	82.2±23.5
	Median	64.0	172.5	84.0	84.0	277.0	112.0	81.0
	Min~Max	2~92	1~413	14~91	1~131	1~302	1~134	4~196
Categories of duration	N	116	1546	98	687	418	600	501
	1-14 days	11 (9.5%)	25 (1.6%)	1 (1.0%)	25 (3.6%)	9 (2.2%)	10 (1.7%)	6 (1.2%)
	15-28 days	8 (6.9%)	18 (1.2%)	1 (1.0%)	16 (2.3%)	4 (1.0%)	18 (3.0%)	4 (0.8%)
	29-42 days	7 (6.0%)	13 (0.8%)	0 (0.0%)	15 (2.2%)	7 (1.7%)	12 (2.0%)	19 (3.8%)
	43-56 days	3 (2.6%)	11 (0.7%)	1 (1.0%)	14 (2.0%)	6 (1.4%)	7 (1.2%)	3 (0.6%)
	57-70 days	43 (37.1%)	14 (0.9%)	1 (1.0%)	53 (7.7%)	8 (1.9%)	49 (8.2%)	120 (24.0%)
	71-84 days	27 (23.3%)	117 (7.6%)	54 (55.1%)	385 (56.0%)	9 (2.2%)	29 (4.8%)	142 (28.3%)
	85-179 days	17 (14.7%)	577 (37.3%)	40 (40.8%)	179 (26.1%)	35 (8.4%)	475 (79.2%)	206 (41.1%)
	180-359 days	0 (0.0%)	252 (16.3%)	0 (0.0%)	0 (0.0%)	340 (81.3%)	0 (0.0%)	1 (0.2%)
	>359 days	0 (0.0%)	519 (33.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative duration								
	≥ 3 months (≥ 90 days)	6 (5.2%)	1290 (83.4%)	7 (7.1%)	48 (7.0%)	370 (88.5%)	462 (77.0%)	172 (34.3%)
	≥ 6 months (≥ 180 days)	0 (0.0%)	771 (49.9%)	0 (0.0%)	0 (0.0%)	340 (81.3%)	0 (0.0%)	1 (0.2%)
	≥ 1 Year (≥ 365 days)	0 (0.0%)	250 (16.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a. Treatment duration = Date of last use - Date of first use +1
b. CD5024 >1% corresponds to CD5024 1% BID
c. CD5024 <1% QD corresponds to CD5024 0.1% QD and 0.3% QD
d. Comparative studies are 18170, 18171, 40106, 2894, 40006, 40027, 40173 (Part A). Non comparative, open label studies are 40051, 40064.
e. Medication dispensing errors occurred in 4 subjects in Studies 18170 and 18171; in the safety assessments, these subjects were analyzed according to the treatment actually received.
Data source: Module 5.3.5.3 SCS Table 1.2

Source: Applicant's Summary of Clinical Safety, pg.44

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Topical Safety

Topical safety was adequately evaluated in the development program and included assessment for local adverse events and dermal safety studies. The number of subjects evaluated in the dermal safety studies was generally as recommended. The local tolerance program included 2 trials to assess cumulative irritancy potential (#19055 and #19081) and 1 trial to assess irritation and sensitization potential (# 40023). The photosensitivity and photoallergy trials were waived due to lack of absorption in the 290 to 700 nm range.

19055

In this trial, the cumulative irritancy potential of ivermectin 1% cream versus vehicle Cream (initial formulation 575.702) and white petrolatum was tested. Materials were applied under occlusive conditions (patches) on 3 separate zones on the upper back of each of 19 healthy subjects, QD for 21 days, 5 days per week (i.e., excluding Saturdays and Sundays, with Friday's patches kept in place until Monday).

Results of 19055

The mean cumulative irritation index (MCII) for ivermectin 1% cream was 0.13 ± 0.03, which was similar to vehicle cream (0.07 ± 0.02) and white petrolatum (0.12 ± 0.04). All 3 products had a low cumulative irritancy potential and none of the products were considered an irritant.

19081

In this trial, the cumulative irritancy potential of 2 vehicle prototypes developed to formulate ivermectin (a vehicle gel-cream formulation 575.214P and vehicle cream formulation 575.754P [vehicle for the to-be-marketed formulation]), versus the initial vehicle cream (575.702P) and white petrolatum were tested. Each test product was applied under occlusive conditions to the upper back of each of 19 healthy subjects QD, 5 days per week (every day except the weekend) for 3 consecutive weeks.

Results of 19081

The MCII for vehicle formulations 575.754P, 575.214P, and 575.702P were 0.151 ± 0.029, 0.148 ± 0.043, and 0.049 ± 0.016, respectively. The MCII for white petrolatum was 0.110 ± 0.028. All 4 products had a low cumulative irritancy potential and none of the products were considered an irritant, including the formulation to be used for the to-be-marketed product, 575.754P.

40023 (RIPT)

In this trial, the potential of repeated applications of 4 concentrations of ivermectin cream (0.03%, 0.1%, 0.3%, and 1%), vehicle cream (formulation 0575.0755P), and white petrolatum ointment (negative control) to induce irritation or sensitization to the skin of 218 healthy subjects with skin phototype I to IV on Fitzpatrick's scale were tested. The study consisted of an induction phase comprising two 48-hour applications and one 72-hour application for 3 weeks (9 applications) under occlusion, a rest period on Weeks 4 and 5, and a challenge phase on Week 6 comprising a single 48-hour application under occlusive conditions.

Results of 40023

Sensitization potential was evaluated at Day 3 and Day 5 of Week 6 for all subjects who remained in the study at that time (207 and 205 subjects, respectively). For all subjects in this study, the sensitization score was negative, regardless of the study product treatment.

It is notable that the RIPT was performed using a formulation with slightly less parabens than the to-be–marketed formulation 575.754 (methylparaben and propylparaben (0.16% w/w and 0.08% w/w, respectively in formulation 0575.0755 and 0.20% w/w and 0.10% w/w, respectively in formulation 575.754). The sponsor asked for a waiver from performing an additional RIPT due to the minimal differences between the 2 formulations and the low likelihood that there would be a difference in the allergenicity related to this difference. This reviewer agrees with the sponsor that an additional trial is not needed and supports the request for a waiver.

Systemic Safety

Systemic safety was adequately evaluated during the course of the development program through safety laboratory testing and assessment of adverse events. No clinically significant signals were identified.

Integrated Analysis

The primary safety population chosen for analysis by this reviewer included all subjects who were randomized and dispensed Ivermectin Cream 1% from “all comparative studies up to 16 Weeks”. This pooling group includes the first 12 weeks of trials 18170, 18171, 40106 and 40027, the first 9 weeks of trials 2894 and 40006 and the first 16 weeks of trial 40173. The first 12 weeks of trials 18170, 18171and 40106 were vehicle-controlled trials. Trials 2894, 40006 and 40027 were active-controlled (metronidazole Bid) and vehicle-controlled. Trial 40173 was active-controlled (metronidazole). All trials were once per day application except for trials 2894, and 40006 which were Bid application. Trial 40027 was the dose-ranging trial and included 3 concentrations of ivermectin Cream (0.1%, 0.3%and 1.0%) applied both once per day and Bid. I will also present analysis for the pooled pivotal phase 3 trials 18170 and 18171.

Demographics

The demographics for the safety population of “all comparative studies up to 16 weeks of treatment” are presented below:

Table 23: Demographic Data and Baseline Characteristics: All Comparative Studies up to 16 Weeks of Treatment

Table 16 Demographic data and Baseline characteristics: all comparative studies up to 16 weeks of treatment

		CD5024 >1%[a]	CD5024 1%	CD5024 <1%[b]	Vehicle	Metronidazole	All
Gender	N	116	1544	98	687	600	3045
	Male	35 (30.2%)	502 (32.5%)	38 (38.8%)	234 (34.1%)	206 (34.3%)	1015 (33.3%)
	Female	81 (69.8%)	1042 (67.5%)	60 (61.2%)	453 (65.9%)	394 (65.7%)	2030 (66.7%)
Race	N	116	1544	98	687	600	3045
	White	115 (99.1%)	1505 (97.5%)	98 (100.0%)	663 (96.5%)	599 (99.8%)	2980 (97.9%)
	Black or african american	0 (0.0%)	12 (0.8%)	0 (0.0%)	7 (1.0%)	1 (0.2%)	20 (0.7%)
	Asian	0 (0.0%)	16 (1.0%)	0 (0.0%)	9 (1.3%)	0 (0.0%)	25 (0.8%)
	Other	1 (0.9%)	11 (0.7%)	0 (0.0%)	8 (1.2%)	0 (0.0%)	20 (0.7%)
Ethnicity	N	116	1066	98	687	116	2083
	Hispanic/Latino	1 (0.9%)	112 (10.5%)	0 (0.0%)	54 (7.9%)	0 (0.0%)	167 (8.0%)
Skin Phototype	N	116	1440	98	581	600	2835
	I	8 (6.9%)	109 (7.6%)	10 (10.2%)	50 (8.6%)	22 (3.7%)	199 (7.0%)
	II	62 (53.4%)	667 (46.3%)	46 (46.9%)	245 (42.2%)	296 (49.3%)	1316 (46.4%)
	III	42 (36.2%)	497 (34.5%)	35 (35.7%)	202 (34.8%)	257 (42.8%)	1033 (36.4%)
	IV	4 (3.4%)	146 (10.1%)	7 (7.1%)	61 (10.5%)	24 (4.0%)	242 (8.5%)
	V	0 (0.0%)	20 (1.4%)	0 (0.0%)	18 (3.1%)	1 (0.2%)	39 (1.4%)
	VI	0 (0.0%)	1 (0.1%)	0 (0.0%)	5 (0.9%)	0 (0.0%)	6 (0.2%)
Age (in Years)	N	116	1544	98	687	600	3045
	18-64 Years	100 (86.2%)	1311 (84.9%)	73 (74.5%)	582 (84.7%)	491 (81.8%)	2557 (84.0%)
	≥ 65 Years	16 (13.8%)	233 (15.1%)	25 (25.5%)	105 (15.3%)	109 (18.2%)	488 (16.0%)
	Mean±STD	50.6±11.8	50.8±12.8	53.1±14.1	51.4±12.4	51.6±13.6	51.2±12.9
	Median	49.0	50.0	51.5	51.0	51.0	51.0
	Min~Max	27~91	18~89	20~84	18~86	18~90	18~91
Severity at Baseline (IGA)	N	116	1544	98	687	600	3045
	1 - Almost Clear	3 (2.6%)	0 (0.0%)	2 (2.0%)	2 (0.3%)	1 (0.2%)	8 (0.3%)
	2 - Mild	52 (44.8%)	20 (1.3%)	33 (33.7%)	50 (7.3%)	53 (8.8%)	208 (6.8%)
	3 - Moderate	55 (47.4%)	1222 (79.1%)	50 (51.0%)	507 (73.8%)	453 (75.5%)	2287 (75.1%)
	4 - Severe	6 (5.2%)	302 (19.6%)	13 (13.3%)	128 (18.6%)	93 (15.5%)	542 (17.8%)
Lesion Counts	N	116	1544	98	687	600	3045
	Mean±STD	27.4±28.5	32.7±14.4	33.0±17.9	31.8±18.1	31.0±14.5	32.0±16.2
	Median	20.0	28.0	28.0	27.0	28.0	28.0
	Min~Max	8~270	15~102	14~108	8~211	8~153	8~270

All Comparative studies up to 16 weeks are 18170 (Part A), 18171 (Part A), 40106, 2894, 40006, 40027, and 40173 (Part A).
Medication dispensing errors occurred in 4 subjects in Studies 18170 and 18171; in the safety assessments, these subjects were analyzed according to the treatment actually received.
a. CD5024 >1% corresponds to CD5024 1% BID
b. CD5024 <1% corresponds to CD5024 0.1% QD and 0.3% QD
Data source: Module 5.3.5.3, SCS Table 3.2.

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Source: Applicant's Summary of Clinical Safety pg.62

A majority of subjects for the safety population of "all comparative studies up to 16 weeks of treatment" were white (>97.9%) and female (66.7%). Subject ages ranged from 18 to 91 years. The mean and median age averaged 51 years old. Of the 2 age categories (18 - 64 and ≥ 65 years), the largest percentage of subjects (84%) were in the age range 18 - 64 years.

The demographics for the population in the pivotal trials 18170 and 18171 discussed in Section 6.1.2 were similar with 95.8% White and 67.5% female with a mean and median age of 50.

7.2.2 Explorations for Dose Response

The applicant conducted one dose-ranging trial #40027. This trial compared 3 doses of ivermectin cream once per day (0.1%, 0.3%, and 1%) and of ivermectin 1% cream BID versus vehicle cream and metronidazole 0.75% cream BID in 296 subjects with PPR over 12 weeks. Safety measurements included recording of AEs, of cutaneous signs and symptoms (e.g., dryness, desquamation, pruritus, stinging/burning) scored on a 4-

point scale (0 to 3) at each study visit, and vital signs at screening, baseline and week 12. Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) and physical examinations (PEs) were performed at screening and week 12.

Table 24: Summary of Adverse Events by Preferred Term (Safety Population) for Trial #40027

TABLE 87: Summary of Adverse Events Related to Study Drug by Preferred Term (Safety Population)

	Ivermectin 0.1% (n=51)	Ivermectin 0.3% (n=47)	Ivermectin 1% once (n=52)	Ivermectin 1% twice (n=48)	Metronidazole (n=48)	Placebo (n=50)
TOTAL NUMBER OF AEs	9	8	5	7	6	6
TOTAL NUMBER (%) OF SUBJECTS WITH AEs	5 (9.8)	6 (12.8)	3 (5.8)	7 (14.6)	4 (8.3)	5 (10.0)
Photosensitivity reaction	1 (2.0)	1 (2.1)	-	-	-	-
Rhinorrhoea	1 (2.0)	-	-	-	-	-
Rosacea	1 (2.0)	1 (2.1)	1 (1.9)	-	2 (4.2)	1 (2.0)
Skin discomfort	1 (2.0)	1 (2.1)	1 (1.9)	1 (2.1)	-	2 (4.0)
Skin exfoliation	1 (2.0)	-	-	-	-	-
Eye irritation	-	1 (2.1)	-	1 (2.1)	-	-
Lacrimation increased	-	1 (2.1)	-	-	-	-
Nasal congestion	-	1 (2.1)	-	-	-	-
Skin burning sensation	-	1 (2.1)	1 (1.9)	2 (4.2)	1 (2.1)	-
Skin irritation	-	1 (2.1)	-	1 (2.1)	1 (2.1)	-
Erythema	-	-	1 (1.9)	-	-	-
Pruritus	-	-	1 (1.9)	-	-	2 (4.0)
Flushing	-	-	-	2 (4.2)	-	-
Dysgeusia	-	-	-	-	1 (2.1)	-
Rash pustular	-	-	-	-	-	1 (2.0)

Adverse events are defined as events occurred after the first use of medication
A subject was counted once per preferred term even if more than one occurrence of the event was experienced

Source: Applicant's Study Report for #40027, pg 17.

There was no obvious dose-relationship with regard to the treatment related adverse events seen in the dose-ranging trial.

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical program was adequate to explore potential adverse reactions. See section 4.3, Nonclinical Pharmacology/Toxicology.

In addition to the usual nonclinical studies, investigations into a possible effect of ivermectin 1% cream on neutrophils were performed, including a preclinical assessment of neutrophil cell counts (NCC) across repeat-dose toxicity studies with ivermectin cream, and investigational in vitro experiments with ivermectin on neutrophils and neutrophil precursors.

7.2.4 Routine Clinical Testing

According to the applicant, laboratory data were collected in selected trials in healthy subjects (PK # 40007 and Thorough QT/QTc # 18120), and in all trials in subjects with PPR except proof of concept # 2894, exploratory efficacy and safety # 40006, and treatment-free follow-up # 40037. All instances of NCC <1.5 G/L were the subject of a specific assessment including retrospective analyses and in vitro investigations. See Section 7.3.5 Submission Specific Primary Safety Concerns for analysis of the neutrophil cell count data.

Clinical testing was adequate in methodology and scheduling.

7.2.5 Metabolic, Clearance, and Interaction Workup

According to the applicant, three (3) in vitro studies were conducted to address drug-drug interaction (DDI) potential for ivermectin 1% cream in clinical practice; Studies 31037, 31038, and 31039. In addition, 1 in vitro study was conducted to complete investigations regarding ivermectin metabolites, M1 and M2 (Study 4830). The applicant stated that the data supports CYP3A4 as the enzyme primarily responsible for the metabolism of [3H]-Ivermectin to 3 metabolites (C1<C2 □C3, based on intrins clearance). See the review by the clinical pharmacologist for further discussion of this topic.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Stromectol

Ivermectin is available orally under the brand name Stromectol. Labeled doses for the treatment of Onchocerciasis and Strongyloides are 150 and 200 ug/kg respectively. See Section 2.3 for details.

IND 57420

Merck has investigated the use of oral Stromectol for head lice under IND 57420. Details on these studies are presented below*:

Table 25: Merck (IND 57-420) Trials for Head Lice

Study	Design	Population	Regimen	AE
064	DB	Head lice (n =90) Children and adults 15 (2-5 yrs) 51 (6-12 yrs) 24 (>12 yrs)	200 mcg/kg for 1, 2 and 3 doses (d 1,4,8)	10 % (n= 9) Most common AEs-cough, abdl pain (in subject who passed intestinal parasites), rash 2 serious AEs 1) MVA on day 5 2) overdose of investigational agent – 3 tabs (≈440mcg/kg) given to child-no ill effects noted
065	DB	Head lice (n= 176) 42 (2-5 yrs) 92 (6-12 yrs) 42 (>12 yrs)	200 mcg/kg (d1, 4, 8) 400 mcg/kg (d 1 + 8) 400 mcg/kg (d1,4, 8)	AE queries done on days 2,4,5,8,9 and 15 22 %, (n=38) Most common AEs-sleeplessness, diarrhea, headache No SAEs

070	DB	Head lice (n = 166) Median age=10 yrs	200 mcg/kg (d 1,8) 400 mcg/kg (d 1, 8)	21.6% (n=36)) Most common AEs- headache, abdl pain, diarrhea, vomiting, pruritis, urticaria (3 of subjects with GI distress all in one household- ? viral) No SAEs
070	DB	OL Head lice	400 mcg/kg	

*Source: IND 57420, Vol 4.1

According to IND 57420 (Vol 4.1), a total of 315 children ages 2-12 years were treated with oral ivermectin during Merck's head lice program. The two serious adverse events seen were one MVA (most likely unrelated) and one case of ivermectin overdose that produced no side effects. The percentage of subjects with AEs ranged from 10-22% and many of the events were symptoms that could represent infections such as cough and GI distress. The study report archived in DARRTS did not contain enough detail to compare events in the treated group with events in the control group so it is not possible to determine causality. These results suggest a rather benign adverse event profile for oral treatment with two-three doses of oral Ivermectin 200-400 mcg/kg.

Relative to liver abnormalities: Merck reviewed its database in April of 2001 (200 million ivermectin exposures) and identified 12 reports of liver enzyme abnormalities or hepatic dysfunction, 8 of these were related to exposure to veterinary formulations. This does not indicate a significant problem with hepatotoxicity with approved use of oral ivermectin.

Published Literature

Labeled doses for the treatment of Onchocerciasis and Strongyloides are 150 and 200 ug/kg respectively. Doses between 150 and 400 ug/kg have been used in trials of scabies treatment and for head lice.

Table 26: Published Literature on Oral Ivermectin Use – Safety Analysis

Citation	Design/ Type	Population	Regimen	AE	Additional notes*
Alleman, Mary 2006 *Filaria Journal*	Review of Mectizan (ivermectin) Donation Program	2005: 62,201,310 Rxs for onchocerciasis 2005: 42,052,583 Rxs combined with a bendazole for filariasis	15-200 ug/kg	No specific assessments done	470 million Rxs total for onchocerciasis by end of 2005 120 million Rxs for filariasis by end of 2005
Brooks, PA 2002 *J. Paediatr. Child Health*	RCT, blinded	Children 6 mo-14 years Vanuatu (n =110)	200 ug/kg x 1 or 10 % Benzyl benzoate topically	More local AE in benzyl benzoate (p =.004), 3 ivermectin developed pustular disorders	No serious side effects Mean age ≈ 5 years
Brown, KR 1998 *Annals of trop med &*	Review of Changes in Use Profile of Mectizan	**Additional notes*** • Initially program excluded children under the age of 5 years, pregnant women, and mothers who were nursing children under the age of 3 months			

Parisit		• Accumulating evidence and new scientific information** led to inclusion of pregnant women living in areas where the risk of loss of sight because of onchocerciasis is very high; and women who are nursing children as young as 1 week of age. ** discovery of the presence of a protective blood-brain barrier protein component (P-glycoprotein) that helps to stop Mectizan from crossing the placenta and from crossing the blood-brain barrier in most animal species, including humans.			
Chouela 1999	DBRCT	Adults (n = 53)	150-200 ug/kg ivermectin + PCB vs. 1 % lindane + PCB	Mild and transient: 1 case each of hypotension, headache, abdominal pain and emesis	Unable to obtain original article for review
Chosidow, O 2010 *NEJM*	RCT	Adults and children (n=812, ages 2 yrs and up) Europe and Israel Median age=10 yrs	400ug/kg (n=398) vs 0.5% malathion lotion (n=414) on days 1 and 8	2 serious AE – one in each arm (both in 6-12 yr age group)- Ivermectin group-seizure on day6-focus found Malathion-severe headache-hospitalized overnight Also-in ivermectin -impetigo(2),N/V(1), gastroenteritis (3) Also-in malathion –rash (3), gastroenteritis (2)	
Colatrella, B 2008 *Annals of trop med & Parisit*	Retrospective on Mectizan (Ivermectin) Donation Program	530 million treatments administered for onchocerciasis since 1987 – one annual dose 1998 – expanded to include treatment of Filariasis – 160 million combined doses with albendazole			
Currie, MJ 2010 *Pediatric Derm*	CT	40 children 5-11 years	200ug/kg on days 1 and 7 vs topical of choice	No adverse events reported	AE telephone queries on days 7 and 14
Glaziou 1993	RCT	Adults and children (n= 44, ages 5-56) French Polynesia	100 ug/kg x 1 vs. 10 % benzyl benzoate x 2 (q 12 h)		Unable to obtain original article for review
Madan 2001	RCT	N = 200	200 ug/kg vs. 1 % topical lindane overnight	Headache	Unable to obtain original article for review
Usha, V 2000 *JAAD*	RCT	Adults and children ages 5 and above (n= 85) India	200 ug/kg x 1 vs. 5 % permethrin	No major side effects observed	

Open Label Trials

	Design/ Type	Population	AE's	Additional notes*
Bockarie MJ 2000	Case control (by village)	Adults and Children Papau New Guinea- 2 communities (31 tx, 60 control)	None	Unable to obtain original article for review
Conti 1999	OL	Adults and children, ages 5-84 n = 38 (Sao Paolo)	84 % tolerance	Unable to obtain original article for review
Dourm-ishev 1998	OL	Adults, n -19	Pruritus increased 24-72 h after tx in 7 patients	Unable to obtain original article for review
Elmogy 1999	OL	Adults n = 120 (Egypt)	AE- 11 % - drowsiness (4), arthralgia (2), dyspnea (3), HA (1), nausea (1), blurry vision (1)	Unable to obtain original article for review
Glaziou, P 1994 *Trop Med Parasitol*	OL	Children 5-17 yrs	200ug/kg single dose	No adverse events reported
Hegazy 1999	OL	Adults and Children (n =		Unable to obtain original article for review

		3147 Egypt)		
Heukelbach 2004 *Bull of WHO*	OL	Adults and Children over 5 yrs , n = 251 (Brazil)	200ug/kg on days 1 and 10	AEs reported in 9.4% - moderate to moderate, transient – abdominal discomfort,
Lawrence 2005 *Bull of WHO*	Case control (by Island)	Children over 15 kg, n = 541 (Solomon Islands) 160-250ug/kg on day 1 and 8	None	No adverse events reported
Muniirathinam, A 2009 *Int J of Derm*		Children ages 6-10 years, n=534 South India 4 arm trial- DEC vs DEC+ALB vs IVR+ DEC vs IVR+ALB vs	DEC - 6 mg/kg ALB – 400mg IVR – 200ug/kg	No discussion of adverse events
Nnoruka 2001	OL	13 children ages 5-14 (of total n = 58) Nigeria	Pruritus with BB	Unable to obtain original article for review
Saez de Ocariz 2002 *Clin + Exp Derm*	OL	18 children (ages 14 month to 17 yrs) 150-200ug/kg	Single dose-15 subjects 2nd dose on day 10 -3 subjects	1 case headache/ dizziness X 4 hours

*Additional Notes from my review of articles
Source: Reviewer's table #28 from clinical MO review for Sklice NDA 202736
Majority of material originally obtained from an internal agency document: Ivermectin Background Information -prepared by MFH in preparation for an internal meeting to discuss the advisability of a written request for oral ivermectin for the treatment of scabies. Additions to document to update by Reviewer

Discussion of Literature review

The articles by Alleman, Brown and Colatrella which document the findings of evaluation of the Mectizan (French Name for Stromectol) Donation Program provide reassuring details on the large number of subjects treated with oral Ivermectin. By 2008, 530 and 160 million people had been treated with oral Ivermectin for onchocerciasis and filariasis respectively. The loosening of restrictions on the program to include some pregnant women and children under age 5 reflect the overall benign adverse event profile seen in this program. The Brown article in addition references some reassuring scientific data regarding the "discovery of the presence of a protective blood-brain barrier protein component (P-glycoprotein) that helps to stop Mectizan from crossing the placenta and from crossing the blood-brain barrier in most animal species, including humans". No laboratory results were available from these studies (in the majority of cases they were not performed) but overall these articles lend support to the safety of ivermectin used orally even in children. This in turn lends support to the safety of a topical version of ivermectin that has been demonstrated to have low systemic bioavailability.

OSE evaluation

In March 2005 the Division of Drug Risk Evaluation conducted a review assessing the risk of seizures and hepatotoxic events associated with the use of oral ivermectin. Their search uncovered 10 unduplicated cases of seizures and 14 unduplicated cases of liver injury, where the majority indicated serious outcome events in reports from non-US sources. There were two cases suggesting a possible association between the use of ivermectin and the development of seizures in patients with no underlying or associated predisposing factors for convulsions.

In all of the 14 AERS cases describing liver toxicity subsequent to ivermectin use that were found there was a temporal association between dosing and the appearance of hepatic adverse events. In many of the cases there were concomitant or predisposing factors for liver disease which make it difficult to determine if the hepatic adverse event was solely due to the ingestion of ivermectin. All 14 cases listed a serious outcome, including two fatalities. The two deaths occurred in younger patients. The fatalities were listed as fulminant hepatitis in a 6-year old, and as associated with Stevens Johnson Syndrome complicated with sepsis and renal failure in a 14-year old.

In the conclusion the OSE reviewer states, “There were a few cases where the information provided did not suggest another plausible etiology for the events other than the use of ivermectin. Because there may be considerable under-reporting and because the serious nature of the adverse events, it may be prudent to update the postmarketing section of the label to include seizures and hepatotoxic events (elevation of liver enzymes, jaundice, hepatitis, and hepatomegaly).

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the 15 clinical studies performed as part of this clinical development program for ivermectin cream 1% for rosacea.

7.3.2 Nonfatal Serious Adverse Events

In total, 111 serious adverse events (SAEs) were reported during the 15 clinical trials in the clinical development program for Ivermectin Cream 1%. No SAEs were reported in healthy subjects. All SAEs were reported in 8 of the 10 studies performed in subjects with PPR. Of the 111 SAEs reported, none were considered by the investigators to be related to ivermectin cream. The 65 SAEs that occurred in subjects on ivermectin cream included abdominal pain (2 subjects), abortion spontaneous (1 subject), alcohol withdrawal syndrome (1 subject), anaphylactic reaction (1 subject presenting with a reaction to amoxicillin), angina pectoris (1 subject), aortic valve disease (1 subject), appendicitis (1 subject), atrial fibrillation (2 subjects), atrioventricular block complete (1 subject), B-cell lymphoma (1 subject), breast cancer (3 subjects), bunion (1 subject), cardiac failure (1 subject), cerebrovascular accident (1 subject), chest pain (2 subjects), cholecystitis (2 subjects), cholelithiasis (1 subject), chronic obstructive pulmonary disease (1 subject), circulatory collapse (1 subject), coronary artery disease (1 subject),

dehydration (1 subject), colonic obstruction (1 subject), dermatitis atopic (1 subject), depression (2 subjects), dysfunctional uterine bleeding (1 subject), esophageal adenocarcinoma (1 subject), esophageal reflux disease (1 subject), esophageal ulcer perforation (1 subject), fall (1 subject), femoral arterial stenosis (1 subject), forearm fracture (1 subject), gastroenteritis viral (1 subject), secondary glaucoma (1 subject), headache (2 subjects), hypertensive crisis (1 subject), influenza-like illness (1 subject), inguinal hernia (4 subjects), intervertebral disc protrusion (1 subject), intra-uterine death (1 subject), ligament rupture (1 subject), multiple sclerosis (1 subject), myocardial infarction (1 subject), myocardial ischemia (1 subject), nephrolithiasis (1 subject), neutrophil count decreased (1 subject), pneumonia (3 subjects), osteoarthritis (2 subjects), psoriatic arthropathy (1 subject), rash pustular (1 subject), sick sinus syndrome (1 subject), skin discomfort (1 subject), skin irritation (1 subject), sinusitis (2 subjects), spinal column stenosis (1 subject), squamous cell carcinoma of skin (1 subject), transitional cell carcinoma (1 subject), traumatic brain injury (1 subject), transient ischemic attack (1 subject), urethral stenosis (1 subject), vasculitis (1 subject), vertigo (1 subject), and whiplash injury (1 subject).

I have reviewed the case narratives for the 65 SAEs that occurred in subjects on ivermectin cream and I agree with the investigators that the above SAEs are unlikely to be related to the investigational product.

7.3.3 Dropouts and/or Discontinuations

The following table from the applicants Integrated Summary of Safety Tables displays the disposition of subjects in the primary safety population

Table 27: Reason for Discontinuation (All Comparative Studies up to 16 weeks)

2. Patient Disposition
Table 2.4 Reason for discontinuation (All Comparative studies up to 16 weeks)

		CD5024 >1%	CD5024 1%	CD5024 <1%	Vehicle	Metronidazole	All
Reason for discontinuation	N	116	1544	98	687	600	3045
	Completed	87 (75.0%)	1437 (93.1%)	94 (95.9%)	603 (87.8%)	547 (91.2%)	2768 (90.9%)
	Lack of Efficacy	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	4 (0.1%)
	Adverse Event	5 (4.3%)	22 (1.4%)	3 (3.1%)	13 (1.9%)	16 (2.7%)	59 (1.9%)
	Withdrawal by Subject	3 (2.6%)	50 (3.2%)	0 (0.0%)	26 (3.8%)	11 (1.8%)	90 (3.0%)
	Protocol Violation	1 (0.9%)	7 (0.5%)	1 (1.0%)	3 (0.4%)	2 (0.3%)	14 (0.5%)
	Lost to Follow-up	0 (0.0%)	18 (1.2%)	0 (0.0%)	17 (2.5%)	3 (0.5%)	38 (1.2%)
	Other	20 (17.2%)	4 (0.3%)	0 (0.0%)	23 (3.3%)	20 (3.3%)	67 (2.2%)
	Pregnancy	0 (0.0%)	4 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	5 (0.2%)

All Comparative studies up to 16 weeks are 18170(Part A), 18171(Part A), 40106, 2894, 40006, 40027, 40173(Part A).
Due to medication dispensing errors in Studies 18170 and 18171, subjects were analyzed according to the treatment actually received.
CD5024 >1% corresponds to CD5024 1% BID
CD5024 <1% corresponds to CD5024 0.1% QD and 0.3% QD

Source: Applicants Integrated Summary of Safety Tables

The majority of the subjects (90.9%) completed the trials. The most common reason for discontinuation for both the ivermectin 1% group (3.2%) and the vehicle group (3.8%) was withdrawal by subject. A small number of subjects discontinued due to adverse events and there was no obvious dose relationship displayed with 4.3% in the ivermectin 1% bid group, 1.4% in the ivermectin 1% group, 3.1% in the ivermectin <1% group and 1.9% in the vehicle group.

Of the subjects who were treated with ivermectin cream 1% in part A of trial 18170, seven subjects discontinued due to AEs. Six of these were in the SOC of Skin and Subcutaneous Tissue Disorders: dermatitis allergic, pain of skin, skin burning sensation (2 events), skin irritation (3 events), and flushing. There were 2 of these subjects where possible allergic contact dermatitis was suspected but both refused patch testing to confirm. The not skin-related AE leading to discontinuation was due to elevated LFTs at day 99. In this subject (8130-007) the LFTs were elevated at both the -2 week visit and at baseline and were not thought by the investigator to be related to ivermectin. I agree with this judgment.

Of the subjects who were treated with ivermectin cream 1% in part A of trial 18171, six subjects discontinued due to AEs. Only one of these events was in the SOC of Skin and Subcutaneous Tissue Disorders. Subject 8040-012 discontinued due to worsening rosacea and dry skin (See further discussion of this subject under section 7.3.4 Significant Adverse Events on pg 81 of this review). The not skin-related AEs leading to discontinuation included Basal Cell Ca, lymphoma, anemia (present at baseline), vertigo and memory loss. None of these not skin-related AEs were thought by the investigator to be related to ivermectin. I agree with this judgment.

7.3.4 Significant Adverse Events

The incidence of severe TEAEs in the SOC of Skin and Subcutaneous Tissue Disorders was identical in the groups of subjects exposed to ivermectin cream compared to subjects exposed to other treatments (vehicle cream, azelaic acid gel, or metronidazole cream). In the comparative studies up to 16 weeks of treatment, the incidence was 0.3% in the ivermectin 1% Cream QD group, 0.3% in the vehicle cream group, and 0.3% in the metronidazole 0.75% cream BID group.

Severe Adverse Events

No severe reactions occurred in trials 40064 and 2894.

I reviewed the narratives for all severe events that occurred in subjects with PPR on ivermectin cream. Below I have provided summarized narratives for those reactions I considered possibly relevant to the ivermectin 1% cream followed by my comments on whether the reactions effect the risk-benefit profile for the investigational product.

There were 15 severe reactions in the ivermectin 1% group in trial 40173. Three severe reactions in 2 subjects were evaluated in depth.

Subject No. 5635-006

Subject 5635-006, a 60-year-old White female with rosacea began treatment with ivermectin 1% cream on 24-Oct-2012. On 03-Nov-2012 (Treatment Day 11), the subject was reported to have a treatment-emergent AE of eczema on treated areas only. The study drug was applied over the whole face and there were unaffected areas in between the eczema areas. Study drug was temporarily discontinued and 9 applications were missed. Corrective treatment included triamcinolone acetonide/clotrimazole ointment 0.05/0.5 kg/L ointment twice daily (05-Nov-2012 to 14-Nov-2012)

After recovery, on 15-Nov2012, the investigator performed epicutaneous test according to the site procedure. The last test was assessed as negative and according to this result, the Investigator was confident to rule out an allergic reaction to the study drug.

On 19-Nov-2012 (Treatment Day 27), the study drug was restarted. From 19-Nov to 21-Nov-2012, small eczema reactions on a few areas occurred. The AE was considered by the Investigator to be severe in intensity and not related to the study drug. Such reactions were attributed to the discontinuation of the local steroid applications.

The subject discontinued from the study on 16-Jan-2013 due to subject request.

Reviewer's Comments

I do not agree with the investigator that the above described eczematous reaction was unrelated. Based on the timing and recurrence upon restarting the ivermectin cream I believe the reaction represents an irritant contact dermatitis to the product. The negative patch test makes an allergic reaction unlikely. Irritant contact dermatitis in some percentage of subjects treated with ivermectin is to be expected. Based on the local tolerability results in the majority of the trials it is not commonly seen.

Subject No. 5635-009

Subject 5635-009, a 44-year-old white female with rosacea began treatment with ivermectin 1% Cream on 27-Nov-2012. The subject's medical history included rosacea (since Jun-1997) and herpes (since 27-Apr-2009).

On 13-Dec-2012 (Treatment Day 17), the subject was reported to have a treatment-emergent AE of "worsening of herpes" (herpes virus infection) on non-treated areas only. Corrective treatment included acyclovir 400 mg tablet (14-Dec-2012 to 24-Dec-2012).

On 25-Dec-2012 (Treatment Day 29), the subject was reported to have a second treatment emergent AE of tooth infection. Corrective treatment included ibuprofen 400

mg tablet 4 times daily (25-Dec-2012 to 26-Dec-2012), septanest 1.7 mL injection once (26-Dec-2012), and clindamycin 150 mg tablet 4 times daily (29-Dec-2012 to 31-Dec-2012).

Both AEs were considered by the Investigator to be severe in intensity and not related to the study drug.

Reviewer's Comments

I agree with the investigator that HSV on an untreated area and a tooth infection are unlikely to be related to the ivermectin treatment.

There were 7 severe reactions in the ivermectin 1% group in trial 18170. One severe reaction was evaluated in depth.

Subject No. 8092-009

Subject 8092-009, a 51-year-old White female with rosacea began treatment with ivermectin 1% Cream on 04 Apr 2012. On 04 Apr 2012 (Treatment Day 1), the subject was reported to have the following 2 treatment emergent AEs located on treated areas: skin burning sensation and pruritus. Three days later, on 07 Apr 2012 (Treatment Day 4), the subject was reported to have the following treatment emergent AE located on treated areas: skin exfoliation (on the face), treated with menthol/ zinc oxide lotion twice daily from 07 to 22 Apr 2012. The subject continued to apply the menthol/ zinc oxide lotion daily (from 23 Apr 2012 to ongoing) as facial moisturizer prophylaxis.

All 3 AEs were considered by the Investigator to be severe in intensity, related to the study drug, and resolved on 22 Apr 2012 (Treatment Day 19). Study drug continued without interruption.

Reviewer's Comments

I agree with the investigator that the above severe dermatitis is likely to be related to the ivermectin treatment. Despite the severity of the reaction the subject was able to continue treatment without interruption. As previously noted, some incidence of irritant contact dermatitis in subjects treated with ivermectin is to be expected. Based on the local tolerability results in the majority of the trials it is not commonly seen.

There were 14 severe reactions in the ivermectin 1% group in trial 18171. Three severe reactions were evaluated in depth.

Subject No. 8353-018

Subject 8353-018, a 43-year-old White female with rosacea began treatment with ivermectin 1% Cream on 26 Jun 2012. On 28 Jun 2012 (Treatment Day 3), the subject

was reported to have a treatment-emergent AE of pruritus on treated areas only. Study drug was discontinued temporarily on 04 Jul 2012 and restarted 3 days later due to the AE of pruritus. The last study drug application occurred on 27 May 2013 and the subject completed the study as planned on 23 Jul 2013.

The AE of pruritus was considered by the Investigator to be severe in intensity, related to the study drug, and resolved on 04 Jul 2012

Reviewer's Comments

I agree with the investigator that the above pruritus was likely related to the ivermectin treatment. The pruritus did not recur with re-institution of the ivermectin and most likely represented a mild irritant reaction.

Subject No. 8360-014

Subject 8360-014, a 45-year-old Asian female with rosacea began treatment with ivermectin 1% Cream on 05 Apr 2012. During the study, the subject was reported to have 2 AEs due to an allergic reaction to dragon fruit (both moderate, not related, located on non-treated areas only): urticaria and pruritus both treated with diphenhydramine from 07 to 09 Jul 2012 and prednisone from 10 to 18 Jul 2012.

On 07 Jul 2012, the subject was reported to have a treatment-emergent AE of rash on non-treated areas only. The rash was of unknown etiology and occurred intermittently, without a confirmed time of day or night. The subject did not recall any contact with allergens. Corrective treatment included hydroxyzine 25 mg tablet as needed since 19 Sep 2012. Study drug was continued unchanged and the last study drug application occurred on 15 Nov 2012. The subject completed the study as planned on 26 Apr 2013.

The AE of rash was considered by the Investigator to be severe in intensity, not related to the study drug, and was ongoing at the time of reporting.

Reviewer's Comments

Though the narrative is confusing it appears the subject had a diagnosis of allergic reaction to dragon fruit that coincided with the timing of the "rash". She had also been receiving hydroxyzine PRN for several months prior to the "rash" AE suggesting intermittent allergies. I agree with the investigator that since the "rash" was a single episode despite continued therapy with ivermectin cream it is unlikely to be related to the investigational product.

Subject No. 8040-012

Subject 8040-012, a 38-year-old White female with rosacea began treatment with ivermectin 1% Cream on 31 May 2012. Concomitant treatment also included Nivea ☐ moisturizer since 2011 for dry skin prophylaxis.

On 07 Jun 2012 (Treatment Day 8), the subject was reported to have 2 treatment-emergent events, including an AE of "worsening rosacea" (rosacea) located on both treated and not treated areas, and an AESI of "facial dry skin" (dry skin) located on treated areas only. The study drug was discontinued permanently on 12 Jun 2012 (Treatment Day 13). The subject ended study participation the next day due to these 2 events.

The AE of rosacea was considered by the Investigator to be severe in intensity, not related to the study drug, and ongoing at the time of reporting.

Reviewer's Comments

I agree with the investigator that worsening of rosacea on treatment day 8 is unlikely due to the ivermectin cream. The AESI of "facial dry skin" was most likely related to the investigational product. The personal history of "dry skin" may have predisposed the subject to "dermatitis", either irritant or allergic.

There was one severe reaction in the ivermectin group in trial 40006 of pneumonia which was unlikely to be related to the investigational product.

There were 12 severe reactions in the ivermectin groups in dose-ranging trial 40027. Three severe reactions in one subject were evaluated in depth. The no treatment follow-up trial to 40027 was 40037. Four severe reactions occurred in trial 40037. None of these were evaluated by this reviewer as related to the investigational product.

Subject No. 9321-5553

Subject 9321-5553 began treatment with ivermectin cream 0.3% on Feb 1, 2007. On Feb 2, 2007 (day two) she complained of "watery eyes" that was rated severe in intensity accompanied by swelling of nasal mucosa initially rated as moderate that worsened to become severe. On Feb 22, 2007 she also complained of "burning of the eyes" rated severe that led to termination from the study on April 9, 2007.

Reviewer's Comments

I agree with the investigator that the above described symptoms of eye irritation are likely due to the ivermectin cream. This is the only subject who experienced this severity

of eye irritation in the development program. This symptom complex should be watched for in the post-marketing period as part of routine surveillance but based on the low incidence in the development program appears to be a rare event.

There were 3 severe reactions in the ivermectin group in trial 40106. One severe reaction was evaluated in depth.

Subject No. 5668-003

Subject 5668-003, a 62-year old Caucasian male, began applications of ivermectin 1% Cream on (b) (6). On (b) (6) (Day 15 of the study), about 2 weeks after commencing treatment, the subject presented with mild pink exanthema and pruritus on both arms, trunk, and both thighs. The subject had a history of rosacea (since Nov 2008), and lymphocytic vasculitis (since 15 Nov 2011). Concomitant medications included bethamethasone 5 g QD topically for lymphocytic vasculitis. On 11 Jan 2011, the subject received trimecain (also known as mesocain) 0.5 mL subcutaneously after analysis of a cutaneous biopsy indicating lymphocytic vasculitis with non-specific signs, possibly of allergic origin. On (b) (6) (Day 29), the subject was hospitalized by his dermatologist because of the presence of cutaneous lesions, especially on the upper extremities on the extensor side of the arms and on the lower extremities on the front and "distant" side. Lesions were bright red in the center, infiltrated, and associated with hyperpigmentation, burning sensation, and pruritus. Arthralgia of the shoulders (present for a considerable period of time) was also noted.

During hospitalization, the subject received parenteral steroids with gradual reduction in dose and switching to oral steroid and antihistamine therapy. Study drug was discontinued on (b) (6) due to concomitant use of prohibited medication. On (b) (6), the subject's status improved, erythema improved, and the subject was discharged from the hospital on (b) (6).

The Investigator considered the event of worsening of lymphocytic vasculitis as severe in intensity and not related to the study treatment.

Reviewer's Comments

I do not agree with the investigator that the above described worsening of lymphocytic vasculitis was unrelated to the ivermectin. Based on the timing of the onset of the worsening and resolution shortly after discontinuing the investigational product it is possible that the ivermectin cream caused an exacerbation. This is the only subject who experienced this adverse reaction in the development program. Drug-induced vasculitis should be watched for in the post-marketing period as part of routine surveillance but based on the low incidence in the development program it appears to be a rare event.

There were 11 severe reactions in the ivermectin group in trial 40051. None of these were thought by this reviewer to merit in depth evaluation.

7.3.5 Submission Specific Primary Safety Concerns

Neutropenia Issue

As previously noted in Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, the applicant's early clinical development program included a 52 week, open-label, uncontrolled long-term safety trial of once daily use of Ivermectin Cream 1%, trial RD.03.SRE.40051 which began on 8/06/2008. The trial was planned to enroll 424 subjects, however the trial was stopped early (at week 10) due to abnormal laboratory findings (namely, low neutrophil counts) in 3 out of 305 subjects who were enrolled in the trial.

In these three subjects, the neutrophil count decreased to below 1.5 Giga cell/L, which the applicant defined as an important threshold for detecting neutropenia. The values for these three subjects were .79 G/L, 1.06 G/L, and 1.23 G/L. The absence of a control arm did not allow for a comparative assessment to see if the findings observed would be representative of the patient population enrolled.

The applicant conducted a Phase 2 trial, Trial RD.03.SPR.40106, starting in September of 2010 to assess the hematological safety of once daily topical ivermectin cream 1%. The trial was performed in Europe. The trial was planned to randomize 200 subjects in a 1:1 fashion to either ivermectin 1% cream or vehicle cream. The FDA statistical review of the protocol for trial 40106 dated 3/17/11 (DDDP only received the trial information after the trial was completed) pointed to numerous flaws in the study design as outlined below:

> Trial 40106 is likely to provide limited information on the safety of ivermectin for the assessment of neutrophil counts. The following are reasons for such a determination.
>
> - The planned treatment duration of the trial is 12 weeks. With such a short term exposure to drug, this trial will not provide data on long term use of the ivermectin and its effects on neutrophil counts.
> - The trial enrollment is for 100 subjects per treatment arm. With a low incidence rate of neutrophil counts below 1.5 G/L (1% for active and an assumed incidence rate of 0.05% for the vehicle per the sponsor's protocol), the trial is not likely to observe many incidences of the safety parameter of interest. Correspondingly, the trial has power below 20% to detect a significant difference between the active and control.

The study report for trial 40106 and the applicant's evaluation of the results were submitted to the Agency as part of the meeting package for a Type B meeting scheduled for Aug 10, 2011. The applicant's evaluation of the results included the following information:

Hematological assessments were performed every two weeks during the month prior to randomization, during the 12-week treatment period, and four weeks after the study treatment discontinuation (i.e. at Week 16).

Four (4) treatment-emergent cases of mild to moderate Neutrophil Cell Count (NCC) values below the defined threshold for neutropenia occurred during the study: 3 in the ivermectin 1% group (2.9%) and 1 in the vehicle group (0.9%). The values were 0.96 G/L, 0.97 G/L, 1.42 G/L and 1.46 G/L.

All treatment-emergent NCC values below the threshold of 1.5 G/L occurred at a single sampling timepoint for each of these 4 subjects (three at week 6 and one at week 10). All of the values returned to normal during the course of the study. In one subject the ivermectin cream 1% was temporarily discontinued (as per protocol) until signs of infection (flu like symptoms) which had coincided with the decrease had resolved. The other three subjects continued treatment without interruption.

Three other subjects reported a total of 4 NCC cases ≤ 1.5G/L during the study:

- One subject, no. 5523-015 in the ivermectin 1 % cream treatment group had an NCC of 1.35 GIL before the first application of study drug, retests were performed and the subsequent retest values were 1.21G/L followed by 3.58 GIL. The subject then withdrew consent.
- Two additional subjects had NCC values once below 1.5G/L before the first application of study drug, and normal values at all post-treatment visits.

On May 20, 2010 an information request (IR) was sent to the applicant asking for a "summary of any additional safety monitoring to be incorporated in ongoing clinical trials" and "an examination of completed trials with an integrated safety analysis including the data on the decline in neutrophil counts among subjects in all studies".

The requested analysis was submitted in December of 2010. The following is a summary of the medical officer's review of this analysis dated April 1, 2011:

Table 28: RD.03.SRE.40051: Subjects with Neutrophil Counts Lower than 1.5 G/L during the Treatment Period

Table 1: RD.03.SRE.40051: Subjects with Neutrophil Counts Lower than 1.5 G/L during the Treatment Period

Subject Number	1st Dose Date	Last Dose Date	Baseline value X 10^9L	Lowest value X 10^9L	Final value X 10^9L	Age/ Sex Years/ M or F	Country
1919	09/30/2008	01/19/2009	2.46	1.06	2.12	35 F	DEU
2111	11/07/2008	01/18/2009	1.15	1.15	2.84	37 M	ISL
5138	10/20/2008	01/01/2009	5.89	1.01	2.69	66 M	HUN
2803	**10/27/2008**	**01/14/2009**	**2.85**	**0.79**	**2.62**	**57 M**	**BGR**
3006	10/23/2008	01/19/2009	1.44	1.44	1.77	34 M	FRA

Source: MO's RV by Melinda McCord dated 4/1/11 for IND 76064

Dr. McCord notes that "The incidence of neutropenia was 0.98 compared with an estimated incidence of neutropenia (below 1.5 G/L) in a population with similar demographics of 0.5% (Hsieh)".

With regard to the integrated analysis of previously completed trials, Dr. McCord noted that only 3 clinical trials in addition to trial 40051 collected data on neutrophil counts, trials 18120 (single dose QT/QTC trial in healthy volunteers), 40027 (12 week dose-ranging trial) and 40106 (ongoing at the time of the review).

In trial 18120, 56 subjects received a single oral dose of ivermectin 6 mg. Two days after treatment there was a decrease in neutrophil count in 48% of ivermectin subjects, 57% of placebo subjects and 76% of moxifloxacin subjects.

In trial 40027 48 subjects received ivermectin 1% Bid, 52 received 1% q day, 98 received either 0.1% or 0.3% q day, 48 received metronidazole 0.75% Bid and 50 received vehicle. A decrease of neutrophil count was observed at Week 12 in 55% (ivermectin 0.3% QD, ivermectin 1 % QD) to 58% (ivermectin 1 % BID) of the subjects. In the vehicle arm, 68% of the subjects had decreased neutrophil counts. In the metronidazole (0.75% BID) arm, 57% of the subjects had decreased neutrophil counts.

The applicant concluded that the decline in neutrophil counts was similar across studies with comparable changes in the control arms for 18120 and 40027. Dr. McCord concluded that "Although the preponderance of information does not indicate a safety signal, the clinical study initiated by the sponsor to evaluate the potential of ivermectin 1% to induce neutropenia in subjects with papulopustular rosacea is inadequate".

In an advice letter (AL) sent on April 20, 2011 DDDP made the following comments:

- Based upon the safety signal detected in Study 40051 and the limitations of the studies having been conducted to date, the proposed Phase 3 protocols should be modified to include periodic laboratory monitoring (including complete blood count with differential).
- You should propose a revised development plan that includes adequate assessment of the effect of ivermectin cream on neutrophil count. Such a study or studies should include long term exposure to ivermectin cream with an adequate control and be powered appropriately. You are encouraged to submit your proposed development plan to assess the safety of your product along with protocols for Agency review.

Based on the potential neutropenia signal, DDDP requested that the Division of Pharmacovigilance (DPV) to search the AERS database to evaluate whether there had been cases of abnormal neutrophil counts reported to the FDA associated with the use of oral ivermectin. DPV's review stated that "Based on the limitations of spontaneous post-marketing data, we cannot make any definitive conclusions regarding the safety of this product concerning abnormal neutrophil counts. However, at this time, there does not appear to be a post-marketing safety signal for abnormal neutrophil counts with oral ivermectin."

Based on the above advice letter, changes were made in the planned phase 3 program which included

- Adding a 40 week investigator-blinded extension comparing the long term safety of ivermectin cream 1% versus azelaic acid 15% gel. The applicant rolled over the placebo arm to azelaic acid in hopes of limiting drop-outs.
- Increasing the number of subjects enrolled into the ivermectin arm by changing the originally planned randomization of 1:1 to 2:1
- Increased lab monitoring, PEs and vital signs
- The creation of an Independent Data Monitoring Committee to periodically review neutrophil counts
- Assessing systemic exposure to ivermectin 1% cream at weeks 12, 32, 52 and 56 in 150 subjects
- Assessing PK in subjects with NCC < 1.5 G/L
- Addition of detailed instructions regarding management of low NCC as a function of value and presence or absence of clinical signs of infection
- Addition of confirmed neutropenia below 0.5 G/L as an SAE

With regard to the integrated analysis of the safety population (all comparative studies up to 16 weeks) and decreased NCC, the following table shows that the percentage of subjects reporting decreased NCC was the same (0.8%) when comparing the ivermectin 1% group with 1523 subjects, the vehicle group with 605 subjects and the metronidazole group with 516 subjects. There was one incident of low NCC in the 90

subjects (1.1%) in the low dose ivermectin group (ivermectin < 1%) and no incidents in the 43 subjects in the high dose (ivermectin 1% Bid) group.

Table 29: Neutrophil Cell Counts below 1.5 G/L (All Comparative Studies up to 16 weeks)

8.2.3 Neutrophil cell counts (All Comparative studies up to 16 weeks)
Table 8.2.3.2 Incidence of NCC values below 1.5G/L (All Comparative studies up to 16 weeks)

	CD5024 >1%	CD5024 1%	CD5024 <1%	Vehicle	Metronidazole
N at risk	43	1523	90	605	516
N<1.5 G/L	0 (0.0%)	12 (0.8%)	1 (1.1%)	5 (0.8%)	4 (0.8%)

Source: Applicant's Integrated Summary of Safety Tables, pg.1852

The pooled data for the pivotal phase 3 trials 18170 and 18171 and their long term extension are presented below

Table 30: Neutrophil Cell Counts below 1.5 G/L (Phase 3 Pivotal Trials - Part A)

8.1.3 Neutrophil cell counts (Phase 3 pivotal studies)
Table 8.1.3.3 Incidence of NCC values below 1.5G/L (Phase 3 pivotal studies)

	CD5024 1%	Vehicle
N at risk	903	455
N<1.5 G/L	4 (0.4%)	3 (0.7%)

Source: Applicant's Integrated Summary of Safety Tables, pg.1836.

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The incidence of decreased NCC was higher in the vehicle group than in the ivermectin 1% group for Part A of the pooled pivotal trials. In Part B, the long term active controlled extension portion of the pivotal trials, the incidence was again higher for the azelaic acid group (2.2%) then for the ivermectin 1% group (1.8%) as displayed below:

Table 31: Neutrophil Cell Counts below 1.5 G/L (Long Term Extension of the Phase 3 Trials)

8.3.3 Neutrophil cell counts (Long term extension of the Phase 3 pivotal studies)
Table 8.3.3.3 Incidence of NCC values below 1.5G/L (Long term extension of the Phase 3 pivotal studies)

		CD5024 1%	Azelaic Acid
Quarter #2	N at risk	830	414
	N<1.5 G/L	3 (0.4%)	4 (1.0%)
Quarter #3	N at risk	785	375
	N<1.5 G/L	7 (0.9%)	4 (1.1%)
Quarter #4	N at risk	743	354
	N<1.5 G/L	7 (0.9%)	4 (1.1%)
Overall	N at risk	831	414
	N<1.5 G/L	15 (1.8%)	9 (2.2%)

I reviewed the case narratives for all subjects with NCC below 1.5 G/L for all trials that assessed hematology values (40051, 40027, 40106, 18170 and 18171). A summary table of these subjects with pertinent details is presented below:

Table 32: Neutrophil Cell Counts below 1.5 G/L (Trials 40051, 40027, 40106, 18170 and 18171)

Subject /Trial #	Date 1st dose	Date last dose	Pre-Treatment Value (X $10^{9)*}$	Lowest Value (X $10^{9)*}$ Visit date/ day /Retest	Final Value (X $10^{9)*}$	Age Sex	AE/If Yes-Severity Related Outcome
5275-1919 40051	09/30/08	01/19/09	2.46	1.06 12/08/08 Day 70 Retest=2.62 on 01/07/09	2.12	35F	Not Reported as an AE
5301-2111 40051	11/07/08	01/18/09	1.15 Pre-Rx 11/05/08	1.15	2.84	37M	Not Reported as an AE
5532-5138 40051	10/20/08	01/01/09	5.89	1.23 12/29/08 Day 71 d/c'd trial Retest=1.01 01/05/09 Re retest=1.08 01/09/09	2.69	66M	Y Mild Not Related Recovered 02/02/09
5650-2803 40051	10/27/08	01/14/09	2.85	0.79 01/12/09 Day 78 Retest=1.9 on 01/20/09	2.62 d/c'd trial at subject request	57M	Y Moderate Related Recovered
5189-4919 40051	11/19/08	01/19/09	1.92	1.43 02/18/09 (one month past d/c Rx) 1.73 on 01/21/09 (Lowest value during Rx) Day 62	1.43 2/18/09 (one month past d/c Rx)	54F	Not Reported as an AE
5536-0207 40051	09/12/08	01/18/09	3.73	1.44 02/20/09 Day 162- 33 days post d/c Rx	2.5 1/25/09	45F	Y Mild Not Related Recovered 02/27/09

5140-3006 40051	10/23/08	01/19/09	1.44 Week-2 10/14/08	1.44 Pre-treatment	1.77	34M	Not Reported as an AE
5140-009 40106	11/10/10	03/03/11	2.24	0.96 12/23/10 Day 44-sample delayed shipment and cold temp exposed Drug inter due to flu with ↓NCC Retest=2.7 on 12/29/10	3.07	42F	Y Mild Not Related Recovered-6 dys
5532-003 40106	12/22/10	03/15/11	2.54	0.97 Day 71 Sample exposed to temp fluctuations Retest=2.03 2 dys later	2.77	58F	Y Mild Not Related Recovered-2 dys
5668-004 40106	12/27/10	03/23/11	3.45	1.42 2/07/11 Day 43 Retest=1.67 2 dys later	4.00	58F	Y Mild Not Related Recovered 2/21/11
5523-015 40106	12/01/10	12/5/10	1.35 12/01/10	1.21 Still pre-treatment 12/03/10 Retest=3.58 On 12/07/10 subject withdrew	3.58	72F	Y Not Related Recovered Withdrew Consent-never treated
5554-005 40106	12/27/10	04/20/11	1.37	1.37 12/27/10 Pre-treatment Retest=2.9 on 12/30/10	3.33	42M	Y Mild Not Related Recovered-2 dys
8005-001	04/27/12	03/31/13	1.8	1.4 05/27/12	2.2	49F	Y- Mild

18170				Day 27 Retest=1.86 on **/**/** ? dys later			Related (IDMC-not related) Recovered
8077-001 18170	05/16/12	02/04/13	5.9	1.3 01/07/13 Week 32 2^0 to chemo for bladder CA d/c'd from trial	1.5	59M	NCC not an AE, Bladder CA-yes
8005-018 18170	05/08/12	08/27/12	3.2	1.2 11/12/12 Day 190 Retest=1.7 on 11/14/12	3.8	61F	Y-Moderate Not related Recovered
8094-011 18170	05/10/12	05/08/13	2.3	1.4 06/05/12 Day 27 Drug inter-cold symptoms Retest=1.7 on 06/8/12 1.4 on 02/14/13 Retest=2.1 on 0314/13	1.9	43 AAF **	Y Mild Not related Recovered
8327-014 18170	04/11/12	04/16/13	2.0	1.2 07/25/12 Day 106 Retest=2.3 on 07/27/12	2.6	54F	Y Moderate Not Related Recovered
8195-026 18170	06/19/12	06/18/13	2.7	1.3 01/29/13 Day 225 Retest=2.1 on 02/04/13	2.6	27F	Y Mild Unlikely Related Recovered
8214-027 18170	06/04/12	04/08/13	2.6	0.6 02/11/13 Day 253 Specimen exposed to cold temps Retest=5.8 on 02/14/13	3.1	58M	Not reported as an AE
8340-	06/04/12	06/02/13	4.6	1.3	3.8	46F	Not reported

014 18170				03/13/13 Day 283 Retest=2.0 on 03/15/13			as an AE
8354-014 18170	05/24/12	05/21/13	2.5	1.2 03/04/13 Day 285 Cold symptoms and treatment Retest=2.5 on 03/07/13	2.4	50F	Not reported as an AE
8373-010 18170	06/11/12	05/27/13	2.3 Week-2 1.7 Week-1 3.9 baseline	1.3 10/01/12 Day 113 Retest=1.8 on 10/03/12 NCC< 1.5 at weeks 32, 36,44,48 and 52	2.1	39F	Not reported as an AE
8038-004 18171	05/09/12	05/15/13	2.1	0.9 01/23/13 Day 260 URI symptoms Drug inter Retest=1.9 on 01/25/13	3.2	37F	Y Mild Not Related Recovered
8069-004 18171	04/16/12	05/08/13	1.9	1.3 02/20/13 Day 311 URI symptoms Drug Inter Retest=0.6 on 02/22/13 Retest=1.8 on 02/25/13	2.5	57F	Y Moderate Not related Recovered
8137-014 18171	04/02/12	04/29/13	2.1	1.4 04/03/13 Day 367 Between 1.3-1.6 04/04 – 04/15/13 Retest=3.5 on	3.5	51F	Y Mild Unlikely Related Recovered 04/29/13

				04/29/13			
8110-026 18171	05/09/12	05/07/13	2.3	1.4 09/25/12 HSV on ear Day 140 Drug inter Retest=1.6 on 10/02/12	2.2	54M	Not reported as an AE
8133-016 18171	04/04/12	04/02/13	2.6	1.1 04/03/13 Day 365 Retest=1.0 on 04/18/13 Retest=2.4 on 04/24/13	2.4	62M	Not reported as an AE
8213-025 18171	05/21/12	12/17/12	2.1	1.4 11/05/12 Day 169 Retest=2.1 on 11/07/12	1.8	57F	Not reported as an AE h/o off/on neutropenia since 2001
8213-028 18171	06/20/12	09/11/12	2.1	1.4 08/15/12 Day 57 Retest=1.5 on 08/30/12	2.1	78F	Not reported as an AE
5375-9400 40027	01/04/07	03/27/07	3.1	1.3 Week 12 Day 83 Final day of trial-lab not repeated	1.3	38F	Not reported as an AE
5554-9232 40027	02/01/07	04/26/07	1.6	1.4 Week 12 Day 85 Final day of trial-lab not repeated	1.4	46F	Not reported as an AE

*normal range trial 40106 (2.1 - 6.9 G/L) *normal range trial 40027 (1.9 – 7.50 G/L) *normal range trial 40051 (1.8 – 7.0 G/L) *normal range trial 18170 + 18171 (1.5 – 7.7 G/L)
**AAF=African American Female
Source: Reviewer's Table

The majority of cases of decreased NCC below 1.5 were asymptomatic and reverted to the normal range on repeat blood work. There were a few cases of persistent low NCCs. One subject 8373-010 had repeated low counts but this subject also had

recorded borderline to low counts during the pre-treatment period and never developed any symptoms of infection. This may represent a subject who tends to run low under normal circumstances. Another subject 5532-5138 was discontinued from the trial but persisted with low NCC for almost a month off treatment.

It is not possible to rule out the ivermectin 1% cream as a contributing factor in these cases. However, the majority of subjects did not evidence any issues with NCC at the to be marketed dose despite long term monitoring of blood counts in the 40 week follow-up (Part B) of the pivotal trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the 7 comparative studies (up to 16 weeks) that were pooled for the primary safety population, a total of 993 treatment emergent adverse events (TEAEs) were reported in 583 subjects (37.8%) in the ivermectin 1% group versus 488 TEAEs in 277 subjects (40.3%) in the vehicle group . The most common TEAEs reported in >1% of subjects in the 7 pooled studies in the ivermectin 1% group versus the vehicle group were nasopharyngitis (4.6% ivermectin 1% vs 4.8% vehicle), headache (2.5% ivermectin 1% vs 1.6 % vehicle), upper respiratory tract infection (1.6% ivermectin 1% vs 1.9% vehicle), influenza (1.2% ivermectin 1% vs 0% vehicle), sinusitis (1.2% ivermectin 1% vs 1.5% vehicle), and back pain (1.2% ivermectin 1% vs 4.8% vehicle).

Table 33: Incidence of Treatment Emergent Adverse Events by System Organ Class and by Preferred Term for All Comparative Studies up to 16 weeks of Treatment Occurring at ≥0.5% Frequency in the Ivermectin 1% Cream QD Group, Safety Population

System Organ Class	Preferred Term	CD5024 >1% (N=116)	CD5024 1% (N=1544)	CD5024 <1% (N=98)	Vehicle (N=687)	Metronidazole (N=600)
TOTAL NUMBER OF AEs	-	71	993	75	488	312
TOTAL NUMBER OF SUBJECTS WITH AEs, n (%)	-	46 (39.7)	583 (37.8)	44 (44.9)	277 (40.3)	190 (31.7)
Blood and lymphatic system disorders, n (%)	ALL	0	19 (1.2)	0	8 (1.2)	5 (0.8)
	Neutropenia	0	8 (0.5)	0	3 (0.4)	3 (0.5)
Gastrointestinal disorders, n (%)	ALL	8 (6.9)	62 (4.0)	3 (3.1)	31 (4.5)	13 (2.2)
	Diarrhoea	0	15 (1.0)	1 (1.0)	5 (0.7)	3 (0.5)
	Abdominal pain	1 (0.9)	7 (0.5)	0	2 (0.3)	2 (0.3)
Immune system disorders, n (%)	ALL	3 (2.6)	16 (1.0)	1 (1.0)	4 (0.6)	3 (0.5)
	Seasonal allergy	2 (1.7)	12 (0.8)	0	4 (0.6)	2 (0.3)
Infections and infestations, n (%)	ALL	17 (14.7)	241 (15.6)	23 (23.5)	124 (18.0)	84 (14.0)
	Nasopharyngitis	7 (6.0)	71 (4.6)	10 (10.2)	33 (4.8)	32 (5.3)
	Upper respiratory tract infection	0	24 (1.6)	0	13 (1.9)	4 (0.7)
	Influenza	0	19 (1.2)	2 (2.0)	5 (0.7)	10 (1.7)
	Sinusitis	0	19 (1.2)	0	10 (1.5)	2 (0.3)
	Urinary tract infection	1 (0.9)	15 (1.0)	0	6 (0.9)	2 (0.3)
	Bronchitis	0	13 (0.8)	0	5 (0.7)	5 (0.8)
	Pharyngitis	1 (0.9)	11 (0.7)	3 (3.1)	5 (0.7)	5 (0.8)
	Oral herpes	2 (1.7)	10 (0.6)	2 (2.0)	8 (1.2)	7 (1.2)
	Rhinitis	1 (0.9)	9 (0.6)	1 (1.0)	6 (0.9)	3 (0.5)
Injury, poisoning and procedural complications, n (%)	ALL	3 (2.6)	58 (3.8)	1 (1.0)	26 (3.8)	6 (1.0)
	Muscle strain	0	10 (0.6)	0	1 (0.1)	0
Investigations, n (%)	ALL	1 (0.9)	22 (1.4)	3 (3.1)	11 (1.6)	3 (0.5)
	C-reactive protein increased	0	7 (0.5)	0	4 (0.6)	0
Musculoskeletal and connective tissue disorders, n (%)	ALL	1 (0.9)	66 (4.3)	3 (3.1)	23 (3.3)	20 (3.3)
	Back pain	1 (0.9)	18 (1.2)	2 (2.0)	6 (0.9)	4 (0.7)
	Pain in extremity	0	8 (0.5)	0	1 (0.1)	0
	Arthralgia	0	7 (0.5)	0	6 (0.9)	6 (1.0)
Nervous system disorders, n (%)	ALL	4 (3.4)	60 (3.9)	6 (6.1)	26 (3.8)	18 (3.0)
	Headache	3 (2.6)	38 (2.5)	4 (4.1)	11 (1.6)	13 (2.2)
Psychiatric disorders, n (%)	ALL	0	19 (1.2)	0	6 (0.9)	7 (1.2)
	Depression	0	8 (0.5)	0	2 0.3)	2 (0.3)
Respiratory, thoracic and mediastinal disorders, n (%)	ALL	2 (1.7)	48 (3.1)	4 (4.1)	15 (2.2)	10 (1.7)
	Cough	0	11 (0.7)	0	2 (0.3)	3 (0.5)
	Oropharyngeal pain	1 (0.9)	11 (0.7)	1 (1.0)	4 (0.6)	2 (0.3)
Skin and subcutaneous tissue disorders, n (%)	ALL	12 (10.3)	101 (6.5)	15 (15.3)	73 (10.6)	27 (4.5)
	Skin irritation	3 (2.6)	14 (0.9)	1 (1.0)	12 (1.7)	5 (0.8)
	Skin burning sensation	2 (1.7)	12 (0.8)	1 (1.0)	11 (1.6)	1 (0.2)
	Erythema	0	11 (0.7)	1 (1.0)	7 (1.0)	2 (0.3)
	Pruritus	0	11 (0.7)	1 (1.0)	9 (1.3)	6 (1.0)
	Rosacea	0	11 (0.7)	2 (2.0)	9 (1.3)	7 (1.2)
	Dry skin	0	7 (0.5)	0	5 (0.7)	1 (0.2)
Vascular disorders, n (%)	ALL	3(2.6)	16 (1.0)	1 (1.0)	12 (1.7)	4 (0.7)
	Hypertension	0	13 (0.8)	0	9 (1.3)	4 (0.7)

Adverse events were defined as events that occurred on the day of the first use of medication or after, with exception of adverse events occurring the same day of first use and coded within "Investigation" or "Blood and lymphatic disorder" or "Hepatobiliary disorders".
Note: The numbers in the columns cannot be added because a given subject could report more than one AE.
CD5024 >1% corresponds to CD5024 1% BID
CD5024 <1% corresponds to CD5024 0.1% QD and 0.3% QD
All Comparative studies up to 16 weeks are 18170 (Part A), 18171 (Part A), 40106, 2894, 40006, 40027, 40173 (Part A).
Medication dispensing errors occurred in 4 subjects in Studies 18170 and 18171; in the safety assessments, these subjects were analyzed according to the treatment actually received.
Data source: Module 5.3.5.3, SCS Table 6.2.4.

Source: Applicant's Summary of Clinical Safety pg. 94-95

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The most common related TEAEs reported in ≥ 0.5% of subjects in the 7 pooled studies in the ivermectin 1% group versus the vehicle group were all in the SOC of Skin and Subcutaneous Tissue Disorders: skin burning sensation (0.8% ivermectin 1% vs 1.6 % vehicle), skin irritation (0.9% ivermectin 1% vs 1.7% vehicle), erythema (0.7% ivermectin 1% vs 1.0% vehicle), and pruritus (0.7% ivermectin 1% vs 1.3% vehicle). It is notable that all of the related TEAEs occurred more commonly in the vehicle group than in the ivermectin 1% group. The applicant speculates that this may reflect the anti-inflammatory nature of ivermectin 1% cream. It certainly argues against any significant irritant effect of the active moiety in the majority of subjects.

In the pooled pivotal trials 18170 and 18171 (up to 12 weeks treatment ie Part A) there were 589 TEAEs in 350 subjects (38.5%) in the ivermectin 1% group and 312 TEAEs in 175 subjects (38.0%) in the Vehicle Cream QD group. Of these 3.4% were considered related in the Ivermectin 1% Cream QD group, which was less than in the Vehicle Cream QD group (45 TEAEs in 33 subjects [7.2%]). The table below from the applicant's Summary of Clinical Safety displays the TEAEs by system organ class (SOC) and by preferred term (PT) occurring in ≥ 0.5%

Table 34: Incidence of Treatment Emergent Adverse Events by System Organ Class and by Preferred Term for Phase 3 Pivotal Studies (Part A) Occurring at ≥ 0.5% Frequency in the Ivermectin 1% Cream QD group, Safety Population

System Organ Class	Preferred Term	CD5024 1% (N=910)	Vehicle (N=461)
TOTAL NUMBER OF AEs	-	589	312
TOTAL NUMBER OF SUBJECTS WITH AEs, n (%)	-	350 (38.5)	175 (38.0)
Gastrointestinal disorders, n (%)	ALL	39 (4.3)	22 (4.8)
	Diarrhoea	7 (0.8)	4 (0.9)
	Toothache	5 (0.5)	0
Immune system disorders, n (%)	ALL	14 (1.5)	4 (0.9)
	Seasonal allergy	12 (1.3)	4 (0.9)
Infections and infestations, n (%)	ALL	113 (12.4)	62 (13.4)
	Nasopharyngitis	22 (2.4)	12 (2.6)
	Upper respiratory tract infection	18 (2.0)	10 (2.2)
	Sinusitis	14 (1.5)	7 (1.5)
	Urinary tract infection	14 (1.5)	3 (0.7)
	Ear infection	6 (0.7)	4 (0.9)
	Influenza	6 (0.7)	1 (0.2)
	Bronchitis	5 (0.5)	4 (0.9)
Injury, poisoning and procedural complications, n (%)	ALL	50 (5.5)	24 (5.2)
	Muscle strain	10 (1.1)	1 (0.2)
	Procedural pain	5 (0.5)	5 (1.1)
Investigations, n (%)	ALL	18 (2.0)	11 (2.4)
	C-reactive protein increased	6 (0.7)	4 (0.9)
Musculoskeletal and connective tissue disorders, n (%)	ALL	39 (4.3)	15 (3.3)
	Back pain	9 (1.0)	1 (0.2)
	Pain in extremity	7 (0.8)	0
	Arthralgia	6 (0.7)	5 (1.1)
Nervous system disorders, n (%)	ALL	38 (4.2)	15 (3.3)
	Headache	22 (2.4)	7 (1.5)
Psychiatric disorders, n (%)	ALL	15 (1.6)	3 (0.7)
	Depression	6 (0.7)	0
	Insomnia	5 (0.5)	0
Respiratory, thoracic and mediastinal disorders, n (%)	ALL	28 (3.1)	8 (1.7)
	Cough	6 (0.7)	0
	Oropharyngeal pain	6 (0.7)	2 (0.4)
Skin and subcutaneous tissue disorders, n (%)	ALL	62 (6.8)	49 (10.6)
	Skin burning sensation	9 (1.0)	10 (2.2)
	Skin irritation	8 (0.9)	11 (2.4)
	Pruritus	7 (0.8)	5 (1.1)
	Dermatitis contact	5 (0.5)	4 (0.9)
	Dry skin	5 (0.5)	3 (0.7)
Vascular disorders, n (%)	ALL	6 (0.7)	7 (1.5)
	Hypertension	5 (0.5)	6 (1.3)

Adverse events were defined as events that occurred on the day of the first use of medication or after, with exception of adverse events occurring the same day of first use and coded within "Investigation" or "Blood and lymphatic disorder" or "Hepatobiliary disorders."

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. Medication dispensing errors occurred in 4 subjects in Studies 18170 and 18171; in the safety assessments, these subjects were analyzed according to the treatment actually received.

Data source: Module 5.3.5.3, SCS Table 6.1.4.

Source: Applicant's Summary of Clinical Safety pg. 104

Reference ID: 3644887

The highlighted terms are those for which the ivermectin 1% group exceeds the vehicle group. None of the highlighted terms seem likely to be related to the investigational product. In fact, in the systems of most concern, the skin and subcutaneous disorders SOC, the vehicle group has a higher incidence of skin burning sensation, skin irritation, pruritus, contact dermatitis and dry skin. As previously noted above, this was also seen when looking at the pooled "all comparative studies up to 16 weeks" group.

7.4.2 Laboratory Findings

Laboratory data were collected in all trials in subjects with PPR except proof of concept trial 2894, exploratory efficacy and safety trial 40006, and treatment-free follow-up trial 40037.

Results

Laboratory abnormalities reported as AEs were examined on an individual basis for the pivotal trials 18170 and 18171. See Attachment A for tables of abnormal laboratories reported as an AE. No laboratory findings were reported as a SAE. The few abnormal laboratory results that led to discontinuation from the pivotal trials are described below:

Subject 8130-007 in Trial 18170, a 46 year old male was discontinued from the trial on day 99 due to increased LFTs graded "moderate". Examination of his baseline and screening values revealed that the LFTs were elevated prior to treatment (ALT=151, AST=67, GGT=442, total bilirubin=0.8). The LFTs fluctuated throughout Part A of the trial and at 12 weeks were ALT=194, AST=153, GGT=654, total bilirubin=1.31. I agree with the investigator that given the elevation prior to treatment it is unlikely that the slight worsening was related to the investigational product.

Subject # 8133-002 in Trial 18171, a 48 year old female, was noted on day 16 of treatment to have anemia graded as "moderate" and was discontinued from the trial. Examination of her baseline and screening values revealed that the anemia was present (Hgb=9.1) prior to treatment. The week 2 Hgb that led to her discharge from the trial was 8.5. I agree with the sponsor that this was unlikely to be related to the investigational product.

Subject #8110-012 in Trial 18171, a 43 year old female was discharged from the trial at week 32 for a "moderate" anemia. Her Hgb at that time was 8.3. She had a baseline Hgb of 10.4 upon entry into the trial. Her Hgb fluctuated between 9.9 and 11.9 during the first 20 weeks of treatment but then began slowly declining between weeks 20 and 32. She was brought back in for termination visits at weeks 52 (Hgb=8.4) and week 56 (Hgb=6.8). At that time she had been off ivermectin for 5 months; this negative de-challenge suggests an alternative cause for the anemia than the investigational product.

One case of marked elevation of transaminases (>10 times the reference range for AST) was reported for Subject 8191-001, a 61 year old female, in the ivermectin group of pivotal Trial 18171 (Part A). This subject presented with acute hepatitis from the Week 12 visit to the Week 16 visit which was reported as a TEAE considered unrelated by the investigator. At the Week 12 visit, the following liver function test (LFT) results were obtained: AST of 704 UI/L (normal: 15 to 41 IU/L), ALT of 527 IU/L (normal: 17 to 63 IU/L), and ALP of 121 U/L (normal: 32 to 92 U/L). The study drug was temporarily discontinued until the Week 16 visit. Two (2) weeks later, all results for LFTs returned to within the normal ranges. The study drug was restarted and the subject completed the study as planned with no other incidence of increased transaminases occurring for the remainder of the study. I agree with the investigator that given the lack of recurrence of increased LFTs with reinstitution of the ivermectin at week 16 it is unlikely that the increase was due to the investigational product.

Examination of the shift tables for hematology and chemistry values for the pivotal trials 18170 and 18171 did not reveal any discernable or worrisome patterns to suggest a drug effect.

7.4.3 Vital Signs

Vital signs data were also collected in 7 of the 10 clinical trials performed in subjects with PPR; Studies 40027, 40051, 40064, 40106, 40173, 18170, and 18171. There were no clinically relevant changes in vital signs noted by this reviewer in the development program for ivermectin 1% cream.

7.4.4 Electrocardiograms (ECGs)

The IRT team reviewed the results of the thorough QT trial #18120 which was submitted on Dec 17, 2010 to IND 76064. The IRT reviewer noted

> No significant QTc prolongation effect of ivermectin 6 mg was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between ivermectin 6 mg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

7.4.5 Special Safety Studies/Clinical Trials

Trial 40106 was designed by the applicant to investigate a concern regarding neutropenia induced by ivermectin cream. Results of this trial are discussed in Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission and Section 7.3.5 Submission Specific Primary Safety Concerns.

7.4.6 Immunogenicity

This is not applicable to this non-biologic product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.2.2 Explorations for Dose Response for discussion of this topic.

7.5.2 Time Dependency for Adverse Events

In examining Parts B and C of the 2 Phase 3 pivotal trials (Trials 18170 and 18171), which evaluated the safety profile of ivermectin 1% Cream QD for up to 56 weeks, there was no trend for increasing incidences of TEAEs over time. There was also no evidence that long-term use of the study drugs conveyed an increased risk of occurrence of any specific type of TEAE.

7.5.3 Drug-Demographic Interactions

See Section 6.1.7 Subpopulations

7.5.4 Drug-Disease Interactions

No formal analyses were performed for drug-disease interactions with this topical drug product.

7.5.5 Drug-Drug Interactions

See the review by the clinical pharmacologist for discussion of this topic.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

According to the applicant, in a 104-week dermal carcinogenicity study in the Swiss CD1 mice daily dermal application (site of application unprotected) of ivermectin cream at concentrations of 0.1%, 0.3% or 1% (corresponding to dose levels of 1, 3 or 10 mg/kg/day) did not induce any treatment-related effects upon in-life observation and did not affect the incidence of tumor-related deaths either from benign or malignant tumors or when all tumors were considered together. The histopathological examination and the statistical analysis did not reveal any effect of the test item on the incidence and morphology of tumors. At the highest dose of 10 mg/kg/day, plasma $AUC_{0\text{-}24h}$ values were 48,519 and 26,461 ng.h/mL in males and females, respectively, representing 645

(for males) and 352 (for females) times the human exposure at the maximum recommended human dose (i.e., $AUC_{0\text{-}24h}$ value of 75.16 ng.h/mL as assessed in the pharmacokinetics study RD.03.SRE.40064 conducted in patients with severe PPR treated under maximal use condition).

According to the applicant, in a 12-month dermal photo-carcinogenicity study conducted in hairless mice with ivermectin cream at concentrations of 0.1%, 0.3% or 1%, repeated topical administration of vehicle cream enhanced UVR-induced skin tumor development, as compared with mice only exposed to UVR. Repeated topical administration of ivermectin cream at concentrations of 0.3% and 1.0% enhanced photocarcinogenesis as compared with Vehicle Cream.

According to the applicant, in a 104-week oral carcinogenicity study in rats, ivermectin was considered not tumorigenic when administered daily at doses up to 3 mg/kg/day. At 3 mg/kg/day, the plasma exposures of animals were 21,226 ng.h/mL in males and 24,780 ng.h/mL in females and represented at least 282 times the human exposure at the MRHD. At the high dose of 9 mg/kg/day, plasma $AUC_{0\text{-}24h}$ values were 62,568 ng.h/mL in males and 69,407 ng.h/mL in females, about 832(males) and 923 (females) times the MRHD. At 9 mg/kg/day, treatment-related pre-neoplastic changes observed only in males were benign hepatocellular adenomas. At this dose level, other findings for which a treatment relationship could not be established with certainty consisted of pancreatic islet cell adenomas in males and carcinomas with no evidence of distant metastasis in females.

7.6.2 Human Reproduction and Pregnancy Data

Oral ivermectin (Stromectol) has a pregnancy category C and states the following in its FDA approved label:

> Pregnancy, Teratogenic Effects
> Pregnancy Category C
>
> Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m2/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.
>
> Nursing Mothers
>
> STROMECTOL is excreted in human milk in low concentrations. Treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

The following pregnancies occurred during the development program for ivermectin 1% cream.

Table 35: Summary of pregnancies occurring in the Ivermectin Cream clinical development program

Subject Number	Study Treatment	Pregnancy Outcome
Study 40173 (Part A)		
5788-005	Ivermectin 1% Cream	Healthy baby[a]
5812-002	Metronidazole 0.75% Cream	Healthy baby[a]
Study 40173 (Part B)		
5202-002[b]	Metronidazole 0.75% Cream	Ectopic pregnancy[a]
5204-018	Metronidazole 0.75% Cream	Healthy baby[a]
5549-008	Ivermectin 1% Cream	Drug exposure before pregnancy Healthy baby[a]
5780-009	Ivermectin 1% Cream	Drug exposure before pregnancy Spontaneous abortion (miscarriage), not related[a]
Study 18170		
8294-007	Ivermectin 1% Cream QD - Part B	Unknown
8198-023	Ivermectin 1% Cream QD - Part A	Subject lost to follow-up
8245-001	Ivermectin 1% Cream QD - Part A	Stillborn, not related
8197-007	Azelaic Acid 15% Gel BID – Part B	Voluntary abortion for personal reasons (on Day 153)
8048-011	Ivermectin 1% Cream QD - Part B	Unknown
8197-015	Ivermectin 1% Cream QD - Part B	Healthy baby[a]
8060-007	Azelaic Acid 15% Gel BID - Part B	Voluntary abortion for personal reasons
8373-004	Ivermectin 1% Cream QD - Part B	Subject lost to follow-up
Study 18171		
8329-018	Ivermectin 1% Cream QD – Part B	Spontaneous abortion (miscarriage), not related
8018-002	Ivermectin 1% Cream QD – Part A	Healthy baby
8212-003	Ivermectin 1% Cream QD – Part B	Healthy baby

[a]New information received after cut-off date of 08 Apr 2013.
[b]A pregnancy was detected in Subject 5202-002 for whom a UPT was performed at the Week 52 visit.
Data source: Subject narratives in RD.03.SRE.40173, Section 14.6, RD.06.SRE.18170, Section 14.3.10, RD.06.SRE.18171, Section 14.3.10.

Source: Addendum to Applicant's ISS pg.44

Narratives for Subjects of Concern

Subject 5780-009

Subject 5780-009, a 29-year-old White female with rosacea, began treatment with ivermectin 1% Cream on 03-Dec-2012 (Part A). No study drug was applied throughout Part B (no retreatment needed). The last study drug application occurred on 26-Mar-2013.

In Jul-2013, around 14 weeks after last application, the subject found out that she was pregnant. The last menstrual period started on 02-Jul-2013 and start of pregnancy was evaluated on 11-Jul-2013. The fetus was thus not exposed to the study drug. The expected date of delivery was Mar-2014.

On 15-Aug-2013, the subject was discontinued from study due to pregnancy. On (b) (6), during a routine gynecologist consultation, the physician found out that the subject had experienced a silent miscarriage. The subject was hospitalized and manual vacuum aspiration of the fetus was performed. On (b) (6), the subject was discharged home in good condition.

Subject 8245-001

Subject 8245-001, a 35-year-old White female with rosacea began treatment with ivermectin 1% Cream on 08 Feb 2012. The subject had 4 previous pregnancies: 1 normal full-term birth, 1 pre-term birth (living child), 1 miscarriage in Mar 2009, and 2 pre-term births (children born at 24 weeks and died 1 week after). She had a Cesarean section on (b) (6).

On 10 Apr 2012 (Treatment Day 63), the subject consulted her gynecologist as she suspected she was pregnant. The obstetrician confirmed the pregnancy and estimated the start of the pregnancy to be 17 Mar 2012; expected due date was 13 Dec 2012. Last menstrual cycle was 01 Mar 2012. The subject was prescribed pre-natal vitamins (since 10 Apr 2012) and citalopram was stopped the same day. The study drug was discontinued immediately (on 11 Apr 2012) and the subject was discontinued from the study on 25 Apr 2012 due to pregnancy.

The fetus was exposed to study drug during the first 26 days of development (first trimester). On 18 Jul 2012, the subject saw her obstetrician-gynecologist. She was 18 weeks pregnant with a baby girl that she could feel moving. The pregnancy was progressing on schedule and the baby was healthy. On (b) (6), the subject gave birth to a stillborn baby (at (b) (6) weeks). No additional information was reported as the subject refused to discuss further about the event.

The cause of fetal death is unknown and no medical records could be obtained. The Investigator assessed this event as serious, severe in intensity, and not related to the study drug.

Subject 8329 – 018

Subject 8329-018, a 34-year-old White Hispanic or Latino female with rosacea began treatment with ivermectin 1% Cream on 14 Jun 2012. The subject had 4 previous pregnancies leading to 2 full term births and 2 miscarriages.

On 28 Dec 2012, at the Week 28 visit, the subject had a questionable urine pregnancy test. Two serum pregnancy tests were performed and the study drug was discontinued permanently (last application occurred on 27 Dec 2012). On 01 Jan 2013, the subject reported that she started her period (without cramping or pain). On 02 Jan 2013, the serum pregnancy tests results (HCG qualitative) were received; 1 was positive and the

other negative. On 04 Jan 2013, the subject's obstetrician advised that she had miscarried on 01 Jan 2013. The start of pregnancy was estimated to be 08 Dec 2012 and so the fetus was exposed to study drug during the first 20 days of development. The expected date of delivery was 06 Sep 2013. The treatment-emergent SAE of spontaneous abortion was considered by the Investigator to be severe in intensity, not related to study drug, and resolved on 01 Jan 2013.

It is difficult to assess causality in the two pregnancies that were exposed to the study drug that resulted in stillbirth and spontaneous abortions. Both subjects had a history of miscarriage but it is not possible to rule out ivermectin as a contributing cause.

A review of the literature regarding exposure to ivermectin during pregnancy is summarized in the table below:

Table 36: Literature review of oral ivermectin exposure during pregnancy

Citation	Design/ Type	Population	Outcome
Chippaux, JP 1993 *Trans Royal Soc Trop Med*	Retrospective report on inadvertent Ivermectin exposure during Pregnancy	2710 women ages 15-45 North Cameroon	Tracking of women who delivered within 40 weeks of Rx : 401 pregnant women not Rxd 110 pregnant women Rxd with Ivermectin Outcome of first trimester pregnancy (early abortion, miscarriage, stillbirth) not different from untreated No malformations or abnormalities in developmental status
Doumbo, P 1992 *Bull Soc Path Ex.*	Retrospective report on inadvertent Ivermectin exposure during Pregnancy	435 women 15-45 yrs Mali	No difference in intrauterine mortality, newborn mortality, malformations
Gyapong, J 2003 *Trop Med + Inter Health*	Retrospective report on effect of inadvertent Ivermectin Rx for Filariasis during Pregnancy	2985 women 15-49 years Ghana	Tracking of women who delivered within 42 weeks of Rx - 343 pregnant women – 50 Rxd with Ivermectin (39 in first trimester) Six malformations (one in IVR group- hearing abnl) Relative risk (RR) for congenital malformation with first trimester exposure= 1.05 RR, RR (overall) = 0.82 12 abortions-9 spontaneous (2 in IVR group) RR for spon abortion = 1.67 P = 0.62
Ndyomugyenyi, R 2008 *Am J Trop Med*	Prospective, open label trial IVR + ALB and each alone for	834 pregnant women Uganda 400mg ALB	198 subjects – Ivermectin - Group A 194 subjects – Albendazole - Group B 199 subjects – IVR + ALB - Group C 241 subjects – untreated controls - Group D

	Helminth infection in 2nd trimester of pregnancy		AEs mild and transient: 48.9% (A), 34% (B), 17% © – abdominal pain, fever, rash/itchiness, headache anorexia/vomiting No serious AEs No effect on birth weight One abortion in ALB group 13 premature deliveries – 3(A), 2 (B), 3 (C) and 5 (D) – no sig differences but not powered to detect a difference 10 stillbirths – 1(A), 5(B), 3(C) and 1 (D) – no sig differences but not powered to detect a difference 2 congenital abnormalities – 1(A-talipes equinovarus of the R foot) and 1(D-cleft palate and talipes equinovarus of the L foot)
Pacque, M 1990 *Lancet*	Retrospective report on inadvertent Ivermectin exposure during Pregnancy	2884 women Liberia	Tracking of women who delivered within 40 weeks of Rx : 739 pregnant women not Rxd 200 pregnant women (203 pregnancy outcomes) Rxd with Ivermectin 10 (4.9%) abnormal outcomes-exposed group o 5 stillbirths o 5 malformations 76 (4.3%) abnormal outcomes-control group o 55 stillbirths/miscarriages o 21 malformations No sig differences- rate of stillbirths, mean birth weight, rate of malformations Rate of major congenital malformations-2.4% in exposed

Source: Reviewer's table #66 from clinical MO review for Sklice NDA 202736

The results of these studies are somewhat reassuring that inadvertent exposure to topical ivermectin during early pregnancy is unlikely to result in a marked increase in risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant has developed Ivermectin 1% Cream for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older. There has been no investigation of the use of ivermectin 1% cream in children in this development program.

The active ingredient, ivermectin, is currently approved in the US in oral form (Stromectol®), with indications for use in strongyloidiasis of the intestinal tract and onchocerciasis in adults and in children with a weight of minimum 15 kg. Ivermectin is

also approved as a lotion indicated for the topical treatment of head lice infestations in patients 6 months of age and older (Sklice®).

The applicant has requested a waiver for all pediatric age groups citing the low prevalence of rosacea in children and expressed concerns regarding the feasibility of clinical studies in this patient population. The waiver request was presented to PERC on July 9, 2014 and a full waiver was approved.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The following information on overdosage appears in the approved labeling for oral ivermectin, Stromectol (Merck, 2009):

> Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg*. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis.
>
> In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.
>
> In case of accidental poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.
>
> *This is 125 to >300 times the labeled oral human dose] and 40 to 50 mg/kg, respectively.

The applicant has proposed the following statement regarding overdose for the label for topical ivermectin 1% cream:

(b) (4)

> In accidental or significant exposure to unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have

been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In case of accidental ingestion, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

DDDP recommended removal of the statement "(b) (4) ."

In addition, precautions such as emphasizing the need to keep the product out of the reach of children have been included in labeling.

A consultation with DMEPA was obtained regarding this issue and they were satisfied with the applicant's approach.

The approved labeling for Stromectol does not contain information on abuse potential, withdrawal or rebound. I agree with the applicant that topical ivermectin is not expected to have these effects.

7.7 Additional Submissions / Safety Issues

The 120 day safety update was received from the sponsor on April 11, 2014. It contained additional safety information from trial 40173 (ongoing at the time of NDA submission). Trial 40173 was a two part (A and B) phase 3 trial conducted in the European Union, Russia and Ukraine. Part A was a 16 week investigator-blind, active-controlled trial of 962 subjects with PPR. Part B was a 36 week extension period to assess relapse and measure pharmacoeconomic parameters in a total of 757 subjects (out of 762 eligible subjects) from Part A. All safety results from Part A and the early data from Part B (up to April 8, 2014) are included in the previously detailed safety review as they were submitted with the NDA. Safety results from Part B through Feb 12, 2014 were included in the 120 day safety update. I have reviewed the safety information from the 120 day safety update. I agree with the applicant that "the additional safety data provided within this document do not impact or change the safety profile of Ivermectin 1% Cream as presented in the initial NDA submission".

8 Postmarket Experience

See Section 7.2.6

9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review.

9.2 Labeling Recommendations

See agreed upon labeling.

9.3 Advisory Committee Meeting

Not-applicable, as no Advisory Committee was convened in response to this application

Table 37: Table of Abnormal Liver Tests reported as an Adverse Event

Subject #/trial #	Age/ sex	AE	Onset day/ duration	D/C study	SAE	Severity	Related	Outcome
8005-018 18170	61/F	↑ LFTs	188/73 Part B	N	N	Mild	Y	Recovered
8036-014 18170	71/M	Liver steatosis	17 Part A	N	N	Moderate	N	Ongoing
8076-017 18170	64/F	↑bilirubin	85/3 Part A	N	N	Moderate	N	Recovered
8094-006 18170	34/M	↑GGT	253/120 Part B	N	N	Mild	N	Recovered
8120-010 18170	57/M	↑AST	394/13	N	N	Mild	N	Recovered
8130-007 18170	46/M	↑ LFTs (LFTs were ↑ at week -2 and baseline)	99 Part A	Y-d/c	N	Moderate d/cd	N	Ongoing
8197-004	55/M	↑bilirubin	169/29 Part B	N	N	Mild	N	Recovered

Reference ID: 3644887

18170		↑GGT ↑LFTs	169/100 Part B 365 Part B	N N	N N	Mild Mild	N N	Recovered Ongoing
8197-015 18170	23/F	↑SGOT	170/7 Part B	N	N	Mild	N	Recovered
8204-002 18170	49/F	↑ALT	1/8 Part A	N	N	Mild	N	Recovered
8250-005 18170	41/M	↑Alk Phos	184	N	N	Moderate	N	Ongoing
8245-015 18170	55/M	↑LFTs	368/20 Part B	N	N	Mild	N	Recovered
8350-013 18170	58/M	↑GGT	395 Part C	N	N	Mild	N	Ongoing
8250-007 18170	78/M	↑bilirubin	113 Part B	N	N	Mild	N	Ongoing
8250-008 18170	59/F	↑Alk Phos ↑GGT	88/94 Part A 88/94	N N	N N	Mild Mild	N N	Recovered Recovered

			Part A					
8250-010 18170	28/F	↑AST ↑GGT	85/31 Part A 85/85 Part A	N N	N N	Mild Mild	N N	Recovered Recovered
8326-015 18170	45/F	Worsening of ↑LFTs	82 Part A	N	N	Moderate	N	Ongoing
8351-010 18170	56/F	Worsening of ↑LFTs	97	N	N	Mild	N	Ongoing
8355-006 18170	30/F	↑LFTs	90/15 Part A	N	N	Mild	N	Recovered
8358-008 18170	64/F	↑GGT	169/86 Part B	N	N	Mild	N	Recovered
8355-016 18170	28/F	↑LFTs	311/58 Part B	N	N	Mild	N	Recovered
8359-006 18171	70/M	↑LFTs	1/113 Part A	N	N	Moderate	N	Recovered
8228-021 18171	62/F	↑AST ↑Alk Phos	93/84 Part B 85/92	N N	N N	Mild Drug inter	N N	Recovered Recovered

		↑GGT	Part A 85/92 Part A	N	N	Mild Drug inter Mild Drug inter	N	Recovered
8213-028	78/F	Alcoholic liver disease	63/23 Part A	N	N	Moderate Drug inter	N	Recovered
8212-007 18171	59/M	Hepatic steatosis	283 Part B	N	N	Mild	N	Ongoing
8208-001 18171	44/M	↑AST ↑ALT ↑GGT	169/85 169/10 169/10	N N N	N N N	Mild Mild Mild	N N N	Recovered Recovered Recovered
8191-001 18171	61/F	Acute hepatitis	92/22 Part A	N	N	Severe Drug inter	N	Recovered
8133-007 18171	46/F	↑AST ↑ALT ↑GGT	169 169 169	N N N	N N N	Mild Mild Mild	N N N	Ongoing
8074-006 18171	22/M	↑LFTs	1/15 Part A	N	N	Mild	N	Recovered

8010-023 18171	60/M	↑LFTs ↑LFTs	1/84 Part A 228/132 Part B	N N	N N	Moderate Moderate	N N	Recovered Recovered
8010-011 18171	74/M	↑AST/↑ALT	393 Part C	N	N	Mild	N	Ongoing

Source: Reviewer's Table

Table 38: Table of Abnormal Lipids Reported as an Adverse Event

Subject #/trial #	Age/ sex	AE	Onset day/ duration	D/C study	SAE	Severity	Related	Outcome
8056-002 18170	66/M	↑lipids	130 Part B	N	N	Mild	N	Ongoing
8195-005 18170	57/F	↑lipids	106 Part B	N	N	Moderate	N	Ongoing
8196-033 18170	38/F	↑lipids	137 Part B	N	N	Moderate	N	Ongoing
8245-012 18170	63?F	↑lipids	10 Part A	N	N	Moderate	N	Ongoing
8327-002 18170	75/M	↑Cholesterol	163 Part B	N	N	Mild	N	Ongoing
8245-015 18170	55/M	↑lipids	14 Part A	N	N	Moderate	N	Ongoing
8355-014 18170	48/M	Worsening of ↑lipids	364 Part B	N	N	Mild	N	Ongoing
8355-	56/F	↑lipids	214	N	N	Mild	N	Ongoing

018 18170			Part B					
8320-008 18171	60/F	↑Cholesterol	277 Part B	N	N	Mild	N	Ongoing
8258-006	63/F	↑lipids	-9/1 Screen	N	N	Mild	N	Recovered
8150-013 18171	48/F	↑lipids	88 Part A	N	N	Moderate	N	Ongoing
8150-009 18171	47/M	↑lipids	12/382 Part A	N	N	Mild	N	Recovered
8143-002 18171	55/F	↑Cholesterol	385 Part C	N	N	Moderate	N	Ongoing
8142-013	53/M	↑Cholesterol	166 Part B	N	N	Mild	N	Ongoing
8113-004 18171	45/M	↑Cholesterol	148 Part B	N	N	Moderate	N	Ongoing

Table 39: Table of Other Abnormal Laboratories Reported as Adverse Events

Subject #/trial #	Age/ sex	AE	Onset day/ duration	D/C study	SAE	Severity	Related	Outcome
8005-021 18170	68/F	↓plts	337 Part B	N	N	Mild	N	Ongoing
8059-005 18170	41/M	Anemia	211 Part B	N	N	Mild	N	Ongoing
8094-011 18170	43/F	↑eos ↓plts	27/3 Part A 190/36 Part B	N N	N N	Mild Mild	N N	Recovered Recovered
8120-004 18170	73/M	Anemia	86 Part B	N	N	Severe	N	Ongoing
8204-003 18170	55/M	↓K	95/202 Part B	N	N	Moderate	N	Recovered
8227-007 18170	47/F	↑neutros ↓plts ↑WBCs	225/29 Part B 365/27 Part B 225/29	N N N	N N N	Mild Mild Mild	N N N	Recovered Recovered Recovered
8250-007 18170	78/M	macrocytic anemia	82 Part A 82/32	N	N	Moderate	N	Ongoing

		Lymphopenia ↑neutros	Part A 82/32 Part A	N N	N N	Moderate Mild	N N	Recovered Recovered
8327-007 18170	47/F	Anemia	291 Part B	N	N	Mild	N	Ongoing
8327-008 18170	67/F	↑eos	301 Part B	N	N	Mild	N	Ongoing
8327-014 18170	54/F	↓Hgb ↑Monocytes ↓plts	106/3 Part A 106/3 Part A 106/3 Part A	N N N	N N N	Mild Moderate Moderate	N N N	Recovered Recovered Recovered
8350-015 18170	46/F	↓Hgb/Hct	290/57 Part B	N	N	Moderate	N	Recovered
8350-016 18170	56/F	↓WBCs	88/19 Part A	N	N	Mild	N	Recovered
8355-016 18170	28/F	↑WBCs	311/27 Part B	N	N	Mild	N	Recovered
8358-004 18170	55/M	Lymphopenia	15 Part A	N	N	Moderate	N	Subject Lost To Follow-Up
8365-010 1817	54/F	↑neutros/↑ WBCs	202/24 Part B	N	N	Mild	N	Recovered

8352-006 18171	39/M	Lymphopenia	86 Part	N	N	Mild	N	Ongoing
8254-005 18171	48/F	↑Lymphocyte	316/27 Part B	N	N	Mild	N	Recovered
8213-025 18171	57/F	↓WBCs	169/3 Part B	N	N	Mild	N	Recovered
8212-004 18171	49/F	Anemia	81 Part A	N	N	Moderate	N	Ongoing
8208-001 18171	44/M	↓plts	169/10 Part B	N	N	Mild	N	Recovered
8191-002 18171	39/M	Anemia	229/163 Part B	N	N	Mild	N	Recovered
8149-011 18171	42/F	↑neutros/↑ WBCs	1/42 Part A	N	N	Mild	N	Recovered
8133-016	62/M	↓plts	113 Part B	N	N	Mild	N	Ongoing
8133-002 18171	48/F	Anemia (Hgb low at baseline) ↑chem (also ↑ at baseline)	16 Part A 34 Part A	Y N	N N	Moderate Drug d/cd Mild	N N	Ongoing Ongoing
8129-017 18171	42/F	Anemia	242/5 Part B	N	N	Mild	N	Recovered
8110-012	43/F	Anemia	226	Y	N	Moderate	N	Ongoing

						Drug d/cd		
8027-006 18171	68/M	↓Hgb	316 Part B	N	N	Moderate	N	Ongoing
8026-014 18171	55/F	Anemia	86/85 Part A	N	N	Moderate	N	Recovered
8026-004 18171	48/F	Lymphopenia	170/22 Part B	N	N	Mild	N	Recovered
8010-023 18171	60/M	↑creatinine	386 Part C	N	N	Mild	N	Ongoing
8010-017 18171	40/F	Lymphopenia	246/34 Part B	N	N	Mild	N	Recovered

Table 40: Investigator List- Trial 18170

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	Name/Address/Tel./Fax	Dates of Participation	Subject Identifier Series
8004	Diane Baker, MD Baker Allergy Asthma and Dermatology Research Center 3975 SW Mercantile Drive Suite 165 Lake Oswego, OR 97035 Tel: 503-534-2622 Fax: 503-534-2722	29Feb2012 – 15May2013	8004-001 – 8004-008
8005	Boni Elewski, MD UAB Department of Dermatology 2000 6th Avenue South 3rd Floor Birmingham, AL 35233 Tel: 205-502-9960 Fax: 205-502-9963	24Apr2012 – 27Jun2013	8005-001, 8005-004, 8005-007, 8005-009, 8005-011, 8005-018 – 8005-021, 8005-030, 8005-005-036 - 8005-037
8030	Adnan Nasir, MD Wake Research Associates 3100 Duraleigh Road Suite 304 Raleigh, NC 27612 Tel: 919-781-2514 Fax: 919-420-6067	05Apr2012 – 26Jun2013	8030-001, 8030-006 – 8030-014, 8030-017 – 8030-018
8036	Richard Thomas, MD Derm Research@888 Inc. 312-888 West 8th Avenue Vancouver, BC V5Z 3Y1 Canada Tel: 604-873-4049 Fax: 604-677-5310	24Apr2012 – 10Jul2013	8036-002 – 8036-018
8048	Joel Schlessinger, MD Skin Specialist, P.C. 2802 Oak Vew Mall Drive Omaha, NE 68144 Tel: 402-697-6599 Fax: 402-334-8622	13Feb2012 – 08Jul2013	8048-001 – 8048-003, 8048-005 – 8048-007, 8048-009 – 8048-012, 8048-014, 8048-016 8048-023
8056	Marshall Shuler, MD Palmetto Clinical Trial Services, LLC 920 Woodruff Road Greenville, SC 29607 Tel: 864-467-1557 Fax: 864-467-1558	14Feb2012 – 17Jul2013	8056-001 – 8056-020

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8057	Kappa P. Meadows, MD The Education & Research Foundation, Inc. 2095 Langhorne Road Lynchburg, VA 24501 Tel: 434-847-8400 Fax: 434-846-1707	09Feb2012 –20Jun2013	8057-001, 8057-003, 8057-004, 8057-009, 8057-010
8059	Pranav Sheth, MD Dermatology Research Center of Cincinnati 379 Dixmyth Avenue Cincinnati, OH 45220 Tel: 513-246-7441 Fax: 513-246-7403	19Mar2012 – 25Jun2013	8059-001 – 8059-006, 8059-008 – 8059-011
8060	Jerry Tan, MD Windsor Clinical Research, Inc. 2224 Walker Road Suite 300B Windsor, ON N8W 5L7 Canada Tel: 519-971-7693 Fax: 519-971-7594	19Apr2012 – 25Jun2013	8060-001 – 8060-003. 8060-05 – 8060-010, 8060-012
8076	Michael Jarratt, MD DermResearch, Inc. 8140 North Mopac Building 3, Suite 120 Austin, TX 78759 Tel: 512-502-9324 Fax: 512-349-9559	28Dec2011 – 25Jun2013	8076-001 – 8076-005, 8076-007 – 8076-009, 8076-012 – 8076-014, 8076-016 – 8076-018, 8076-020 – 8076-024, 8076-027, 8076-028
8077	Richard Langley, MD Eastern Canada Cutaneous Research Associates 5743 University Avenue Halifax, NS B3H 0A2 Canada Tel: 902-423-0482 Fax: 902-423-0666	16May2012 – 25Jun2013	8077-001, 8077-003, 8077-004, 8077-006
8089	Simon Nigen, MD Innovaderm Research, Inc. 1851 Sherbrooke Street East Suite 502 Montreal, QC H2K 4L5 Canada Tel: 514-421-4285 Fax: 514-906-0659	16Mar2012 – 10Jul2013	8089-001 – 8089-003, 8089-005 – 8089 012, 8089-014 – 8089-016, 8089-018 – 8089-022

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8090	Wayne Carey, MD Siena Medical Research 4 Westmount Square Suite 100 Montreal Quebec H3Z 2S6 Canada Tel: 514-788-3203 Fax: 514-788-3202	10Apr2012 – 10Jul2013	8090-001 – 8090-012
8092	Leonard Kircik, MD Derm Research, PLLC 1169 Eastern Parkway Suite 2310 Louisville, KY 40217 Tel: 502-451-9000 Fax: 502-456-2728	06Mar2012 – 26Jun2013	8092-001 – 8092-010, 8092-012 – 8092-018
8094	Linda Stein-Gold, MD Henry Ford Medical Center New Center One Dept. of Dermatology 3031 West Grand Blvd. Detroit, MI 48202 Tel: 313-916-1984 Fax: 313-916-9857	13Mar2012 – 11Jul2013	8094-001 – 8094-003, 8094-005 – 8094-007, 8094-009, 8094-011, 8094-012, 8094-014, 8094-015
8095	Michael J. Maloney, MD Cherry Creek Research, Inc. 3773 Cherry Creek North Drive Suite 970 Denver, CO 80209 Tel: 303-388-5629 Fax: 303-321-7586	28Mar2012 – 11Jun2013	8095-002 – 8095-008, 8095-010, 8095-012
8120	John W. Toole, MD Dermadvances Research 203 Edmonton Street Winnipeg, Manitoba R3C 1R4 Canada Tel: 204-947-1630 Fax: 204-957-0185	28Mar2012 – 02Jul2013	8120-001 – 8120-005, 8120-008 – 8120-011, 8120-013, 8120-014, 8120-016, 8120-017
8123	Norman R. Wasel, MD Dermadvances Research 203 Edmonton Street Winnipeg, Manitoba R3C 1R4 Canada Tel: 204-947-1630 Fax: 204-957-0185	28Feb2012 – 05Jul2013	8123-001 – 8123-013, 8123-005 – 8123-007, 8123-009 – 8123-011, 8123-013 – 8123-015

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8130	Howard Sofen, MD Dermatology Research Associates 8930 S. Sepulveda Blvd. #114 Los Angeles, CA 90045 Tel: 310-337-7171 Fax: 310-337-1081	28Feb2012 – 17Jun2013	8130-001, 8130-005 – 8130-007, – 8130-009 – 8130-015
8147	Ian Landells, MD Nexus Clinical Research 120 Stavanger Driver Suite 102 St. John's, NL A1A 5E8 Canada Tel: 709-726-3386 Fax: 709-729-5898	14May2012 – 19Jun2013	8147-001 – 8147-004
8186	Alan Fleischer, MD Dept. of Dermatology Wake Forest University Health Sciences 4618 Country Club Road Winston, Salem, NC 27104 Tel: 336-716-7465 Fax: 336-713-4355	21Mar2012 – 29Jul2013	8186-001 – 8186-013, 8186-015 – 8186-018, 8186-020 – 8186-024
8192	Stephen K. Tyring, MD Center for Clinical Studies 6655 Travis Suite 120 Houston, TX 77030 Tel: 713-528-8818 Fax: 713-528-8848	29Feb2012 – 15Jul2013	8192-001 – 8192-003, 8192-005 – 8192-011, 8192-013, 8192-015 – 8192-019
8195	Robert Haber, MD Haber Dermatology and Cosmetic Surgery 26949 Chagrin Blvd. Suite #300 Beachwood, OH 44122 Tel: 216-932-5200 Fax: 216-932-5212	22Mar2012 – 16Jul2013	8195-001 – 8195-006, 8195-008 – 8195-011, 8195-013, 8195-017, 8195-018, 8195-020 – 8195-029
8196	Holly Harris, MD The South Bend Clinic, LLP 211 N. Eddy Street South Bend, IN 46617 Tel: 574-237-9391 Fax: 574-204-6439	29Feb2012 – 08Jul2013	8196-002 – 8196-011, 8196-014, 8196-015, 8196-017 – 8196-024, 8196-026 – 8196-033
8197	Mark S. Lee, MD Progressive Clinical Research, P.A. 4499 Medical Drive Suite 145 San Antonio, TX 78229 Tel: 210-614-5557 Fax: 210-614-5556	17Feb2012 – 14May2013	8197-001, 8197-002, 8197-004 – 8197-009, 8197-012, 8197-014 – 8197-018

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8198	Craig Leonardi, MD (Replacement) Michael Heffernan, MD Central Dermatology, PC 1034 S. Brentwood Blvd. Suite 600 St. Louis, MO 63117 Tel: 314-721-5565 Fax: 314-721-6122	01Mar2012 – 17Jun2013	8198-001 – 8198-005, 8198-007 – 8198-009, 8198-013 – 8198-024
8204	Lesly Davidson, MD Davidson Dermatology 901 Von Kolinitz Road Suite 100 Mount Pleasant, SC 29464 Tel: 843-849-1880 Fax: 843-849-1383	08Mar2012 – 31May2013	8204-002 - 8204-005
8206	Paul Gillum, MD Central Sooner Research 900 North Porter Suite 207 Norman, OK 73071 Tel: 405-329-0474 Fax: 405-364-0933	08Mar2012 – 08Jul2013	8206-001 – 8206-0003, 8206-005 – 8206-009, 8206-011 – 8206-014
8214	Leonard Swinyer, MD Dermatology Research Center,Inc. 1548 East 4500 South Suite 201 Salt Lake City, UT 84117 Tel: 801-269-0135 Fax: 801-288-0170	14Feb2012 – 01Jul2013	8214-001, 8214-002, 8214 – 006, 8214-007, 8214-010, 8214-014, 8214-016, 8214-017, 8214-025 – 8214-027
8226	Steven Grekin, MD Grekin Skin Institute 13450 E. 12 Mile Road Warren, MI 48088 Tel: 586-759-5525 Fax: 586-759-4765	06Mar2012 – 20Jun2013	8226-001 – 8226-004, 8226-06 – 8226-008
8227	Mark Russell Ling, MD MedaPhase, Inc. 710 Newnan Crossing Bypass Suite B Newnan, GA 30263 Tel: 770-252-6900 Fax: 770-252-0794	27Feb2012 – 10Jul2013	8227-001, 8227-002, 8227-004, 8227-005, 8227-007, 8227-010 – 8227-019
8245	Jennifer Clay Cather, MD Modern Research Associates, PLLC 9101 North Central Expressway Suite 170 Dallas, TX 75231 Tel: 214-361-2008 Fax: 214-361-2004	08Feb2012 – 09Jul2013	8245-001 – 8245-0006, 8245-009 – 8245-018

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8250	Frank E. Schiavone, MD (Replacement) Jonathan Kantor, MD North Florida Dermatology Associates, PA 1551 Riverside Avenue Jacksonville, FL 32204 Tel: 904-353-3662 Fax: 904-634-8840	23Jan2012 – 24May2013	8250-001, 8250-003, 8250-005, 8250-007 – 8250-010, 8250-014 – 8250-015
8259	Francisco Flores, MD FXM Research Miramar 3000 SW 148th Avenue Suite 216 Miramar, FL 33027 Tel: 954-430-1097 Fax: 305-675-3152	10Apr2012 – 10Jul2013	8259-001, 8259-003 - 8259-007, 8259-009 – 8259-012, 8259-014 – 8259-017, 8259-020
8289	C. William Hanke, MD Laser & Skin Surgery Center of Indiana 13400 N. Meridian Street Suite 290 Carmel, IN 46032 Tel: 317-660-4900 Fax: 317-660-7113	22Mar2012 – 07May2013	8289-001, 8289-002, 8289-004
8294	Russell D. Mader, MD Dermatology Associates of Kingsport, SC 2300 West Stone Drive Kingsport, TN 37660 Tel: 423-230-3133 Fax: 423-989-3693	02Mar2012 – 09Jul2013	8294-001, 8294-003, 8294-004 – 8294-009
8302	Brian Berman, MD The Center for Clinical & Cosmetic Research 2925 Aventura Blvd. Suite 205 Aventura, FL 33180 Tel: 305-933-6716 Fax: 305-933-3853	21Feb2012 – 10May2013	8302-001, 8302-003, 8302-005
8326	Catherine J. Pointon, MD PMG Research of Charlotte 12611 North Community House Road Suite 102 Charlotte, NC 28277 Tel: 704-527-6672 Fax: 704-527-4622	15Feb2012 – 03Jul2013	8326-001, 8326-002, 8326-004, 8326-005, 8326-008 – 8326-020
8327	Timothy Gardner, MD TriCities Skin and Cancer 1009 N. State of Franklin Access Rd. Johnson City, TN 37604 Tel: 423-989-3105 Fax: 423-989-3693	05Mar2012 – 10Jul2013	8327-002 – 8327-004, 8327-006– 8327-020

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8336	Anatoli Freiman, MD Toronto Research Centre, Inc. 4256 Bathurst Street Suite 400 Toronto, ON M3H 5Y8 Canada Tel: 416-633-0001 Fax: 416-633-0002	26Mar2012 – 10Jul2013	8336-002 – 8336-006, 8336-008 – 8336-012, 8336-014 – 8336-025
8340	Melinda Gooderham, MD SKiN Centre for Dermatology 743 Lansdowne Street West Peterborough, Ontario K9J 1Z2 Canada Tel: 705-775-0295 Fax: 705-775-3376	13Mar2012 – 10Jul2013	8340-001 – 8340-015
8350	Vincent Afsahi, MD Research Across America 999 N. Tustin Avenue Suite 120 Santa Ana, CA 92705 Tel: 714-542-3008 Fax: 714-542-3617	09Mar2012 – 18Jul2013	8350-002 – 8350-004, 8350-006 – 8350-008, 8350-010 – 8350-016
8351	Kim Abson, MD The Polyclinic Madison Center 904 7th Avenue Seattle, WA 98104 Tel: 206-860-5433 Fax: 206-726-6023	07Feb2012 – 10Jul2013	8351-002, 8351-004 – 8351-012, 8351-015 – 8351-020
8354	Lawrence J. Green, M.D., LLC 1505 Shady Grove Road Suite 440 Rockville, MD 20850 Tel: 301-610-0663 Fax: 301-610-5420	27Feb2012 – 20Jun2013	8354-001 – 8354-015
8355	Cheryl Hull, MD Northwest AR Clinical Trials Center, PLLC / Hull Dermatology, PA 500 S. 52nd Street Rogers, AR 72758 Tel: 479-876-8205 Fax: 479-876-8049	17Feb2012 – 11Jul2013	8355-001 – 8355-006, 8355-08 – 8355-010, 8355-013 – 8355-019
8358	Walter K. Nahm, PhD, Inc. 7695 Cardinal Court Suite 200 San Diego, CA 92123 Tel: 858-278-8470 Fax: 858-633-0167	29Feb2012 – 17Jul2013	8358-001 – 8358-010, 8358-012 – 8358-021, 8358-023 – 8358-025

RD.06.SRE 18170 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address/Tel./Fax**	**Dates of Participation**	**Subject Identifier Series**
8365	Marta L. Rendon, MD The Dermatology and Aesthetic Center Skin Care Research 880 NW 13th Street Suite 3C Boca Raton, FL 33486 Tel: 561-750-0544 Fax: 561-750-9873	14Feb2012 – 12Jul2013	8365-001, 8365-003, 8365-005 – 8365-007, 8365-009 – 8365-021, 8365-023
8366	Scott Guenthner, MD The Indiana Clinical Trials Center (ICTC) 1100 Southfield Drive Suite 1240 Plainfield, IN 46168 Tel: 317-838-9911 Fax: 317-837-6080	05Apr2012 – 09Jul2013	8366-001, 8366-003 – 8366-013, 8366-015 – 8366-019
8373	Peter Jenkin, MD PLLC dba Dermatology Associates 1730 Minor Avenue Suite 1000 Seattle, WA 98101 Tel: 206-267-2100 Fax: 206-267-2101	15May2012 – 11Jul2013	8373-002 – 8373-006, 8373-009 – 8373-012, 8373-014
8380	Jane Lee, MD Anderson & Collins Clinical Research, Inc. 1 Ethel Road Suite 106B Edison, NJ 08817 Tel: 732-287-5130 Fax: 732-287-9175	02May2012 – 03Jul2013	8380-001 – 8380-007, 8380-009

Table 41: Investigator List- Trial 18171

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8003	Karan Sra, MD Center for Clinical Studies 451 North Texas Avenue Webster, TX 77598	24Jan2012 - 25Jul2013	8003-001 – 8003-013
8009	Dowling Stough, MD Burke Pharmaceutical Research 3633 Central Avenue, Suite 1 Hot Springs, AR 71913	14Mar2012 – 07May2013	8009-001, 8009-003 – 8009-004, 8009-006 – 8009-010
8010	Melanie Appell, MD Total Skin and Beauty Dermatology Center, PC 2100 16th Avenue South Suite 202 Ash Place Birmingham, AL 35205	14Feb2012 – 08Jul2013	8010-002 – 8010-005, 8010-007 – 8010-009, 8010-011, 8010-013 – 8010-015, 8010-017, 8010-020 – 8010-021, 8010-023 – 8010-028
8017	Kimberly Grande, MD The Skin Wellness Center 10215 Kingston Pike, Suite 200 Knoxville, TN 37922	01Mar2012 – 25Jul2013	8017-001 – 8017-019
8018	David Gratton, MD International Dermatology Research, Inc. #740 3550 Cote des Neiges Montreal, QC H3H 1V4 Canada	20Mar2012 – 28May2013	8018-001 – 8018-002, 8018-004 – 8018-010
8021	Eugene Huang, MD Therapeutics Clinical Research 9025 Balboa Avenue, Suite 105 San Diego, CA 92123	26Jan2012 – 30Jul2013	8021-001 – 8021-011, 8021-013 – 8021-017
8026	Charles Lynde, MD Lynderm Research, Inc. 5762 Highway 7 East, Suite 201 Markham, ON L3P 1A8 Canada	23Mar2012 – 25Jul2013	8026-003 – 8026-007, 8026-009 – 8026-012, 8026-014 – 8026-015, 8026-017, 8026-019 – 8026-023, 8026-025
8027	Ann G. Martin, MD Dermatology Clinical Trials Unit Washington University 969 Mason Road, Suite 225 St. Louis, MO 63141	21Mar2012 – 24Jul2013	8027-001 – 8027-002, 8027-004 – 8027-007, 8027-009, 8027-011 – 8027-012, 8027-018 – 8027-020, 8027-022 – 8027-025, 8027-027 – 8027-028, 8027-030
8028	Stephen Miller, MD Stephen Miller, MD, PA 16110 Via Shavano San Antonio, TX 78249	03May2012 – 26Jun2013	8028-002 – 8028-004, 8028-007, 8028-009

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8038	Ronald Vender, MD Dermatrials Research 132 Young Street Hamilton, ON L8N 1V6 Canada	20Mar2012 – 02Jul2013	8038-001 – 8038-007
8040	William Harwell, MD Dermatology Research Associates 1900 Patterson St., Suite 104 Nashville, TN 17203	26Mar2012 – 23Jul2013	8040-001 – 8040-004, 8040-007 – 8040-010, 8040-012, 8040-015 – 8040-016
8045	Yves Poulin, MD Centre de Recherche Dermatologique du Quebec Metropolitain CRDQ 2880 Chemin Quatre-Bourgeois Suite 105 Quebec, QC G1V 4X7 Canada	12Apr2012 – 18Jul2013	8045-001 – 8045-003, 8045-005 – 8045-014
8052	Joseph Samady, MD Dermatology Specialists, Inc. 3629 Vista Way Oceanside, CA 92056	29May2012 – 18Jun2013	8052-003
8069	Joseph Fowler, MD Dermatology Specialists Research 501 South Second Street Louisville, KY 40202	11Apr2012 – 29Jul2013	8069-001 – 8069-002, 8069-004 – 8069-0016
8074	Ava Shamban, MD ATS Clinical Research 2021 Santa Monica Blvd. Suite 600 East Santa Monica, CA 90404	06Mar2012 – 26Mar2013	8074-001 – 8074-006
8091	Lyn Guenther, MD The Guenther Dermatology Research Center 835 Richmond Street London, Ontario N6A 3H7 Canada	25Apr2012 – 26Jul2013	8091-001 – 8091-005, 8091-007 – 8091-009, 8091-011 – 8091-012, 8091-015 – 8091-016, 8091-018 – 8091-020, 8091-023
8110	Zoe Draelos, MD Zoe Diana Draelos, MD 2444 North Main Street High Point, NC 27262	29Feb2012 – 17Jul2013	8110-001 – 8110-007, 8110-010, 8110-012, 8110-014 – 8110-017, 8110-019 – 8110-023, 8110-025 – 8110-033
8113	Tiffani K. Hamilton, MD Atlanta Dermatology, Vein & Research Center, LLC 11800 Atlantis Place Alpharetta, GA 30022	29Mar2012 – 26Jul2013	8113-001, 8113-004 – 8113-010

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8121	Darryl Toth, MD XLR8 Medical Research, Inc. 2425 Tecumseh Road East, Suite 210 Windsor, Ontario N8W 1E6 Canada	22Mar2012 – 09Jul2013	8121-001 – 8121-008, 8121-010, 8121-013 – 8121-018
8129	Fasahat Hamzavi, MD Hamzavi Dermatology 2950 Keewahdin Road Fort Gratiot, MI 48059	16Feb2012 – 02Jul2013	8129-001 – 8129-002, 8129-004, 8129-006 – 8129-008, 8129-011 – 8129-012, 8129-014 – 8129-025
8132	Rodion A. Kunynetz, MD Ultranova Skincare 125 Bell Farm Road, Suite 104 Barrie, ON L4M 6L2 Canada	19Mar2012 – 21Jun2013	8132-001 – 8132-007
8133	Angela Moore, MD Arlington Research Center, Inc. 711 East Lamar Blvd., Suite 100 & 200 Arlington, TX 76011	05Jan2012 – 25Jul2013	8133-001 – 8133-003, 8133-005 – 8133-019, 8113-023 – 8133-028, 8133-030 – 8133-031, 8133-033
8134	Jeffrey Moore, MD Gary Waterman, MD Deaconess Clinic, Inc. 421 Chestnut Street Evansville, IN 47713	13Apr2012 – 31Jul2013	8134-003, 8134-007 – 8134-008
8135	Les Rosoph, MD North Bay Dermatology Centre 500 Cassells Street North Bay, ON P1B 3Z7 Canada	19Mar2012 – 01Aug2013	8135-001, 8135-003 – 8135-014, 8135-016, 8135-018 – 8135-023
8137	Eduardo Tschen, MD Academic Dermatology Associates 1203 Coal Avenue, SE Albuquerque, NM 87106	28Feb2012 – 26Jun2013	8137-001 – 8137-004, 8137-006 – 8137-022
8142	Kenneth Dawes, MD Dawes Fretzin Clinical Research Group, LLC 8103 Clearvista Parkway, Suite 260 Indianapolis, IN 46256	29Mar2012 – 18Jul2013	8142-001 – 8142-003, 8142-005 – 8142-007, 8142-009 – 8142-010, 8142-013
8143	Hector Wiltz, MD FXM Research Corp. 11760 Bird Road, Suite 452 Miami, FL 33175	11Apr2012 – 17Jul2013	8143-001 – 8143-005, 8143-007 – 8143-008, 8143-010, 8143-012, 8143-014 – 8143-017, 8143-020 – 8143-026, 8143-028 – 8143-034, 8143-036
8149	Jerry Bagel, MD The Psoriasis Treatment Center of Central NJ 59 One Mile Rd., Suite G East Windsor, NJ 08520	21Feb2012 – 12Jul2013	8149-001, 8149-003 – 8149-004, 8149-006 – 8149-008, 8149-011

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8150	Elyse Rafal, MD Derm Research Center of New York, Inc. 2500 Route 347, Building 22A Stony Brook, NY 11790	13Jan2012 – 29Jul2013	8150-001 – 8150-007, 8150-009 – 8150-013, 8150-015 – 8150-017, 8150-019 – 8150-021
8155	George Murakawa, MD Somerset Skin Centre 255 Kirts Boulevard, Suite 100 Troy, MI 48084	13Mar2012 – 26Jul2013	8155-001 – 8155-013
8161	Lorne Albrecht, MD Guildford Dermatology Specialists 15300 105th Avenue, Suite 20 Surrey, British Columbia V3R 6A7 Canada	10Apr2012 – 17Jul2013	8161-001 – 8161-002, 8161-004 – 8161-014
8188	Diane Thiboutot, MD Penn State Hershey Medical Center Department of Dermatology UPCII - Room 2010 500 University Drive Hershey, PA 17033-0850	12Apr2012 – 29May2013	8188-001 – 8188-007
8191	Bethanee Schlosser, MD Northwestern University Department of Dermatology 676 N. St. Clair Street, Suite 1600 Chicago, IL 60611	10Apr2012 – 17Jul2013	8191-001 – 8191-005, 8191-007, 8191-009 – 8191-010, 8191-012 – 8191-014, 8191-018 – 8191-019
8208	David Greenstein, MD Northeast Dermatology Associates 138 Conant Street Beverly, MA 01915	07Mar2012 – 16Jul2013	8208-001 – 8208-002, 8208-004 – 8208-006, 8208-008 – 8208-013, 8208-015, 8208-017
8212	Phoebe Rich, MD Oregon Dermatology and Research Center 2565 NW Love Joy, Suite #200 Portland, Oregon 97210	13Mar2012 – 27Jun2013	8212-002 – 8212-005, 8212-007 – 8212-018
8213	James Solomon, MD Leavitt Medical Associates of FL / dba Ameriderm Research 725 West Granada Blvd., Suite 44 Ormond Beach, FL 32174	25Jan2012 – 30Jul2013	8213-001 – 8213-002, 8213-007, 8213-013, 8213-015 – 8213-016, 8213-018, 8213-020 – 8213-026, 8213-028 – 8213-030, 8213-032 – 8213-033
8228	Andrew Pollack, MD Philadelphia Institute of Dermatology 501 Office Center Drive, Suite 195 Fort Washington, PA 19034	08Feb2012 – 29Jul2013	8228-001 – 8228-006, 8228-008 – 8228-016, 8228-018 – 8228-025
8254	David Fivenson, MD, PLC 3001 Miller Road Ann Arbor, MI 48103	27Feb2012 – 10Jun2013	8254-001 – 8254-003, 8254-005 – 8254-009

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8255	Lawrence Parish, MD Paddington Research 1760 Market Street, Suite 301 Philadelphia, PA 19103	08Feb2012 – 29Jul2013	8255-001 – 8255-018, 8255-021 – 8255-024
8258	Fred Bodie, MD Coastal Clinical Research, Inc. 100 Memorial Hospital Drive Annex Building / Suite 3-B Mobile, AL 36608	24Jan2012 – 18Jul2013	8258-002, 8258-004, 8258-006 – 8258-007, 8258-009, 8258-013, 8258-015 – 8258-016
8297	Jeffrey Sugarman, MD Redwood Dermatology Research / Redwood Family Dermatology 2725 Mendocino Avenue Santa Rosa, CA 95403	26Jan2012 – 29Jul2013	8297-001 – 8297-012
8303	Martin Steinoff, MD University of California-San Francisco 1701 Davisadero St., Room 430 San Francisco, CA 94115	12Apr2012 – 17Jul2013	8303-001 – 8303-002, 8303-003, 8303-005 – 8303-006, 8303-008 – 8303-011
8320	Scott Gottlieb, MD Dermatology and Skin Surgery Center 501 Gordon Drive Exton, PA 19341	21Feb2012 – 10Jul2013	8320-002 – 8320-008, 8320-010, 8320-012, 8320-017 – 8320-019
8329	Steven Davis, MD Dermatology Clinical Research Center of San Antonio 7810 Louis Pasteur, Suite 200 San Antonio, TX 78229	26Jan2012 – 14May2013	8329-001, 8329-003 – 8329-006, 8329-011, 8329-018
8338	Mani Raman The Centre for Dermatology 312 Highway 7 East Richmond Hill, ON L4B 1A5 Canada	24Mar2012 – 18Jul2013	8338-002, 8338-004 – 8338-007, 8338-010 – 8338-032
8352	Suephy Chen Emory University 1525 Clifton Road, 3rd Floor Dermatology Atlanta, GA 30322	11May2012 – 26Jun2013	8352-001, 8352-004 – 8352-007
8353	Richard Fried, MD Yardley Dermatology Associates 903 Floral Vale Blvd. Yardley, PA 19067	16Feb2012 – 23Jul2013	8353-001 – 8353-002, 8353-004 – 8353-012, 8353-015 – 8353-016, 8353-018
8359	Ethan Nguyen, MD Integrated Research Group, Inc. 4646 Brockton Avenue, Suite 202-3/301 Riverside, CA 92506	28Feb2012 – 12Jun2013	8359-001 – 8359-006

RD.06.SRE.18171 PRINCIPAL INVESTIGATORS			
Site #	**Name/Address**	**Dates of Participation**	**Subject Identifier Series**
8360	Rebekah Oyler, MD PMG Research of Raleigh, LLC 3521 Haworth Drive, Suite 100 Raleigh, NC 27609	06Jan2012 – 10Jul2013	8360-001, 8360-005, 8360-009, 8360-011, 8360-013 – 8360-014, 8360-016 – 8360-019, 8360-021 – 8360-022, 8360-025, 8360-027 – 8360-028, 8360-031
8367	Michael Bukhalo, MD Altman Dermatology Associates 1100 W. Central Road Suite 200 Arlington Heights, IL 60006	03Apr2012 – 22Jul2013	8367-001, 8367-003 – 8367-016, 8367-018 – 8367-021

Attachment C

Table 42: Clinical Investigator Financial Disclosures for Trials 18171, 40027, 18170 and 40106

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206255

Submission Date(s): 12-20-13

Applicant: Galderma Research and Development, LLC

Product: (ivermectin) Cream, 1%

Reviewer: Jane Liedtka, MO, DDDP

Date of Review: Jan 31, 2014

Covered Clinical Study (Name and/or Number): 18171

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 50		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[3] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

1.3.4 FINANCIAL DISCLOSURE

Details of Discloseable Financial Arrangements

Dr. (b) (6)

- Consulting and Research Fees (including travel costs) totaling $45,852

Minimization of Potential Bias

Study RD.06.SRE.18171 was a multicenter, randomized, double-blind, vehicle-controlled clinical trial that involved 50 investigational sites and enrolled 689 subjects. Dr. (b) (6) enrolled relatively few patients for this study (b) (6)% and as such, there is little potential for bias resulting from these disclosed financial arrangements.

Dr. (b) (6)

- Consulting and Research Fees (including travel costs) totaling $297,904

Minimization of Potential Bias

Study RD.06.SRE.18171 was a multicenter, randomized, double-blind, vehicle-controlled clinical trial that involved 50 investigational sites and enrolled 689 subjects. Dr. (b) (6) enrolled relatively few patients for this study (b) (6)% and as such, there is little potential for bias resulting from these disclosed financial arrangements.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206255

Submission Date(s): 12-20-13

Applicant: Galderma Research and Development , LLC

Product: (ivermectin) Cream, 1%

Reviewer: Jane Liedtka, MO, DDDP

Date of Review: Jan 31, 2014

Covered Clinical Study (Name and/or Number): 40027

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 26		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ Not applicable	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ Not applicable	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[4] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206255

Submission Date(s): 12-20-13

Applicant: Galderma Research and Development , LLC

Product: (ivermectin) Cream, 1%

Reviewer: Jane Liedtka, MO, DDDP

Date of Review: Jan 31, 2014

Covered Clinical Study (Name and/or Number): 18170

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 50		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[5] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Details of Discloseable Financial Arrangements

Dr. (b) (6)

- Consulting and Research Fees (including travel costs) totaling $102,213

Minimization of Potential Bias

Study RD.06.SRE.18170 was a multicenter, randomized, double-blind, vehicle-controlled clinical trial that involved 50 investigational sites and enrolled 683 subjects. Dr. (b) (6) enrolled relatively few patients for this study (b) (6)% and as such, there is little potential for bias resulting from these disclosed financial arrangements.

Dr. (b) (6)

- Consulting and Research Fees (including travel costs) totaling $56,969

Minimization of Potential Bias

Study RD.06.SRE.18170 was a multicenter, randomized, double-blind, vehicle-controlled clinical trial that involved 50 investigational sites and enrolled 683 subjects. Dr. (b) (6) enrolled relatively few patients for this study (b) (6)% and as such, there is little potential for bias resulting from these disclosed financial arrangements.

Dr. (b) (6)

- Consulting and Research Fees (including travel costs) totaling $60,884

Minimization of Potential Bias

Study RD.06.SRE.18170 was a multicenter, randomized, double-blind, vehicle-controlled clinical trial that involved 50 investigational sites and enrolled 683 subjects. Dr. (b) (6) enrolled relatively few patients for this study (b) (6) % and as such, there is little potential for bias resulting from these disclosed financial arrangements.

The statistical reviewer did the calculations to remove these centers from the results for trial 18170. He states, “the removal of the centers with financial disclosures actually made the treatment effect for both endpoints slightly larger”.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206255

Submission Date(s): 12-20-13

Applicant: Galderma Research and Development , LLC

Product: (ivermectin) Cream, 1%

Reviewer: Jane Liedtka, MO, DDDP

Date of Review: Jan 31, 2014

Covered Clinical Study (Name and/or Number): 40106

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 23		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[6] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Details of Discloseable Financial Arrangements

(b) (6)

- Consulting and Research Fees (including travel costs) totaling $82,845

Minimization of Potential Bias

Study RD.06.SRE.40106 was a multicenter, randomized, double-blind, vehicle-controlled Phase 2 clinical trial that involved 24 investigational sites and enrolled 210 subjects. (b) (6) enrolled relatively few patients for this study (b) (6)% and as such, there is little potential for bias resulting from these disclosed financial arrangements.

This phase 2 trial would not significantly impact the findings as it was only supportive.

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

/s/

JANE E LIEDTKA
10/17/2014

JILL A LINDSTROM
11/05/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206255 **Applicant:** Galderma Research and Development, LLC **Stamp Date:** 12/20/13

Drug Name: Ivermectin 1% Cream **NDA/BLA Type:** standard

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical overview pg 60
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2)-literature for peri and post natal info
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 40027 Study Title: ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR ROSACEA OVER 12 WEEKS Sample Size: 296 Arms:6 Location in submission: 5.3.5.1	X			
EFFICACY					

Reference ID: 3446551

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 #18170 A Phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1 % cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel Indication: papulopustular rosacea Pivotal Study #2 #18171 A Phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1 % cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel Indication: papulopustular rosacea	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			See SPA letter dated 10-22-2008
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

Reference ID: 3446551

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MEDRA 12
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No deaths in the development program
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Documentation for waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

No issues from clinical reviewer

Jane Liedtka, MD 1/29/14

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3446551

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

/s/

JANE E LIEDTKA
02/03/2014

JILL A LINDSTROM
02/03/2014