

Clinical Pharmacology Review

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| NDA #: | 202736 |
| Submission Date: | April 07, 2011 |
| Brand Name: | Sklice |
| Generic Name: | Ivermectin |
| Dosage Form: | Lotion |
| Dosage Strength: | 0.5% |
| Reviewer: | Chinmay Shukla, Ph.D. |
| Team Leader: | Doanh Tran, Ph.D. |
| OCP Division: | DCP-3 |
| OND Division: | Division of Dermatology and Dental Products |
| Sponsor: | Topaz Pharmaceuticals, Inc. |
| Relevant IND(s): | 073,134 |
| Submission Type: | Original |
| Indication: | Topical treatment of head lice (b) (4) in patients 6 months of age and older |

Table of Contents

| | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|----|
| 1. Executive Summary | * | * | * | * | * | * | * | * | 1 |
| 1.1 Recommendation | * | * | * | * | * | * | * | * | 2 |
| 1.2 Post-Marketing Requirements/Commitments | | | | * | * | * | * | * | 2 |
| 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings | * | | | | | | | | 2 |
| 2. Question Based Review | * | * | * | * | * | * | * | * | 3 |
| 2.1 General Attributes of the Drug | | * | * | * | * | * | * | * | 3 |
| 2.2 General Clinical Pharmacology | * | * | * | * | * | * | * | * | 6 |
| 2.3 Intrinsic Factors | * | * | * | * | * | * | * | * | 8 |
| 2.4 Extrinsic Factors | * | * | * | * | * | * | * | * | 9 |
| 2.5 General Biopharmaceutics | | * | * | * | * | * | * | * | 9 |
| 2.6 Analytical Section | * | * | * | * | * | * | * | * | 10 |
| 3. Detailed Labeling Recommendations | | | * | * | * | * | * | * | 12 |
| 4. Individual Study Review | * | * | * | * | * | * | * | * | 13 |
| 5. Appendix - Sponsor proposed original package insert (Section 8.3 and 12) | | | | | | | | * | 25 |

1. Executive Summary

With this NDA, the Sponsor is seeking approval for ivermectin lotion, 0.5% for the topical treatment of head lice (b) (4) in patients 6 months of age and older.

Ivermectin (22, 23-dihydroavermectin B_{1a} [H₂B_{1a}] + 22, 23-dihydroavermectin B_{1b} [H₂B_{1b}]) is a mixture of avermectins, a class of highly active broad-spectrum antiparasitic agent isolated from the fermentation products of naturally occurring bacterium *Streptomyces avermitilis*. It contains not less than 90% of H₂B_{1a} (major component).

Oral ivermectin (Stromectol[®]) was approved on 11/22/1996 (NDA 050742) for the treatment of strongyloidiasis of the intestinal tract due to nematode parasite *Strongyloides*

stercoralis and for the treatment of onchocerciasis due to nematode parasite *Onchocerca volvulus*. To date, no topical form of ivermectin has been approved by the Agency.

For this application the Sponsor is following a 505(b)(1) regulatory pathway and has obtained a right of reference from Merck Sharp & Dohme Corp. to reference NDA 050742 (Stromectol®).

1.1 Recommendation

From a Clinical Pharmacology standpoint, the Sponsor has met the requirements under 21 CFR 320 and the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Post-Marketing Requirements/ Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA the Sponsor has completed 7 clinical trials and pharmacokinetics (PK) was evaluated only in 2 trials shown below, under maximal use conditions in subjects with head lice.

| Trial Number | Subject Age | Formulation |
|--------------|---------------------|--|
| TOP001 | 4 to 10 years | Old topical formulation of ivermectin, 0.5% |
| TOP008 | 6 months to 3 years | To-be-marketed topical formulation of ivermectin, 0.5% |

Ivermectin lotion was administered as a single treatment by the clinical staff in a quantity sufficient to saturate the hair and scalp. The formulation was left for 10 minutes and then rinsed off. Primary PK data are available from Trial TOP008 which was conducted using the to-be-marketed formulation, with additional supporting information from Trial TOP001 which was conducted using a slightly different formulation. The original formulation was modified during development (b)(4)

Trial TOP008 was an open-label study to assess the bioavailability, safety, local tolerance and efficacy of 0.5% ivermectin lotion in subjects 6 months to 3 years of age with *Pediculus humanus capitis* (head lice infestation). 30 male and female subjects aged 6 months to 3 years were enrolled but PK was assessed only in 20 subjects. PK data are available from 19 subjects (ivermectin concentrations in the remaining 1 subject were below LLOQ of 0.05 ng/mL). The results showed that C_{max} (mean \pm SD) and AUC_{tlast} (mean \pm SD) were 0.24 ± 0.23 ng/mL, and 6.70 ± 11.23 hr*ng/mL respectively.

Trial TOP001 was a randomized study to compare the safety, local tolerance, PK, and efficacy of 0.5% ivermectin in a topical shampoo/conditioner preparation compared to

oral ivermectin (Stromectol[®]) and a topical placebo in subjects aged 4 to 10 years with head lice infestation. 26 male and female subjects were enrolled and randomized to a treatment arm. Particularly, there were 15 subjects in the topical ivermectin arm, 5 subjects in the topical placebo arm, and 6 subjects to oral ivermectin arm. The results indicated that all plasma concentrations of ivermectin following topical administration were below the LLOQ of 5 ng/mL. Following oral administration of a single dose of 150 µg/kg, 4 out of 6 subjects were included in the PK analysis (2 subjects were excluded due to lack of availability of 2 post-treatment PK blood samples). The C_{max} (mean ± SD) following oral administration was 41.83 ± 20.44 ng/mL. Calculation of AUC was not possible due to sparse data.

Since oral C_{max} in Trial TOP001 was 41.83 ± 20.44 ng/mL and all systemic concentrations following topical administration were below the LLOQ of 5 ng/mL, one can infer that the C_{max} following topical administration was at least 8-fold lower than the C_{max} following the oral dose.

Comparing the PK results from trial TOP001 and TOP008, the mean C_{max} following topical administration (0.24 ± 0.23 ng/mL) was ~ 175 fold lower than the mean C_{max} following oral administration (41.83 ± 20.44 ng/mL) (This is cross study comparison and both studies used different analytical methods).

Based on information from NDA 050742 (Stromectol[®]), following administration of 165 µg/kg oral dose the mean C_{max} from 2 trials is reported as 46.6 ng/mL and 30.6 ng/mL and the mean AUC₍₀₋₇₂₎ is reported as 726 hr*ng/mL and 513 hr*ng/mL respectively. Comparing the mean C_{max} (0.24 ng/mL) and mean AUC_{last} (6.70 hr*ng/mL) following topical administration of ivermectin for 10 minutes (Trial TOP008), the mean C_{max} following topical administration was ~ 194 and 128 fold lower than those observed following 165 µg/kg oral dose and corresponding AUC was ~ 108 and 77 fold lower (this observation is based on cross study comparison).

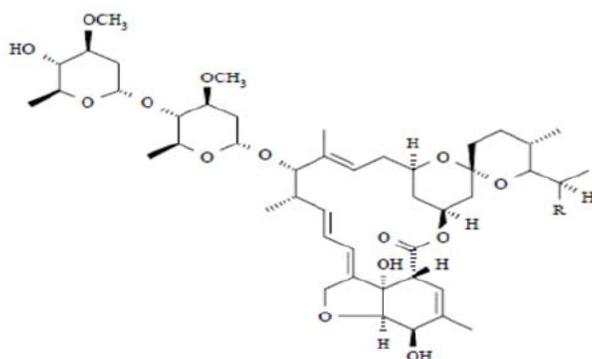
Clinical Pharmacology Briefing: An optional intra-division level Clinical Pharmacology briefing was conducted on 11/17/2011 with the following in attendance: Chinmay Shukla, Doanh Tran, Jane Liedtka, Manuela Vieira, Abimbola Adebawale, Hae-Young Ahn, and E. Dennis Bashaw.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance: Ivermectin contains not less than 90% of H₂B_{1a} (major component). The molecular formula of H₂B_{1a} and H₂B_{1b} is C₄₈H₇₄O₁₄ and C₄₇H₇₂O₁₄, respectively and the molecular weight of H₂B_{1a} and H₂B_{1b} is 875.1 and 861.1, respectively. The chemical structure of ivermectin is shown in Figure 1.



Component H₂B_{1a}: R = CH₂CH₃ Component H₂B_{1b}: R = CH₃

Figure 1: Structure of Ivermectin

Formulation: Table 1 below shows the composition of to-be-marketed ivermectin lotion, 0.5% w/w.

Table 1: Composition of the to-be-marketed ivermectin lotion, 0.5% w/w

| Component | Quality Standard | Function | %w/w |
|----------------------|------------------|----------------|------|
| Ivermectin | USP | Drug Substance | 0.5 |
| Purified Water | USP | (b) (4) | |
| Olive Oil | NF | | |
| Crodalan AWS | In house | | |
| Oleyl alcohol | NF | | |
| Lanolin alcohol | NF | | |
| Cyclomethicone | NF | | |
| Shea butter | In house | | |
| Sorbitan tristearate | In house | | |
| Methylparaben | NF | | |
| Propylparaben | NF | | |
| Citric Acid | USP | | |
| Sodium Citrate | USP | | |

Change in formulation: Microbial contamination was discovered in the original drug product. Hence the Sponsor modified the formulation (b) (4)

Trial TOP001 was conducted using the old formulation while trial TOP008 was conducted using the to-be-marketed formulation. Table 2 below shows comparison between formulations used in trials TOP001 and TOP008.

Table 2: Comparison between the original formulation (used in Study TOP001) and the to-be-marketed formulation (used in Study TOP008)

| Ingredient | Formulation #2440 used in TOP001 study | Final Drug Product Formulation used in TOP008 study |
|----------------------|--|---|
| Crodalan AWS | | (b) (4) |
| Oleyl Alcohol, NF | | |
| Ivermectin | 0.50 | 0.50 |
| Olive Oil, NF | | (b) (4) |
| Lanolin Alcohol, NF | | |
| Cyclomethicone, NF | | |
| Shea Butter | | |
| Sorbitan Tristearate | | |
| Methylparaben, NF | | |
| Propylparaben, NF | | |
| Purified Water, USP | | |
| Citric Acid, USP | | |
| Sodium Citrate, USP | | |

Reviewer comments: *The formulation in the original application was denoted as a cream. However, the Sponsor changed it to lotion based on CMC recommendation (See communication in DARRTS dated 10/14/2011).*

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: Ivermectin is a member of the avermectin class of broad-spectrum anti-parasitic agents which have a unique mode of action. Compounds of the class cause death of the parasite primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels.

Therapeutic indication: Topical treatment of head lice (b) (4) in patients 6 months of age and older

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical

Proposed dosage: Apply ivermectin topical lotion, 0.5% to dry hair in an amount sufficient (up to 1 tube*) to thoroughly coat hair and scalp. When the application is

complete, the formulation should be left on the hair and scalp for 10 minutes, and then rinsed off with water.

* The formulation will be supplied in a 4 oz. (120 mL) tube and the tube is intended for single use and should be discarded after use.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies and what is the PK of ivermectin topical lotion, 0.5%?

Systemic exposure: PK was evaluated in 2 trials in subjects with head lice under maximal use conditions.

| Trial Number | Subject Age |
|--------------|---------------------|
| TOP001 | 4 to 10 years |
| TOP008 | 6 months to 3 years |

Ivermectin lotion was administered as a single treatment by the clinical staff in a quantity sufficient to saturate the hair and scalp. The formulation was left for 10 minutes and then rinsed off. Primary PK data are available from Trial TOP008 which was conducted using the to-be-marketed formulation, with additional supporting information from Trial TOP001 which was conducted using a slightly different formulation. The original formulation was modified during development (b) (4)

Primary maximal use PK trial: Trial TOP008 was an open-label study to assess the bioavailability, safety, local tolerance and efficacy of 0.5% ivermectin lotion in subjects 6 months to 3 years of age with *Pediculus humanus capitis* (head lice infestation). 30 male and female subjects aged 6 months to 3 years were enrolled but PK was assessed only in 20 subjects. PK data are available from 19 subjects (ivermectin concentrations in the remaining 1 subject were below LLOQ of 0.05 ng/mL). The results showed that C_{max} (mean \pm SD) and AUC_{last} (mean \pm SD) were 0.24 ± 0.23 ng/mL, and 6.70 ± 11.23 hr*ng/mL respectively. The concentration versus time profile up to 24 hours is shown in Figure 2 below. There were only 2 subjects with quantifiable concentrations on Day 8 (168 hour time point) and the concentrations were 0.065 ng/mL and 0.050 ng/mL.

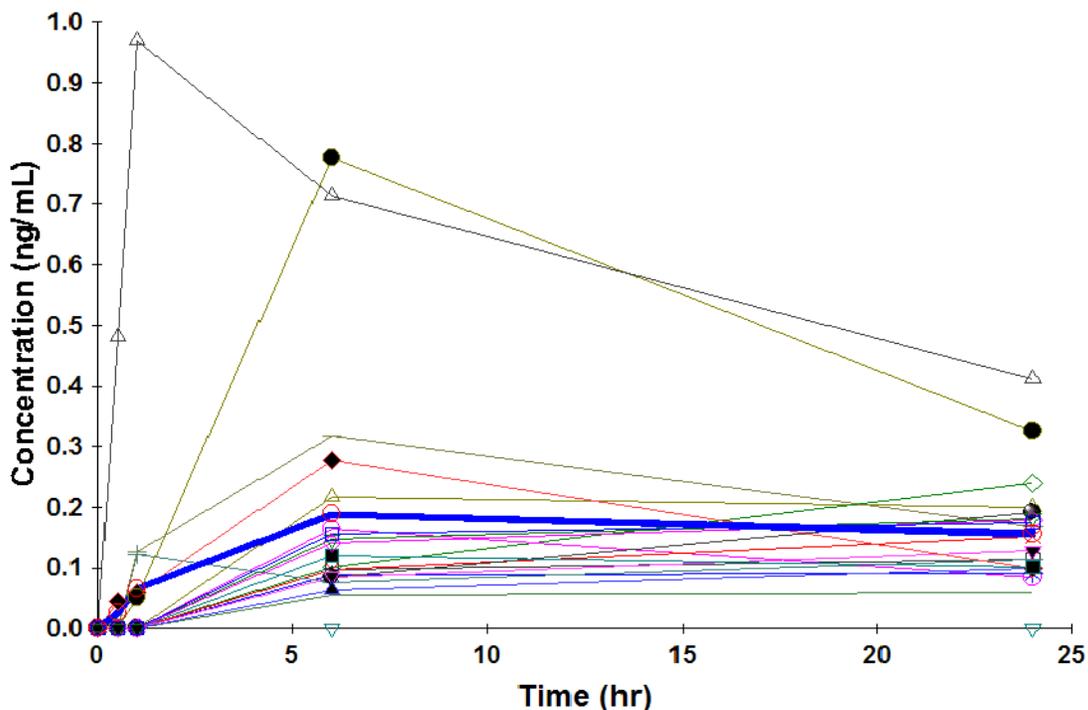


Figure 2: Individual subject ivermectin concentration versus time profile up to 24 hours following topical administration in subjects with head lice (Trial TOP008). The mean profile is shown in the bold blue line.

Supportive PK trial: Trial TOP001 was a randomized study to compare the safety, local tolerance, PK, and efficacy of 0.5% ivermectin in a topical shampoo/conditioner preparation compared to oral ivermectin (Stromectol[®]) and a topical placebo in subjects aged 4 to 10 years with head lice infestation. 26 male and female subjects were enrolled and randomized to a treatment arm. Particularly there were 15 subjects in the topical ivermectin arm, 5 subjects in the topical placebo arm, and 6 subjects to oral ivermectin arm. 5 of 15 subjects in the topical ivermectin arm and 2 of 6 subjects in the oral ivermectin arm discontinued prematurely. All the discontinued subjects were replaced. All subjects in the topical placebo arm completed the study. The results indicated that all plasma concentrations of ivermectin following topical administration were below the LLOQ of 5 ng/mL. Following oral administration of a single dose of 150 µg/kg, 4 out of 6 subjects were included in the PK analysis (2 subjects were excluded due to lack of availability of 2 post-treatment PK blood samples). The C_{max} (mean ± SD) following oral administration was 41.83 ± 20.44 ng/mL. Calculation of AUC was not possible due to sparse data.

The PK samples from trial TOP001 were reanalyzed using a modified (more sensitive) bioanalytical method (LLOQ 0.05 ng/mL) which was later developed. Ivermectin concentrations were quantifiable in 4 out of 6 subjects following oral administration and in 7 out of 15 subjects following topical administration. The results showed that the (mean ± SD) C_{max} (mean ± SD) following oral administration was 35.68 ± 12.53 ng/mL and following the first dose of topical administration was 0.16 ± 0.12 ng/mL. AUC

estimation was not possible due to sparse data. The Sponsor failed to provide adequate long term stability data to support the stability of the reanalyzed PK samples. Hence, the reanalyzed data from trial TOP001 are not considered reliable and no definitive conclusions can be derived.

Relative systemic exposure compared to oral ivermectin: Since oral C_{max} in Trial TOP001 was 41.83 ± 20.44 ng/mL and all systemic concentrations following topical administration were below the LLOQ of 5 ng/mL, one can infer that the C_{max} following topical administration was at least 8-fold lower than the C_{max} following the oral dose.

Comparing PK results from trial TOP001 and TOP008, the mean C_{max} following topical administration (0.24 ± 0.23 ng/mL) was ~ 175 fold lower than the mean C_{max} following oral administration (41.83 ± 20.44 ng/mL) (This is cross study comparison and both studies used different analytical methods).

Based on information from NDA 050742 (Stromectol[®]), following administration of 165 μ g/kg oral dose the mean C_{max} from 2 trials is reported as 46.6 ng/mL and 30.6 ng/mL and the mean $AUC_{(0-72)}$ is reported as 726 hr*ng/mL and 513 hr*ng/mL respectively. Comparing the mean C_{max} (0.24 ng/mL) and mean AUC_{tlast} (6.70 hr*ng/mL) following topical administration of ivermectin for 10 minutes (Trial TOP008), the mean C_{max} following topical administration was ~ 194 and 128 fold lower than those observed following 165 μ g/kg oral dose and corresponding AUC was ~ 108 and 77 fold lower (this observation is based on cross study comparison).

Reviewer comments: *With this application there is PK data available (Trial TOP008) with the to-be-marketed formulation under maximal use conditions in the lowest age group (6 months to 3 years). The results of this trial produced low drug exposure following a 10 minute topical application compared to oral administration (based on cross study comparison) and did not result in any safety signals. Since safety can be extrapolated upwards to older population, the available PK data appear to be adequate to support this NDA.*

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.2 Effect of Gender

The effect of gender on the PK parameters was not evaluated by the Sponsor in this submission.

2.3.2.1 Pediatric patients

The Sponsor has evaluated PK with their to-be-marketed formulation under maximal use conditions in 20 subjects (13 of these subjects were below 15 kg) with head lice of age 6 months to 3 years (Trial TOP008). The C_{max} (mean \pm SD) and $AUC_{0-t_{last}}$ (mean \pm SD) were 0.24 ± 0.23 ng/mL was 6.70 ± 11.23 hr*ng/mL respectively.

The Sponsor has requested for a waiver of pediatric studies in subjects from birth to less than 6 months of age due to the stated reasons of too few patients to study and evidence strongly suggesting that the drug would be unsafe (for more information, see review by Dr. Elizabeth Durmowicz in DARRTS dated 08/30/2011).

2.3.2.2 Renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK. Low levels of absorption and the indication does not justify the study requirement.

2.3.2.3 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK. This study is not justified given the low level of absorption and the indication.

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

There were no studies for ivermectin lotion, 0.5% conducted in pregnant women. As per the approved labeling for oral ivermectin, ivermectin is excreted in human milk in low concentrations.

2.4 Extrinsic Factors

2.4.1 Drug-drug interactions

The Sponsor has not evaluated drug-drug interactions following topical administration of ivermectin. However, from the approved labeling for oral ivermectin, the clinically relevant concentrations of ivermectin following oral administration did not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.

Since the C_{max} following topical administration for 10 minutes was approximately 175 fold lower than following oral administration (although this is based on cross study comparison and the studies used different analytical methods), drug-drug interactions are highly unlikely following topical ivermectin administration.

2.5 General Biopharmaceutics

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

Not Applicable

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

The pivotal Phase 3 clinical trials (TOP011 and TOP012) and the primary PK trial (TOP008) used the to-be-marketed formulation.

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

Not applicable.

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

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

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of ivermectin were determined using high performance liquid chromatography (HPLC) coupled with fluorescence detection. Ivermectin concentrations in the urine were not determined.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites of ivermectin were not selected for analysis.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentrations of ivermectin (unbound and bound) were measured.

2.6.4 Was the analytical method modified during development?

Yes. Initially the sponsor had an assay with LLOQ of 5 ng/mL, which was used for analysis of samples from trial TOP001. A more sensitive assay with LLOQ of 0.05 ng/mL was developed later during the development program and was used to analyze samples from study TOP008. The samples of trial TOP001 were reanalyzed using the more sensitive assay (LLOQ 0.05 ng/mL).

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

| Trial | Range (ng/mL) |
|--------------|----------------------|
| TOP001 | 5 - 500 |
| TOP008 | 0.05 - 10 |

All the concentrations following topical administration in trial TOP001 were below LLOQ (5 ng/mL) while trial TOP008 (LLOQ = 0.05 ng/mL) did produce quantifiable ivermectin concentrations in the plasma. Hence the range of 5 - 500 ng/mL for trial TOP001 was not sensitive enough.

2.6.6 What are the accuracy and precision at LLOQ?

| Trial | LLOQ (ng/mL) | % Accuracy | | % Precision | |
|--------------|---------------------|-------------------|-----------------|--------------------|-----------------|
| | | Intraday | Interday | Intraday | Interday |
| TOP001 | 5 | - 1.9 | - 2.0 | 2.8 | 2.7 |
| TOP008 | 0.05 | -13.3 | -1.5 | 10.1 | 15.0 |

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

The results shown below were adequate to support the stability of ivermectin PK samples.

Trial TOP001

| | |
|---|--------------------|
| Stability of stock solutions at -70°C | 6 weeks |
| Auto-sampler stability at 20°C | 36 hours |
| Stability in plasma at room temperature | 4 hours |
| Long term stability at - 70°C | 92 days |
| Freeze and thaw stability | 3 cycles at - 70°C |

Trial TOP008

| | |
|--|--------------------|
| Stability of stock solutions at 5°C | 35 days |
| Stability of working solutions at 5°C | 14 days |
| Stability in plasma at room temperature | At least 20 hours |
| Short term stability in whole blood at 5°C | 4 hours |
| Long term stability at - 80°C | 148 days |
| Long term stability at - 20°C | 112 days |
| Freeze and thaw stability | 3 cycles at - 70°C |
| Stability of extract at 5°C | 72 hours |

2.6.8 Were any of the trials conducted by Cetero Research in Houston, Texas?

In response to Agency information request dated September 15, 2011, the Sponsor confirms that there were no studies conducted by Cetero Research in Houston, Texas

during the period of concern (April 1, 2005 to June 15, 2010) submitted to NDA 202736 (See communication in DARRTS dated 10/4/2011).

Analysis of samples from trial TOP008 was performed by (b) (4) and for trial TOP001 original PK samples were analyzed by (b) (4)

3. Detailed Labeling Recommendations

The following changes are recommended in the Sponsor's proposed labeling (Sponsor's proposed labeling language is shown in the appendix). The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strike through~~ text indicates recommended deletion.

8.3 Nursing Mothers

Following oral administration, ivermectin is (b) (4) excreted in human milk in low concentrations. Excretion of ivermectin in human milk has not been evaluated following topical administration. (b) (4)

12.2 Pharmacodynamics

Pharmacodynamics of SKLICE Topical Lotion is unknown.

12.3 Pharmacokinetics

The absorption of ivermectin from SKLICE Topical (b) (4) **Lotion** was evaluated in (b) (4) a clinical study (b) (4) in subjects aged from 6 months to (b) (4) 3 years. (b) (4)

This (b) (4) study (b) (4) evaluated pharmacokinetics in 20 lice infested subjects (b) (4) and (b) (4) 13 of these subjects weighed 15 kg or less (overall weight range 8.5-23.9 kg). All enrolled subjects received a single treatment with SKLICE Topical (b) (4) Lotion. (b) (4)

The systemic ivermectin exposure was evaluated using an assay with a lower limit of quantitation of 0.05 ng/mL- (b) (4) The mean (\pm standard deviation) plasma maximum concentration (C_{max}) and area under the concentration-time curve from 0 to time of last measurable concentration ($AUC_{0-t_{last}}$) were (0.24 (b) (4) \pm 0.23 (b) (4)- ng/ml and- (b) (4) $6.7 \pm 11.2 \text{ hr}^* \text{ ng/mL}$ respectively. These levels are much lower than those observed following oral administration of 165 mcg/kg dose of ivermectin. (b) (4)

4. Individual Study Review

Trial TOP008:

Title: An open-label study to assess the bioavailability, safety, local tolerance and efficacy of 0.5% ivermectin lotion in subjects 6 months to 3 years of age with *Pediculus humanus capitis* (head lice infestation).

Study objectives:

Primary

- The primary objective of this study was to determine the bioavailability of 0.5% ivermectin lotion in a pediatric population 6 months to 3 years of age.

Secondary

- Determine the efficacy of 0.5% ivermectin lotion as demonstrated by rapid and sustained eradication (absence) of live head lice by Day 2 and maintained through Day 8 and Day 15 (14 -16 days after treatment).
- Assess the safety and local tolerance of 0.5% ivermectin lotion

Study plan: This was an open-label, multi-center, single application trial to assess the safety and efficacy of a single application of 0.5% ivermectin lotion in subjects 6 months to 3 years of age who had head lice infestation (i.e., presence of at least 1 live louse prior to treatment).

30 subjects with at least 1 live louse were enrolled in this trial and among these, PK was determined in 20 subjects (shown below). Subjects were required to weigh ≤ 15 kg (33 lb) and be within the age range of 6 to 36 months.

The study consisted of 4 scheduled visits: Day 1 (Visit 1), Day 2 (Visit 2), Day 8 (Visit 3 ± 1 day), and Day 15 (14 – 16 days after treatment). All 30 enrolled subjects were treated topically with 0.5% ivermectin lotion on Day 1. Personnel at the study site applied 0.5% ivermectin lotion to thoroughly coat hair and scalp, left the applied product in place for 10 minutes and then rinsed with water. Each subject's parent/guardian was given an inert shampoo (i.e., no known activity against head lice or nits) to use on the subject for the duration of the study, and an FDA-approved over-the-counter lice treatment was provided for use on other affected household members.

Blood samples for PK analysis of H₂B_{1a} (major component) were collected in 20 subjects on Day 1 at pre-dose and at 0.5 hours (± 10 min.), 1 hour (± 10 min.) and 6 hours (± 15 min.), Day 2 (~ 24 hours), and Day 8 (~ 168 hours) post-treatment.

Assessments for safety by collection of safety blood samples, recording of adverse events (AEs), and concomitant medications were performed at each visit. Laboratory safety tests included liver function tests (LFT) and complete blood count (CBC) was also assessed.

On Day 28 (± 2), all treated subjects were followed-up via telephone call to assess occurrence of AEs since their last visit. A post-treatment efficacy assessment (visual

examination of the scalp and hair for live lice) was performed on Days 2, 8, and 15. If live lice were observed on the subject at any of these evaluations, the subject was given an FDA-approved OTC rescue treatment.

Table 3 below provides information about age and weight of the subjects enrolled in this trial.

Table 3: Age and weight of subjects enrolled in Trial TOP008

| Subject ID | Age (months) | Wt (kg) | Remarks |
|-------------------|---------------------|----------------|--------------------|
| TOP008-13-01 | 8 | 7.8 | Not in PK analysis |
| TOP008-14-01 | 34 | 15.0 | Not in PK analysis |
| TOP008-14-02 | 22 | 12.4 | Not in PK analysis |
| TOP008-16-01 | 25 | 13.2 | |
| TOP008-16-02 | 45 | 23.9 | |
| TOP008-16-03 | 45 | 16.8 | |
| TOP008-16-04 | 30 | 14.0 | |
| TOP008-16-05 | 14 | 9.2 | |
| TOP008-16-06 | 17 | 10.3 | |
| TOP008-16-07 | 13 | 10.9 | |
| TOP008-16-08 | 43 | 23.7 | |
| TOP008-16-09 | 35 | 18.5 | |
| TOP008-16-10 | 25 | 11.7 | |
| TOP008-16-11 | 26 | 13.8 | |
| TOP008-16-12 | 20 | 13.2 | |
| TOP008-16-13 | 33 | 15.3 | |
| TOP008-16-14 | 26 | 12.7 | |
| TOP008-16-15 | 22 | 19.2 | |
| TOP008-16-16 | 6 | 8.5 | |
| TOP008-16-17 | 34 | 13.4 | |
| TOP008-16-18 | 37 | 12.1 | |
| TOP008-16-19 | 34 | 10.1 | Not in PK analysis |
| TOP008-16-20 | 34 | 14.4 | Not in PK analysis |
| TOP008-16-21 | 26 | 11.4 | Not in PK analysis |
| TOP008-16-22 | 13 | 9.6 | |
| TOP008-16-23 | 21 | 16.4 | |
| TOP008-16-24 | 9 | 10.9 | Not in PK analysis |
| TOP008-16-25 | 33 | 17.2 | Not in PK analysis |
| TOP008-16-26 | 12 | 11.6 | Not in PK analysis |
| TOP008-16-27 | 22 | 12.4 | Not in PK analysis |

Treatment failures were not evaluated further for efficacy but continued to be evaluated for PK and safety. Eye irritation was assessed within 60 minutes prior to treatment and 6 hours post treatment and on Day 2 (24 hours post treatment). Scalp/skin irritation was assessed within 60 minutes prior to treatment and 6 hours post treatment, and on Day 2, 8 and 15 visits.

Reviewer comments: *Since this trial enrolled subjects with at least one head lice, which was lower than the enrollment criteria for other clinical trials which enrolled subjects with at least 3 head lice, an information request (IR) was sent to the Sponsor (see communication in DARRTS dated 07/22/2011) to provide information regarding number of lice identified at enrollment in each subject. In response the Sponsor stated that since the enrollment criteria in the protocol for Trial TOP008 required enrolling subjects with at least 1 live louse, the total lice count was not captured (see communication in DARRTS dated 07/28/2011).*

In order for a trial to be considered to be under maximal use, it should be conducted in subjects with the dermatological disease of interest at the upper range of severity. An e-mail was sent to Dr. Jane Liedtka and in her response (dated 07/14/2011), she compared the % excoriation in the subjects enrolled in different trials as a measure of disease severity and provided data shown in table below.

| | TOP003 | | TOP008 | TOP010 | | TOP011 | | TOP012 | |
|--------------------|-------------|-------------|-------------|--------------|-------------|--------------|--------------|--------------|--------------|
| | IC* n=57 | VC# n=23 | IC* n=30 | IC* n=192 | VC# n=55 | IC* n=211 | VC# n=199 | IC* n=169 | VC# n=202 |
| Pruritus | 95% | 100% | 50% | 70% | 66% | 60% | 68% | 72% | 72% |
| Erythema | 9.1% | 13% | 6.7% | 13.5% | 9.1% | 7.6% | 11.6% | 26% | 26% |
| Excoriation | 5.5% | 4.3% | 23.3% | 16.2% | 12.7% | 7.6% | 19.1% | 24.9% | 22.8% |
| Pyoderma | 0% | 0% | 0% | 0.5% | 1.8% | 0% | 1.5% | 1.2% | 1.2% |

* IC – Ivermectin

VC - Vehicle

From the table above, Dr. Liedtka pointed out that the % excoriation in subjects enrolled in trial TOP008 was comparable with the values in other clinical trials and based on this data it was concluded that trial TOP008 was conducted under maximal use conditions.

Treatments administered: All subjects were treated with 0.5% ivermectin lotion as a single application on Day 1. Treatment remained on the hair and scalp for 10 minutes prior to rinsing. Treatment was administered by experienced study personnel in the same manner for every subject. Sufficient medication was used to allow thorough application to the scalp and hair. Application began at the scalp, covered the hair closest to the scalp, and then worked outward to cover the entire length of hair.

Demographic information: Details are shown in Table 4 below.

Table 4: Demographic information for Trial TOP008

| | | |
|---------------|---|--------------|
| GENDER | N | 30 |
| | FEMALE | 23(76.7%) |
| | MALE | 7(23.3%) |
| AGE (months) | N | 30 |
| | MEAN | 25.8 |
| | SD | 11.0 |
| | MEDIAN | 26.0 |
| | RANGE | (6.0, 45.0) |
| HEIGHT (inch) | N | 30 |
| | MEAN | 34.3 |
| | SD | 4.2 |
| | MEDIAN | 34.2 |
| | RANGE | (25.5, 41.6) |
| WEIGHT (lb) | N | 30 |
| | MEAN | 30.1 |
| | SD | 8.7 |
| | MEDIAN | 28.5 |
| | RANGE | (17.3, 52.6) |
| ETHNICITY | N | 30 |
| | HISPANIC | 28(93.3%) |
| | NOT HISPANIC OR LATINO | 2(6.7%) |
| RACE | N | 30 |
| | BLACK | 0(0.0%) |
| | ASIAN/PACIFIC ISLANDER | 0(0.0%) |
| | INDIAN/ALASKAN NATIVE | 0(0.0%) |
| | MULTI RACIAL | 0(0.0%) |
| | OTHER | 0(0.0%) |
| | WHITE | 30(100%) |
| HAIR LENGTH | N | 30 |
| | LONG (PAST SHOULDER LENGTH TO MID-BACK) | 1(3.3%) |
| | MEDIUM (SHOULDER LENGTH) | 13(43.3%) |
| | SHORT (EAR LENGTH OR SHORTER) | 15(50.0%) |
| | VERY LONG (PAST MID-BACK) | 1(3.3%) |
| HAIR TEXTURE | N | 30 |
| | COARSE | 4(13.3%) |
| | FINE | 11(36.7%) |
| | MEDIUM | 15(50.0%) |
| HAIR VOLUME | N | 30 |
| | MEDIUM | 13(43.3%) |
| | THICK | 6(20.0%) |
| | THIN | 11(36.7%) |
| HAIR SHAPE | N | 30 |
| | CURLY | 5(16.7%) |
| | STRAIGHT | 17(56.7%) |
| | WAVY | 8(26.7%) |

Definition of PK Parameters:

- AUC_{0-t} or AUC_{last} : Area under the plasma concentration versus time curve from administration through time of last quantifiable concentration.
- AUC_{0-24} : Area under the plasma concentration versus time curve from administration through 24 hours.
- C_{avg} : Time averaged plasma ivermectin concentration (ng/mL) over 24-hours.
- C_{max} : Observed maximum plasma ivermectin concentration (ng/mL).
- T_{max} : Time (hour) at which C_{max} occurs.
- K_{el} : Elimination rate constant.
- $t_{1/2}$: Apparent elimination half-life, calculated as $\ln(2)/K_{el}$.

Pharmacokinetic Results: Plasma samples were analyzed using a validated HPLC method coupled with fluorescence detection with a lower limit of quantification (LLOQ) of <0.050 ng/mL. The PK parameters were calculated using a non-compartmental approach.

PK analysis was performed for 19 of the 20 subjects, the remaining one subject's (Subject 16-23) drug concentrations were below the LLOQ. The mean (\pm standard deviation) plasma maximum concentration (C_{max}) and area under the concentration-time curve from 0 to time of last measurable concentration ($AUC_{0-t_{last}}$) were 0.24 ± 0.23 ng/ml and 6.7 ± 11.2 ng/mL respectively. Concentrations of one subject (16-23) were below LLOQ for all time points. Only one subject (16-03) had sufficient samples containing quantifiable ivermectin to allow calculation of terminal half life ($t_{1/2}$) and it was 49.4 h.

The mean plasma concentrations of ivermectin at each time point are shown in Table 5 below and the concentration versus time profile is shown in Figure 3. Summary of PK parameters is shown in Table 6.

Table 5: Ivermectin concentrations at each time point following topical administration for 10 minutes in trial TOP008

| Time (h) of post application sample collection | Mean ivermectin concentration (ng/mL) | SD ⁽²⁾ | RSD ⁽³⁾ | N ⁽⁴⁾ |
|--|---------------------------------------|-------------------|--------------------|------------------|
| 0 | 0.00000 | 0.00000 | nc ⁽⁵⁾ | 20 |
| 0.5 | 0.02528 | 0.11018 | 435.9% | 19 |
| 1 | 0.08192 | 0.22695 | 285.2% | 19 |
| 6 | 0.20075 | 0.20456 | 101.9% | 19 |
| 24 | 0.16325 | 0.08983 | 55.0% | 18 |
| 168 | 0.05767 | nc | nc | 2 |

⁽¹⁾ BLQ concentrations in the lag time between time zero and the first concentration \geq LLOQ were set at zero, and those between 2 concentrations \geq LLOQ were considered as missing. Trailing concentrations <LLOQ were not used in calculations.

⁽²⁾ SD: standard deviation.

⁽³⁾ RSD: percent coefficient of deviation.

⁽⁴⁾ N: number of used values for calculation.

⁽⁵⁾ nc: not calculated.

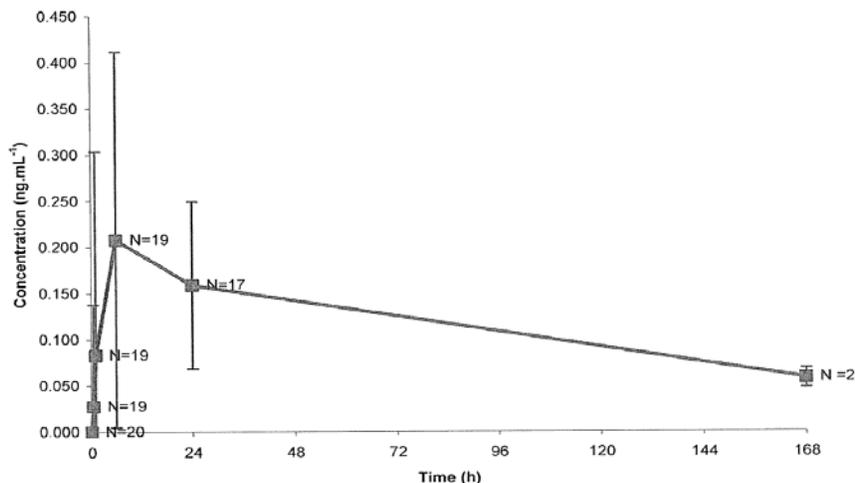


Figure 3: Mean (\pm SD) concentration versus time profile of ivermectin following topical administration in subjects with head lice

Table 6: Summary of PK parameters following topical administration of ivermectin in trial TOP008

| Subject | Dose (mg/kg) | C _{max} (ng/mL) | C _{avg} (ng/h/mL) | T _{max} (h) | AUC _{last} (ng h/mL) | AUC ₀₋₂₄ (ng h/mL) | t _{1/2} (h) | k _{el} (h ⁻¹) |
|---------|--------------|--------------------------|----------------------------|----------------------|-------------------------------|-------------------------------|----------------------|------------------------------------|
| 16-01 | 35.4 | 0.17556 | 0.06632 | 24 | 3.37438 | 3.37438 | NC | NC |
| 16-02 | 20.7 | 0.17875 | 0.06393 | 24 | 3.22887 | 3.22887 | NC | NC |
| 16-03 | 28.8 | 0.96837 | 0.51495 | 1 | 49.2023 | 14.8223 | 49.423 | 0.01402 |
| 16-04 | 25.3 | 0.18204 | 0.06582 | 24 | 3.36608 | 3.36608 | NC | NC |
| 16-05 | 21.5 | 0.77552 | 0.23063 | 6 | 11.9954 | 11.9954 | NC | NC |
| 16-06 | 11.9 | 0.11940 | 0.04420 | 6 | 2.28759 | 2.28759 | NC | NC |
| 16-07 | 14.9 | 0.27811 | 0.08721 | 6 | 4.25122 | 4.25122 | NC | NC |
| 16-08 | 19.8 | 0.09982 | 0.03264 | 24 | 1.62702 | 1.62702 | NC | NC |
| 16-09 | 22.8 | 0.12941 | 0.04300 | 24 | 2.14886 | 2.14886 | NC | NC |
| 16-10 | 25.4 | 0.19247 | 0.05545 | 24 | 20.1786 | 2.70708 | NC | NC |
| 16-11 | 17.6 | 0.05919 | 0.02299 | 24 | 1.17418 | 1.17418 | NC | NC |
| 16-12 | 6.9 | 0.31665 | 0.12265 | 6 | 5.51546 | 5.51546 | NC | NC |
| 16-13 | 6.6 | 0.12143 | 0.06226 | 1 | 2.23166 | 2.23166 | NC | NC |
| 16-14 | 14.8 | 0.15118 | 0.04948 | 24 | 2.46704 | 2.46704 | NC | NC |
| 16-15 | 13.8 | 0.09099 | 0.03597 | 24 | 1.84068 | 1.84068 | NC | NC |
| 16-16 | 3.7 | 0.16521 | 0.05004 | 6 | 2.66491 | 2.66491 | NC | NC |
| 16-17 | 16.0 | 0.11444 | 0.04252 | 24 | 2.15891 | 2.15891 | NC | NC |
| 16-18 | 40.5 | 0.23922 | 0.06808 | 24 | 3.31632 | 3.31632 | NC | NC |
| 16-22 | 17.4 | 0.21722 | 0.08338 | 6 | 4.29497 | 4.29497 | NC | NC |
| 16-23 | 26.8 | NC | 0.00000 | NC | NC | NC | NC | NC |
| N | 19 | 19 | 20 | 19 | 19 | 19 | 1 | 1 |
| Mean | 19.1 | 0.241 | 0.08708 | 15.9 | 6.701 | 3.972 | NC | NC |
| SD | 9.4027 | 0.23372 | 0.11102 | 10 | 11.23 | 3.5142 | NC | NC |
| Min | 3.7 | 0.05919 | 0.00000 | 1 | 1.1742 | 1.1742 | NC | NC |
| Max | 40.5 | 0.96837 | 0.51495 | 24 | 49.202 | 14.822 | NC | NC |

SD: standard deviation
NC: Not calculated

Summary of efficacy: Ivermectin lotion was efficacious in eradicating head lice in 96.7% of subjects on Day 2, 89.7% on Day 8 and 89.3% on Day 15. Eradication was maintained through Day 8 and Day 15 in 86.2% of subjects.

Reviewer comments: *The efficacy results reported here are those that have been reported by the sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical and Biostatistics reviews.*

Summary of safety: According to the Sponsor, clinical observations showed that 0.5% ivermectin lotion was well tolerated and all adverse events were mild or moderate in intensity. Six subjects experienced 6 AEs (erythema, 5; pruritus, 1) which were considered possibly treatment-related. One subject was hospitalized due to acute gastroenteritis, dehydration and diaper dermatitis and these severe AEs were considered to be not treatment related by the investigator. No subject discontinued from the study due to an AE. 0.5% ivermectin lotion was effective in reducing the signs and symptoms of head lice infestation; local scalp/skin excoriation and pruritus were significantly reduced post treatment.

Reviewer comments: *The safety results reported here are those that have been reported by the sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.*

Trial TOP001:

Title: A randomized study to compare the safety, local tolerance, pharmacokinetics, and efficacy of 0.5% ivermectin in a topical shampoo/conditioner preparation compared to

ivermectin orally (Stromectol[®]) and a topical placebo in children with head lice infestation

Study objectives:

Primary

- To compare the safety and tolerability of the topical ivermectin, 0.5%, to a topical placebo (identical with the exception of ivermectin) and to compare the PK (including bioavailability) of topical ivermectin, 0.5%, to the currently marketed oral formulation of ivermectin (Stromectol[®]).

Secondary

- To compare the efficacy of topical ivermectin, 0.5%, to a topical placebo.

Study plan: This was a randomized study, with double-blind and open-label components, designed to compare the safety, local tolerance, PK, and efficacy of a topical 0.5% ivermectin shampoo/conditioner preparation to oral ivermectin or a topical placebo in children with head lice infestation. Safety, tolerability, and PK were the primary objectives of the study.

At admission (Visit 1, Day 1), subjects were verified as having an active head lice infestation. After the inclusion and exclusion criteria were evaluated and the, the subjects with at least 3 live lice that were deemed appropriate were randomized to receive oral therapy or topical treatment. Residents of the subject's household were treated outside the protocol, according to the standard of care for the community, to reduce the possibility of subjects becoming re-infested.

Subjects who received topical treatment, and demonstrated eradication of their infestation (i.e. no active lice) 24 (\pm 2) hours (Visit 2) were asked returned 9 to 11 days later (Visit 3) for a second treatment. Topically treated subjects with persistence of their infestation and oral ivermectin subjects regardless of their infestation status completed the study at Visit 2.

A long term follow-up phone interview (Visit 6) was conducted 30 days after each subject's last dose of study medication to assess serious adverse events (SAEs). Local tolerability (skin and scalp exam), vitals signs, and adverse events (AEs) were assessed at all visits, except Visit 6. Blood and urine for clinical laboratory safety tests (hematology, clinical chemistry, and urinalysis) were drawn at Admission, Visit 2, and Visit 4 (24 hours post Visit 3).

Blood for assay of ivermectin plasma levels was obtained at admission, before dosing (at 0 hour) and after dosing (at 1, 2, and 6 hours), and Visit 2 (24 hours post dose). For subjects who continued in the study, a single blood sample for assay of ivermectin plasma levels was also taken at Visit 4 (24 hours post second dose administered at Visit 3).

A clinical assessment, lice and nit counts, was made at admission, before dosing (at 0 hour) and after dosing (at 1, 2, and 6 hours), and once at all other on-site visits. Subjects

who received topical treatment and withdrew from the study for any reason, other than clinical failure, before completion of Visit 4 did not complete the study and were replaced. Oral ivermectin subjects completed the study at Visit 2, regardless of their lice infestation status.

Treatments:

- Oral ivermectin (Stromectol®) (Dose administered was 150 µg/Kg)
- Topical ivermectin, 0.5%
- Topical placebo

The topical ivermectin, 0.5%, and the topical placebo formulations were decanted in their entirety (60 mL containers) and applied onto the scalp and into dry hair with gloved hands by the investigative staff. After application, the topical treatments remained in place for 10 minutes and were rinsed out with tepid water. Hair was allowed to air-dry, but was not blown dry. Hair may have been gently towel dried (by patting) if deemed necessary by study center staff. These steps of topical application were repeated at Visit 3 (Day 9 to 11) in subjects for whom eradication occurred after the first administration.

Single dose of oral ivermectin formulation (Stromectol®) was administered at a dosage of approximately 150 µg per Kg of body weight, with 6 ounces of water.

Demographic information: Details are shown in Table 7 below.

Table 7: Demographic information for Trial TOP001
(Protocol TOP001)

| Number (%) of Subjects | Oral Ivermectin (N=6) | | Topical Ivermectin (N=15) | | Topical Placebo (N=5) | | Total (N=26) | |
|------------------------|-----------------------|---------|---------------------------|---------|-----------------------|---------|--------------|---------|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Gender | | | | | | | | |
| Male | 1 | (16.7) | 2 | (13.3) | 1 | (20.0) | 4 | (15.4) |
| Female | 5 | (83.3) | 13 | (86.7) | 4 | (80.0) | 22 | (84.6) |
| Race | | | | | | | | |
| White | 6 | (100.0) | 15 | (100.0) | 5 | (100.0) | 26 | (100.0) |
| Ethnicity | | | | | | | | |
| Hispanic or Latino | 5 | (83.3) | 10 | (66.7) | 3 | (60.0) | 18 | (69.2) |
| Not Hispanic or Latino | 1 | (16.7) | 5 | (33.3) | 2 | (40.0) | 8 | (30.8) |
| Age (yrs) | | | | | | | | |
| N | 6 | | 15 | | 5 | | 26 | |
| Mean | 8.0 | | 8.1 | | 8.2 | | 8.1 | |
| SD | 1.90 | | 1.75 | | 2.49 | | 1.85 | |
| Median | 8.0 | | 9.0 | | 9.0 | | 8.5 | |
| Min | 5 | | 4 | | 4 | | 4 | |
| Max | 10 | | 10 | | 10 | | 10 | |
| Height (cm) | | | | | | | | |
| N | 6 | | 15 | | 5 | | 26 | |
| Mean | 123.7 | | 128.4 | | 130.2 | | 127.7 | |
| SD | 13.52 | | 9.82 | | 10.89 | | 10.72 | |
| Median | 123.5 | | 129.0 | | 131.0 | | 128.3 | |
| Min | 106.0 | | 106.5 | | 114.0 | | 106.0 | |
| Max | 145.0 | | 142.0 | | 141.0 | | 145.0 | |
| Weight(kg) | | | | | | | | |
| N | 6 | | 15 | | 5 | | 26 | |
| Mean | 30.1 | | 32.1 | | 34.2 | | 32.0 | |
| SD | 16.31 | | 9.12 | | 10.23 | | 10.88 | |
| Median | 24.4 | | 29.2 | | 33.3 | | 28.3 | |
| Min | 21.0 | | 21.0 | | 22.0 | | 21.0 | |
| Max | 63.0 | | 55.2 | | 47.0 | | 63.0 | |
| ECG | | | | | | | | |
| Normal | 6 | (100.0) | 15 | (100.0) | 5 | (100.0) | 26 | (100.0) |
| QTc Value | | | | | | | | |
| Within normal range | 6 | (100.0) | 15 | (100.0) | 5 | (100.0) | 26 | (100.0) |
| Hair Length | | | | | | | | |
| Short | 4 | (66.7) | 8 | (53.3) | 3 | (60.0) | 15 | (57.7) |
| Long | 2 | (33.3) | 7 | (46.7) | 2 | (40.0) | 11 | (42.3) |

NOTE: Long hair was defined as hair that reached at least 2 inches overhanging the neck to shoulder length, but no longer. Short hair was defined as hair that did not exceed 1 inch overhanging the neck.
KEY: n = Number of subjects contributing to summary statistics; N = Number of subjects in the analysis population by treatment group; % = n/N*100

Subject withdrawal: Overall, 26 subjects were enrolled and randomly assigned to treatment (15 subjects to topical ivermectin, 5 subjects to topical placebo, and 6 subjects to oral ivermectin). Seven subjects (26.9%) discontinued the study prematurely as shown in Table 8 below.

Table 8: Discontinued subjects for trial TOP001
(Protocol TOP001)

| Number (%) of Subjects | Oral Ivermectin (N=6) | | Topical Ivermectin (N=15) | | Topical Placebo (N=5) | | Total (N=26) | |
|---|-----------------------|--------|---------------------------|--------|-----------------------|---------|--------------|--------|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Total Completed | 4 | (66.7) | 10 | (66.7) | 5 | (100.0) | 19 | (73.1) |
| Primary Reason for Discontinuation from Study | | | | | | | | |
| Subject/Parent/Guardian Choice | 0 | | 1 | (6.7) | 0 | | 1 | (3.8) |
| Lost to Follow-up | 0 | | 1 | (6.7) | 0 | | 1 | (3.8) |
| Other | 2 | (33.3) | 3 | (20.0) | 0 | | 5 | (19.2) |
| Total Discontinued | 2 | (33.3) | 5 | (33.3) | 0 | | 7 | (26.9) |

KEY: n = Number of subjects contributing to summary statistics; N = Number of subjects in the analysis population by treatment group; % = n/N*100

5 of 15 subjects in the topical ivermectin group discontinued prematurely, 3 of these subjects discontinued after Visit 1 and 2 subjects discontinued after Visit 2. All 5 discontinued topical ivermectin subjects were replaced. 2 of 6 subjects in the oral ivermectin group discontinued prematurely, both subjects failed to return for Visit 2 and were replaced. All topical placebo subjects completed the study.

Exclusions from the PK population: From among the subjects that completed the study, 9 subjects were excluded from the PK analysis. Particularly, subject 108 and 110 from the oral ivermectin arm, subjects 107, 113, 116 and 129 from the topical ivermectin arm and subject 126 from the topical placebo arm were excluded due to lack of 2 post-treatment blood samples (one of them was a sample at 6 hours post treatment). Additionally there were 2 other exclusions due to no pretreatment blood sample and these excluded subjects were subject 122 of the topical ivermectin arm and subject 127 of the topical placebo group. According to the Sponsor, none of these excluded subjects had detectable levels of ivermectin in the plasma at any other assessed time points.

Reviewer comments: *Since ivermectin concentrations following topical administration was not quantifiable (below the LLOQ), subject withdrawal did not affect PK results. Oral administration produced PK results in 4 out of 6 subjects. 2 subjects were excluded due to lack to availability of 2 post treatment blood samples.*

PK results: The PK results from this trial are considered supportive due to a different formulation used compared to the to-be-marketed formulation used in Trial TOP008 (for additional information on formulation, refer to Section 2.1.1).

Ivermectin was not detected in the plasma of subjects treated with topical ivermectin or topical placebo (limit of quantitation: 5 ng/mL).

Ivermectin was detected in the plasma of all subjects (n = 4) treated with oral ivermectin (Stromectol[®]). The mean dose for oral ivermectin subjects was 168.7 µg/kg (range: 133.3 to 228.1 µg/kg).

Blood samples for assay of H₂B_{1a} (major component) were drawn at 1, 2, and 6 hours after dosing and at Visits 2 (24 hours post treatment) and Visit 4 (24 hours post second treatment at Visit 3, only in case of topical ivermectin). The C_{max} (mean ± SD) following oral administration was 41.83 ± 20.44 ng/mL (calculation of AUC was not possible due to sparse data).

Reviewer comments: *Since oral C_{max} was 41.83 ± 20.44 ng/mL and all systemic concentrations following topical administration were below the LLOQ of 5 ng/mL, one can infer that the C_{max} following topical administration was at least 8-fold lower than the C_{max} following the oral dose.*

Table 9 below shows the mean ivermectin concentration at each time point in 4 subjects that received oral administration. The PK sampling in this arm ended with the 24 hour blood sample.

Table 9: Ivermectin concentrations at each time point following oral administration of 150 µg/kg in trial TOP001

| Visit | Mean (ng/mL) | SD | Median (ng/mL) | Range (min - max) (ng/mL) |
|------------------------|--------------|------|----------------|---------------------------|
| 1 (Pre dose) | 0.0 | 0.0 | 0.0 | 0.0 - 0.0 |
| 1 (1 hour post dose) | 8.4 | 11.8 | 4.3 | 0.0 - 25.0 |
| 1 (2 hours post dose) | 30.0 | 30.8 | 24.2 | 0.0 - 71.7 |
| 1 (6 hours post dose) | 32.3 | 12.3 | 31.5 | 19.2 - 47.1 |
| 2 (24 hours post dose) | 7.8 | 6.1 | 8.5 | 0.0 - 14.2 |

Reviewer comments: *Based on information from NDA 050742 (Stromectol[®]), following administration of 165 µg/kg oral dose the mean C_{max} from 2 trials is reported as 46.6 ng/mL and 30.6 ng/mL and the mean AUC₍₀₋₇₂₎ is reported as 726 hr*ng/mL and 513 hr*ng/mL respectively. Comparing the mean C_{max} (0.24 ng/mL) and mean AUC_{last} (6.70 hr*ng/mL) following topical administration of ivermectin for 10 minutes (Trial TOP008), the mean C_{max} following topical administration was ~ 194 and 128 fold lower than those observed following 165 µg/kg oral dose and corresponding AUC was ~ 108 and 77 fold lower (this observation is based on cross study comparison).*

Dosing variability: All enrolled subjects received at least one dose of study medication. 10 of 15 (66.7%) topical ivermectin subjects returned at Visit 3 and received a second treatment.

All topical treatments were provided as 60 mL doses to be decanted in their entirety. All subjects received <60 mL doses due to the inability of study personnel to fully decant the treatment containers.

The topical ivermectin and placebo groups received similar doses at Visit 1. The mean dose for the topical ivermectin group at Visit 1 (n=15) was 53.1 g (range: 47.3 to 55.7 g). The mean dose for the topical placebo group at Visit 1 (n=5) was 54.7 g (range: 53.4 to 56.1 g). The mean dose for the topical ivermectin group at Visit 3 (n=10) was 53.4 g (range: 50.2 to 55.1 g).

These results indicate that dose variability was low within and across the topical treatment groups and the topical ivermectin group received similar doses at Visits 1 and 3.

Summary of efficacy: Twelve of 12 (100%) topical ivermectin subjects demonstrated eradication of lice at Visit 2, while all of the topical placebo subjects had persistence of their infestations. A majority of these topical ivermectin subjects, 7/12 (58.3%), demonstrated eradication by 4 hours after treatment, and 3 more subjects, for a total of 10/12 (83.3%), achieved eradication by 6 hours after treatment.

10 subjects treated with topical ivermectin at Visit 1 returned for retreatment at Visit 3. 2 of these subjects, both with long hair, had viable lice present at Visit 3. Subject 101 had 3 active lice at Visit 3, compared to 15 active lice at baseline, and Subject 104 had 1 active louse at Visit 3, compared to 15 active lice at baseline. Both the subjects had either a decrease or no change in their nit count, indicating that no new eggs had been laid since the last assessment.

After receiving their second topical treatment at Visit 3, all 10 topical ivermectin subjects demonstrated eradication of their infestation at Visit 4 (24 hours after the second treatment at Visit 3) and remained free of lice infestation at Visit 5 (13-15 days post treatment at Visit 3).

Reviewer comments: *The efficacy results reported here are those that have been reported by the sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical and Biostatistics reviews.*

Summary of safety: All 26 enrolled subjects were included in the safety analyses. At least 1 adverse event (AE) was reported for 3 subjects (11.5%) and 4 AEs were reported overall. No deaths, severe AEs, or AEs leading to discontinuation occurred during the course of the study.

2 of 6 subjects (33.3%) in the oral ivermectin group reported at least one AE considered drug-related in the opinion of the study doctor. No drug related AEs were reported in the topical ivermectin or topical placebo treatment groups.

Overall AEs were reported for 1/15 (6.7%) subjects in the topical ivermectin group and 2/6 (33.3%) subjects in the oral ivermectin group. No AEs were reported for the topical placebo group (n=5).

1 topical ivermectin subject experienced moderate erythema of the antecubital fossa and this was deemed not related to study therapy by the study doctor. 2 oral ivermectin subjects (105 and 106) experienced moderate headaches on Day 1. These events were deemed to have probable relationships to study therapy by the study doctor. On Day 1, Subject 105 also experienced moderate dizziness which was deemed to have a probable relationship to study therapy. Subject 106 was treated with Tylenol for headache which resolved after 1 day. Subject 105's headache and dizziness both resolved after 2 day

Reviewer comments: The safety results reported here are those that have been reported by the sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.

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/s/

CHINMAY SHUKLA
11/22/2011

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11/22/2011