CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name	Sklice
Therapeutic Class	Anti-lice Product
Applicant	Topaz Pharmaceuticals
Formulation(s)	Lotion 0.5%
Dosing Regimen	One 10 minute application
Indication(s)	Head Lice (b) (4)
Intended Population(s)	Patients 6 months and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant submitted a new drug application for a lotion formulation of ivermectin 0.5% proposed for the topical treatment of head lice (b) (4) infestation in subjects 6 months of age and older. This product is the first topical product to have ivermectin as an active ingredient. Oral ivermectin is available as Stromectol which received FDA approval (NDA 050742) for the treatment of onchocerciasis and strongyloidiasis in 1996.

Two well-controlled Phase 3 trials were conducted with the objective of establishing the superiority of a single 10 minute application of ivermectin 0.5% lotion to vehicle. In both Phase 3 trials, ivermectin 0.5% lotion demonstrated superiority over vehicle. Safety data included seven studies conducted under the clinical development program. The incidence of adverse events was low for both the active and vehicle arm, none of which were considered serious.

The applicant provided sufficient clinical data to establish safety and efficacy of their drug product for topical treatment of head lice infestation in patients 6 months of age and older.

Therefore, I recommend approving this NDA.

1.2 Risk Benefit Assessment

In the United States, it is estimated that between 6 and 12 million people per year are diagnosed with head lice. The highest incidence is found in children aged 3 to 11 years. Head lice are more frequent in girls due to the tendency to have longer hair and to exchange hair care accessories.[1] Head lice are uncommon in African-Americans because anatomic differences in American lice do not allow for proper positioning of the female in order to lay eggs on coarse, curly hair.[2,3] Genetic resistance to pyrethroids and to lindane is common in the United States.[4] Available treatments without resistance documented in the United States include malathion 0.5% lotion, benzyl alcohol 5% lotion and Spinosad 0.9% suspension. Malathion is limited to use in children 6 years and older and resistance has been reported in the United Kingdom. Spinosad is limited to use in children 4 years and older. There is a public health need for products for the treatment of head lice with a favorable side effect profile and approval for use in children less than 4 years of age.

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Sklice (Ivermectin Lotion 0.5%) has demonstrated robust efficacy in comparison to vehicle with a single 10 minute treatment for head lice in subjects 6 months of age and older.

Safety was evaluated in the two pivotal trials. Supportive safety data is also available from five other sponsor-conducted Phase 1 and 2 trials. In the clinical development program no deaths occurred and 3 SAEs, all occurring in one subject, were not considered related to study drug. Adverse events which occurred in less than 1% of subjects included conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation . Evaluation of cutaneous safety, scalp irritation (Phases 1, 2, 3) and ocular irritation (Phase 3), did not reveal clinically notable signals.

A theoretical concern about medication errors that might result in the ingestion of the ivermectin product (particularly in young children) resulted in a recommendation for a post-marketing commitment for the sponsor to investigate the feasibility of a child – resistant closure for this product.

The adverse event profile observed reveals a product safe for use in children as young as 6 months. The demonstration of efficacy with a single 10 minute treatment is unique amongst anti-lice products and will likely improve compliance. Sklice (Ivermectin Lotion 0.5%) represents a significant addition to the current armamentarium for the treatment of head lice.

[1] Jacobson CC and Abel EA. Periodic Synopsis: Parasitic Infections. Journal of the American Academy of Dermatology 2007;56:1026-43.
[2] Burkhart CN and Burkhart CG. Head lice: Scientific assessment of the nit sheath with clinical ramifications and therapeutic options. Journal of the American Academy of Dermatology 2005; 53:129-133.
[3] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.
[4] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007; 119; 965-974.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a specific postmarketing risk management plan. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this drug at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

A theoretical concern about medication errors that might result in the ingestion of the ivermectin product (particularly in young children) arose during review of the ivermectin product (See Section 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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for details). I recommend a post-marketing commitment for the sponsor to investigate the feasibility of a child –resistant closure for their product.

2 Introduction and Regulatory Background

2.1 Product Information

The drug substance, ivermectin, is manufactured by Hovione. According to the CMC reviewer, “the applicant has provided an LOA to reference the DMF and VMF for all CMC information”.

The drug product is an off-white to tan topical lotion containing 0.5% (w/w) ivermectin to be marketed under the name Sklice®. The lotion is packaged in a single use white laminate tube (b) (4) It will be a blind end tube, and the cap will not be in contact with the drug product. The drug product is intended to be applied once to the head for the treatment of head lice (b) (4)

There are three novel excipients used in the formulation and according to the CMC reviewer, “an adequate toxicological assessment has been provided by the Applicant in support of their use, which was further assessed by the toxicologist and deemed satisfactory”. All additional excipients are either USP or NF grade and controlled according to the compendial requirements.

The proposed commercial dosage form is a topical lotion of ivermectin (0.5%) referred to by the Applicant as “Ivermectin Cream, (b) (4) Ivermectin Lotion or drug product” throughout the application; all refer to the same product. Per the request of the Agency on 23-SEP-2011 the dosage form was changed from cream to lotion. The official name to be used for this submission is Sklice (Ivermectin) Lotion 0.5%.

2.2 Tables of Currently Available Treatments for Proposed Indications

FDA approved pharmaceutical products for the treatment of head lice include the following:

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Table 1: Treatments for Head Lice

Treatment	Formulations	Rx/OTC	Resistance[1, 2]	Instructions	Ages	Pregnancy Category
Permethrin (e.g.NIX)	1% lotion	OTC	common	Repeat if needed in 7-days	>2 mos	B
Pyrethrin & piperonyl butoxide (e.g. RID)	mousse, shampoo	OTC	common	2 treatments required	>2 yrs	unclassified
Benzyl alcohol (Ulesfia)	5% lotion	Rx	Not yet reported	2 treatments required	> 6 mos	B No teratogenic effects in animal studies
Malathion 0.5% (Ovide)	0.5% lotion	Rx	Not yet reported in US but common in United Kingdom	Repeat if needed in 7-days	> 6 yrs	B No teratogenic effects in animal studies
Lindane 1%	1% lotion	Rx	common	Do not re-treat	Caution < 110 lbs	C neurologic developmental abnormalities in animals
Spinosad (Natroba)	0.9% suspension	Rx	Not yet reported	Repeat if needed in 7 days	> 4 yrs	B No teratogenic effects in animal studies

[1] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007; 119:965-974.
[2] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.
Source: Reviewer's Table

Permethrin and the pyrethrins work by impeding sodium channel closure thereby causing delayed repolarization of the neuron. This causes hyperstimulation of the nervous system, paralyzing the louse and preventing it from feeding.[5] In individuals using pyrethrin-based products, rare cases of exacerbation of asthma and even death have been reported.[6]

NDA 22-129 ULESFIA (benzyl alcohol) Lotion, 5% was approved April 9, 2009 containing 5% benzyl alcohol as the active. The indication is topical treatment of head lice infestation in patients 6 months and older. For ULESFIA, the most common adverse

reactions (> 1% and more common than with placebo) are: ocular irritation, applicant site irritation, and application site anesthesia and hypoesthesia (from the approved product labeling).

Malathion 0.5% and Lindane 1% are discussed in section 2.4 below.

NDA 022408 Natroba (Spinosad 0.9% suspension) was approved Jan 18, 2011. The indication is topical treatment of head lice infestation in patients 4 years and older. As per the FDA approved label, Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die. For Natroba, the most common adverse reactions are application site erythema, ocular erythema and application site irritation (from the approved product labeling).
.
Pharmaceutical products that are used off-label to treat head lice include oral ivermectin (discussed further in Section 7.2.6) with a potential for neurotoxicity and trimethoprim/ sulfamethoxazole with a risk of allergic rash and of Stevens Johnson syndrome.

Physical, non-pharmacologic methods for treating lice include hair removal and occlusion (petroleum jelly, olive oil, mayonnaise, etc.). Another non-pharmacologic method is nit combing. Devices have been approved for the treatment of head lice and include Lice Comb, Lockomb, Licemeister, and others.

[5] Lebwohl M, Clark L, and Levitt J. Op.cit
[6] Wax PM and Hoffman RS. Fatality Associated with Inhalation of a Pyrethrin Shampoo. Clinical Toxicology 1994:32;457-460.

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

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(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

Products which are marketed as insecticides and drugs that are FDA approved prescription products for the indication treatment of head lice include Lindane 1% lotion/shampoo and Malathion lotion 0.5%.

Lindane is γ-benzene hexachloride. By noncompetitively inhibiting the γ-amino butyric acid (GABA) receptor which binds GABA, an inhibitory neurotransmitter, lindane causes neuronal hyperstimulation with ensuing paralysis of the louse and death due to inability to feed.[7] Lindane carries a boxed warning for neurologic toxicity (from the PI):

> Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (59kg) as they may be at risk of serious neurotoxicity.

In addition, Lindane is a pregnancy category C drug.

Malathion is an organophosphate insecticide which, after conversion to malaoxin in the louse, irreversibly inhibits acetylcholinesterase. The ensuing excess cholinergic activity causes neuronal hyperexcitability, preventing feeding. Potential risks associated with Malathion use include flammability due to the high concentration of isopropyl alcohol in the formulation. With accidental oral ingestion, cholinesterase depletion could occur leading to severe respiratory distress. However, according to Lebwohl et al[8], reports of accidental ingestion are exceedingly rare and there are no known reports of bodily injury resulting from the isopropyl alcohol catching fire.

[7] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007; 119:965-974.
[8] Ibid

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

Sklice (ivermectin Lotion) 0.5% was developed under commercial IND 73,134 submitted on April 20, 2007. Principal meetings are outlined in the following table:

Table 2: Principal Presubmission Regulatory Activity

Type of Meeting	Date	Objective
Pre-IND	7/24/06	To provide general guidance on the content and format of the proposed Investigational New Drug Application under 21 CFR 312.
Guidance	11/14/08	To provide advice regarding the need for conducting adequate dose ranging trials prior to conducting Phase 3 trials.
EOP2 Meeting	8/12/09	The objectives of the meeting were to agree upon the proposed CMC, toxicology, and clinical plans to support an NDA submission for Ivermectin Lotion (Sklice) for the treatment of human head lice.
Pre-NDA	1/12/2011	To discuss the content and format of the NDA for Ivermectin Lotion (Sklice) for the proposed indication of the treatment of human head lice.

A **Pre-IND meeting** was held on 7/24/06. The Agency had the following comments and recommendations:

- Include a systemic treatment arm (using the approved Stromectol tablet) in the PK protocol.
- Document the amount of shampoo that will be applied to each patient.
- Investigate the safety and efficacy at various ranges of concentration, duration of application, and frequency of treatment.
- Conduct two well controlled clinical studies for phase 3 to establish efficacy and safety.
- Phototoxicity and photoallergenicity studies may be waived if there are no ingredients in the product that absorb in the 290 – 700 nM spectrum.

The applicant has complied with each of the above requests during the course of their development program.

A **Guidance Meeting** was held via teleconference on 11/14/08. The Agency recommended a Phase 2 dose-ranging trial. The applicant conducted the suggested trial TOP003, the results of which are included in the NDA submission.

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An **EOP2 Meeting** was held on 8/12/09. The Agency had the following comments and recommendations:

- A waiver for subjects under 6 months of age appears reasonable.
- The population enrolled in your pivotal trials needs to include subjects aged 6 months and older. To accomplish this, you will need to have completed your PK study in the youngest cohort prior to initiation of your pivotal trials. Enrollment of sufficient numbers of younger aged subjects will be needed to achieve an indication down to 6 months of age.
- For your PK study we recommend that you enroll a minimum of 15 subjects with a minimum of 12 evaluable subjects completing the study with at least half of the subjects below the age of 2.
- The data from the PK study in the youngest cohort could inform the need for laboratory monitoring in the phase 3 trials.
- Provide a written list of the detailed instructions to be given to the subject that includes the duration of therapy and any ancillary recommendations.
- You propose to conduct the appropriate topical safety studies, a cumulative irritation study in 30 subjects and a contact sensitization study in 200 subjects.
- Submit your rationale for a waiver of QTc studies and data to support that rationale to the NDA.

The applicant has complied with each of the above requests during the course of their development program. There were 11 subjects under the age of 2 in the PK and Safety Study TOP008.

The design of the two pivotal studies was the subject of a **Special Protocol Assessment** (SPA) procedure, originally submitted on 11/17/09. A SPA Agreement was reached on 12/23/09. The following is an excerpt from that letter:

> The following agreements and disagreements are based upon the review of Protocol TOP011 but would apply to both Phase 3 protocols should they be identical as stated in your cover letter. The following are acceptable:

- The general design of your study
- Two identical, well-controlled trials to establish the efficacy of ivermectin Lotion
- Definition of the index subject as the youngest family member presenting with at least 3 live lice
- The proposed dose regimen (single treatment with 0.5% ivermectin Lotion)
- The proposed primary efficacy measure, the absence of live lice in index subjects on day 15 (14 days after last treatment)

- The proposed primary efficacy endpoint, the proportion within each treatment group of index subjects who are lice free on day 15 (14 days post last treatment)
- The proposed primary time point for efficacy assessment (day 15, fourteen days after product administration)
- Active assessment of cutaneous and ocular irritation as proposed
- Generation of the randomization schedule prior to study initiation and randomizing
- Households stratified by investigative site
- The eligibility criteria as defined in the protocol
- Testing the superiority of ivermectin Lotion to vehicle Lotion based on the proportion of INDEX subjects who are lice free at day 15 at the two-sided a=0.05 level using a Cochran-Mantel-Haenszal test stratified by investigative site
- The imputation approach of using LOCF as the primary method and imputing all missing as failures as a sensitivity analysis
- The sensitivity analysis to assess the impact of extreme centers by deleting the most extreme centers after a significant Breslow-Day test (a=0.10)

An agreement **has not been reached** on the following issues:

- Definition of the Intent to Treat (ITT) population – the preferred definition is all INDEX subjects randomized and dispensed medication regardless of whether or not they were treated. For a superiority trial in head lice, the ITT population is considered to be the primary analysis population and the PP population is considered to be supportive.
- The need for laboratory assessments as a part of the safety monitoring for your Phase 3 studies cannot be determined until the full results of study TOP008 (PK and safety study in ages 6 months to three years) are made available and review of these results are completed.

The following comments were also included in the SPA letter:

- Your proposed secondary efficacy endpoint, the proportion within each treatment group of all subjects who are "lice free" on day 15 will not be included in labeling and cannot be used to establish efficacy, as the inclusion criteria for the subjects in this cohort are not the same as those for the index subjects in that subjects in the household cohort are only required to have 1 live louse.
- You propose a clinically meaningful difference of 30%. Taking into account the observed treatment effect from the Phase 2 trial, you should power your Phase 3 trials to ensure that the lower bound of the 95% confidence

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interval is greater than the proposed clinically meaningful difference of 30%.

- The number of sites planned should be defined in the protocol. The study should be planned to enroll at least 8 households per treatment arm. (This statement was later clarified in a teleconference held on 2/5/10 to be "at least 8 households per treatment arm per center".)

With regard to the items under Non-agreements, the applicant subsequently changed the definition of the ITT population to the one the Agency preferred. The applicant did not perform laboratory assessments in the pivotal phase 3 trials. The applicant references the reassuring results of the PK and safety trial TOP008 and the Agency statement made at the EOP2 meeting that results of this trial could "inform the need for laboratory monitoring in the phase 3 trials". Subsequent to the EOP2 meeting the Agency became aware of a safety signal seen in another IND ((b) (4) using Ivermectin Cream 1% in inflammatory rosacea (see section 7.2.6 for details) that prompted us to request that the applicant perform lab evaluations in the phase 3 trials. Our advice letter containing this request was sent on May 14, 2010. On May 24, 2010 we received an email communication from the applicant stating that since enrollment for the trials had been completed and they were ongoing it was not possible for them to incorporate lab evaluation in the trials. This issue will be further discussed in section 7, the safety section of the review.

There is an additional issue with stratification. According to the December 23, 2009 Special Protocol Agreement Letter, randomization in Phase 3 trials were planned to be stratified by site. However, in the NDA submission, the applicant states that "the statistician inadvertently used central randomization and not stratified randomization" for treatment allocation and that the applicant identified the error on April 16, 2010. Consequently, the applicant revised the randomization scheme to be stratified by site beginning on April 16, 2010. A letter was sent to the applicant on May 27, 2011 asking for the following:

Please clarify the following:

- how randomization was generated by the study statistician, whether any factors were used in the process of generating the randomization code, and whether computer software was used in the randomization process. Provide the program along with listing the factors (if any) over time, used in the randomization.

- the observed imbalance of treatment allocation within sites.

- how the error of the randomization scheme was discovered almost halfway through the trials, and whether the Agency was informed about this issue.

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The stratification issue is discussed in detail in the statistical review for this NDA and in Section 6.1.10 of this review.

On 9/15/10 a letter to the applicant was sent by DMEPA informing them that the proprietary name proposed, Sklice is acceptable. This letter also stated the following "if your future development program includes expansion of the indication of use of this product, we would find the proposed name Sklice misleading for other indications since the proposed proprietary name misleadingly implies that the product treats only lice".

A **Pre-NDA Meeting** was held on 1/12/2011. The Agency had the following comments and recommendations:

- Case Report Forms (CRFs) should be submitted as well as electronic links for: a) death B) all Serious Adverse Events C) all Severe Adverse Events D) all patients who discontinued for whatever the reason (not just because of adverse events).
- Data from the Safety Population should be presented for the following subgroups: Age Group (6 months to <2 years, 2 to <4years, 4 to <12 years, 12 to 16 years, and >16 years old), Gender (male or female), and Race (White or Non-white).
- Please provide the following in the ISS and elsewhere in your submission as appropriate: shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant, group means for irritancy safety study results and frequency tables for sensitivity safety study results.
- The success rated and 95% confidence intervals for the primary efficacy endpoint will be presented for the following subgroups within each population: Age Group (6 months to <2 years, 2 to <4 years, 4 to <12 years, 12 to 16 years, and >1 years old), Gender (male or female) and Race (White or Non-white).
- Provide a detailed examination of study to study differences in results. Critical study design differences should be discussed and compared. The extent to which the results of the relevant studies reinforce or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed, and any areas needing further exploration should be identified.
- Provide a discussion of the high vehicle response rate demonstrated in your studies, including possible explanations.
- Provide the Agency with SAS transport files in electronic form.

The applicant has complied with each of the above requests in the NDA submission.

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Department of Scientific Investigations (DSI) inspections were requested for 4 sites with the following rationales:

Table 3: DSI Inspection Sites

Site #	Study #	Investigator/ Sub-investigator	Location	Rationale
#5	TOP011	Patti J. Perry, MD	Yuma, Az	A large treatment effect was noted at this site. A large difference in treatment response between active and control arms was also noted.
#5	TOP012:	Katie Sheperd Sub-I: (b) (6)	Nashville, TN	A large treatment effect was noted at this site. A large difference in treatment response between active and control arms was also noted
#6	TOP011	Miguel S. Restrepo, MD	Dinuba, Ca	This site enrolled 20 subjects rapidly under the central randomization scheme*. After the correction, only an additional 4 subjects were enrolled. In addition, this site had a very high efficacy rate for the control group.
#3	TOP011	Rossmeri Montalvo, MBA, CCRC (b) (6)	West Palm Beach, Fla	This site had a significant change in the treatment effect after the change in the randomization scheme* was instituted.

*Randomization (according to the SPA letter-dated 12/23/09) was planned to be stratified by site. However, randomization was centralized from study onset thru till April 16, 2010 when this error was identified and corrected by the sponsor

All four sites received a final classification of “No deviations from regulations” (NAI).

At site #5 for TOP011 (Dr. Perry’s site) it was noted that 2 overweight tubes (≈178 grams) were dispensed to subjects 205-01 and 205-02. No explanation for this was determined during inspection (i.e. whether a weighing error or larger tube was actually

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dispensed). After discussion with the review team regarding this incident it was determined that this was unlikely to have a significant effect on the safety or efficacy determination.

3.2 Compliance with Good Clinical Practices

According to the clinical study reports, the sponsor conducted the 7 studies in the clinical development program in compliance with GCPs.Clinical investigations and informed consent were reviewed and approved by an Institutional Review Board prior to study initiation. Informed consent was obtained.

3.3 Financial Disclosures

The applicant submitted form FDA 3454, certifying that they, the applicant, had not entered into any financial arrangements with the clinical investigators. A list of the clinical investigators for the Natroba clinical development program was provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.2 Clinical Microbiology

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 “There is no significant safety concern for systemic toxicity after the use of SKLICE Lotion product due to limited systemic exposure to ivermectin… This NDA is approvable from a pharmacology/toxicology perspective.”

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class cause death 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. In addition, ivermectin does not readily cross the blood-brain barrier in humans.

4.4.2 Pharmacodynamics

No pharmacodynamic information is available for Sklice.

4.4.3 Pharmacokinetics

The absorption of ivermectin from SKLICE Topical Lotion was evaluated in a clinical study in subjects aged from 6 months to 3 years. This study evaluated pharmacokinetics in 20 lice infested subjects, and 13 of these subjects weighed15 kg or less (overall weight range 8.5 – 23.9 kg). All enrolled subjects received a single treatment with SKLICE Topical Lotion. The systemic ivermectin exposure was evaluated using an assay with a lower limit of quantitation of 0.05 ng/mL. The mean (± standard deviation) plasma maximum concentration (Cmax) and area under the concentration-time curve from 0 to time of last measurable concentration (AUC0-tlast) were 0.24 + 0.23 ng/ml and 6.7 ± 11.2 ng/ml respectively. These levels are much lower than those observed following oral administration of 165 mcg/kg dose of ivermectin.

In vitro studies using human liver microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the in vitro method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Table of Trials for Efficacy or PK Data

Study # Phase # of Sites	**Ages of Subjects**	**Design/Control ***	**Dose regimen**	**# of subjects exposed to Ivermectin 0.5% Lotion ****	**Age Range (years)**
TOP011 n=410 Phase 3 8 sites	ITT1 Population 6 mo to < 4 yrs IC-15 (21%) VC-12 (16%) 4 to < 12 years IC-46 (65%) VC-52 (70%) 12 to 16 years IC-7 (9.9%) VC- 8 (11%) > 16 years IC-3 (4.2%) VC- 2 (2.7%)	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC n=211 VC n= 199	.75-55
TOP012 n=371 Phase 3 8 sites	ITT1 Population 6 mo to < 4 yrs IC-19 (27%) VC-16(21.6%) 4 to < 12 years IC-34 (49%) VC-47 (64%) 12 to 16 years IC-10 (14%) VC- 7 (9.5%) > 16 years IC- 7 (10%) VC- 4 (5.4%)	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC n=169 VC n= 202	0.5-68
TOP010 n=247 Phase 2b 12 sites	2 to < 4 yrs IC-8 (4.2%) VC-0 (0%) 4 to < 12 years IC-90(47%) VC- 25(46%) 12 to 16 years IC- 44(23%) VC- 9 (16.4%) > 16 years IC-50 (26%) VC- 21 (38%)	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC n=192 VC n= 55	2-59
TOP003 n=78 Phase 2 Single site	2 yrs to 11 yrs IC - 31/55 (56%) VC-15/23 (65%) 12 yrs to 18 yrs IC- 11/55 (20%) VC-6 (26.1%) > 18 yrs IC- 13/55 (23.6%) VC- 2 (8.7%)	R, DB, PC, PG **dose-ranging** study in subjects with head lice	One 10 minute application at study site	0.15% IC n=18 0.25% IC n=18 0.5% IC n= 19 VC n=23	2-62
TOP001 n=26 Phase1 Single site	4 to 10 years IC- 15/15 (100%) VC- 5/5 (100%) Oral- 6/6 (100%)	R, PG, controlled study in **children** with head lice	Up to two topical applications at study site, Single dose of oral ivermectin (Stromectol)	0.5% IC n= 15 Oral Stromectol n=6 VC n=5	4-10
TOP008	6 mo to < 4 yrs IC- 30 (100%)	**Open-label,** MC	One 10 minute	0.5% IC n=30	0.5-3

n=30 Phase1 Single site		study in **children** with head lice	application at study site		

Source: Reviewer's Table
This table omits Study TOP007 which was for safety purposes only. See Section 7.4.5 for discussion of TOP007.

5.2 Review Strategy

The pivotal trials, TOP011 and TOP012 were reviewed in detail for safety and efficacy. Review of TOP010 which had different entry criteria, provided supportive evidence of efficacy and was reviewed in detail for safety. TOP001 provided supportive evidence for efficacy but differed from the pivotal trials in that 2 treatments were administered. TOP008 was open-label and was therefore not considered in the efficacy review. Both TOP001 and TOP008 were reviewed in detail for the safety review. TOP003 provided supportive evidence for the efficacy review and was reviewed in detail for safety. TOP007 was reviewed in detail for safety but not considered for efficacy since the population was healthy adults.

5.3 Discussion of Individual Studies/Clinical Trials

Study Design

Pivotal Studies: Protocol Number TOP011 and TOP012

The pivotal studies, TOP011 and TOP012 were identical in design, but were conducted independently at eight study sites each. The pivotal studies were the subject of a SPA agreement and the protocol presented below adheres to the agreements made.

Title: A double-blind randomized study to compare the efficacy, safety and local tolerability of a 0.5% ivermectin Lotion compared to a topical vehicle control in subjects with *Pediculus humanus capitis* infestation.

Investigators

Table 5: Investigators for Study TOP011

Investigator/Study Coordinator	Study Site
Dewitt L. Bolton, MD	Spence Medical Research 1018 6th Avenue, Suite A Picayune, MS 39466 601-799-4044
Bryan H. Merrick, MD	McKenzie Medical Research

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	205 Hospital Drive, Suite A McKenzie, TN 38201 731-352-1561
Rossmeri Montalvo, MBA, CCRC Sub-Investigator: (b) (6)	Lice Solutions 6758 N. Military Trail, Suite H West Palm Beach, FL 33407 561-842-9969
Daniel M. Pariser, MD, FAAD. FACP	Virginia Clinical Research, Inc. 601 Medical Tower Norfolk, VA 23507 757-625-0151
Patti J. Perry, MD	Cactus Kids Pediatrics 1832 South 8th Avenue Yuma, AZ 85364 928-782-6830
Miguel S. Restrepo, MD	Universal BioPharma Research Institute 888 N. Alta Avenue Dinuba, CA 93618 559-595-1861
Lidia Serrano Sub-Investigator: (b) (6)	Lice Source Services 6971 W. Sunrise Boulevard #102 Plantation, FL 33313 954-791-0711
Dennis J. Ward, DO	Hill Top Research 6088 Main Street, PO Box 138 Miamiville, OH 45147 513-831-3114 Ext. 2822

Source: Reviewer's Table

Table 6: Investigators for Study TOP012

Investigator/Study Coordinator	Study Site
W. Michael Brown, MD	Hill Top Research 6699 13th Avenue North St. Petersburg, FL 33710 727-344-7602
Anton L. Duke, MD	Arkansas Pediatric Clinic Research 500 S. University Avenue, Suite 200 Little Rock, AR 72205 501-661-0308 Ext.130 / 501-661-0308 Ext. 141
Paula J. Lane, MD	Lovelace Scientific Resources 2441 Ridgecrest Drive SE

	Albuquerque, NM 87108 505-348-9398 / 505-348-9373
Elisabeth Rivera Sub-Investigator: Shahida Anjum, MD	Lice Cleanique 5353 W. Atlantic Avenue, Suite 400-A Delray Beach, FL 33484 561-495-0166
Katie Sheperd Sub-Investigator: (b) (6)	Lice Solutions 604 Gallatin Avenue #105 Nashville, TN 37206-3476 561-635-2884 / 615-227-3919
Dow B Stough, MD, CCRI	Burke Pharmaceuticals 3633 Central Avenue Hot Springs, AR 71913 501-620-4449
Nora U Torres, MD	Northeast Houston Pediatric Clinic 13018 Woodforest Boulevard, Suite A Houston, TX 77015 713-455-0200
Stephen J Wall, MD	Haywood Pediatrics and Adolescent Medicine 15 Facility Drive Clyde, NC 28721 828-452-2211

Source: Reviewer's Table

The phase 2 Study TOP003 was conducted at a single site. There were 12 sites for the phase 2b study TOP010 (See Study Report for Study TOP010 for listing).

Protocol

Protocol Amendments

On Jan 21, 2010 the applicant submitted SD#48 which contained protocol amendments requested by the Agency in the SPA Agreement letter dated 12/23/2009 and clarified during a teleconference on 1/8/2010. The following requested changes were included:

- Adjustment to the sample size determination stating that the expected success rate will be < 25% in the vehicle group and > 70% in the active treatment group.
- Adjustment to the sample size determination stating that "The sample size is based on the estimated lower bound of the 95% confidence interval for the difference between the two treatment groups exceeding 30%".
- The statement that "a total of 66 subjects will be needed for each group for the study to be adequately powered (~90%).

- The statement that "The intent-to-treat population consists of all index subjects who were randomized and were dispensed active ingredient or vehicle".

Objectives

The primary objective of these Phase 3 trials was to compare the efficacy of a single application of 0.5% ivermectin Lotion to a vehicle control formulation, under at-home use conditions, in subjects infested with head lice (Pediculus humanus capitis).

The secondary objectives were to compare the safety and local tolerability of a 0.5% ivermectin Lotion to a vehicle control formulation in subjects with head lice infestation.

Overall Study Design

The pivotal studies were identical multi-site, randomized, double-blind, vehicle controlled, two-arm, parallel studies in healthy male and female subjects aged 6 months and above who were infested with *Pediculus humanus capitis*. The duration of the study was approximately 15 days for each subject. Visits to the site consisted of a screening visit (Day 1) at which time subjects with live head lice were randomly assigned to treat with either the 0.5% Ivermectin Lotion or vehicle control which was then dispensed as a single tube (4 oz) for home administration. Subjects received written instructions to thoroughly coat dry hair and scalp with product, then to leave product in place on hair and scalp for 10 minutes before rinsing out with water. Subjects were requested to return used tubes on Day 2 for weighing. All qualifying members of a household infested with head lice and enrolled in the study received the same treatment, with the youngest enrolled member acting as the index case. Follow-up visits occurred on Days 2, 8, and 15.

A trained evaluator provided efficacy (presence or absence of live lice) and safety assessments at the site on Days 2, 8, and 15. The lice examination was conducted for no less than 15 minutes unless live lice were identified in less time. The start time and end time of the evaluation was recorded in the source documents and the total number of minutes for the evaluation was transcribed to the case report form. If live lice were present on Days 2, 8, or 15, the subject received an FDA-approved over-the-counter (OTC) rescue treatment and their study participation was considered complete. The study schedule is presented below:

Table 7: Study Schedule for Pivotal Studies

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Best Available Copy

Procedure	Screening[a] / Day 1	Day 2[d] (+/- 12 hrs)	Day 8[d] (+/- 1 day)	Day 15[d] (+2 days)
HIPAA	X			
Informed Consent / Assent (minors)	X			
Head Lice Evaluations	X*	X	X	X
Nit Presence Assessment	X*			
Skin/Scalp Irritation Safety Assessments	X*	X	X	X
Ocular Irritation Assessment	X*	X		
Urine Pregnancy Test[b] (females of child bearing potential only)	X*			
Subject Demographics / Medical History / Review / Subject Weight	X*			
Inclusion – Exclusion Criteria / Review	X*			
Concomitant Medications / Review	X*	X	X	X
Adverse Events		X	X	X
Subjects Instructions	X*	X	X	
Subject Randomization	X*			
Test Article Distribution	X*			
Self-Application of Assigned Treatment	X[c]			
Distribute rescue medication to infested subjects		X	X	X
Study Compliance Confirmation		X	X	X
Test Article Return		X	X[e]	X[e]

a – The Screening and Day 1 visits may occur on separate days up to 7 days apart. When this occurs, the procedures with an asterisk (*) must be performed on Day 1 (even if they were also performed during the Screening visit).
b – Urine Pregnancy Test will be conducted for all female subjects and female caregivers who are not treated who are of child-bearing potential. Child bearing age is defined as from the onset of menses to one year post menopause
c – Subjects (or caregivers) will apply their designated treatment at home on Day 1 following their visit to the study site.
d – All subjects (whether lice free or with lice present) will complete all procedures for that particular visit.
e – If test article is not returned on Day 2, it should be collected at the next scheduled visit.

Source: Applicant Protocol for Study TOP011 pg. 24

Primary safety endpoints included assessments of reported adverse events, observed skin/scalp reactions and ocular irritation assessments (See Section 7.4.1 for details). The conjunctivae of all subjects were assessed for the presence or absence of irritation on Day 1 (baseline, prior to treatment) and Day 2 (post treatment). Clinically significant changes in physical condition (including skin/scalp or ocular irritation), based on the opinion of the investigator were considered as AEs that were subject to the same criteria as all other AEs.

If an AE occurred, the subject, under the direction of the Investigator (or designee) was referred to a consultant physician for treatment. All AEs were followed until resolution to the extent possible (e.g., medical attention by subject's primary care physician) or were

explained as not being study drug related. The resolution or the outcome of the events was documented.

The scale for assessment of skin/scalp reactions is presented below:

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Table 8: Skin/Scalp Irritation Assessment Scale for Pivotal Studies

Rating	Type of Irritation			
	Pruritus	Erythema	Excoriation	Pyoderma
None = 0	The scalp does not itch.	No redness of the scalp.	No broken skin on the scalp.	No lesions visible on the scalp.
Mild = 1	Occasional episodes of itching, not bothersome.	Faint, barely perceptible erythema with limited distribution.	One or two areas on the scalp on which skin is broken.	One or two lesions visible with crusting or other evidence of infection.
Moderate = 2	Frequent, several times a day, bothersome.	Diffuse pink areas of scalp are readily visible.	More than two separate areas of the scalp with broken skin but not generalized across the scalp.	Presence of more than two lesions with crusting or other evidence of infection, but not generalized across the scalp.
Severe = 3	Nearly constant, frequent scratching, very bothersome.	Large areas of the scalp are red.	Widespread breaking of the skin involving most of the scalp.	Lesions with crusting or other evidence of infection, involving most of the scalp.

Pruritus = Itching.
Erythema = Redness of the scalp.
Excoriation = Breaking of skin, usually caused by scratching.
Pyoderma = Sores filled with clear fluid, pus or crusting.

Source: Applicant's Protocol for Study TOP011, pg. 28.

Laboratory evaluation was not performed in Studies TOP011 and TOP012. Agreement on the need for laboratory assessments as part of the safety evaluations for the pivotal studies was not included in the SPA agreement. At that time, the Agency had not yet reviewed the results of the PK and safety Study TOP008 which included laboratory assessments on 30 subjects between the ages of 6 months to two years. The applicant elected not to include laboratory assessments based on the lack of findings in Study TOP008. (See section 2.5 for further discussion of this topic.)

Phase 2 Study TOP003 differed from the pivotal studies in that the investigational product was applied at the study site by study personnel. Phase 2b Study TOP010 did employee a self-administered (or caretaker administered) at home design similar to the pivotal trials.

Inclusion Criteria

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1) Index subjects must have an active head louse infestation defined as: At least 3 live lice (adults and/or nymphs) present on the scalp and/or hair, as determined by a trained evaluator. The index subject must be the youngest family member presenting with at least 3 live lice. After the index subject has been identified, additional infested household members (see b below) will be enrolled.

2) Household subjects must have an active head louse infestation defined as: At least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator (with the exception of the male head of household who may self-assess as being lice free).

3) Subject is male or female.

4) Subject is at least 6 months of age at time of enrollment.

5) Subject is in good general health based on medical history.

6) Each subject must have an appropriately signed Informed Consent agreement. A caregiver must sign an Informed Consent agreement for children not old enough to do so. Children of a specified age will be administered a child's assent form.

7) The caregiver of a subject must be willing to allow all household members to be screened for head lice. If other household members are found to have an active head lice infestation, according to the criteria b (above), they must be willing and able to participate in the study. No more than one working male per household may be excluded from evaluation if he is assessed as being lice free by himself or the caregiver and cannot come in due to his work schedule. If this individual may have lice, he must come to the test facility; otherwise the entire household will be excluded from study participation.

8) Subject and/or their caregiver must be physically able and wiling to apply the test article.

9) Subject agrees not to use any other form of lice treatments (commercial, community-anecdotal, or mechanical/manual) while participating in the study.

10) Following application and rinsing of the test article, subject agrees not to shampoo, wash, or rinse their hair or scalp until the 24-hour post-treatment evaluation has been completed.

11) Subject agrees to not cut or chemically treat their hair while participating in the study.

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12) Subject agrees to follow all study instructions.

13) Female subjects of childbearing potential (including a female caregiver even if she is not being treated) must be willing to have a urine pregnancy test.

14) In the event of a subject judged to be incapable of self-treating, the household must have a caregiver willing to apply the treatment at home.

The Phase 2b study TOP010 differed from the pivotal studies in that inclusion criteria required one live louse for participation. The phase 2 Study TOP003 required 5 viable appearing nits as well as 3 live lice for participation. Both phase 2 studies required a weight of 15 kg (33 lbs) to participate. This resulted in the youngest subject in these phase 2 studies being 2 years old.

Exclusion Criteria

1) History of irritation or sensitivity to ivermectin or the Lotion components, pediculicides or hair care products.

2) Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation, such as an erythema score that is > 2, blisters, vesicles which, in the opinion of the investigative personnel or sponsor, will interfere with safety and/or efficacy evaluations.

3) Presentation at the treatment site with eczema or atopic dermatitis.

4) Treatment for head lice (OTC, home remedy and/or Rx) in the last 7 days.

5) Any condition or illness that; in the opinion of the investigator, may compromise the objective of the protocol.

6) Is receiving any other treatment which, in the opinion of the investigator or study monitor, may interfere with the study results.

7) Females (including caregivers who come in contact with the investigational product) who are pregnant, nursing or planning a pregnancy. (NOTE: female caregivers and all enrolled females of childbearing potential must have a negative urine pregnancy test prior to treatment). If a household has a pregnant female who has an active case of lice, the entire household is excluded from participation. If this pregnant household member does not have an active infestation, this individual must NOT be the caregiver (one who provides treatment to other household members).

8) Is of child-bearing potential and unwilling to use an adequate method of contraception for the duration of the study. Adequate methods of contraception

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include: abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, IUD, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly, surgical sterilization.

9) Participation in a previous investigational drug study within the past 30 days.

10) Prior participation in any ivermectin trials.

11) Does not understand the requirements for study participation and/or may likely exhibit poor compliance, in the opinion of the investigator.

12) Does not have a known household affiliation with their household members (i.e., do not stay in one household consistently, sleeping at one place several nights and then at another place or location). Household is defined as living in a shared area or space (for example the same house or apartment unit).

Blinding:

For masking purposes, all test articles were packaged in identical containers. The ivermectin Lotion and the vehicle Lotion were identical in appearance. Blinding was maintained through the use of randomization procedures. This appears to be adequate.

Data Analysis

The primary efficacy endpoint in the pivotal studies TOP011 and TOP012 was

> The proportion within each treatment group of index subjects who are lice free (without live lice) on Day 15.

This was agreed to in the SPA agreement dated 12/23/09.

The secondary efficacy endpoint in the pivotal studies TOP011 and TOP012 was

> The proportion within each treatment group of all subjects who are lice free on Day 15.

With regard to the secondary efficacy endpoint, the following statement was included as an additional comment in the SPA letter dated 12/23/09:

> Your proposed secondary efficacy endpoint, the proportion within each treatment group of all subjects who are “lice free” on day 15 will not be included in labeling and cannot be used to establish efficacy, as the inclusion criteria for the subjects in this cohort are not the same as those

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for the index subjects in that subjects in the household cohort are only required to have 1 live louse.

Treatment success was defined as the absence of live lice at all post treatment visits. Differences between treatment groups were assessed using a 1 degree of freedom chi-square test. Binomial proportion comparisons will also be made using two-sided 95% confidence intervals of the differences in proportions.

Study Populations

Qualified index subjects within a household who were enrolled into the study, randomized and dispensed medication were considered as the Intent to Treat (ITT1) population for efficacy endpoints.

The ITT2 population consisted of all enrolled household members (including the index subjects) who were randomized and dispensed medication.

The Per Protocol (PP) population is a subset of the ITT population, excluding index subjects with major protocol deviations or violations.

The superiority of ivermectin Lotion to vehicle Lotion was based on the proportion of INDEX subjects who were lice free at day 15 at the two-sided α=0.05 level using a Cochran-Mantel-Haenszal test stratified by investigative site.

The imputation approach was to use LOCF as the primary method and to impute all missing as failures as a sensitivity analysis.

The primary efficacy endpoint in the Phase 2b Study TOP010 differed from the pivotal studies; it was “The proportion within each treatment group of all subjects who are lice free (without live lice) on Day 15”. Similarly the phase 2 Study TOP003 assessed the subjects as a single population (as opposed to the ITT1 and ITT2 for the pivotal studies). The primary efficacy endpoint for Study TOP003 was “The percentage of subjects who demonstrate eradication by Day 2 that is maintained through Day 8 and Day 15”.

6 Review of Efficacy

Efficacy Summary

Two pivotal phase 3 trials, TOP011 and TOP012 (which were multi-center, randomized, double-blind, vehicle-controlled, parallel group studies) were conducted with the objective of establishing the superiority of a 10 minute application of Sklice (Ivermectin Lotion 0.5%) to vehicle. These trials were of adequate design and sufficiently powered to study the safety and efficacy of the investigational product. The pivotal trials were the

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subject of a SPA (See Section 2.5) and the key parameters were agreed upon with the Agency prior to the conduct of the trials.

TOP011 was conducted in eight centers across the U.S. and enrolled a total of 410 subjects (145 index subjects used for the primary efficacy evaluation). TOP012 was conducted in an additional eight U.S. centers and enrolled a total of 371 subjects (144 index subjects). The youngest subject from each household who qualified for the study was designated as the index subject for inclusion in the Primary Treatment Cohort (ITT1). The Primary Treatment Cohort was the population evaluated for the primary efficacy outcome.

A majority of subjects exposed to Sklice, Ivermectin Lotion 0.5%, (the safety population) were Caucasian (95.2%) with a mean age of 14.5 years. A total of 17.5% were male and 82.5% were female. These demographic characteristics were similar for both treatment and vehicle control arms.

For the ITT1 population for the pivotal trials, a majority of the population was white (95.7%) with a mean age of 7.8 years. A total of 17% were male and 83% were female. These demographic characteristics were relatively balanced across the treatment arms.

The primary endpoint was defined as “the proportion within each treatment group of index subjects who are lice free (without live lice) on Day 15”. The analysis group was pre-specified in the statistical analysis plan to be the intent-to-treat (ITT1) population. Results from both studies showed that Sklice (Ivermectin Lotion 0.5%) was statistically superior to vehicle with p-values below 0.0001.

Supportive analysis for the primary efficacy endpoint was also performed on the per protocol (PP) population. Results from this supportive analysis were consistent with results from the ITT1 population which found that Sklice (Ivermectin Lotion 0.5%) was statistically superior to vehicle.

The secondary efficacy endpoint “the proportion within each treatment group of all subjects who are lice free on Day 15” also showed that Sklice (Ivermectin Lotion 0.5%) was statistically significantly superior to vehicle with p-values below 0.0001.

The results for the primary endpoint for a pooled analysis of Studies TOP003, TOP011 and TOP012 were examined in the subpopulations gender, race, and age. Response rates for females (79.2%) were somewhat higher than for males (68%) but both groups showed a statistically significant difference between Ivermectin Lotion 0.5% and the Vehicle.

The majority of subjects among the primary (ITT1) population were white. Response rates for both whites and non-whites showed a statistically significant difference between Ivermectin 0.5% Lotion and vehicle. Definitive conclusions regarding response

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rates among the other races analyzed; African American, American Indian or Alaskan Native and multiracial are precluded due to small numbers.

The sponsor performed subgroup analysis for efficacy by age groups 0.5 to 2 years , 2 to 4 years, 4 to 12 years, 12 to 16 years and >16 years. For three of the five age subgroups the results of this subgroup analysis are consistent with the findings in the pivotal studies showing a statistically significant difference between Ivermectin Lotion 0.5% and the Vehicle. Despite the pooling, the low number of subjects in some subpopulations (for example - age group 0.5 to 2 yrs) was proposed by the sponsor as an explanation for the failure to achieve a statistically significant result in two of the five subgroups.

6.1 Indication

The proposed indication is for the topical treatment of head lice (b) (4) in patients 6 months of age and older.

6.1.1 Methods

The efficacy evaluation will focus upon a detailed review of the Phase 3 Pivotal Trials TOP011 and TOP012. Supportive efficacy data were provided by phase 2b TOP010 and phase 2 dose-ranging TOP003.

6.1.2 Demographics

The demographic characteristics of the population that participated in the pivotal trials, TOP011 and TOP012 are presented below in Table 7.

Table 9: Demographics for Studies TOP011 and TOP012: ITT Population

Characteristic		**TOP011**		**TOP012**	
		0.5% Ivermectin (N = 71)	**Vehicle Control (N = 74)**	**0.5% Ivermectin (N = 70)**	**Vehicle Control (N =74)**
Gender: n (%)	Female	60 (84.5%)	61 (82.4%)	57 (81.4%)	54 (73.0%)
	Male	11 (15.5%)	13 (17.6%)	13 (18.6%)	20 (27.0%)
Age (yrs)	n	71	74	70	74
	Mean (SD)	7.18 (4.94)	7.84 (6.35)	8.37 (7.75)	9.15 (9.70)
Age (yrs): n (%)	6 mos to < 4 yrs	15 (21.1%)	12 (16.2%)	19 (27.1%)	16 (21.6%)
	4 to < 12 yrs	46 (64.8%)	52 (70.3%)	34 (48.6%)	47 (63.5%)
	12 to 16 years	7 (9.9%)	8 (10.8%)	10 (14.3%)	7 (9.5%)

	>16 yrs	3 (4.2%)	2 (2.7%)	7 (10.0%)	4 (5.4%)
Ethnicity (%)	Hispanic /Latino	35 (49.3%)	32 (43.2%)	22 (31.4%)	25 (33.8%)
	Not Hispanic /Latino	36 (50.7%)	42 (56.8%)	48 (68.6%)	49 (66.2%)
Race: n (%)	Black	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
	Indian/Alaskan Native	1 (1.4%)	0 (0.0%)	0 (0.0%)	2 (2.7%)
	Multi-Racial: White/Black	1 (1.4%)	2 (2.7%)	4 (5.7%)	1 (1.4%)
	White	69 (97.2%)	71 (95.9%)	66 (94.3%)	71 (95.9%)
Weight (kg)	n	71	74	70	74
	Mean (SD)	30.75 (17.4)	32.43 (21.1)	32.76 (23.2)	30.77(17.2)

Source: Reviewer's Table

A majority of subjects were White (>94%) and female (>80% except for the vehicle control group in TOP012 which was 73%). Head lice are more frequent in girls due to the predilection for longer hair and habits of exchanging hair care accessories.[9]More than 50% of subjects in each treatment group reported their ethnicity as Not Hispanic or Latino.

The mean age was 7-9 years old. Of the 4 age categories (6 months to < 4 years, 4 to < 12 years, 12 to 16 years, and > 16 years), the largest percentage of subjects were in the age range of 4 to < 12 years. In the United States the highest incidence of head lice is found in children aged 3 to 11 years.

As compared with that for the U. S. population (from the census bureau statistics for 2005-2007), the demographics of the population studied in the pivotal trials show a relative under-representation of African-Americans and a relative over-representation of Hispanics. In African-Americans head lice are less common than in other races because anatomic differences in American lice do not allow for proper positioning of the female in order to lay eggs on coarse, curly hair.[10,11] The over representation of Hispanic ethnicity is unlikely to affect applicability of study results to the U.S. target population.

Demographic and baseline characteristics were balanced between treatment groups.

[9] Jacobson CC and Abel EA. Periodic Synopsis: Parasitic Infections. Journal of the American Academy of Dermatology 2007; 56:1026-43.
[10] Burkhart CN and Burkhart CG. Head lice: Scientific assessment of the nit sheath with clinical ramifications and therapeutic options. Journal of the American Academy of Dermatology 2005; 53:129-133.
[11] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. 2009.

6.1.3 Subject Disposition

Two phase three studies were included in the applicant's NDA submission; TOP0011 and TOP012. No subjects dropped out due to an adverse event in the phase 3 studies.

The following table (Table 8) presents the summary of subjects who discontinued from Study TOP011 and TOP012.

Table 10: Disposition of Subjects: Study TOP011 and TOP012

	Study TOP011		**Study TOP012**	
# of subjects	**0.5% Ivermectin (N = 211)**	**Vehicle Control (N = 199)**	**0.5% Ivermectin (N =169)**	**Vehicle Control (N =202)**
Randomized	211 (100.0%)	199 (100.0%)	169 (100.0%)	202 (100.0%)
Completed Study	210 (99.5%)	196 (98.5%)	161(95.3%)	198 (98.0%)
Did Not Complete Study	1 (0.5%)	3 (1.5%)	8 (4.7%)	4(2.0%)
Discontinued due to:				
Protocol Violation /Deviation	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Withdrawal	0 (0.0%)	3 (1.5%)	1 (0.6%)	2 (1.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	7 (4.1%)	0 (0.0%)
Non-compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)

Source: Reviewer's Table

Study TOP011 enrolled 410 subjects and 406 completed. Among subjects randomized a similar percentage completed the study in the ivermectin and the vehicle control group, 99.5% and 98.5% respectively. Four subjects, 1% (all in the ITT2 population) did not complete the study. Three of the subjects in the vehicle group were withdrawn do to the "parent no longer wanting to participate" and one subject (03-208-07) in the 0.5% ivermectin group) was withdrawn due to a protocol deviation (the subject did not use the treatment).

Study TOP012 enrolled 371 subjects and 359 completed. Among subjects randomized a similar percentage completed the study in the ivermectin and the vehicle control group, 95.3% and 98.0% respectively. Twelve subjects (3.2%) did not complete the study. 1 subject in the 0.5% ivermectin group and 2 subjects in the vehicle control group withdrew from the study, 7 subjects (all in the 0.5% ivermectin group) were lost to follow-up, and 2 subjects (both in the vehicle control group) were withdrawn due to non-compliance with treatment.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint in the pivotal studies TOP011 and TOP012 was "The proportion within each treatment group of index subjects who are lice free (without live lice) on Day 15."

Table 11: Primary Efficacy Analysis- ITT1 Population – TOP011 and TOP012
(Day 15 - LOCF Imputation)

	TOP011		**TOP012**	
	0.5% Ivermectin (N = 71)	Vehicle Control (N = 74)	0.5% Ivermectin (N = 70)	Vehicle Control (N = 74)
Number of Subjects	71	74	70	74
Number Lice Free (%)	54 (76.1%)	12 (16.2%)	53 (75.7%)	15 (20.3%)
P value	< 0.0001		< 0.0001	

Source: Reviewer's Table

Results from both studies show that Ivermectin Lotion 0.5% is statistically superior to Vehicle with p values below 0.0001 in each study.
As a supportive analysis to the ITT1 population, Table 10 presents efficacy for the PP population for the index subjects.

Table 12: Primary Efficacy Analysis- PP Population – TOP011 and TOP012
(Day 15 - LOCF Imputation)

	TOP011		**TOP012**	
	0.5% Ivermectin (N = 71)	Vehicle Control (N = 74)	0.5% Ivermectin (N = 70)	Vehicle Control (N = 74)
Number of Subjects	70	73	64	72
Number Lice Free (%)	53 (75.7%)	11(15.1%)	48 (75.0%)	13 (18.1%)
P value	< 0.0001		< 0.0001	

Source: Reviewer's Table

Results from this supportive analysis are consistent with results from the ITT1 population which finds that Ivermectin Lotion 0.5% is statistically superior to Vehicle with p values below 0.0001 in each study.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoint in the pivotal studies TOP011 and TOP012 was "The proportion within each treatment group of all subjects who are lice free on Day 15.

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Table 13: Secondary Efficacy Analysis- ITT2 Population – TOP011 and TOP012 (Day 15 - LOCF Imputation)

	TOP011		TOP012	
	0.5% Ivermectin (N =211)	Vehicle Control (N =199)	0.5% Ivermectin (N =169)	Vehicle Control (N = 202)
Number of Subjects	211	199	169	202
Number Lice Free (%)	172 (81.5%)	44 (22.1%)	131(77.5%)	47 (23.3%)
P value	< 0.0001		< 0.0001	

Source: Reviewer's Table

Results from this analysis are consistent with the ITT1 and the PP population results which find that Ivermectin Lotion 0.5% is statistically superior to Vehicle with p values below 0.0001 in each study.

Phase 2 Efficacy Results

The phase 2b Study TOP010 differed from the pivotal trials in that only one live louse was required for entry. In addition, the primary efficacy endpoint included the entire population (i.e. all members of each family studied).For this reason efficacy results are not integrated with the pivotal trials and are not to be considered for labeling.

Table 14: Primary Efficacy Analysis- ITT Population – TOP010 (Day 15)

	TOP010	
	0.5% Ivermectin (N =192)	Vehicle Control (N =55)
Number of Subjects	185	54
Number Lice Free (%)	141 (76.2%)	19 (35.2%)
P value	< 0.001	

Source: Reviewer's Table

The overall results of this analysis are consistent with the findings in the pivotal studies. However there is a much higher vehicle response relative to that seen in TOP011 and TOP012 (range of vehicle response 15.1- 23.3). One possible explanation for this proposed by the applicant is that the single head louse required for participation in this study may have been below the threshold required to develop a clinical infestation in some cases. This might result in some "cures" for the vehicle group who were never actually infested. This seems a reasonable explanation. The vehicle response seen in pivotal trials for Ulesfia, approved by the FDA in 2009 (4.8 to 26.2%) are consistent with those seen in the pivotal studies for Ivermectin Lotion. The design of the pivotal trials for Ulesfia did require a minimum of three live lice for entry.

The phase 2 dose-ranging Study TOP003 also included the entire population (i.e. all members of each family studied) in the primary efficacy evaluation.

Table 15: Primary Efficacy Evaluation: Active Treatments Versus Placebo: Study TOP003

Eradicated at Visit:		0.15% Ivermectin (N = 18)	0.25% Ivermectin (N = 18)	0.50% Ivermectin (N = 19)	Placebo (N = 23)
Maintained Day 2, 8 and 15	n (%)	10 (55.6%)	9 (50.0%)	14 (73.7%)	2 (8.7%)
	p-value[a]	0.0034	0.0091	< 0.0001	
	95% C.I.	0.16, 0.77	0.11, 0.72	0.37, 0.93	

[a] p-values based on a 2-group continuity-corrected chi-square test of equal proportions (odds ratio=1).
N = total number of subjects per treatment group; n = number (percentage) of subjects with a value.
Source: Applicant's Clinical Study Report TOP003 pg 22

The results of TOP003 are consistent with those seen in the pivotal trials. The Ivermectin 0.5% arm showed efficacy in 73.7%.

Overall, the primary efficacy results shown by Ivermectin Lotion 0.5% in both phase 2 and phase 3 trials are within a fairly narrow range: 75.7%, 76.1%, 76.2% and 73.7% for TOP011, TOP012, TOP010 and TOP003 respectively. This provides strong support for the efficacy of the investigational product.

6.1.6 Other Endpoints

No other relevant endpoints were reviewed for this application.

6.1.7 Subpopulations

The applicant submitted evaluations of efficacy for a pooled population that included the index subjects from TOP003, TOP011 and TOP012 in order to allow analysis of subpopulations by age group, gender and race. Study TOP010 had different entry criteria (only one live louse required for participation), Study TOP001 allowed for two treatments and Study TOP008 was open-label and therefore none of these studies were included in the pooling. Study TOP007, which was a dermal safety study in healthy volunteers was also excluded. This pooling strategy appears reasonable.

<u>Subgroup Analysis by Age Group</u>

Despite the pooling, the number of subjects in some subpopulations (for example - age group 6 mo to 2 yrs) was small enough that statistical interpretation of results is difficult. Lice infestation is less common in this youngest age group which may be related to the decreased amount and density of hair and the decreased direct exposure (during play) due to the majority of this age group not yet walking or interacting with their peers.

The efficacy presented by age group for the ITT population for Studies TOP003, TOP011 and TOP012 are presented below in Table 14.

Table 16: Primary Efficacy Evaluation- ITT population- pooled TOP003, TOP011 and TOP012 - Subgroup Analysis by Age Group

Subgroup	Treatment Success	0.5% Ivermectin	Vehicle Control	Chi-square p-value
0.5 to <2	n	4	4	
		4 (100.0%)	3 (75.0%)	0.2850
2 to <4	n	33	26	
		26 (78.8%)	2 (7.7%)	< 0.0001
4 to <12	n	83	104	
		67 (80.7%)	18 (17.3%)	< 0.0001
12 to 16	n	18	17	
		9 (50.0%)	4 (23.5%)	0.1053
>16	n	12	7	
		10 (83.3%)	0 (0.0%)	0.0004

Source: Reviewer's Table

For three of the five age subgroups the results of this subgroup analysis are consistent with the findings in the pivotal studies. The age groups 0.5 to < 2 and 12 to16 do not show a statistically significant difference between Ivermectin Lotion 0.5% and the vehicle control. The applicant proposes that this may be related to the small size of these subgroups and this is a reasonable possibility. The youngest age group showed a very high (75%) vehicle response rate while the adolescent age group showed a decrease in the percentage of subjects responding to ivermectin. It is certainly possible that these findings are due to chance alone. I am not aware of a scientific reason why adolescents with head lice would be more prone to failure when treated with Ivermectin Lotion. One alternative explanation for the low treatment response in the adolescent age subgroup is that compliance in this age group (who may have self-administered the treatment) might be less than with younger or older subjects. Compliance with treatment is often an issue with adolescents.

The efficacy presented by age group for the ITT2 population for Studies TOP003, TOP011 and TOP012 are presented below in Table 14. This larger group included family members who were only required to have one live louse for participation.

Table 17: Primary Efficacy Evaluation- ITT2 population- pooled TOP003, TOP011 and TOP012 - Subgroup Analysis by Age Group

Subgroup	Treatment Success	0.5% Ivermectin	Vehicle Control	Chi-square p-value
0.5 to <2	n	9	8	
		9 (100.0%)	3 (37.5%)	0.0048
2 to <4	n	49	40	
		40 (81.6%)	4 (10.0%)	< 0.0001
4 to <12	n	276	236	
		208 (75.4%)	39 (16.5%)	< 0.0001
12 to 16	n	103	66	
		80 (77.7%)	22 (33.3%)	< 0.0001
>16	n	154	129	
		128 (83.1%)	45 (34.9%)	< 0.0001

The larger group size may be the reason why all 5 age subgroups in this analysis showed a statistically significant difference between Ivermectin 0.5% and the vehicle. The subgroup ages 0.5 to <2 continues to show high efficacy (100%) but in this case the vehicle response was lower (37.5%). This vehicle response rate is still high relative to that seen for the overall response for the ITT population not divided by age. A similar high vehicle response is seen in the 12 to 16 and >16 subgroups as well (33.3% and 34.9% respectively). As previously noted this could be in part due to the fact that the single head louse required for participation in this population may have been below the threshold required to develop a clinical infestation in some cases. This might result in some “cures” for the vehicle group who were never actually infested.

Subgroup Analysis by Gender

The efficacy presented by gender for the ITT population for Studies TOP003, TOP011 and TOP012 are presented below in Table 15.

Table 18: Primary Efficacy Evaluation- ITT population- pooled TOP003, TOP011 and TOP012 - Subgroup Analysis by Gender

Subgroup	Treatment Success	0.5% Ivermectin	Vehicle Control	Chi-square p-value
Female	n	125	125	
		99 (79.2%)	20 (16.0%)	< 0.0001
Male	n	25	33	
		17 (68.0%)	7 (21.2%)	0.0003

Source: Reviewer’s Table

The results of this subgroup analysis are consistent with the findings in the pivotal studies. Both female and male subjects showed a statistically significant difference between Ivermectin Lotion 0.5% and the Vehicle.

Subgroup Analysis by Race

The efficacy presented by race for the ITT population for Studies TOP003, TOP011 and TOP012 are presented below in Table 16.

Table 19: Primary Efficacy Evaluation- ITT population- pooled TOP003, TOP011 and TOP012 - Subgroup Analysis by Race

Subgroup	Treatment Success		0.5% Ivermectin	Vehicle Control	Chi-square p-value
White	n		143	152	
			109 (76.2%)	25 (16.4%)	< 0.0001
Non-White	n		7	6	
			7 (100.0%)	2 (33.3%)	0.0094
	American Indian or Alaska Native	n	2	2	
			2 (100.0%)	0 (0.0%)	0.0455
	African American	n	0	1	
			0 (0.0%)	1 (100.0%)	N/A
	Multi-Racial	n	5	3	
			5 (100.0%)	1 (33.3%)	0.0350

Source: Reviewer's Table

As noted in Section 6.1.2, the majority of subjects in the development program for Ivermectin Lotion 0.5% were white (>94% in the pivotal trials). Both the White and the Non-White subgroups showed a statistically significant difference between Ivermectin 0.5% Lotion and vehicle. However, when the non-white group is further broken down the numbers are too small to expect any clinically meaningful pattern to emerge. There was a single African-American subject in the pooled efficacy population (control group), 4 Native Americans and 8 subjects of multi-racial descent.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In-Vitro testing was performed to assist in dose-selection. Two in-vitro studies were performed.

The first *in-vitro* study, entitled "Mortality Response of the Human Head Louse, *Pediculus humanus capitis*, to Ivermectin Pediculicide Formulations using the Hair Tuft Bioassay" was performed at (b) (4) [redacted]. This study compared

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3 formulations of Ivermectin (1%, 0.5%, and 0.25% concentrations) to 1% permethrin (Nix), 0.5% malathion (Ovide), ivermectin vehicle and water. The lice were obtained from infested children in (b) (4) and maintained in an *in-vitro* "rearing system" at (b) (4). The timing of mortality (measured starting after a ten minute application followed by 5 minutes of washing and drying) was the primary endpoint.

Results

All lice exposed to Ovide were already dead when the assessment began. All three of the ivermectin formulations were superior to Nix and both controls. Nix was superior to the controls. The mortality response of the 1% ivermectin treatment was significantly faster compared to the 0.5%, 0.5% with a 5 min exposure, 0.5% with a 3 min exposure and the 0.25% ivermectin treatments, respectively. The mortality response of the 0.5% ivermectin treatment was significantly faster compared to the 0.5% with a 5 min exposure and the 0.25% ivermectin treatments.

The second study, TNC-09001 was an "*In Vitro* Dose-Ranging Study of Five Topical Ivermectin (TPZ-0434) Formulations to Evaluate the Effectiveness against Head Lice (*Pediculus Humanus Capitis*)" and was performed at (b) (4). This study compared the killing activity over time of 5 ivermectin formulations (0.05%, 0.15%, 0.25%, 0.5% and 1%) to vehicle and water controls against *Pediculus Humanus Capitis* obtained from naturally infested volunteers.

Results

There was no difference in activity found between concentrations of Ivermectin Lotion 0.5% and 1% with regard to killing of head lice and nits which started at 2 hours post treatment. These concentrations were superior to lower concentrations tested. The 0.05% Ivermectin was equivalent to vehicle and water with regard to activity against *Pediculus Humanus Capitis.* The 0.15% and 0.25% outperformed the controls but not until 5 hours and 10 hours post treatment, respectively.

Based on the above studies, the applicant had established that the killing effect of Ivermectin Lotion plateaued at a concentration of 0.5% and that a ten minute application time was optimal. The applicant chose to perform a clinical dose-ranging trial comparing Ivermectin Lotion 0.5%, 0.25% and 0.15% applied for 10 minutes compared to vehicle. I agree with the selection of doses chosen for this trial, TOP003 (see Section 7.5.1 for discussion of TOP003 safety results).

Study TOP003 was designed to evaluate whether lower doses of Ivermectin Lotion might be as effective as Ivermectin Lotion 0.5% in eradicating head lice with a single 10 minute treatment.

Results of this study are shown below:

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Table 20: Live Lice Eradication: Primary Efficacy Evaluation: Active Treatments versus Placebo

Eradicated at Visit:		0.15% Ivermectin (N = 18)	0.25% Ivermectin (N = 18)	0.50% Ivermectin (N = 19)	Placebo (N = 23)
Maintained Day 2, 8 and 15	n (%)	10 (55.6%)	9 (50.0%)	14 (73.7%)	2 (8.7%)
	p-value*	0.0034	0.0091	< 0.0001	
	95% C.I.	0.16, 0.77	0.11, 0.72	0.37, 0.93	

* p-values based on a 2-group continuity-corrected chi-square test of equal proportions (odds ratio=1).
N = total number of subjects per treatment group; n = number (percentage) of subjects with a value.
C.I. = confidence interval

Source: Applicant's Clinical Study Report TOP003, pg. 37

All of the concentrations tested were superior to placebo but the 0.5% concentration was better than either 0.15% or 0.25%. The two lower concentrations were very similar in their efficacy. The applicant has adequately demonstrated that the Ivermectin Lotion 0.5% concentration is the most effective dose. There was no demonstrated increase in safety concerns with the 0.5% dose versus the lower concentrations of the investigational product. Based on Study TOP003 the applicant proceeded with their development program using the Ivermectin Lotion 0.5% concentration applied for a single 10 minute interval for the treatment of head lice.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of persistence of efficacy and/or tolerance were not performed. Efficacy beyond Day 15 was not evaluated.

6.1.10 Additional Efficacy Issues/Analyses

As was presented briefly in Section 2.5, according to the Dec 23, 2009 SPA Letter, randomization in Phase 3 trials was planned to be stratified by site. However, in the NDA submission, the applicant states that "the statistician inadvertently used central randomization and not stratified randomization" for treatment allocation and that the applicant identified the error on April 16, 2010. Consequently, the applicant revised the randomization scheme to be stratified by site beginning on April 16, 2010. The effects of this error were evaluated by the statistical reviewer who stated:

> Randomization by site led to treatment imbalance for some sites. To investigate the impact of this error on the randomization we compared the efficacy results for subjects enrolled prior to April 19th with those for subjects enrolled after April 19th. Table 2 present the efficacy results depending on the subject enrollment time (before or after April 19th):

Table 2: Proportion of Head Lice Free ITT Subjects by Subgroup Resulted by Randomization Method (LOCF)

Study	Stratification Method	Placebo		Skylice		Difference (95% CI)	P-value
		n/N	%	n/N	%		
Top-11	Pre-4/19*	7/41	17.1	29/39	74.4	57.3 (36.9, 77.7)	<.001
	Post-4/19**	5/33	15.2	25/32	78.1	63.0 (41.1, 84.9)	<.001
Top-12	Pre-4/19*	5/33	15.2	22/33	66.7	51.5 (28.3, 74.8)	<.001
	Post-4/19**	9/41	22.0	28/37	75.7	53.7 (32.4, 75.0)	<.001

Source: Reviewer's analysis after correcting the errors in LOCF (See footnote in Table 1)
* Study-wide randomization (not according to the protocol)
** Protocol-specified, site-specific randomization.

Source: Statistical Reviewer's Midcycle Review pg2

The result of this table show that the efficacy results are comparable for the two periods; thus indicating that no bias in findings occurred due to the change in the randomization.

I agree with the statistical reviewer that the error in randomization did not affect the reliability of the results obtained in the pivotal trials.

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, TOP011 and TOP012 which were conducted in the United States. Supportive safety data is also available from five other sponsor-conducted Phase 1 and 2 trials. The safety information available for oral ivermectin (Stromectol) in the literature and from the approved labeling adds additional supportive data. Finally, investigations of other topical ivermectin formulations in clinical development have been reviewed for the safety database.

Information from the Sklice clinical development program includes 1651 subjects of whom 992 were exposed to the investigational product. Of these 992, 590 were head lice infested subjects exposed to a single treatment of the "to be marketed formulation" for a ten minute duration at the proposed dose in Phase 2 and 3 studies. The safety population consists of the 1089 subjects participating in the phase 2 and 3 trials (excluding those in TOP003 treated with alternative doses) and the subjects from TOP001 treated topically (excluding oral ivermectin subjects).

In the Phase 2 studies, the minimum age for inclusion was 2 years. In the Phase 3 clinical trials and one of the phase 1 studies (an open label PK and safety study-TOP008), the minimum age was 6 months. Pediatric exposure (ages 6 months to 16 years) included 327 subjects, 88 of these under 4 years and 21 under 2 years. This database is adequate to assess the safety of Sklice for the treatment of head lice in patients 6 months and older (See Section 7.6.3 for detailed discussion).

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The safety measurements were assessment of adverse events, laboratory evaluation (in TOP001 and TOP008) and skin/scalp/ocular evaluation.

No deaths were seen in the Sklice clinical development program. There were 3 serious adverse events reported all in one subject in Study TOP008 who experienced acute gastroenteritis, dehydration, and diaper dermatitis seven days after she was treated with 0.5% Ivermectin Lotion. This event was not felt to be related to the investigational product by the investigator or by this reviewer. No subject in the safety population was withdrawn from the study due to an adverse event.

A total of 97 AEs were reported in a total of 79 subjects in the safety population (48 [7.9%] in the 0.5% ivermectin group and 31 [6.4%] subjects in the vehicle control group. Approximately 86% of the AEs in each treatment group were mild in severity, and more than 97% of the AEs in each treatment group were either mild or moderate. Only 2 AEs were severe (see Section 7.3.4) in the safety population and these were felt to be unrelated to the investigational product.

The most commonly experienced treatment emergent AEs (seen in greater than 0.1%) in the integrated safety population were pruritus, upper respiratory tract infection (URI) and conjunctivitis. However, only pruritus was seen in a greater percentage of treated versus vehicle subjects and this was only slightly greater, 1.8% in the treated population versus 1.4% in the vehicle control. Evaluation of adverse events across the development program did not reveal any safety signal.

The results of the pooled analysis of the safety population for each of the skin/scalp assessments (pruritus, erythema, excoriation and pyoderma) revealed no signal for irritation. Overall, as the studies progressed all of the skin/scalp reactions lessened with time in both treatment groups. This lack of irritation is supported by the results of the dermal safety study TOP007 (See Section 7.4.5). In addition, based on the findings of the ocular irritation assessments there does not appear to be a signal for significant ocular irritation associated with Ivermectin 0.5% Lotion when treating head lice.

Potential safety issues for the ivermectin moiety that have arisen from other formulations and indications for the product include hepatotoxicity, seizures and neutropenia. No signal for hepatotoxicity, seizures or neutropenia were detected in the Sklice clinical development program (See Sections 7.2.6 and 7.4.2 for detailed discussions.) No significant laboratory abnormalities were noted in the 56 subjects tested (30 of whom were below the age of 3 years) in the phase 1 Studies TOP001 and TOP008.

Available pharmacokinetic data from the phase 1 Studies TOP001 and TOP008 (See Section 4.4 for details) indicate very low (sub-nanomolar) absorption of Ivermectin 0.5% Lotion when applied to the scalp for a 10 minute application in lice infested subjects.

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This safety database appears adequate to assess the safety of Sklice (Ivermectin Lotion 0.5%) for the treatment of head lice in patients 6 months and older.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from seven studies sponsored by the applicant were submitted in the marketing application. The two phase 3 pivotal studies TOP011 and TOP012 were identical in design and enrolled 410 and 371 subjects respectively. Two phase 2 studies TOP010 and TOP003 enrolled 247 and 78 subjects respectively. TOP001, a phase one PK study enrolled 26 subjects. TOP008 a phase one, open-label PK and safety study enrolled 30 subjects. TOP007, a phase one sensitization/irritation study enrolled 256 healthy subjects.

Table 21: Studies Providing Safety Information

Study # Phase	**Design/Control***	**Dose regimen**	**# of subjects exposed to Ivermectin 0.5% Lotion ****	**Age Range (years)**
TOP011 n=410 Phase 3	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC, n=211 VC n= 199	1-55
TOP012 n=371 Phase 3	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC, n=169 VC n= 202	0.5-68
TOP010 n=247 Phase 2b	R, DB, PC, PG, MC study in subjects with head lice	One 10 minute application at home	0.5% IC, n=192 VC n= 55	2-59
TOP003 n=78 Phase 2	R, DB, PC, PG **dose-ranging** study in subjects with head lice	One 10 minute application at study site	0.15% IC n=18 0.25% IC n=18 0.5% IC n= 19 VC n=23	2-62
TOP001 n=26 Phase1	R, PG, controlled study in **children** with head lice	Up to two topical applications at study site, Single dose of oral ivermectin (Stromectol)	0.5% IC n= 15 Oral ivermectin (Stromectol) n=6 VC n=5	4-10
TOP008 n=30	**Open-label,** MC study in **children**	One 10 minute application at	0.5% IC, n=30	0.5-3

Phase1	with head lice	study site		
TOP007 n=256 Phase1	R, DB **contact sensitization-cumulative irritation** combination study in **healthy adults**	Drug product applied as a patch	Group A (Irritation) n=36 Group B (Sensitization) n=220	18-65

* R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, MC=multi-center
**Ivermectin Lotion=IC, Vehicle Control=VC
Source: Reviewer's Table

The safety review of the applicant's product will focus on adverse events, systemic safety (laboratory evaluation) and local safety (cutaneous signs and symptoms at application sites).

Safety was assessed through reported adverse events (AEs) at Days 1, 2, 8 and 15 for Studies TOP003, TOP008, TOP010, TOP011, and TOP012. The schedule differed for Studies TOP001 (two applications of the investigational product were applied) and TOP007 (product applied as patches to back) but occurred at each visit.

Assessments of observed skin/scalp reactions (pruritus, erythema, excoriation, and pyoderma) occurred on Days 1, 2, 8 and 15 for Studies TOP003, TOP008, TOP010, TOP011, and TOP012. Study TOP001 did not assess skin irritation and for Study TOP007 irritation was a primary endpoint and was assessed daily starting on visit 3.

Assessments of ocular irritation occurred on Days 1 and 2 for Studies TOP003, TOP008, TOP010, TOP011, and TOP012. Studies TOP001 and TOP007 did not assess ocular irritation.

Each adverse event was evaluated for severity, duration, and whether the event may have been associated with the study drug.

Integrated Analysis

The safety population included all subjects who were randomized and dispensed Ivermectin 0.5% Lotion from studies TOP011, TOP012, TOP010, TOP001 (excluding oral Ivermectin subjects), TOP003 (excluding subjects who received 0.15% and 0.25% Ivermectin). Some of the studies had slightly different entry criteria regarding the number of live lice required for eligibility. In Study TOP010 subjects had to have at least 1 live louse present at baseline. In TOP003, subjects had to have at least 3 live lice present at baseline. In Studies TOP011 and TOP012, the index subject for each household was the youngest individual within the household who had at least 3 live lice present at baseline, while non-index household members had at least 1 live louse

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present. Studies TOP011, TOP012 and TOP010 utilized an at home treatment design, while in Studies TOP001 and TOP003 the treatment was administered by qualified clinical trial professionals on site.

Study results for alternative doses from Study TOP003 which included 0.25% and 0.15% Ivermectin Lotion and oral ivermectin from study TOP001 are not included in the pooled analysis (see Section 7.5.1 Dose Dependency for Adverse Events for safety discussion of dose-ranging study TOP003). Study results from TOP008 which was open-label are not included in the pooled analysis (see Section 7.4.1, subsection Analysis of Common Adverse Events: Study TOP008 (ages 6 months to 3 years) for safety discussion of Study TOP008). Study results from TOP007 are also not included as these were healthy adults who only received ivermectin Lotion 0.5% to small patches on the back.

There were 1651 subjects enrolled in the Applicant studies, a total of 672 subjects with head lice received study medication throughout the clinical development program. There were 327 pediatric subjects (ages 6 months to 16 years) who received treatment. Of these pediatric subjects, 88 were under the age of 4 years and 21 under 2 years. The youngest subjects (under 4 years of age) are discussed further under Section 7.4.1, subsection Analysis of Common Adverse Events: Study TOP008 (ages 6 months to 3 years).

For all clinical studies serious adverse events and clinically important adverse events were examined. Deaths were not seen in the clinical development program.

Additional (Secondary) Data Sources

See Section 7.2.6 for discussion of literature.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the MedDRA® dictionary (version 12.1) and were tabulated by system organ class and preferred terms. For the pivotal studies TOP011 and TOP012 the applicant's classification of verbatim terms to preferred terms appears acceptable.

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

As noted above in Section 7.1.1, the integrated analysis includes the subjects treated with topical 0.5% Ivermectin Lotion from all 5 studies that were controlled and these subjects were compared to vehicle (TOP001, TOP003, TOP010, TOP011 and TOP012). The number of treatments (one) was the same with the exception of study TOP001 which allowed a second treatment between days 9-11 (which was given to 10

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out of the 15 subjects treated). Study TOP007 was a contact sensitization and cumulative irritation study in which all subjects received 0.5% Ivermectin Lotion as a patch. Therefore, subjects from TOP007 were excluded. Study TOP008 was open-label and therefore was also excluded. This pooling strategy appears reasonable.

Separate non pooled analysis of adverse events was performed for study TOP008 which enrolled only younger (6months to 3 years) subjects (see Section 7.4.1).

7.2 Adequacy of Safety Assessments

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

The total number of subjects with active head lice infestation exposed to the Ivermectin Lotion 0.5% in the clinical development program are presented below:

Table 22: Subjects with Infestation exposed to Ivermectin Lotion

Study	# of subjects exposed To Ivermectin Lotion 0.5%*	# of applications	Treatment amount (mean dose)	Treatment duration
TOP001	15	One or two (10 subjects)	1st - 53.1 g 2nd - 53.4 g	10 min
TOP003	0.15% IC n=18 0.25% IC n=18 0.5% IC n= 19	One	99.30 g 98.63 g 100.07 g	10 min
TOP008	30	One	6.3 – 98.8 g	10 min
TOP010	192	One	12.6 – 143.8 g	10 min
TOP011	211	One	76.57 g	10 min
TOP012	169	One	75.58 g	10 min
Total	672			

*except as noted in the dose-ranging Study TOP003
Source: Reviewer's table

Of the 672 subjects exposed, 635 were exposed at the proposed dose of 0.5% Ivermectin Lotion. The mean dose by weight of study medication used to treat each subject was 78.14 g (range 0.00–213.84 g) for the 0.5% ivermectin group. The mean dose by weight per kg of body weight was 2.34 g/kg for the 0.5% ivermectin group. In the home treatment studies (TOP010, TOP011 and TOP012) the subjects/caretakers were instructed to bring the tube back in for weighing post treatment to determine the amount used.

The demographics for the safety population are presented below:

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Table 23: Demographic Characteristics: Safety Population: All Studies

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Integrated Summary of Safety: Revised Safety Population

Table 1.2
Demographic Characteristics
Revised Safety Population: TOP001, TOP003, TOP010, TOP011 and TOP012

Characteristic		0.5% Ivermectin (N =605)	Vehicle Control (N =484)
Gender: n (%)	Female	499 (82.5%)	383 (79.1%)
	Male	106 (17.5%)	101 (20.9%)
Age (years)	n	605	484
	Mean (Std Dev)	14.52 (12.59	15.37 (13.60
	Median	10.00	10.00
	Min, Max	0.50, 68.00	0.75, 64.00
Age (years): n (%)	0.5 to < 2	9 (1.5%)	8 (1.7%)
	2 to < 4	49 (8.1%)	40 (8.3%)
	4 to < 12	291 (48.1%)	241 (49.8%)
	12 to 16	103 (17.0%)	66 (13.6%)
	> 16	153 (25.3%)	129 (26.7%)
Ethnicity: n (%)	Hispanic or Latino	270 (44.6%)	202 (41.7%)
	Not Hispanic or Latino	335 (55.4%)	282 (58.3%)
Race: n (%)	American Indian/Alaskan Native	7 (1.2%)	9 (1.9%)
	Black	0 (0.0%)	1 (0.2%)
	Multi-Racial	20 (3.3%)	7 (1.4%)
	Other	2 (0.3%)	0 (0.0%)
	White	576 (95.2%)	467 (96.5%)
Weight (kg)	n	605	484
	Mean (Std Dev)	46.24 (27.28	45.20 (26.23
	Median	40.00	39.77
	Min, Max	8.18, 136.36	7.27, 134.09

Note: N = Total number of subjects per treatment group; n = number of subjects with a value

Source: Applicant's Revised Integrated Summary of Safety

A majority of subjects were White (>90%) and female (>79%). As previously noted in Section 6.1.2, head lice are more frequent in girls. More than 55% of subjects in each treatment group reported their ethnicity as Not Hispanic or Latino.

Subject ages ranged from 6 months to 68 years. The mean age was 14 to 15 years old. The median age was ten years. Of the 4 age categories (6 months to < 4 years, 4 to < 12 years, 12 to 16 years, and > 16 years), the largest percentage of subjects were in the age range of 4 to < 12 years. As previously noted in Section 6.1.2, in the United States the highest incidence of head lice is found in children aged 3 to 11 years.

As with the demographics for the population in the pivotal trials TOP011 and TOP012 discussed in Section 6.1.2, compared with that for the U. S. population this represents a relative under-representation of African-Americans and a relative over-representation of Hispanics. As noted in 6.1.2, head lice are less common in African-Americans. With

regard to safety, the over representation of Hispanic ethnicity is unlikely to affect adverse events.

Demographic and baseline characteristics were relatively balanced between treatment groups.

Adequacy of Clinical Exposure:

An adequate number of subjects were exposed to Ivermectin Lotion 0.5% at the proposed dosing regimen to assess safety for use. A total of 657 subjects were exposed to the to be marketed formulation.

Pediatric Exposure

In the development program, pediatric exposure in the 4 years and younger age group appears adequate (88 subjects), in the youngest age group 6 to 24 months (21 subjects) were treated. (See Section 7.4.2 for further discussion of pediatric exposure.)

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

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. This might be expected since, topical application as studied in PK trials did not result in significant systemic absorption.

7.2.2 Explorations for Dose Response

The applicant conducted one dose-ranging study, TOP003. This study compared doses of Ivermectin Lotion 0.15%, 0.25% and 0.5% to vehicle control (placebo). There were 22 Adverse Events (AEs) reported by 20 subjects.

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Table 24: Summary of Treatment-emergent Adverse Events: TOP003

Parameter	0.15% Ivermectin (N = 18)	0.25% Ivermectin (N = 18)	0.50% Ivermectin (N = 19)	Placebo (N = 23)
Number (%) of Subjects with at Least One AE	6/ 18 (33.3%)	3/ 18 (16.7%)	5/ 19 (26.3%)	6/ 23 (26.1%)
Number of AEs	7	3	6	6
Number (%) of Serious AEs	0/ 7 (0.0%)	0/ 3 (0.0%)	0/ 6 (0.0%)	0/ 6 (0.0%)
Number (%) of AEs by Severity				
Mild	7/ 7 (100.0%)	2/ 3 (66.7%)	5/ 6 (83.3%)	6/ 6 (100.0%)
Moderate	0/ 7 (0.0%)	1/ 3 (33.3%)	1/ 6 (16.7%)	0/ 6 (0.0%)
Severe	0/ 7 (0.0%)	0/ 3 (0.0%)	0/ 6 (0.0%)	0/ 6 (0.0%)

N = total number of subjects per treatment group; n = number (percentage) of subjects with a value.

Source: Applicant's Clinical Study Report TOP003 pg 43.

No serious adverse events occurred in Study TOP003. I was unable to detect a dose-response when analyzing the relationship between dose and adverse events in Study TOP003; however the study was small and not powered to detect such a difference. The highest incidence of AEs was seen in the lowest concentration of Ivermectin Lotion (0.15%). The incidence of AEs in the Ivermectin Lotion 0.5% was similar to that seen in the placebo group. The incidence in the Ivermectin Lotion 0.25% was even less than placebo. The majority of the AEs seen were rated as mild (90.9%). Only 2 AEs (one in Ivermectin Lotion 0.25% and one in Ivermectin Lotion 0.5%) were rated as moderate. There were no AEs leading to discontinuation in this study.

There was also no discernable dose-relationship with regard to AEs presented by System Organ class. The table below shows the AEs by system organ class and preferred terms for Study TOP003.

Table 25: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class	Preferred Term	0.15% Ivermectin (N = 18)	0.25% Ivermectin (N = 18)	0.50% Ivermectin (N = 19)	Placebo (N = 23)
Eye disorders	Conjunctivitis	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
	Eye pruritus	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Erythema	0 (0.0%)	0 (0.0%)	1 (5.3%)	3 (13.0%)
	Folliculitis	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (4.3%)
	Pruritus	5 (27.8%)	2 (11.1%)	4 (21.1%)	1 (4.3%)
	Skin irritation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)

If a subject experienced the same event more than once, the first occurrence was tabulated.
N = total number of subjects per treatment group; n = number (percentage) of subjects with a value.

Source: Applicant's Clinical Study Report TOP003 pg 44.

Only conjunctivitis (one case, 5.3% in the 0.5% group vs 0 cases in placebo), eye pruritus (one case, 5.6% in the 0.15% group vs 0 cases in placebo) and pruritus (5 cases, 27.8% in the 0.15% group, 2 cases, 11.1% in the 0.25% group and 4 cases, 21.1% in the 0.50% group vs 1 case, 4.3 % in placebo) occurred more commonly in the treated versus the controls. As with the incidence of adverse events above, I was unable to detect a dose-response when analyzing the relationship between dose and adverse events by System Organ Class and Preferred Term in Study TOP003. The highest percentage of subjects experiencing pruritus (27.8%) was in the lowest concentration (Ivermectin 0.15%) of the investigational product.

The types of AEs seen in Study TOP003 are very similar to that of the overall safety population. However the incidences of these side effects are considerably higher in this smaller study (see Section 7.4.1).

Table 26: Comparison of AEs in Study TOP003 to the Safety Population

	Study TOP003		**Safety Population**	
	Ivermectin	Placebo	Ivermectin	Placebo
Pruritus	20%	4.3%	1.8%	1.4%
Conjunctivitis	5.3%	0.0%	0.5%	0.0%
Eye Pruritus	5.6%	0.0%	0.0%	0.0%

Source: Reviewers Table

The applicant has adequately demonstrated that the Ivermectin Lotion 0.5% concentration is the most effective dose. There was no demonstrated increase in safety concerns with the 0.5% dose versus the lower concentrations of the investigational product.

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7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3.

7.2.4 Routine Clinical Testing

The routine clinical testing performed in Study TOP001 included CBC with Diff, Absolute Neutrophil Count (ANC) ALT, AST, Alk Phos, BUN, CO_2, Cl, Crt, LDH, K, Na and urinalysis. The routine clinical testing performed in Study TOP008 included CBC with Diff, ALT, AST, Alk Phos, Bilirubin and LDH. The applicant was asked to calculate Absolute Neutrophil Count (ANC) for Study TOP008 and complied. These evaluations were adequate to assess the safety and efficacy of use for Ivermectin Lotion 0.5% (see Section 7.4.2).

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant did not perform any assessment of drug-drug interactions. Metabolism and clearance were not studied as no significant systemic absorption was noted.

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 Stromectol for head lice under IND 57420. Details on these studies are presented below*:

Table 27: 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)	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

		Median age=10 yrs		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 28: Published Literature on Oral Ivermectin Use – Safety Analysis

Citation	Design/ Type	Popul	Regimen	AE	Additional notes*
Alleman, Mary 2006 *Filaria Journal*	Review of Mectizan (ivermectin) Donation Program	2005: (b) (4) Rxs for onchocerciasis 2005: (b) (4) Rxs combined with a bendazole for filariasis	15-200 ug/kg	No specific assessments done	(b) (4) Rxs total for onchocerciasis by end of 2005 (b) (4) 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 & Parisit*	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 • 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 = 3147 Egypt)		Unable to obtain original article for review

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 article
Source: Obtained from an internal Agency document: Ivermectin Background Information -prepared by (b) (4) in preparation for an internal meeting to discuss the advisability of a written request for oral ivermectin for treatment of (b) (4) 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 5 reflect the overall benign adverse event profile seen in this program. (See section 7.6.2 for further discussion of treatment during pregnancy) The Brown article in addition references some reassuring new 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 very 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 underreporting 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).

IND (b) (4)

Ivermectin Cream 1% is being developed by Galderma under IND (b) (4) for the topical treatment of inflammatory lesions of papulopustular rosacea. The applicant’s early clinical development program included a 52 week, open-label, uncontrolled long-term safety study of once daily use of Ivermectin Cream 1%, Study RD.03.SRE.40051 (b) (4)

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

Reference ID: 3067484

> 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.

The applicant has conducted a Phase 2 study, Study RD.03.SPR.40106 (Study 40106), to assess the hematological safety of once daily topical ivermectin Cream 1%. The study was performed in Europe. The study was planned to randomize 200 subjects in a 1:1 fashion to either CD5024 1% cream or vehicle cream. The FDA statistical review of the protocol for Study 40106 pointed to numerous flaws in the study design as outlined below:

> Study 40106 is likely to provide limited information on the safety of CD5024 for the assessment of neutrophil counts. The following are reasons for such a determination.
>
> - The planned treatment duration of the study is 12 weeks. With such a short term exposure to drug, this study will not provide data on long term use of the CD5024 and its effects on neutrophil counts.
>
> - The study 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 study is not likely to observe many incidences of the safety parameter of interest. Correspondingly, the study has power below 20% to detect a significant difference between the active and control.

The study report and the sponsor's evaluation of the results were recently submitted to the Agency as part of the meeting package for a Type B meeting scheduled for Aug 10, 2011. The sponsor'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 CD5024 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

Reference ID: 3067484

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 CD5024 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.

In addition, as part of the meeting package for the August, 2011 meeting for IND (b) (4) the sponsor included data regarding the bioavailability of Ivermectin 1% Cream when used daily in subjects with Rosacea (results of PK studies). The systemic levels of ivermectin seen were substantially higher than that seen in the development program for Sklice, see Table presented below:

Table 29: Comparison PK data for IND (b) (4)

	PK Study Results RD.06.SRE.18120 IND (b) (4) Oral Ivermectin (single 6 mg dose)	**PK Study Results RD.03.SRE.40064 IND (b) (4) Topical 1% Ivermectin Cream** (daily use-14 day results)	**PK Study Results TOP008 NDA 202736 Topical Ivermectin Lotion 0.5%** (single application-10 minutes)	
	(b) (4)		AUC_{0-24hr} ng.h/ml	Cmax (ng/mL)
mean			3.972	0.241

It is not suprising that the bioavailability of Ivermectin Lotion 0.5% in NDA 202736 is markedly lower than that seen in IND (b) (4) In IND (b) (4) Ivermectin Cream 1% is applied daily for chronic use to facial skin (often erythematous skin as is seen with rosacea). In NDA 202736 Ivermectin Lotion 0.5% is applied once, left in place on the scalp for 10 minutes and then rinsed off.

In addition, if the signal seen in IND (b) (4) is real (not yet clear) the problem seems to develop after chronic use (the earliest case was at 6 weeks despite close monitoring of WBC in the study above). These two differences between the exposure patterns for IND (b) (4) and NDA 202736 are reassuring with regard to development of a problem with neutropenia for Ivermectin Lotion 0.5% as used for head lice treatment.

Though vigilance for a signal in the post-marketing period will be important to maintain I think it unlikely that a problem with neutropenia will present itself for NDA 202736. Careful analysis of the WBC and absolute neutrophil counts from studies TOP001 and TOP008 also failed to show any such signal (see Section 7.4.2).

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the 7 studies conducted in the development of Ivermectin Lotion 0.5%.

7.3.2 Nonfatal Serious Adverse Events

During the 7 studies conducted during the development of Ivermectin Lotion 0.5% one subject experienced 3 serious adverse events. This subject was an 8 month old female subject enrolled in TOP008 (subject #TOP008-13-01) who experienced acute gastroenteritis, dehydration, and diaper dermatitis seven days after she was treated with 0.5% Ivermectin Lotion. She was hospitalized eleven days post-treatment, was given fluids intravenously, and was released the next day. She recovered without sequelae. These SAE were not considered by the investigator to be related to her treatment with Ivermectin Lotion 0.5%. I agree with the treating investigator that these events are unlikely to be related to the study product.

Dropouts and/or Discontinuations

Pooled Disposition

The following table displays the pooled disposition for the safety population for all studies:

Table 30: Subject Disposition, Safety Population, All Studies

Table 1.1
Subject Disposition
Revised Safety Population: TOP001, TOP003, TOP010, TOP011 and TOP012

Number of Subjects	0.5% Ivermectin (N =605)	Vehicle Control (N =484)
Safety Population	605 (100.0%)	484 (100.0%)
Completed Study	584 (96.5%)	476 (98.3%)
Did Not Complete Study+	21 (3.5%)	8 (1.7%)
Discontinued due to:		
Subject Withdrawal	2 (0.3%)	2 (0.4%)
Lost to Follow-up	15 (2.5%)	1 (0.2%)
Non-compliance	4 (0.7%)	2 (0.4%)
Other	0 (0.0%)	3 (0.6%)

+ Treatment failures on Day 2 or Day 8 have completed the study

Note: N = Total number of subjects per treatment group; n = number of subjects with a value

Source: Applicant's Revised Integrated Summary of Safety

Overall, a similar percentage of subjects completed the studies in the ivermectin and vehicle control group, 96.5% and 98.3% respectively. The number of subjects who did not complete the study was small, 3.5% in the Ivermectin group versus 1.7% in the vehicle control group.

No subjects in the safety population withdrew due to an adverse event. (One subject withdrew due to an adverse event in Study TOP007 which was not included in the safety population. See discussion of disposition for Study TOP007 for details). The majority of the subjects who did not complete in the ivermectin group were lost to follow-up. There were a larger percentage of subjects "lost to follow-up" in the treatment group, 2.5% versus the vehicle control group, 0. 2%. There were a larger percentage of subjects who were discontinued due to non-compliance in the ivermectin group (0.8%) versus in the vehicle control group (0.7%).

7.3.4 Significant Adverse Events

There were four "severe" events that occurred in the development program.

Table 31: Severe Adverse Events

Study/ Subject #	Event	Rx Group	Related	Outcome
TOP012 01-305-03	#1 - Pain in extremity (right heel)	Vehicle	unrelated	resolved
TOP010 03-108-05	#2 - Conjunctivitis (right eye) present at screening visit	ivermectin	unrelated	Ongoing at study completion
TOP007 264	#3 and #4 - Fever, Nausea	Ivermectin patch	unrelated	resolved

Source: Reviewer's Table

Conjunctivitis was an adverse event of special interest. According to the case report form, Subject 03-108-05 presented at baseline with conjunctivitis of the left eye on Oct 14, 2009. She was treated with Ivermectin Lotion 0.5% and returned for follow-up on Day 2 and was noted to have conjunctivitis of both eyes. She was started on Sulfonamide eye drops on day 2. She was noted to have live lice on exam at day 2 and was discharged from the study to be treated with an FDA approved OTC treatment for head lice. At the time of her discharge (Day2) she had ongoing conjunctivitis. A telephone call to discern resolution date for this adverse event was made but the subject's phone had been disconnected. A letter was sent to her address on file but no reply was received. The investigator did not feel that the conjunctivitis (which was present before treatment) was related to the investigational product. I agree with this assessment.

The investigators did not attribute any of the above SAE's to the investigational product. I agree with this assessment after review of the relevant case report forms for each event.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class for discussion of concerns regarding leukopenia/neutropenia, LFT elevations and seizures with other formulations of ivermectin.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events were elicited in this development program both by open-ended questions and in certain studies (to be detailed under "Active Assessments: Scalp Irritation and Ocular Irritation" later in this Section) by specific queries and targeted examinations.

Pooled Analysis of Common Adverse Events: Safety Population

There were 1651 subjects enrolled in the Applicant studies and 1089 subjects in the safety population. A total of 97 AEs were reported in a total of 79 subjects (48 [7.9%] in the 0.5% ivermectin group and 31 [6.4%] subjects in the vehicle control group. Approximately 86% of the AEs in each treatment group were mild in severity, and more than 97% of the AEs in each treatment group were either mild or moderate. Only 2 AEs were severe (see Section 7.3.4) in the safety population. (An additional 2 severe adverse events occurred in one subject in Study TOP007.) The majority of AEs in the 0.5% ivermectin group (71%) were considered by the investigator to be unrelated to the study medication.

Table 32: Summary of Treatment-emergent Adverse Events: Safety Population: All Studies

Table 2.1
Summary of Treatment-emergent Adverse Events
Revised Safety Population: TOP001, TOP003, TOP010, TOP011 and TOP012

	0.5% Ivermectin (N =605)	Vehicle Control (N =484)
Number (%) of Subjects with AE	48 (7.9%)	31 (6.4%)
Number (%) of Subjects with Serious AE	0 (0.0%)	0 (0.0%)
Number of AEs	59	38
Number (%) of Serious AEs	0 (0.0%)	0 (0.0%)
Number (%) of AEs by Severity		
Mild	52 (88.1%)	33 (86.8%)
Moderate	6 (10.2%)	4 (10.5%)
Severe	1 (1.7%)	1 (2.6%)
Number (%) of AEs by Relationship		
Unrelated	42 (71.2%)	18 (47.4%)
Possible	14 (23.7%)	19 (50.0%)
Probable	3 (5.1%)	1 (2.6%)
Definite	0 (0.0%)	0 (0.0%)

Note: N = Total number of subjects per treatment group; n = number of subjects with a value

Source: Applicant's Revised Integrated Summary of Safety

The most commonly experienced treatment emergent AEs (seen in > 0.1%) in the integrated safety population are presented by body system and preferred terms (MedDRA version 12.1). below in Table 33.

Table 33: Occurrence of Treatment-emergent Adverse Events+ (> 0.1% in Either Treatment Group) by Body System and Preferred Term: Safety Population

Table 2.2
Occurrence of Treatment-emergent Adverse Events+ by Body System and Preferred Term
Revised Safety Population: TOP001, TOP003, TOP010, TOP011 and TOP012

Body System	Preferred Term	0.5% Ivermectin (N =605)	Vehicle Control (N =484)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHADENOPATHY	0 (0.0%)	1 (0.2%)
EYE DISORDERS	CONJUNCTIVITIS	3 (0.5%)	0 (0.0%)
	EYE IRRITATION	1 (0.2%)	0 (0.0%)
	OCULAR HYPERAEMIA	1 (0.2%)	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOOTHACHE	1 (0.2%)	0 (0.0%)
	VOMITING	0 (0.0%)	1 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PRURITUS	1 (0.2%)	1 (0.2%)
	PYREXIA	0 (0.0%)	1 (0.2%)
INFECTIONS AND INFESTATIONS	IMPETIGO	0 (0.0%)	1 (0.2%)
	INFLUENZA	2 (0.3%)	0 (0.0%)
	NAIL BED INFECTION	1 (0.2%)	0 (0.0%)
	OTITIS MEDIA	0 (0.0%)	1 (0.2%)
	PHARYNGITIS	1 (0.2%)	0 (0.0%)
	PHARYNGITIS STREPTOCOCCAL	1 (0.2%)	0 (0.0%)
	PYODERMA	1 (0.2%)	0 (0.0%)
	SWINE INFLUENZA	1 (0.2%)	0 (0.0%)
	TONSILLITIS	1 (0.2%)	0 (0.0%)
	UPPER RESPIRATORY TRACT INFECTION	5 (0.8%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	CONTUSION	1 (0.2%)	0 (0.0%)
	EXCORIATION	9 (1.5%)	9 (1.9%)
	INJURY	0 (0.0%)	1 (0.2%)
	SCRATCH	1 (0.2%)	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MUSCULOSKELETAL PAIN	0 (0.0%)	1 (0.2%)
	PAIN IN EXTREMITY	0 (0.0%)	1 (0.2%)
NERVOUS SYSTEM DISORDERS	HEADACHE	1 (0.2%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	1 (0.2%)	0 (0.0%)
	COUGH	2 (0.3%)	0 (0.0%)
	DYSPNOEA	1 (0.2%)	0 (0.0%)
	OROPHARYNGEAL PAIN	2 (0.3%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DANDRUFF	1 (0.2%)	0 (0.0%)

Table 2.2
Occurrence of Treatment-emergent Adverse Events+ by Body System and Preferred Term
Revised Safety Population: TOP001, TOP003, TOP010, TOP011 and TOP012

Body System	Preferred Term	0.5% Ivermectin (N =605)	Vehicle Control (N =484)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	1 (0.2%)	0 (0.0%)
	ERYTHEMA	6 (1.0%)	9 (1.9%)
	FOLLICULITIS	0 (0.0%)	1 (0.2%)
	PRURITUS	11 (1.8%)	7 (1.4%)
	RASH MACULO-PAPULAR	1 (0.2%)	0 (0.0%)
	SKIN BURNING SENSATION	1 (0.2%)	0 (0.0%)
	SKIN IRRITATION	0 (0.0%)	1 (0.2%)

+ If a subject experiences the same event more than once, the first occurrence is tabulated.
Note: N = Total number of subjects per treatment group; n = number of subjects with a value

Source: Applicant's Revised Integrated Summary of Safety

The most commonly experienced treatment emergent AEs (seen in greater than 0.5%) in the integrated safety population were pruritus, upper respiratory tract infection (URI) and conjunctivitis. However, only pruritus and conjunctivitis were seen in a greater percentage of treated versus vehicle subjects and for pruritus this was only slightly greater (1.8% in the treated population versus 1.4% in the vehicle control).

The following adverse events occurred more commonly in the treatment group then in the vehicle control group (presented in decreasing incidence): Pruritus 11 (1.8%) vs 7 (1.4%), Upper Respiratory Tract Infection 5 (0.8%) vs 0 (0.0%), Conjunctivitis 3 (0.5%) vs 0 (0.0%), Influenza 2 (0.3%) vs 0 (0.0%), Cough 2 (0.3%) vs 0 (0.0%), Oropharyngeal Pain 2 (0.3%) vs 0 (0.0%), Headache 1 (0.2%) vs 0 (0.0%), Pharyngitis 1 (0.2%) vs 0 (0.0%), Toothache 1 (0.2%) vs 0 (0.0%), Eye irritation 1 (0.2%) vs 0 (0.0%), Nail bed infection 1 (0.2%) vs 0 (0.0%), Streptococcal pharyngitis 1 (0.2%) vs 0 (0.0%), Pyoderma 1 (0.2%) vs 0 (0.0%), Swine influenza 1 (0.2%) vs 0 (0.0%), Tonsillitis 1 (0.2%) vs 0 (0.0%), Contusion 1 (0.2%) vs 0 (0.0%), Asthma 1 (0.2%) vs 0 (0.0%), Dyspnea 1 (0.2%) vs 0 (0.0%), Dandruff 1 (0.2%) vs 0 (0.0%), Dry skin 1 (0.2%) vs 0 (0.0%), Maculopapular rash 1 (0.2%) vs 0 (0.0%) and Skin burning sensation 1 (0.2%) vs 0 (0.0%).

These results are presented graphically in Table X below:

Table 34: Table of Treatment Emergent Adverse Events (Seen in > 0.1%) in the Integrated Safety Population

Body System	Preferred Term	0.5% Ivermectin Lotion	Vehicle control
Skin and Subcutaneous Disorders	Pruritus	11 (1.8%)	7 (1.4%)
Infections and Infestations	Upper Respiratory Tract Infection	5 (0.8%)	0 (0.0%)
Eye Disorders	Conjunctivitis	3 (0.5%)	0 (0.0%)
Infections and Infestations	Influenza	2 (0.3%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	Cough	2 (0.3%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal Pain	2 (0.3%)	0 (0.0%)
Nervous System Disorders	Headache	1 (0.2%)	0 (0.0%)
Infections and Infestations	Pharyngitis	1 (0.2%)	0 (0.0%)
Gastrointestinal Disorders	Toothache	1 (0.2%)	0 (0.0%)
Eye Disorders	Eye irritation	1 (0.2%)	0 (0.0%)
Infections and Infestations	Nail bed infection	1 (0.2%)	0 (0.0%)
Infections and Infestations	Streptococcal pharyngitis	1 (0.2%)	0 (0.0%)
Infections and Infestations	Pyoderma	1 (0.2%)	0 (0.0%)
Infections and Infestations	Swine influenza	1 (0.2%)	0 (0.0%)
Infections and Infestations	Tonsillitis	1 (0.2%)	0 (0.0%)
Skin and Subcutaneous Disorders	Contusion	1 (0.2%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	Asthma	1 (0.2%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	1 (0.2%)	0 (0.0%)
Skin and Subcutaneous Disorders	Dandruff	1 (0.2%)	0 (0.0%)
Skin and Subcutaneous Disorders	Dry skin	1 (0.2%)	0 (0.0%)
Skin and Subcutaneous Disorders	Maculopapular rash	1 (0.2%)	0 (0.0%)
Skin and Subcutaneous Disorders	Skin burning sensation	1 (0.2%)	0 (0.0%)

Source: Reviewer's Table

There is only one AE occurring in greater than 1% of the population with an incidence greater in the treatment group than in the control group: pruritus. The difference in incidence of this event between the treatment arms is small and this may be due to chance alone.

The next most common event that occurs more in the treated than in the control group is Upper Respiratory Tract Infection which is unlikely to be related to the investigational product.

Many of the events occurring more commonly in the treated group are infectious in origin. A possible explanation for the larger number of adverse events in the infectious categories might be imbalance in the age distribution between the treated and the vehicle groups since infections are seen more commonly in younger age groups. Looking at the table below, however, the arms were relatively well balanced with regard to age.

Table 35: Age Distribution for Safety Population

Characteristic		**0.5% Ivermectin (N = 901)**	**Vehicle Control (N = 750)**
Age (years): n (%)	0.5 to <2	9 (1.5 %)	8 (1.7%)
	2 to <4	49 (8.1%)	40 (8.3%)
	4 to <12	291 (48%)	241 (49.8%)
	12 to 16	103 (17%)	66 (13.6%)
	>16	153 (25%)	129 (26.7%)

Source: Reviewer's Table

Pooled Analysis of Pivotal Trials: Common Adverse Events

The AEs for the pivotal trials TOP011 and TOP012 were pooled. The pattern of treatment-emergent AEs was similar to the pattern of AEs seen in the Integrated Safety Population (see section 7.4.1 above), though the incidence was less. There were 35 subjects who experienced an AE with a similar incidence comparing the Ivermectin group 16 (4.2%) to the vehicle control group 19 (4.7%). No serious AEs were seen in the pivotal trials. One severe AE was seen in the vehicle control group (pain in the right heel), which was felt by the investigator to be unrelated to the investigational product.

Table 36: Summary of Treatment-emergent Adverse Events: Safety Population: TOP011 and TOP012

	0.5% Ivermectin (N =379)	Vehicle Control (N =401)
Number (%) of Subjects with AE	16 (4.2%)	19 (4.7%)
Number (%) of Subjects with Serious AE	0 (0.0%)	0 (0.0%)
Number of AEs	17	26
Number (%) of Serious AEs	0 (0.0%)	0 (0.0%)
Number (%) of AEs by Severity		
Mild	16 (94.1%)	22 (84.6%)
Moderate	1 (5.9%)	3 (11.5%)
Severe	0 (0.0%)	1 (3.8%)
Number (%) of AEs by Relationship		
Unrelated	7 (41.2%)	14 (53.8%)
Possible	8 (47.1%)	12 (46.2%)
Probable	2 (11.8%)	0 (0.0%)
Definite	0 (0.0%)	0 (0.0%)

Note: N = Total number of subjects per treatment group; n = number of subjects with a value
Source: Section 5.3.5.3.1, Integrated Summary of Safety, Table 11.1

Source: Applicant's Summary of Clinical safety Section 2.7.4 pg 54

The most commonly experienced treatment emergent AEs in the pooled pivotal trials were pruritus (1.5% in the control group vs 0.8% in the Ivermectin group), erythema (1.2% in the control group vs 0.5% in the Ivermectin group) and excoriation (1.2% in the control group vs 0.3% in the Ivermectin group). In each of these AEs however, the incidence in the vehicle control group exceeded that of the ivermectin group. Using the criteria of a "common adverse event" being one that occurs in greater than 1% of the population and in the treated group more than control there were no common adverse events seen in the pooled pivotal trials.

The following table displays the treatment emergent AEs (seen in > 0.1%) in the pooled pivotal trials where the incidence in the treated group exceeds the incidence in the control group.

Table 37: Occurrence of Treatment-emergent Adverse Events+ by Body System and Preferred Term Safety Population: TOP011 and TOP012

Body System	Preferred Term	0.5% Ivermectin (n=379)	Vehicle Control (n=401)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	2 (0.5%)	0 (0.0%)
EYE DISORDERS	CONJUNCTIVITIS	1 (0.3%)	0 (0.0%)
“ ”	EYE IRRITATION	1 (0.3%)	0 (0.0%)
“ ”	OCULAR HYPERAEMIA	1 (0.3%)	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOOTHACHE	1 (0.3%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	PHARYNGITIS STREPTOCOCCAL	1 (0.3%)	0 (0.0%)
“ ”	TONSILLITIS	1 (0.3%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DANDRUFF	1 (0.3%)	0 (0.0%)
“ ”	DRY SKIN	1 (0.3%)	0 (0.0%)
“ ”	SKIN BURNING SENSATION	1 (0.3%)	0 (0.0%)

Source: Reviewer’s Table

<u>Analysis of Common Adverse Events: Study TOP008 (ages 6 months to 3 years)</u>

TOP008 was an open-label PK and safety study that enrolled subjects 6 months to 3 years of age. As such, it provides the opportunity to look at adverse events in this age group, though without a control the information obtainable is less than for subjects participating in the controlled studies. We can obtain controlled information regarding AEs in the younger age group from the subgroup analysis on the safety population done by the applicant which will be discussed below, but the number of subjects in the youngest age group is low for this subgroup analysis.

TOP008 enrolled 30 subjects of whom 13 (43.3%) experienced 18 mild or moderate adverse events. This is a rate considerably higher than seen for the overall safety population which experienced an AE in 7.9 % of treated subjects and 6.4 % of vehicle control subjects.

Table 38: Occurrence of Treatment-emergent Adverse Events+ by Body System and Preferred Term Safety Population: TOP008

Body System	Preferred Term	0.5% Ivermectin (n=30)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Erythema	5 (16.7%)
INVESTIGATIONS	ALT Increased	2 (6.7%)
INFECTIONS AND INFESTATIONS	Nasopharyngitis	2 (6.7%)
“ ”	Upper Respiratory Infection (URI)	2 (6.7%)
“ ”	AST Increased	1 (3.3%)
GASTROINTESTINAL DISORDERS	Diarrhea	1 (3.3%)
“ ”	Vomiting	1 (3.3%)
INFECTIONS AND INFESTATIONS	Gastroenteritis	1 (3.3%)
METABOLISM AND NUTRITION DISORDERS	Dehydration	1 (3.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dermatitis Diaper	1 (3.3%)
“ ”	Pruritus	1 (3.3%)

Source: Reviewer’s Table

There were 6 subjects who experienced 6 AEs which were considered possibly treatment-related by the investigator (5 episodes of erythema and one episode of pruritus). This is difficult to interpret since there is no control group for comparison. Scalp erythema and pruritus are commonly seen as manifestations of the disease undergoing treatment, i.e. head lice. In study TOP008 baseline pruritus (prior to treatment) was seen in 50% of subjects and baseline erythema in 6.7% (see Table 38: Baseline Skin/Scalp reactions for Studies in development program for Ivermectin).

One subject (13-01 discussed in detail in Section 7.3.2) was hospitalized due to three AEs (acute gastroenteritis, dehydration and diaper dermatitis) which resolved without sequelae and were not considered treatment related by the investigator. No subject discontinued from the study due to an AE.

Subgroup Analyses- Age

The highest rate of adverse events is seen in the youngest population, 6 mos to 2 years but this was only in the control group who had an incidence of 25%. The treatment group for the same age group had no adverse events suggesting that the rate in the vehicle group was due to chance. The next highest rate was seen in the 4 to 12 yr olds at 9.6% in the treated group which did exceed the 5.4% seen in the control group.

Looking at the subgroup analysis of the safety population divided by age I do not see any obvious meaningful pattern.

Table 39: Summary of Treatment-emergent Adverse Events Safety Population: By Age Group

Age Group (years)		0.5% Ivermectin Lotion	Vehicle Control
0.5 to <2	Number (%) of Subjects with AE	0/ 9 (0%)	2/ 8 (25.0%)
2 to <4	Number (%) of Subjects with AE	2/ 49 (4.0%)	2/ 40 (5.0%)
4 to <12	Number (%) of Subjects with AE	28/291 (9.6%)	13/241 (5.4%)
12 to 16	Number (%) of Subjects with AE	9/103 (8.7%)	5/ 66 (7.6%)
>16	Number (%) of Subjects with AE	9/153 (5.9%)	9/129 (7.0%)

Source: Reviewer's Table

Subgroup Analyses- Gender and Race

Table 40: Summary of Treatment-emergent Adverse Events Safety Population: By Gender

Gender		0.5% Ivermectin Lotion	Vehicle Control
Female	Number (%) of Subjects with AE	40/499 (8.0%)	26/383 (6.8%)
Male	Number (%) of Subjects with AE	8/106 (7.5%)	5/101 (5.0%)

Table 41: Summary of Treatment-emergent Adverse Events Safety Population: By Race

Race		0.5% Ivermectin Lotion	Vehicle Control
White	Number (%) of Subjects with AE	45/576 (7.8%)	30/467 (6.4%)
Non-White	Number (%) of Subjects with AE	3/29 (10.3%)	1/17 (5.9%)

Looking at the subgroup analysis of the safety population divided by gender and race I do not see any obvious meaningful pattern. Particularly for the non-white category the numbers are small enough that statistical interpretation of results is difficult.

Active Assessments: Scalp Irritation and Ocular Irritation

Scalp Irritation

Assessments of observed skin/scalp reactions (pruritus, erythema, excoriation, and pyoderma) were evaluated on Days 1, 2, 8 and 15 for Studies TOP003, TOP008, TOP010, TOP011, and TOP012. Study TOP001 did not assess skin irritation and for Study TOP007 irritation was a primary endpoint (see Section 7.4.5).

Irritation, including erythema, pruritus, excoriation, and pyoderma, were evaluated according to the scale presented below. Pruritus scoring was completed from a scalp assessment and questioning of the subject.

Table 42: Rating of Type of Skin/Scalp Irritation

	Type of Irritation			
Rating	**Pruritus**	**Erythema**	**Excoriation**	**Pyoderma**
None = 0	The scalp does not itch.	No redness of the scalp.	No broken skin on the scalp.	No lesions visible on the scalp.
Mild = 1	Occasional episodes of itching, not bothersome.	Faint, barely perceptible erythema with limited distribution.	One or 2 areas on the scalp on which skin is broken.	One or 2 lesions visible with crusting or other evidence of infection.
Moderate = 2	Frequent, several times a day, bothersome.	Diffuse pink areas of scalp are readily visible.	More than 2 separate areas of the scalp with broken skin but not generalized across the scalp.	Presence of more than 2 lesions with crusting or other evidence of infection, but not generalized across the scalp.
Severe = 3	Nearly constant, frequent scratching, very bothersome.	Large areas of the scalp are red.	Widespread breaking of the skin involving most of the scalp.	Lesions with crusting or other evidence of infection, involving most of the scalp.

Pruritus = Itching
Erythema = Redness of the scalp
Excoriation = Breaking of skin, usually caused by scratching
Pyoderma = Sores filled with clear fluid, pus or crusting

Source: Applicant's Table Clinical Study Report TOP011 pg 32.

Assessment of skin/scalp reactions that might have been due to the investigational agent was complicated by the fact that the condition being treated (head lice infestation) causes a significant amount of skin/scalp reaction at baseline.

Table 43: Baseline Skin/Scalp reactions for Studies in the Development Program for Ivermectin

	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%

*Ivermectin Lotion **Vehicle Control
Source: Reviewer's Table

Pruritus was the most common finding at baseline in both treatment groups in all of the studies that measured this parameter. Erythema and excoriation at baseline were seen less often than pruritus but were still common. Pyoderma was a relatively rare finding at any point in the studies.

The results of the pooled analysis of the safety population for each of the skin/scalp assessments (pruritus, erythema, excoriation and pyoderma) are presented below. These tables present the mean rating (0=none, 1=mild, 2=moderate, 3=severe) for the safety population on each of the days on which the assessment was performed. Day 1 provides the baseline before treatment.

Overall, as the studies progressed all of the skin/scalp reactions lessened with time in both treatment groups. It is important to note the large decrease in the number of subjects in the vehicle control group between days 2 and 8 which is due to the exit of failed subjects from the study (to receive an FDA approved OTC rescue treatment) once live lice were noted on exam.

Table 44: Assessment of Skin/Scalp Pruritus Safety Population-Analysis of Variance – Mean

	0.5% Ivermectin Lotion (n=635)	Vehicle Control (N=484)
Day 1-baseline	1.09 (n=635)	1.12 (N=484)
Day 2	0.28 (n=629)	0.67 (n=482)
Day 8	0.16 (n=589)	0.21 (n=168)
Day 15	0.06 (n=524)	0.11 (n=132)

Source: Reviewer's Table

The finding of pruritus at baseline was balanced between the two groups (mean of 1.09 and 1.12 respectively for the treatment versus the control groups) with each scoring

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close to 1 (1=mild rating on scale). The reduction in pruritus on Day 2 was statistically significantly greater in the 0.5% ivermectin group than in the vehicle control group. This was a pre-specified analysis (See SAP). Both groups displayed a marked improvement in pruritus relative to baseline as the study progressed.

Table 45: Assessment of Skin/Scalp Erythema Safety Population-Analysis of Variance – Mean

	0.5% Ivermectin Lotion (n=635)	**Vehicle Control (N=484)**
Day 1-baseline	0.16 (n=635)	0.22 (N=484)
Day 2	0.11 (n=629)	0.17 (n=482)
Day 8	0.04 (n=589)	0.02 (n=168)
Day 15	0.02 (n=524)	0.01 (n=132)

Source: Reviewer's Table

The finding of erythema at baseline was low but was somewhat greater in the vehicle control group (mean of 0.16 and 0.22 respectively for the treatment versus the control groups) with each scoring close to zero (0= no erythema, 1=mild rating on scale). The difference between the 2 treatment groups in reduction in erythema on Day 2 was not statistically significant. Both groups displayed an improvement in erythema relative to baseline by Day 15.

Table 46: Assessment of Skin/Scalp Excoriation Safety Population-Analysis of Variance – Mean

	0.5% Ivermectin Lotion (n=635)	**Vehicle Control (N=484)**
Day 1-baseline	0.17 (n=635)	0.25(n=484)
Day 2	0.15 (n=629)	0.24 (n=482)
Day 8	0.06(n=589)	0.11 (n=168)
Day 15	0.02 (n=524)	0.05 (n=132)

Source: Reviewer's Table

The finding of excoriation at baseline was low but was somewhat greater in the vehicle control group (mean of 0.17 and 0.25 respectively for the treatment versus the control groups) with each scoring close to zero (0= no erythema, 1=mild rating on scale). The difference between the 2 treatment groups in reduction in excoriation on Day 2 was not statistically significant. Both groups displayed an improvement in excoriation relative to baseline by Day 15.

Table 47: Assessment of Skin/Scalp Pyoderma Safety Population-Analysis of Variance – Mean

	0.5% Ivermectin Lotion (n=635)	**Vehicle Control (N=484)**
Day 1-baseline	0.01 (n=635)	0.02 (n=484)
Day 2	0.01 (n=629)	0.02 (n=482)
Day 8	0.01 (n=589)	0.02 (n=168)
Day 15	0.01 (n=524)	0.01 (n=132)

Source: Reviewer's Table

Pyoderma was rare at baseline in both groups. There was no reduction in pyoderma in either group on Day 2.

Skin/Scalp irritation was also analyzed by age group, gender and race. Ratings were similar across comparisons i.e. no age, gender or race –related trends were observed.

The findings from the skin/scalp assessments presented above suggest that Ivermectin Lotion 0.5% does not cause a worsening of any of the parameters measured to assess irritation. This is supported by the results of the dermal safety study TOP007 (See Section 7.4.5).

Ocular Irritation

Assessments of ocular irritation occurred on Days 1 and 2 for Studies TOP003, TOP008, TOP010, TOP011, and TOP012. Studies TOP001 and TOP007 did not assess ocular irritation. The results of the pooled analysis are presented below.

Table 48: Ocular Irritation for the Safety Population

Visit	Ocular Irritation Found	0.5% Ivermectin Lotion	Vehicle Control	p-value
Day 1-baseline	Yes	13 (2.1%)	9 (1.9%)	0.7982
Day 2	Yes	6 (1.0%)	8 (1.8%)	0.2874

Source: Reviewer's Table

Ocular irritation was rare at baseline (2.1% in the Ivermectin Group and 1.9% in the vehicle control group) in the safety population. There was a decrease in ocular irritation in the Ivermectin group that was greater than that in the control group but the difference was not statistically significant.

Ocular Irritation - Individual Studies

No ocular irritation occurred in studies TOP003 and TOP011. In Study TOP008, 5 subjects had baseline ocular irritation (attributed to allergies) of which 2 resolved by day 2 and the other 3 persisted. There were 8 subjects (4 in each group) who had baseline ocular irritation in Study TOP010. Of these, 1 persisted and 3 resolved in the Ivermectin group and 3 persisted and 1 resolved in the vehicle control group.

The only study in which subjects developed new onset of ocular irritation on Day 2 (with a normal baseline exam) was Study TOP012. In this study, 3 subjects (1 in ivermectin group, 2 in the vehicle control group) developed ocular irritation that might have been related to the investigational product.

No age-related trends were noted in ocular irritation.

There does not appear to be a signal for significant ocular irritation associated with Ivermectin 0.5% Lotion when treating head lice.

7.4.2 Laboratory Findings

Laboratory evaluations were performed in Studies TOP001 and TOP008. In Study TOP001 the formulation used was slightly different and two topical treatments (day 1 and day 10) of this earlier version of Ivermectin Lotion 0.5% were applied. The results for these studies will therefore be presented separately.

<u>Leukocyte Counts</u>

According to the label for Stromectol, 3% of subjects in clinical trials experienced a decrease in leukocyte count. There was also a potential safety signal seen in IND (b) (4) decreases in leukocyte counts with chronic use of topical Ivermectin Lotion 1% for inflammatory rosacea (see Section 7.2.6).

<u>Study TOP008</u>

The laboratory evaluations performed in Study TOP008 (a PK and safety study) included CBC with differential performed on days 1, 2, 8 and 15 in 30 subjects between the ages of 6 months and 3 years.

The results for the leukocyte counts are presented below:

Table 49: WBC Counts (x 10^3m / cum) for study TOP008 (normal reference range 6.0 to 17.5)

(b) (4)

↑ increased overall, ↓ decreased overall − no overall trend
Yellow highlight = below limit of normal
Source: Reviewer's Table

Examination of the serial results does not demonstrate any consistent trend in leukocyte counts post treatment with Ivermectin Lotion 0.5% in Study TOP008. The majority of the

subjects (48.3%) showed a trend towards increasing leukocyte counts throughout the course of the study as shown below:

Table 50: Trends in WBC Counts for Study TOP008

Trend Seen	# of subjects	% of subjects in study (n= 29 evaluable subjects)
↑ increased overall	14	48.3%
↓ decreased overall	8	27.6%
no overall trend	7	24.1%

Source: Reviewer's Table

Five subjects had WBC counts that dipped below normal at some point during the study. Two of these subjects (subject # 16-17 and subject 16-19) started with low counts prior to treatment and increased as the study progressed. One of the subjects (subject 16-20) had only one blood draw (on day 2) which was just slightly below normal range. Of the two remaining subjects (subject 16-01 and subject 16-06) only subject 16-06 demonstrated a consistent decrease in leukocyte count through the course of the study. Even this subject was found to have a normal count on the final day of the trial.

Absolute neutrophil counts (ANC) were calculated by the applicant at the Agency's request for subjects in Study TOP008 and are presented below. There is no reference range for ANC since it is a calculated value. From a clinical point of view, most physicians consider a count below 1.5 to be considered a clinically significant value with regard to an increased risk of infection. Below 0.5 is considered a dangerously low level.

Table 51: Absolute Neutrophil Counts for Study TOP008 (x 10^3m / cum)

(b) (4)

*↑ increased overall, ↓ decreased overall − no overall trend
Yellow highlight = worrisome value
Source: Reviewer's Table

Examination of the serial results does not demonstrate any consistent trend in ANC post treatment with Ivermectin Lotion 0.5% in Study TOP008.

Table 52: Trends in ANC for Study TOP008

Trend Seen	# of subjects	% of subjects in study (n= 29 evaluable subjects)
↑ increased overall		31.1%
↓ decreased overall		17.2%
no overall trend		51.7%

Source: Reviewer's Table

One subject (Subject 16-11) showed a decrease in ANC through the course of the study that dipped into the range considered clinically significant. This subject rebounded by Day 15 to a value higher than baseline and well within normal limits. Such a rapid recovery argues against a drug-related effect. The other 4 subjects (Subjects 16-13, 16-16, 16-21 and 16-24) whose ANC decreased through the course of the study never entered what would be considered an abnormal range. There were 2 subjects whose lab work revealed worrisomely low ANC values (Subjects 16-19 and 16-20). Subject 16-19 had a low value at baseline but recovered to normal values by the end of the study. Subject 16-20 had a low value on Day 2 (missing baseline blood draw) and no further blood work drawn after this value for comparison.

It is unlikely that these mild and transient changes in ANC represent clinically significant changes.

TOP001

Laboratory evaluations were also performed in Study TOP001 which was a comparative bioavailability and safety study with an earlier formulation of topical Ivermectin Lotion 0.5% (n=15 subjects) compared to oral ivermectin (n=6 subjects) and topical placebo (n=5 subjects). These labs included a CBC with differential performed on days 1, 2, and 10 in subjects between the ages of 4 to 10 years. Compliance with blood drawing was poor but the results that are available for leukocyte count and absolute neutrophil counts are presented below.

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Table 53: WBC Counts (x 10^3m / cum) for study TOP001 (normal reference range 4.0 to 13.5)

(b) (4)

[redacted]

↑ increased overall, ↓ decreased overall − no overall trend
*oral ivermectin
&topical Ivermectin Lotion 0.5%
+topical placebo
Source: Reviewer's Table

Only one subject had a WBC count below normal (Subject 123) and that was the baseline value. This subject was in the oral ivermectin group and the value was back up to normal at the next visit. Two subjects (Subject 112 and Subject 127, both in the topical placebo group) did experience a decrease in counts throughout the study but the values were within normal limits at all times.

Absolute neutrophil counts (ANC) were calculated for subjects in Study TOP001 and are presented below.

Table 54: Absolute Neutrophil Counts (x 10^3m / cum) in Study TOP001 (Normal 1.5 - 7.8)

(b) (4)

↑ increased overall, ↓ decreased overall − no overall trend
*oral ivermectin
[&]topical ivermectin Lotion 0.5%
[+]topical placebo
Source: Reviewer's Table

There was only one subject with an abnormal ANC (Subject 106) who was in the oral ivermectin group. This subject had a high value at baseline but then was back within normal limits at the subsequent visit. Four additional subjects (Subjects 124, 116, 112 and 127) showed an overall trend towards decreasing values throughout the study but remained within normal limits.

I do not see a signal for an effect on leukocyte counts or absolute neutrophil counts from the Ivermectin 0.5% Lotion. This is not surprising given the low systemic bioavailability, the single treatment and the short contact time for this product.

Liver Function Tests (LFTs)

According to the label for Stromectol, 2% of subjects in clinical trials experienced an increase in ALT or AST and 1% experienced an increase in bilirubin.

TOP008

Evaluation was performed of the results of transaminases and bilirubin which were performed on days 1, 2, 8 and 15 in Study TOP008.

Table 55: Alanine Aminotransferase (ALT) Values (U/L) for study TOP008 (normal reference range 3.0 to 30)

(b) (4)

(b) (4)

*↑ increased overall, ↓ decreased overall − no overall trend
Yellow highlight = above limit of normal (reference range 3-30)
Source: Reviewer's Table

Table 56: Trends in ALT Values for Study TOP008

Trend Seen	# of subjects	% of subjects in study (n= 30 evaluable subjects)
↑ increased overall	3	10%
↓ decreased overall	0	0%
no overall trend	27	90%

Source: Reviewer's Table

The values for ALT were highly variable both within and across subjects. In the three instances (Subjects 16-11, 16-24 and 16-25) where an increase seemed to occur with the correct timing for being related to the administration of the investigational agent (i.e. day 2 or later) the values decreased again substantially by the next reading. Subject 16-26 started with a highly abnormal value then decreased after the administration of the investigational agent then increased again then decreased again without ever dipping into normal. This seems a random pattern rather than being related to the investigational agent.

Given that the oral version of Ivermectin has been reported to cause an increase in LFTs it is possible that these changes are related to the drug. However, the degree of the changes (< 3X the upper limit of normal in most cases) and the fleeting nature of the changes also suggest the possibility of random variability. Since no control group was available for this study it is not possible to rule this out. None of the subjects in the study with increased ALT possibly related to the investigational drug were symptomatic.

Subject 13-01 who developed gastroenteritis and was hospitalized during the latter portion of the study started with a very slightly elevated value then during the period of GI symptoms normalized. The subject was back to baseline health with regard to symptoms when the ALT went back up again slightly on Day 15.

Table 57: Aspartate Aminotransferase (AST) Values (U/L) for study TOP008 (normal reference range: lower limit =0, Upper limit 55-78)

(b) (4)

*↑ increased overall, ↓ decreased overall − no overall trend
Yellow highlight = above limit of normal (reference range: lower=0, Upper 55-78)
Source: Reviewer's Table

Table 58: Trends in AST Values for Study TOP008

Trend Seen	# of subjects	% of subjects in study (n= 30 evaluable subjects)
↑ increased overall	1	3.3%
↓ decreased overall	0	0%
no overall trend	29	96.7%

Source: Reviewer's Table

As was the case for ALT, the values for AST were highly variable both within and across subjects. In the one instance (Subject 16-25) where an increase seemed to occur with the correct timing for being related to the administration of the investigational agent, the increase was minor (< 3x upper limit of normal) and the value decreased again (back to within normal limits) by the next reading. Subject 16-25 was the only subject who experienced a possibly related increase in both of his transaminase levels. Subject 16-27 (as with his ALT levels) started with a highly abnormal value then decreased back into normal range after the administration of the investigational agent then increased again then decreased. As noted above under ALT evaluation, this seems a random pattern rather than being related to the investigational agent.

Table 59: Bilirubin Values (mg/dL) for study TOP008
(normal reference range: 0.3 – 1.5)

(b) (4)

[redacted]

(b) (4)

*↑ increased overall, ↓ decreased overall − no overall trend
Yellow highlight = above limit of normal (reference range: .3 – 1.5)
Below normal range
Source: Reviewer's Table

Table 60: Trends in Bilirubin Values for Study TOP008

Trend Seen	# of subjects	% of subjects in study (n= 30 evaluable subjects)
↑ increased overall	0	0%
Overall low values	11	36.6%
no overall trend	19	63.4%

Source: Reviewer's Table

There were no significant changes noted in the bilirubin values for Study TOP008. The majority of the subjects fell within normal range throughout the study. A minority of subjects fell below normal range which is not likely to be of clinical significance.

TOP001

Transaminase levels were performed in Study TOP001 on days 1, 2, and 10 in subjects between the ages of 4 to 10 years. Bilirubin values were not evaluated in this study. As previously mentioned, compliance with blood drawing was poor but the results that are available for transaminase levels are presented below.

Table 61: ALT values (IU/L) for Study TOP001 (normal 0-40)

(b) (4)

↑ increased overall, ↓ decreased overall − no overall trend
*oral ivermectin
[&]topical ivermectin Lotion 0.5%
[+]topical placebo
Source: Reviewer's Table

Only two subjects (Subject 104 and 113, both in the topical ivermectin group) had abnormal values for ALT. These were both abnormal at baseline and normalized by the next blood draw in Subject 104. subject 113 did not have any blood draws beyond the baseline visit.

Table 62: AST values (IU/L) for Study TOP001 (normal 0-60)

(b) (4)

↑ increased overall, ↓ decreased overall − no overall trend
*oral ivermectin
[&]topical ivermectin Lotion 0.5%
[+]topical placebo
Source: Reviewer's Table

There were no abnormalities in AST in Study TOP001. One subject (Subject 104) showed an overall trend to decreasing values but remained within normal limits. This is unlikely to be clinically significant.

In my opinion, taken together, the results of the laboratory evaluation of transaminases and bilirubin do not constitute a safety signal with regard to liver toxicity for the topical

application of Ivermectin Lotion 0.5%. Labeling for the topical product should, however, reflect the finding of LFT abnormalities with the oral formulation and the possibility that such could be seen with the topical should significant absorption occur.

7.4.3 Vital Signs

Vital Signs were only obtained in Study TOP001. These were performed at baseline, visit 2 (day 2) and for the topical ivermectin group only on visit 3 (day 9-11). There were no significant changes in blood pressure, temperature, heart rate or respiratory rate observed.

7.4.4 Electrocardiograms (ECGs)

ECG's were performed in Study TOP001 pre and post dosing on day 1. QTc (msec) remained within the normal range (< 450msec) for all subjects. The applicant has submitted a request for a waiver of TQT studies with the NDA submission based on systemic exposures of Ivermectin 100-200 fold less than that observed with approved oral therapeutic doses. In addition, they cited the lack of Qt effects seen in animal and human studies of oral and topical ivermectin. The request for a waiver of TQT studies seems reasonable.

7.4.5 Special Safety Studies/Clinical Trials

Combined skin irritation and sensitization study

A special safety study, TOP007, a combined skin irritation and sensitization study, was done in a population of healthy adult subjects. This was a Phase 1, single center, evaluator-blinded, placebo-controlled, within-subjects randomized study. The study was performed in compliance with Good Clinical Practice, Sept 1, 2009 to Nov 21, 2009.

The primary objective was to evaluate a test article for the induction of contact sensitization by repetitive application to the skin of human subjects.

The secondary objective was to evaluate the test articles for their potential to cause irritation after 21 days of 24 hour patch application.

266 healthy male and female subjects 18 to 65 years of ages, who met the study criteria, were enrolled in the study. A total of 220 subjects completed the study and made up the contact sensitization group. There were 36 subjects in the cumulative irritation group. Of the 220 subjects, 61.9% were female and 38.1% were male. The mean age was 45.5 years.

One subject (#008) withdrew due to an adverse event (see below) which was not considered by the investigator to be related to the test article. Three subjects discontinued because of non-compliance with study treatment, 39 subjects (14.7%) withdrew consent and two were lost to follow-up. One subject was enrolled but not treated due to pregnancy.

The study consists of three phases (induction, rest, and challenge).

Test products were Ivermectin Lotion 0.5%, vehicle control (placebo), 0.9% sodium chloride as the negative control and 0.1% sodium dodecyl sulfate (SDS) as the positive control. Subjects received 200 uL of the test products on each patch. The test products were applied under occlusive patches consisting of a Webril® non-woven cotton pad (~2 x 2 cm) covered by and secured on all sides by occlusive hypoallergenic tape (Blenderm™) (~ 4 x 4 cm).

Subjects were assigned to Group A (the cumulative irritation endpoint) and Group B (the sensitization endpoint).

- Group A received 21 applications of all 4 patches during the Induction Phase of the study. Each set of patches were worn for 24 (±1) hours.

- Group B received nine applications of the 0.5% Ivermectin Lotion and vehicle control Lotion patches during the Induction Phase of the study. Each set of patches were worn for 48 (±1) hours or for 72 (±1) hours if over the weekend.

During the Induction Phase, skin reactions were evaluated at least 30 (+15) minutes post supervised patch removal. Following the induction phase, all subjects entered an approximate 2-week Rest Phase, during which time no patch applications were made. During the Challenge Phase, sensitization was assessed after a single 48-hour application of both patches to naïve skin sites. Skin evaluations were made at least 30 minutes and at approximately 24, 48, and 72 hours after the supervised patch removal. A trained and blinded evaluator performed the skin assessments during the Induction and Challenge Phases using the Hill Top Scoring System.

Safety was monitored by assessing adverse events (AEs) during the study. Other safety parameters included the skin irritation and sensitization assessments. All study procedures were performed on an “outpatient” basis, with subjects arriving on assigned days for patch application, removal, and evaluation.

The following scales were used for Group A - cumulative irritation:

Berger and Bowman Scale

Numeric Scores

0 = No evidence of irritation
1 = Minimal erythema, barely perceptible
2 = Moderate erythema, readily visible; or minimal edema; minimal popular response
3 = Strong erythema; or erythema and papules
4 = Definite edema
5 = Erythema, edema and papules
6 = Vesicular eruption
7 = Strong reaction spreading beyond test site

Letter Grades (always in upper case)

A = Slight glazed appearance
B = Marked glazing
C = Glazing with peeling and cracking
F = Glazing with fissures
G = Film of dried serous exudate covering all or a portion of the patch site
H = Small petechial erosions and/or scabs

During the Challenge Phase to determine sensitization, the HTR Sensitization Scale was utilized. Numeric Scores may have been appended with a Letter Grade.

Skin Inflammatory Responses – Numeric Scores

0 = No visible reaction
+ = Slight, confluent or patchy erythema
1 = Mild erythema (pink)
2 = Moderate erythema (definite redness)
3 = Strong erythema (very intense redness)

Skin Inflammatory Responses – Letter Grades (always upper case)

E = Edema – swelling, spongy feeling when palpated
P = Papule – red, solid, pinpoint elevation
V = Vesicle – small elevation containing fluid
B = Bulla reaction – fluid-filled lesion (blister)
S = Spreading – evidence of the reaction beyond the pad area
W = Weeping – result of a vesicular or bulla reaction – serous exudate
I = Induration – solid, elevated, hardened, thickened skin

Superficial Skin Effects – Letter Grades (always lower case)

g = glazing
y = peeling

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c = scab, dried film of serous exudates of vesicular or bulla reaction
d = hyperpigmentation (reddish-brown discoloration of test site)
h = hypopigmentation (loss of visible pigmentation at test site)
f = fissuring – grooves in the superficial layers of the skin

The Intent-to-Treat (ITT) population included all subjects enrolled who received at least one patch application. This population was used for the safety outcomes. There was no Intent-to-Treat population for irritation and sensitization endpoints.

Per-Protocol (PP) Population

Irritation Endpoint (Group A):

- The per-protocol population for the cumulative irritation endpoint included all subjects that wore test articles for the entire 21 days to be valid for the cumulative irritation evaluation OR if a patch was removed due to excessive irritation, it was included using Last Observation Carried Forward (LOCF).

- The per-protocol population included subjects who did not miss a visit and had no major protocol violations.

Sensitization Endpoint (Groups A and B):

- To be considered an evaluable subject (PPP) for sensitization assessment, subjects in Group A must have received 21 applications and subjects in Group B must have received 9 applications of the test articles and no fewer than 8 readings during Induction and one 48-hour application of Challenge test article followed by subsequent reading during Challenge.

RESULTS

A total of 220 subjects completed the study and made up the contact sensitization group. There were 36 subjects in the cumulative irritation group. One subject (#008) withdrew due to an adverse event (see below). Three subjects discontinued because of non-compliance with study treatment, 39 subjects (14.7%) withdrew consent and two were lost to follow-up. One subject was enrolled but not treated due to pregnancy.

Safety Results

The assessment of the safety was based on the frequency of adverse events. There were no serious adverse events reported during this study. There were 64 AEs reported by 45 subjects during the course of the study. One subject (#008) withdrew due to an adverse event not considered by the investigator to be related to the test article (mild hypertension and moderate migraine headache).

Of these, 37 were classified as possibly, probably or definitely related to the test articles, all of which were considered mild: pruritus (14 events), presyncope (1 event), paresthesia (3 events), dysaesthesia (2 events), nausea (1 event), gastroenteritis (3 events). The remaining AEs were felt not to be related to study conditions and included: hypertension (1 event), migraine headache (1 event), gastroenteritis (2 events), upper respiratory tract infection (3 events), fatigue (1 event), blurred vision (1 event), myalgia (4 events), headache (1 event), cough (1 event), abdominal discomfort (1 event), pruritus (3 events), epistaxis (1 event), diarrhea (1 event), ear infection (1 event), pyrexia (1 event), nausea (1 event), influenza (1 event), toothache (1 event), wrist fracture (1 event).

Irritation Results

A standard approach for scoring and classifying cumulative irritation was used to analyze the data. The letter grades were converted to numerical equivalents in the following way: A=0, B=1, C=2, and F, G, and H=3. For each subject, a combined score was derived by adding the numerical grade and the numerical equivalent of the letter grade at each evaluation time point (e.g., 2C=2+2=4). However, at each evaluation time point or application a maximum score of 3 was allowed for each observed site and was the score carried forward for any application sites discontinued due to skin irritation grades of 3 or greater.

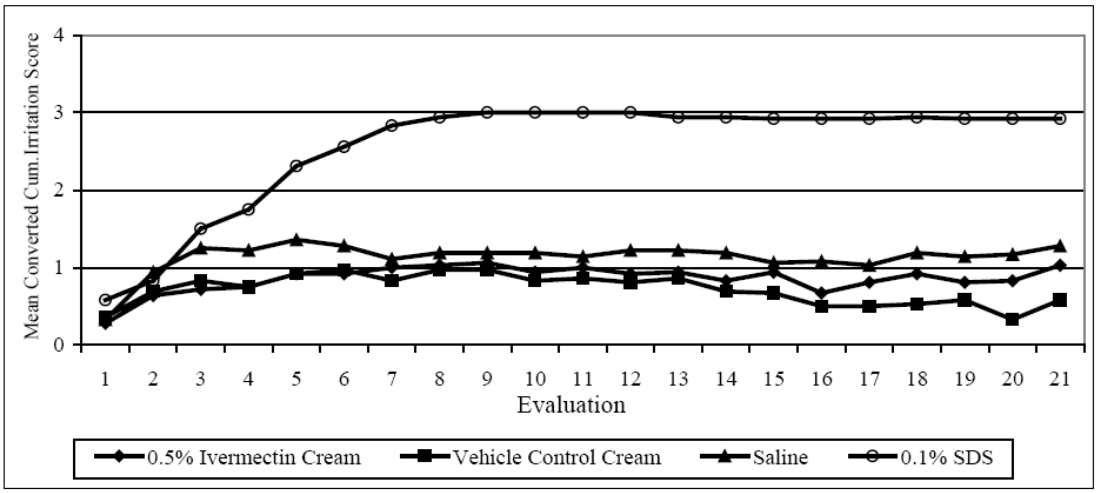
Table 63: Ranking by Mean Overall Cumulative Irritation Scores

Treatment	Overall Score	Std. Dev.
Vehicle Control Cream	0.72	0.32
0.5% Ivermectin Cream	0.85	0.51
Saline	1.13	0.58
0.1% SDS	2.55	0.25

Source: Post-text Table 14.2.3

Source: Applicant's Clinical Study Report TOP007, pg 41.

Table 64: Mean Cumulative Irritation Scores at Each Patch Scoring



Source: Post-text Table 14.2.3
Note: Scores were recorded at 30 (+15) minutes following patch removal.

Source: Applicant's Clinical Study Report TOP007, pg 42.

The results indicate that both Ivermectin Lotion 0.5% and its vehicle are less irritating than the saline (negative control) and significantly less irritating than the 0.1% SDS (positive control). This was demonstrated to be the case over the 21 day course of the study.

Sensitization Results

The interpretation of data was based on the pattern of reactivity of the test article during induction when compared to the severity and persistence of the reaction(s) observed at Challenge. Increased reactivity noted during the first week of Induction to test articles that were considered non-irritating or minimally irritating generally indicated a pre-sensitized condition. Comparable reactivity during the third week, if it appeared suddenly, was suggestive of the initiation of sensitization. Cumulative irritation generally developed more gradually and resolved with a comparable sequence after patch removal.

Positive reactions, at Challenge, were generally more intense and persistent than reactions noted during the Induction Phase, particularly those noted early in the test. Characteristically, they were eczematous (papulovesicular, edematous) rather than strictly erythematous with surface damage. These comparisons, however, were not always diagnostic and borderline or suggestive responses were to be rechallenged.

Rechallenge was to be conducted at least 2-4 weeks after resolution of the original reactions, in order to avoid the conditioned response (angry-back syndrome). The immune response retained its specificity and sensitivity for an extended period, where as hyperirritability should subside.

Table 65: Number and Proportion of Subjects with a Sensitization Reaction

Sensitization	0.5% Ivermectin Cream		Vehicle Control Cream	
N=220	N	%	N	%
Positive	0	0%	0	0%
Negative	218	99.09%	219	99.55%
Inconclusive	2	0.91%	1	0.45%

Source: Post-text Table 14.2.18

Source: Applicant's Clinical Study Report TOP007, pg 45.

Discussion of Results

Two subjects (Subject Nos. 009 and 023) were determined by the investigator to be inconclusive for sensitization reactions to 0.5% Ivermectin Lotion and one subject (Subject No. 009) was determined to be inconclusive for a sensitization reaction to the vehicle control Lotion. According to the applicant, for both subjects, it was determined that the Challenge patches were not worn for a sufficient length of time to make a conclusive determination of positive or negative.

Examination of the raw data revealed that subject No. 9 wore the ivermectin and vehicle Lotion patches for 34 hours (out of the expected 48). Subject No. 9 was scored as a + (+ = Slight, confluent or patchy erythema) at the 24 hour reading and as no reaction for the 48 and 72 hour readings for Ivermectin Lotion. Subject No. 9 was scored as 0P (no reaction but with a papule present) at the 30 minute reading and as a + at the 72 hour reading for the vehicle Lotion. I agree with the investigator that this is inconclusive and does not most likely represent sensitization.

Subject No. 23 wore the ivermectin patch for 30 hours and the vehicle Lotion patch for 44 hours. Subject No. 23 was scored as a 0 (no reaction) for all readings for Ivermectin Lotion. Subject No. 23 was scored as 0 (no reaction) at the 30 minute reading and as a 0d (hyperpigmentation) at the 24, 48 and 72 hour readings for the vehicle Lotion. I agree with the investigator that this is inconclusive and does not most likely represent sensitization.

The applicant states that Subject No. 022 responded to the 0.5% Ivermectin Lotion and the vehicle control Lotion with mild erythema and papules at Challenge which persisted through the 72 hour evaluation, which were not considered strong enough to determine sensitization. Examination of the raw data reveals that Subject No. 22 was scored as 1P (1 = Mild erythema (pink), P= papule) for all 4 readings for the ivermectin Lotion. Subject No. 22 was scored as 1 at the 30 minute and 24 hour readings, as a + at the 48 hour reading and as a 1P at the 72 hour reading for the vehicle Lotion. I would place this subject in the inconclusive category with regard to possible sensitization.

The applicant states that Subject No. 259 “appears to demonstrate reactions indicative of pre-sensitization to both the 0.5% Ivermectin Lotion and the vehicle control Lotion. This subject responded with moderate to strong erythema responses to both test articles by the first evaluation (24 hour) after exposure during the Induction Phase”. I agree that these findings suggest that the subject was already allergic (due most likely to previous exposure to one of the excipients).

Worse case scenario given the above findings would be a total of 4 cases of sensitization to either Ivermectin Lotion or its vehicle out of 220 subjects, a rate of 1.8%. The drug product contains four excipients [redacted] (b) (4) lanolin alcohol (felt by Fisher* to be the main ingredient in lanolin responsible for allergy to lanolin), Crodalan AWS [redacted] (b) (4) methylparaben and propylparaben. Lanolin sensitivity is highest in subjects with a history of eczematous (particularly stasis) dermatitis. The parabens are [redacted] (b) (4) known to cause allergy in about 1% of the population when used in topical therapeutics but rarely to cause problems in cosmetic products. This is felt to be most likely related to the application to “intact skin” versus “damaged skin. The above study was performed in healthy volunteers to normal skin of the back. The results of this study may therefore represent an underestimation of the sensitization likely to be seen in real world use to the often itchy, excoriated scalp seen with infestation by head lice. However, the fact that the product is applied for a short contact time (10 minutes) on a one-time basis makes it less likely to induce allergy than products left on or used chronically.

Conclusion

This degree of potential sensitization is acceptable for this product given its dosing regimen.

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

7.5.2 Time Dependency for Adverse Events

The majority of the subjects experience adverse events during the active treatment phase (at the time of application).

7.5.3 Drug-Demographic Interactions

See Section 7.4.1 subheading subgroup analysis.

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

No exploration of drug-drug interactions was performed.

7.6 Additional Safety Evaluations

There were no additional safety evaluations.

7.6.1 Human Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of SKLICE Topical Lotion or ivermectin. Ivermectin was not genotoxic in vitro in the Ames test, the mouse lymphoma assay, or the unscheduled DNA synthesis assay in human fibroblasts.

7.6.2 Human Reproduction and Pregnancy Data

The applicant has requested a pregnancy category (b) (4) for topical Ivermectin 0.5% Lotion. 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 Applicant provides the following rationale for the request for a different pregnancy category than the approved oral ivermectin:

(b) (4)

The sponsor provided articles on this topic. Key points from these articles have been summarized below.

Table 66: Literature review of oral ivermectin exposure during pregnancy

Citation	Design/ Type	Population	Outcome
(b) (4)			

(b) (4)

The following is an excerpt from the “Pregnancy Labeling Outline” (2007)

Table 67: Pregnancy categories

(b) (4)	Classify as "C" if:
	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Or There are no animal reproduction studies and no adequate and well-controlled studies in humans.

Since animal reproductive studies have shown an adverse effect the applicant is basing their request for category (b) (4) on the second option presented. (b) (4) None of the studies presented by the Applicant as their evidence meet these criteria. Only one study was prospective, (b) (4). This study however, was open label. The other studies were all retrospective.

(b) (4) These studies, based on their design do not provide sufficient evidence to label topical ivermectin 0.5% Lotion as a category (b) (4) pregnancy risk.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pivotal trials included children 6 months of age and older and the original NDA application included a waiver for pediatric studies for children less than 6 months of age as per 21 CFR 201.23(c)(2)(i)(B) and (C)ii. The Applicant's waiver request cited the following reasons:

- Under 21 CFR § 314.55(c)(3)(ii), a waiver is appropriate when necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small (Section 505B(a)(4)(B)(i) of PREA).

The Applicant went on to add that head lice infestation below the age of 6 months has not been reported.

- Under 21 CFR § 314.55(c)(3)(iii), a waiver is appropriate when there is evidence strongly suggesting that the drug would be unsafe in that age group (Section 505B(a)(4)(B)(ii) of PREA).

  The applicant stated that there is a potential for increased absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier in patients under 6 months old.

Pediatric and Maternal Health Staff (PMHS) Consult

The Pediatric and Maternal Health Staff were consulted regarding the adequacy of the safety database in patients less than two years of age. They concluded that the safety database for subjects' ages 6 months to 2 years was adequate provided no signals arose during review of the safety data. No such signals have arisen and I agree with the pediatric reviewer that the safety database is adequate in subjects 6 months of age and older.

The consultation from PMHS also included an analysis of the safety of ivermectin use in patients 6 months and younger since the pediatric reviewer was concerned about off label use (b) (4)

The pediatric reviewer confirmed that the biggest concern in the unapproved age group for the approved ivermectin product (that is subjects under 15 kg) was "the potential for ivermectin to cross the blood-brain barrier and interfere with glutamate and GABA transmission". The presence of Ivermectin in the brain can lead to serious toxicity, including depression, tremors, ataxia, coma and breathing difficulties.[12] "P-gp is located in brain capillary endothelial cells and plays an important role in the blood-brain barrier by actively transporting a large variety of substances, including, drugs such as ivermectin, out of the cell"[13,14]Unfortunately there is little data available on this system in humans. Studies in mice and rats have indicated that "the fetal brain expresses a relatively low level of P-gp, but expression dramatically increases by term[15.] The pediatric reviewer concluded that "data do not appear to be available to determine when the blood-brain barrier and P-gp are mature in young infants".

This effects the decision regarding on what basis to waive the need for studies in subjects under the age of 6 months. There are multiple potential reasons including those cited by the applicant above 1) when necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small and 2) there is evidence strongly suggesting that the drug would be unsafe in that age group.

The pediatric reviewer recommended the second reason "safety" for the waiver in subjects below age 3 months. She states that

> Although definitive data are lacking, the blood-brain barrier may be immature in young infants. In addition, increased systemic absorption may occur due to the immature dermis and the relatively larger head to total body surface area. If a partial waiver is granted secondary to safety, the information regarding potential neurotoxicity must be included in labeling. Presuming off-label use for (b) (4) may be anticipated, discouraging use in young infants may be prudent.

(b) (4)

and I agree with the pediatric reviewer that emphasizing the potential concern for the product's use in this age group is a good precedent to establish.

The label that is currently under negotiation with the sponsor contains the following statement under pediatric use

> The safety and effectiveness of SKLICE Topical Lotion have been established in pediatric patients 6 months of age and older {see Pharmacokinetics (12.3) and Clinical Studies (14)}.

(b) (4)

[12]Burkhart and Burkhart. Therapeutic Advances/Therapeutic Controversies Before Using Ivermectin for Scabies. *Pediatric Dermatology* 1999; 16 (6): 478-480.
[13]Iqbal M, Gibb W, Matthews SG. Corticosteroid Regulation of P-Glycoprotein in the Developing Blood-Brain Barrier. *Endocrinology*.2011; 152(3):1067-79.
[14]Schinkel AG. P- Glycoprotein, a gatekeeper in the blood-brain barrier. *Advanced Drug Delivery Reviews.*1999; 36:179-194
[15]Ek CJ, Wong A, Liddelow SA, Johansson PA, Dziegielewska KM, Saunders NR. Efflux mechanisms at the developing brain barriers: ABC-transporters in the fetal and postnatal rat. *Toxicol Lett*.2010; 197(1):51-9.

Assessment of Effect on Growth

Assessment of effect on growth was not performed as part of the clinical development program. Effect on growth is unlikely since studies involved one application of study drug (except for study TOP001) and both PK Studies demonstrated minimal absorption.

Studies on effect on growth would also be impractical based on the short duration (15 days) of the studies for head lice.

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: (b) (4)

(b) (4)

(b) (4)

In addition, precautions such as emphasizing the need for disposal of the remaining product in the tube after use and keeping the product out of the reach of children should be stressed in labeling.

A consultation with DMEPA was obtained regarding this issue; the response was dated Oct 14, 2011 and contained the following statements

1. The container closure should be re-designed to decrease the risk of accidental ingestions. Additionally, the container closure should resemble a shampoo or scalp product rather than a topical hand Lotion or lotion. If the container closure can not be redesigned then at a minimum the closure should be child-resistant.

2. The proposed quantity of 4 oz (b) (4) is more than the usual quantity of 60 gram (or 60 mL) normally seen with lice treatment products. The large quantity of 4 oz may provide more opportunity for unused portions of the product to remain, and therefore a higher risk for accidental pediatric exposures. If possible, limit the amount of product. We defer to the Division to determine if the proposed quantity of 4 oz is appropriate for this product.

3. The Dosage and Administration Section of the Highlights and the Full Prescribing Information contains the wrong route of administration statement (b) (4) The statement should be revised to state 'For topical use on the scalp hair and scalp only. Sklice Topical Lotion should not be administered by any other routes of administration.

I agree with DMEPA that a child resistant closure would decrease the risk of accidental ingestion. With regard to redesigning the container to resemble a shampoo bottle, I am concerned that this might lead to a higher chance of ingestion by adults since the shampoo bottle would more closely resemble the type of container that ingestible liquids are dispensed in (example of ingestions with lindane). In addition, DDDP anticipates that this product may be useful in other conditions (b) (4) and so redesign as a lotion tube would then be necessary were this additional indication to be approved.

With regard to quantity, decreasing the quantity dispensed to 60 gms as suggested by DMEPA would not be practical. The mean amount of product used in pivotal trials was 72-77 gms with a range up to 115 grams (current tube size is 120 gms.

I agree with DMEPA that changing the language in the Dosage and Administration Section of the Highlights and the Full Prescribing Information to emphasize the currently Sklice is for “topical use on the scalp hair and scalp only” may help to reduce medication errors such as applying the product to other areas of the body.

In addition, DMEPA had multiple recommendations for the container closure system designed to improve the visibility of important messages such as “single use only” and “discard after use” which I agree will decrease the likelihood of medical errors. All of the labeling changes are under negotiation with the sponsor at the time of this review.

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

With regard to the 120 day safety update the following was received from the sponsor:

There is no new safety information learned about the drug to report. Safety data for all completed clinical and nonclinical studies were submitted in the original NDA. There were no ongoing studies at the time of original NDA submission and no new studies have been initiated. The product is not marketed in any country.

8 Postmarket Experience

See Section 7.2.6

Reference ID: 3067484

9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review. See Section 7.2.6 and Section 7.6.2 for details.

9.2 Labeling Recommendations

Assessment of labeling is ongoing at the time of this review.

9.3 Advisory Committee Meeting

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

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

/s/

JANE E LIEDTKA
01/05/2012

JILL A LINDSTROM
01/13/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202736 **Applicant:** Topaz Pharm **Stamp Date:** April 7, 2011

Drug Name: Sklice (ivermectin) Topical Cream 0.5% **NDA/BLA Type:** original

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			eCTD
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			2.5.6
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)(1)
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: **TP003** Study Title: **A Double-blind, Placebo-controlled Study to Compare the Safety, Local Tolerance, and Efficacy of 3 Strengths of Ivermectin Treatment Conditioner and Placebo Following Application of Treatment to Subjects with *Pediculus humanus capitis* (Head Lice) Infestation** Sample Size: **78 subjects** Arms: **4 arms (.15%,.25%,.5% and placebo)** Location in submission: **5.3.5.1**	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			

Reference ID: 2952817

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 **TP011** Indication: **head lice** Pivotal Study #2 **TP012** Indication: **head lice**				
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			SPA agreement on endpoint- letter dated 12/23/09
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	All studies were done in US
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		Applicant has requested a waiver of QT study
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 exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 12.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	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.

[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).

Reference ID: 2952817

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Irritation and contact sensitivity
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			
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			No deaths, one SAE, One WD
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 Disclosure information?	X			
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.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2952817

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

None

Jane Liedtka, MD	5/17/2011
Reviewing Medical Officer	Date
Clinical Team Leader	Date

Reference ID: 2952817

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
05/26/2011

JILL A LINDSTROM
05/31/2011