

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-129**

**MEDICAL REVIEW(S)**

**Medical Officer's Review of NDA 22-129:  
COMPLETE RESPONSE TO APPROVABLE LETTER**

**Application TypeNDA:** 505(b)(2)  
**Document type:** E  
Complete Response to Approvable Letter  
**Type Sequence #:** 001  
**Submission Code:**

**Letter Date:** 10/17/08  
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**PDUFA Goal Date:** 04/17/09

**Established name:** TRADENAME (benzyl alcohol), 5% Lotion  
**Trade name:** Undetermined  
**Therapeutic Class:** Pediculicide  
**Applicant:**

Sciele® Pharma, Inc.  
5 Concourse Parkway  
Suite 1800, Atlanta, GA 30328

**Priority Designation:** S

**Formulation:** Lotion  
**Dosing regimen:** Two 10-minute applications one week apart  
**Indication:** For patients infected with *Pediculus humanis capitis* (head lice and their ova) of the scalp hair  
**Intended Population:** Six months of age and older

**Reviewer Name:** Gordana Diglisic, M.D.  
**Team Leader:** Jill Lindstrom, M.D.  
**RPM:** Nichelle Rashid  
**Review start date:** 12/12/08  
**Review completion date:** 02/06/09

## **EXECUTIVE SUMMARY**

This application was submitted as a “complete response” by the applicant to an approvable action letter issued by the division dated July 14, 2008.

The original application was submitted on Jun 15, 2007. The applicant submitted a new drug application for a lotion formulation of benzyl alcohol 5% (TRADENAME, 5% Lotion) proposed for the topical treatment of head lice (*Pediculosis capitis*) infestation in

subjects 6 months of age and older. This product is the first drug product to have benzyl alcohol as an active ingredient (NME).

Two well-controlled Phase 3 trials were conducted with the objective of establishing the superiority of two 10 minute application of TRADENAME, 5% Lotion one week apart to vehicle. In both Phase 3 trials, TRADENAME, 5% Lotion demonstrated superiority over vehicle. Safety data included eight studies conducted in the clinical development program. The incidence of adverse events was low for both the active and vehicle arms; none were considered serious.

(The reader is referred to the Clinical Review of the original NDA in DFS dated 6/27/08)

However, the original NDA received “Approvable” action for the following deficiencies:

1. Insufficient information regarding the systemic bioavailability of benzyl alcohol from their drug product and potential safety impact resulting from systemic absorption of benzyl alcohol (including but not limited to infant gasping syndrome):

*“The in vivo pharmacokinetic study SU-01-2007 resulted in a number of plasma concentrations of benzyl alcohol. While the median value of all 32 positive samples was ~2.7ug/mL, the upper quartile of them were above 48 ug/mL. Because the plasma concentrations of benzyl alcohol observed are sporadic, it is difficult to adequately interpret the observed high concentrations of benzyl alcohol. Since these plasma concentrations of benzyl alcohol are used to support the systemic safety of the drug product, it is important that you provide further clarification (e.g. are they true representative concentrations) as to why these plasma concentrations were observed and their potential safety impact, including but not limited to, a discussion vis a vis the reported association of plasma levels of benzyl alcohol and infant gasping syndrome.”*

(See Approvable Letter, 07/14/08)

2. Inspection of the drug substance manufacturing facility did not meet cGMP requirements.

(The reader is referred to Appendix 1 for the entire contents of the Approvable Letter)

To address the first deficiency, the applicant conducted the second bioavailability study (Sc-LA-08-01). The objective of this study was to evaluate the bioavailability of benzyl alcohol following a single, exaggerate 30- minute application of TRADENAME, 5% Lotion in subjects with head lice infestation. Quantifiable benzyl alcohol concentrations were observed in 4 of the 19 subjects (21%). Three of these were in the 6 months to 3 years cohort at 0.5 hour post- treatment (ranging from 1.97 to 2.99 mcg/mL), and one in the 4 to 11 year cohort at 1 hour post -treatment (1.63 mcg/mL).

None of subjects experienced adverse events.

Additionally, the applicant provided discussion regarding the relationship between benzyl alcohol and infant gasping syndrome (authored by Neil Buist, M.D.), and a review (authored by the (b) (4) ) of publicly-available benzyl alcohol safety data.

Based on above data, the applicant has provided sufficient and adequate information regarding the systemic bioavailability of benzyl alcohol from their drug product and potential safety impact resulting from systemic absorption of benzyl alcohol in pediatric and adult population.

Regarding the second deficiency, an “Acceptable” site recommendation from the Office of Compliance has been made.

(The reader is referred to the CMC Review, T. Mehta, M.Sc dated 02/11/09)

### **Current Submission:**

On October 17, 2008, the applicant submitted a “**Complete Response to Approvable Letter**” containing the following:

1. **Response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, and the potential safety impact, resulting from systemic absorption of benzyl alcohol in children.** To address this issue, the sponsor submitted:
  - a. Copy of the label from the bottles of NaCl/benzyl alcohol which were used as catheter flush in the first bioavailability study (SU-01-2007)
  - b. Study Report from the second bioavailability study (Sc-LA-08-01)
  - c. Discussion regarding the relationship between benzyl alcohol and infant gasping syndrome by Neil Buist, M.D.
  - d. Review authored by the (b) (4) of publicly available benzyl alcohol safety data
2. **Update on a final response to the PAI inspection deficiencies**
3. **Draft labeling carton/container and PI**
4. **Safety update**

### **Discussion:**

1. **Response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, and the potential safety impact, resulting from systemic absorption of benzyl alcohol in children:**
  - a. Bioavailability Study SC-LA-09-01:

In response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, the sponsor stated that the elevated (> 3 mcg/mL) and sporadic plasma concentration of benzyl alcohol in Study SU-01-2007 were due to an intermittent use of a bacteriostatic saline (NaCl with 0.9% benzyl alcohol as a preservative) catheter flush, and thus were not “true”, representative plasma concentrations (reflective of cutaneous exposure). The NaCl plus benzyl alcohol flush was used to clear the indwelling catheters that facilitated certain blood draws in some subjects. The applicant provided a copy of labeling from the bottles of NaCl plus benzyl alcohol which were used as the catheter flush. However, the phlebotomist did not adequately document the use of the benzyl alcohol containing flush in the study protocol. For that reason, the applicant conducted a second bioavailability study (Sc-LA-08-01) in which any catheter flush used was free of benzyl alcohol.

The objective of this single center, open-label study was to evaluate the bioavailability of benzyl alcohol following a single, exaggerated 30- minute application of TRADENAME, 5% Lotion in subjects (6 month to 11 years old) with active (at least 3 live lice) head lice infestation. All subjects (N=19) were observed to have at least moderate pruritus and excoriation of the scalp. Clinic staff applied a sufficient amount of the clinical material to thoroughly saturate the subject’s hair and scalp for 30 minutes. Blood samples were collected for analysis of plasma benzyl alcohol concentration before application of TRADENAME, 5% Lotion (time 0) and at specified times after completing treatment application.

A total of 102 unique samples were analyzed. Quantifiable benzyl alcohol concentrations were observed in 4 of the 19 subjects (21%). Three of these were in the 6 months to 3 years cohort at 0.5 hour post- treatment (ranging from 1.97 to 2.99 mcg/mL), and one in the 4 to 11 year cohort at 1 hour post -treatment (1.63 mcg/mL). No pharmacokinetic analyses were performed since only single benzyl alcohol concentrations were detected in any subject.

**Table 1: Plasma Concentration (µg/mL) of Benzyl Alcohol – 6 Month to 3 Years Old Subjects (Cohort 1)**

Time (h)	SUBJECT I.D.					
	003	004	008	009	010	018
Pretreatment	BQL	BQL <sup>a</sup>	BQL	BQL	BQL	BQL
0.5	NSR	BQL	1.97	2.99	1.97	BQL
1	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL <sup>a</sup>	BQL	BQL	BQL	BQL <sup>a</sup>
6	BQL	BQL	BQL	BQL	BQL	BQL

<sup>a</sup> Sample appeared hemolyzed

BQL - Below the Quantifiable Limit < 1.00 ug/mL

NSR - No sample received

**Table 2: Plasma Concentration (µg/mL) of Benzyl Alcohol – 4 Years to 11 Years Old Subjects (Cohort 2)**

Time (h)	Subject I.D.												
	002	005	006	007	011	012	013	014	015	016	017	019	020
Pre-treatment	BQL	BQL <sup>a</sup>	BQL	BQL	BQL	BQL	BQL <sup>a</sup>	BQL	BQL	BQL	BQL	BQL	BQL
0.5	BQL	NSR	BQL	NSR	BQL	BQL	NSR	BQL	NSR	BQL <sup>a</sup>	BQL	BQL	BQL
1	BQL	BQL	BQL	1.63 <sup>a</sup>	BQL <sup>a</sup>	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL	BQL <sup>a</sup>	BQL	BQL <sup>a</sup>	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
12	BQL <sup>a</sup>	BQL	BQL	NSR	BQL	BQL	BQL	BQL	BQL	BQL <sup>a</sup>	BQL	BQL	BQL

<sup>a</sup> Sample appeared hemolyzed

BQL - Below the Quantifiable Limit < 1.00 ug/mL

NSR - No sample received

None of subjects experienced adverse events.

The maximum plasma concentration of benzyl alcohol (2.99 mcg/mL) obtained in this second bioavailability study was about 44 fold lower than the C<sub>max</sub> (131.3 mcg/mL) obtained in the first bioavailability study in subjects 6 months to 11 years old. In addition, the plasma concentrations of benzyl alcohol were closer in their range of values (ranging from 1.63 to 2.99 mcg/mL) in study Sc-LA-08-01 compared to the sporadic values (1.2 to 131.3 mcg/mL) observed in study SU-01-2007. (See Clinical Pharmacology Review, 01/26/09).

The highest plasma concentration of benzyl alcohol (2.99 mcg/mL) that was observed in the second bioavailability study was ~ 37 fold lower than serum mean concentration of benzyl alcohol obtained from 6 infants with gasping syndrome (109.2 mcg/mL or 1.01 mmol/L)<sup>1</sup>

#### Reference

1. The New England Journal of Medicine; 1982 Nov 25; Vol 307; Issue 22; p1384-8; The gasping Syndrome and Benzyl Alcohol Poisoning; Garshanik, J.; Boecler, B.; Ensley, H.; McCloskey, S.; George, W.

Based on above data, the applicant has provided sufficient and adequate information regarding the systemic bioavailability of benzyl alcohol from their drug product.

- Discussion regarding the relationship between benzyl alcohol and infant gasping syndrome by Neil Buist, M.D., Professor Emeritus, Oregon Health & Science University; (dated August 29, 2008). Dr. Nail Buist was the lead investigator that identified the occurrence and cause of “gasping syndrome”.

The applicant submitted the document authored by N. Buist, M.D. in which Dr. Buist discusses the data from study SU-01-2007, and states that “*the dosage exposures, and proven blood levels provided and the ages of the subjects are orders of magnitude less than that caused the gasping syndrome in preemies.*”

c. Review authored by the (b) (4) of publicly available benzyl alcohol safety data

The (b) (4) conducted searches of publicly accessible database to identify information on the safety and human exposure to benzyl alcohol. The searches included published literature, internet, and U.S. and foreign government database.

Based on these searches, data were identified demonstrating that:

- Gasping syndrome is a relevant concern only for small premature infants, population distinct from the proposed patient population for TRADENAME, 5% Lotion
  - The infants who developed infant gasping syndrome were low-birth-weight premature neonates with limited ability to metabolize and excrete benzyl alcohol and its metabolite
  - Benzoic acid was accumulated because of immature livers of the preterm infants (unable to conjugate the benzoic acid with glycine and excrete the product, hippuric acid, in the urine)<sup>1, 2</sup>
  - Preterm infants also have low glomerular filtration rate (GFR). Adult levels of GFR are typically achieved by 2.5 to 5 months of age. Thus, inability to filter and excrete benzoic acid may also have contributed to the build up of serum benzoic acid and the resulting acidosis.<sup>3</sup>
  - Even the youngest proposed users of 5% L.A.(6months) have greatly superior metabolic and excretory capabilities compared to preterm neonates
  - A review of the literature identifies no cases of gasping syndrome in full term infants.
- Numerous topical cosmetic and drug products containing benzyl alcohol are present on the market that could potentially yield higher exposure to benzyl alcohol than would be expected if the TRADENAME, 5% Lotion is used according to labeling instructions
  - Benzyl alcohol is used in large number of topical cosmetic products either as preservative, fragrance, solvent, or viscosity-decreasing agent (Table 3) (Cosmetic Safety Database 2008a)

**Table 3: Cosmetic Products Containing Alcohol**

<b>Product Category</b>	<b>Number Containing Benzyl Alcohol</b>
Hair Color and Bleaching	274
Sunscreen with SPF 15 and Above	195
Facial Moisturizer/Treatment	193
Moisturizer	168
Conditioner 154	154
Anti-aging	111
Shampoo	83
Facial Cleanser	69
Fragrance for Women	66
Anti-itch/Rash Cream	42
Others	294

- It is considered by the Cosmetic Ingredient Review Expert Panel to be safe at concentration of up to 5% in cosmetic formulations and up to 10% in hair dyes (CIREP 2001)
- Although actual concentrations used in products are not available, use at concentration of 1-3% has been recommended for preservative use (Beauty Products Made Easy 2008)
- Of 1,649 products currently on the market that contain benzyl alcohol, 39 are marketed for infants according to the Cosmetic Safety Database (Table 4)

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**Table 4: Topical Baby Products Containing Benzyl Alcohol**

Product Types	Products
Moisturizer	Aveeno Daily Baby Moisturizing Lotion Aveeno Baby Daily Baby Lotion Aveeno Baby Lotion Daily Moisture Aloe Vesta 2-n-1 Skin Conditioner Cream Moistural Therapeutic Lotion, Dry Sensitive Skin Formula Therapeutic Lotion Dry Sensitive Skin Formula Aveeno Baby Calming Comfort Baby Lotion Aveeno Baby Lotion Calming Comfort Johnson & Johnson Johnson's Baby Lotion, Bedtime Arbonne Baby Care (ABC) Body Lotion Johnson & Johnson Johnson's Baby Lotion Aloe Vera & Vitamin E Johnson & Johnson Johnson's Baby Bedtime Lotion Johnson & Johnson Johnson's Baby Lotion, Original Rite Aid Gentle Baby Lotion Johnson & Johnson Johnson's Bedtime Lotion Johnson & Johnson Johnson's Baby Lotion
Shampoo	Jason Natural Cosmetics Earth's Best Shampoo & Body Wash by JASON
Sunscreen	AVON SUN Baby Sunscreen Lotion, SPF 40 (2005 formulation) Avalon Baby Natural Mineral Sunscreen, SPF 18 Avalon organics Baby Natural Mineral Sunscreen SPF 18 Rite Aid Baby Sunscreen, SPF 45 (2005 formulation) Coppertone Water BABIES Lotion Sunscreen, SPF 50 CVS Baby Sunscreen Lotion, SPF 50 Coppertone Water BABIES Lotion Sunscreen, SPF 50 Walgreens Baby Sunscreen, SPF 50 Coppertone Water BABIES Quickcover Lotion Spray Sunscreen, SPF 50 Preferred Plus Products Sunblock Baby Lotion, SPF 45 Preferred Plus Products Sunblock Baby Lotion, SPF 30 Walgreens Baby Sunscreen Lotion Spray, SPF 50 Walgreens Baby Sunblock
Anti-Itch/Rash Cream	A+D Ointment Zinc Oxide
Baby Wipes	Pampers Wipes Natural Aloe Unscented Pampers Baby Wipes Unscented Luvs Natural Touch Tub with Lightly Scented Wipes Pampers Kandoo Flushable Wipes, Magic Melon Pampers Lavender Calming Baby Wipes Pampers Kandoo Flushable Wipes Tub Magic Melon

- While it is likely that above baby products contain lower concentrations of benzyl alcohol than TRADENAME, 5% Lotion, their application may result in greater benzyl alcohol absorption because of the difference in the way that the product are used( e.g. TRADENAME, 5% Lotion. product is applied to scalp and hair, left for 10 minutes and than rinsed off; while the baby products listed above may be applied over most of the skin surface area, applied repeatedly over the course of the day, may not be rinsed off between application, and are frequently covered by diapers or clothing resulting in an occluded application site\*).

\*Occlusion of the application site increase benzyl alcohol absorption (32% over 24 hour from an unoccluded site versus 80% from an occluded site; Bronaugh et al 1990)

- Benzyl alcohol is also used as an excipient in a variety of topical over-the-counter and prescription drugs (Physician Desk Reference 2008; Table 5)

**Table 5: Prescription and Non-Prescription Drugs Listed With Benzyl Alcohol**

<b>Product Name</b>
Aldara <sup>™</sup> Cream 5%
Anbesol <sup>®</sup> Cold Sore Therapy Ointment
Anbesol <sup>®</sup> Junior Gel
Maximum Strength Anbesol <sup>®</sup> Gel and Liquid
Bactroban Cream <sup>®</sup> 2%
Desenex <sup>®</sup> Athletes Foot Cream
Head and Shoulders <sup>®</sup> Intensive Solutions Dandruff Shampoo
IvyBlock <sup>®</sup>
LamisilAT <sup>®</sup> Creams
Lotrimin <sup>®</sup> Cream
Lotrisone <sup>®</sup> Lotion
Mentax <sup>®</sup> Cream
Naftin <sup>®</sup> Cream

- Although the percentages of benzyl alcohol present in the creams, lotion, and ointments are less than is present in TRADENAME, 5% Lotion the directions for use of these products allow for longer time exposures (the products are not rinsed off) and potential occlusion of the application site.

**2. Update on a final response to the PAI inspection deficiencies**

- The cGMP issues have been resolved
  - As a corrective action, the drug substance containers were changed from a (b) (4)
  - Drug substance manufacturer, (b) (4), passed a re-inspection by the (b) (4) during the week of November 3, 2008.

**3. Draft labeling carton/container and PI**

- Draft labeling has been submitted:
  - The Division's comments have been incorporated into the present versions of the package insert, carton label, immediate container label and patient direction leaflet.
- The sponsor states that, other than bioavailability study, no additional information relating to safety or effectiveness has become available and that the label has been updated to reflect the data collected in the second clinical bioavailability study.

**4. Safety update:**

- The applicant stated that there is no new safety information to report

## SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### CMC

From the Chemistry review:

#### Container Closure System [Tradename (benzyl alcohol) 5% Lotion]

##### Satisfactory

- The proposed container/closure system for the drug product is an 8 oz (b) (4)

Information provided for the proposed container/closure is deemed adequate.

- Based on the adequate 24 months stability data, the expiration-dating period of 30 months is granted.

##### Drug Substance

- (b) (4) manufactures the benzyl alcohol. The chemistry, manufacturing, and controls information on the drug substance is provided in DMF (b) (4), which is deemed adequate to support this application.

#### Container Closure System [Benzyl Alcohol NF]

##### Satisfactory

- (b) (4)

However, during the site inspection Office of Compliance found them unsatisfactory. Therefore, DMF holder replaced the storage container to (b) (4) (amendment 0030 December 30, 2008).

##### Post approval Stability Protocol and Stability Commitment

- The applicant commits to place the first three production batches of the drug substance manufactured by (b) (4) and stored in (b) (4) on stability at 25°C/60% RH condition with following timetable: 3, 6, 9, 12, 18 and 24 months. Thereafter, applicant will include at least one lot of drug substance per year for long-term stability (cover letter amendment 0030).
- Applicant commits to conduct the stability studies on the first three commercial lots of the drug product after approval of this application. Once the initial stability protocol met the requirements, one batch per calendar year will be placed on the stability at long-term storage condition. The applicant has agreed to perform full-scale ICH stability studies on first three commercial batches to support the switch to the natural bottles.

##### Labeling and Package Insert:

Sponsor revised the labeling and carton labels (see Appendix 1- Approvable Letter, 07/14/08)

- Insert labeling deemed adequate for CMC prospect
- Immediate container label is deemed adequate.
- Carton and immediate container labels are deemed adequate.

**Recommendation and Conclusion on Approvability:**

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An “Acceptable” site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.”

(See CMC Review dated 02/11/09, Tarun Mehta, M.Sc., Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment II; Branch III)

**Animal Pharmacology/Toxicology**

There was no pharmacology/toxicology issues in the Approvable Letter dated July 14, 2008.

From the pharmacology/toxicology review:

“This NDA submission is a 505(b)(2) application because the sponsor is relying on literature references to satisfy some aspects of nonclinical toxicology information needed to support the safety of benzyl alcohol (primarily systemic repeat dose toxicology and genetic toxicology). No specific listed drug products are referred to in these literature references. In addition, the sponsor conducted 14-day dermal toxicity studies with the lice asphyxiator drug product in rats and dogs and oral embryofetal development studies with benzyl alcohol in rats and rabbits. Based on the nonclinical data submitted to NDA 22-129 for benzyl alcohol and the lice asphyxiator drug product, Pharmacology/Toxicology recommended approval of NDA 22-129 provided that the recommended changes in the label described in the review were incorporated into the drug product label. The reader is referred to the Pharmacology/Toxicology review of the original NDA entered into DFS on February 19, 2008 for additional details, if needed.”

**“Conclusion:** This NDA can be approved from a Pharmacology/Toxicology perspective”

(See Pharmacology/Toxicology Memorandum dated 01/30/09, B. Hill, PhD, Pharmacology/Toxicology Supervisor)

**Clinical Pharmacology**

From the clinical pharmacology review:

“The systemic exposure (ranging from 1.63 to 2.99 mcg/mL) obtained in the second bioavailability study (Sc-LA-08-01) did not indicate any elevated or

sporadic benzyl alcohol plasma concentrations approximating the sporadic plasma concentrations observed in the first bioavailability study (SU-01-2007). The maximum plasma concentration of benzyl alcohol (2.99 mcg/mL) obtained in the second bioavailability study (Sc-LA-08-01) was about 44 fold lower than the Cmax (131.3 mcg/mL) obtained in the first bioavailability study (SU-01-2007) in subjects aged 6 months to 11 years old.

In study SU-01-2007, following a 30-minute exposure period of L.A. 5 %, benzyl alcohol plasma concentrations ranging from 1.2 mcg/mL to 131.3 mcg/mL were observed in 10 of the 18 subjects at 0.5 to 12 hours post-treatment for all three age cohorts evaluated. Two of these subjects were in the 6 months to 3 years cohort at 0.5-1.0 hour post-treatment (ranging from 1.18 mcg/mL to 2.28 mcg/mL), six subjects were in the 4 to 11 years cohort at 0.5 to 13 hours post-treatments (ranging from 1.97 mcg/mL to 131.3 mcg/mL) and, two subjects were in the 12 years and older cohort at 0.5 to 1 hour post- treatment (ranging from 2.40 to 30.9 mcg/mL).”

“Therefore, the data provided in study Sc-LA-08-01 supports the applicant’s position that it was the benzyl alcohol in the flush, rather than the drug product that was responsible for the sporadic, fluctuating plasma concentrations of benzyl alcohol observed in the first bioavailability study SU-01-2007. Based on the aforementioned, the applicant has provided adequate information on the true representative systemic bioavailability of benzyl alcohol from their drug product.”

### **Other Relevant Materials:**

#### TRADENAME:

The applicant initially submitted two tradenames, (b) (4). The Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the use of those names from a promotional perspective. Thus, the Applicant submitted the names (b) (4) and (b) (4) for review. However, those names were withdrawn by the Applicant on March 28, 2008. Subsequently, the Applicant submitted the names (b) (4) and (b) (4). The Division of Medication Error Prevention and Analysis (DMEPA) objected to the name (b) (4) due to look-alike similarities with (b) (4), and to the name (b) (4) due to orthographic similarities to (b) (4) and orthographic and phonetic similarities to (b) (4).

Subsequently, the name (b) (4) was submitted. DMEPA did not object to the use of the proprietary name (b) (4). However, DDDP objected to the name (b) (4) due to sound-alike similarity with (b) (4) (OTC product) which could cause confusion that subsequently leads to medication errors (oral ingestion) in the clinical setting.

## **Conclusion:**

- The applicant has 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.
- Because of the potential for systemic exposure, it would be prudent to contraindicate the use of 5% L.A. in children less than 6 months of age.
- The cGMP issues has been be resolved
- Draft labeling has been submitted

Therefore, this submission adequately addressed all deficiencies outlined in the action letter (dated 07/14/08).

## **Recommendation on Postmarketing Actions:**

### Risk Management activities

- 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.

### Required Phase 4 Commitments

- There are no Phase 4 Commitments

## **Recommendation for Regulatory Action**

It is recommended that from a clinical perspective, NDA 22-129, for TRADENAME (benzyl alcohol) Lotion 5%, for the topical treatment of head lice (*Pediculosis capitis*) infestation in patient 6 months of age and older, be approved.

## **APPENDIX 1**

### **Approvable Letter – July 14, 2008**

NDA 22-129

Sciele Pharma, Inc.  
ATTENTION: Debra Hayes, RAC  
Five Concourse Parkway  
Suite 1800  
Atlanta, GA 30328

Dear Ms. Hayes:

Please refer to your new drug application (NDA) dated June 15, 2007, received June 15, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (benzyl alcohol) Lotion 5%.

We acknowledge receipt of your submissions dated July 19, August 31, September 17, September 21, September 28, October 12, and December 28, 2007; January 25, February 5, March 4, March 19, April 14, May 23, and June 5, 2008.

We also acknowledge receipt of your submission dated July 10, 2008. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

The in-vivo pharmacokinetic study SU-01-2007 resulted in a number of plasma concentrations of benzyl alcohol. While the median value of all 32 positive samples was ~2.7ug/mL, the upper quartile of them were above 48 ug/mL. Because the plasma concentrations of benzyl alcohol observed are sporadic, it is difficult to adequately interpret the observed high concentrations of benzyl alcohol. Since these plasma concentrations of benzyl alcohol are used to support the systemic safety of the drug product, it is important that you provide further clarification (e.g. are they true representative concentrations) as to why these plasma concentrations were observed and their potential safety impact, including but not limited to, a discussion vis a vis the reported association of plasma levels of benzyl alcohol and infant gasping syndrome.

Also, it will be necessary for you to submit draft labeling. The draft texts for the package insert and the patient package insert should be revised according to the enclosed labeling.

The draft texts for the immediate container and carton labels should be revised as follows.

1. Delete the proposed tradename, (b) (4)
2. Change the dosage form statement from (b) (4)” to “Lotion.”
3. Delete the (b) (4) designation after the dosage form statement.
4. Relocate the wording (b) (4) from the side panel of the carton label to the principal display panel and increase the size of the wording to make it more prominent on the label. Consider rewording this statement to (b) (4) in order to make the warning more specific.
5. Add “Warning: Keep out of reach of children” on both the immediate container and carton labels to help prevent accidental oral ingestion of the product. Also, consider adding the warning, “Harmful if swallowed” to both the immediate container and carton labels.
6. The instructions for use in the Dosage and Administration, as presented on the side panel of the carton label, are incomplete. Revise the statement, (b) (4) to “See package insert, including the patient information section, for complete information.”
7. Delete Product Description, including the indication statement. Reword the section as follow: Contents Description: TRADENAME is supplied as a white topical lotion containing benzyl alcohol, 5%. Inactive ingredients in this formulation are water, mineral oil, sorbitan monooleate, polysorbate 80, carbomer 934P and trolamine.
8. Decrease the size of the distributor’s name logo.
9. Increase the size of the statement of strength “8 oz. (227 g),” slightly, in order to increase its visibility on the label.
10. Add Lot #, Expiration Date, and barcode on the immediate container label.

In addition, your container/closure proposal, consisting of an orifice reducing plug (b) (4) and current cap, should be implemented.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

During a recent inspection of the manufacturing facility for this application, our field investigator conveyed deficiencies to the facility’s representative. Satisfactory resolution to these deficiencies is required before this application may be approved.



## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling.

To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

5901-B Ammendale Road  
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Maria Walsh, Project Management Officer, at (301) 796-1017.

Sincerely,

*{See appended electronic signature page}*

Daniel Shames, M.D.

Deputy Director

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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

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Gordana Diglisic  
2/17/2009 02:02:20 PM  
MEDICAL OFFICER

Jill Lindstrom  
2/19/2009 05:08:06 PM  
MEDICAL OFFICER

## Summary Review for Regulatory Action

<b>Date</b>	11July08
<b>From</b>	Susan J. Walker, M.D.
<b>Subject</b>	Division Director Summary Review
<b>NDA</b>	22-129/ 505(b)(2)
<b>Relevant IND</b>	50,076
<b>Applicant Name</b>	Summers Laboratories, Inc.
<b>Date of Submission</b>	15June 2007
<b>PDUFA Goal Date</b>	15July2008
<b>Proprietary Name / Established (USAN) Name</b>	Undetermined/ Benzyl Alcohol 5% Lotion
<b>Dosage Forms / Strength</b>	Topical Lotion, 5% (w/w)
<b>Proposed Indication(s)</b>	1. Treatment of Pediculus humanus capitis
<b>Action/Recommended Action for NME:</b>	<i>Approvable</i>

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of discipline reviewers</b>
Medical Officer Review	Gordana Diglisic, M.D.
Statistical Review	Mat Soukup, Ph.D., Mohamed Al Osh, Ph.D.
Pharmacology Toxicology Review	Barbara Hill, Ph.D.
CMC Review	Tarun Mehta, Ph.D/Moo-Jhong Ree, Ph.D.
Clinical Pharmacology Review	Abimbola Adebawale, Ph.D./Lydia Velazquez, Pharm.D. 01May08
DDMAC	Iris Masucci, PharmD
CDTL Review	Jill Lindstrom, M.D.
OSE/DMETS/DMEP	Loretta Holmes, PharmD.
OSE/DRM	Nancy Carothers; Jodi Duckhorn
Pediatrics and Maternal Health Staff	Hari Sachs, M.D.

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS/DMEP=Division of Medication Errors and Technical Support; Division of Medication Error Prevention

DSI=Division of Scientific Investigations

DRM= Division of Risk Management

CDTL=Cross-Discipline Team Leader

## 1. Introduction

This applicant proposes the topical treatment of head lice (*pediculus humanus capitis*) with a lotion containing benzyl alcohol as the active ingredient. Although benzyl alcohol is present in other products as an excipient, it has not previously been approved as a new drug.

Head lice are wingless insects that are obligate ectoparasites of humans, and humans are their only known host. Head lice spend their entire life cycle on the human scalp, and feed exclusively on human blood. The insects generally cling to the hair shafts where they lay their eggs, and crawl down to the scalp for their blood meal. Head lice and body lice are closely related, but are not identical and infest different anatomic areas on the human host.

Treatment of head lice is a well studied indication and there are multiple approved products, both prescription and over-the-counter. The intended result of treatment of head lice is to eradicate the live lice from the scalp/hair. Living head lice crawl on the scalp for feeding and also cling to the scalp hair, depositing eggs that become “glued” on the hair shaft, generally to the proximal portion of the hair shaft. The female lays approximately 6 eggs every 24 hrs, usually at night, and may lay up to 150 in her lifetime. Eggs incubate in about 8-9 days, and reach adulthood in about 15 days. An effective product must kill the live lice (pediculicides), but must also provide for eradication of any new lice which may hatch from viable eggs (nits). If these eggs are not killed by the treatment product (ovicide) or removed (combing), the cycle of infestation will continue. Products claiming pediculocidal and ovicidal activity may demonstrate efficacy with one application, while products without ovicidal activity may require an additional application(s) to eradicate any lice hatching from viable eggs.

For studies to support an indication of treatment of head lice, the recommended primary efficacy variable is the status of lice infestation (live lice present/absent) and the usual primary efficacy evaluation time point is 14 days after the last treatment. Patients are dichotomized into success/failure based upon this day 14 post-treatment evaluation. The proportion of subjects who are a “success” is compared to the proportion of subjects who are determined to be “failures” at day 14 following the second treatment.

The applicant should provide adequate dose ranging studies (dose, duration, frequency) to establish the appropriate treatment regimen based upon their products performance profile. All patients should be evaluated for local and systemic safety. The primary efficacy evaluation time point is generally 2 weeks after the last treatment. This time point is chosen because it is difficult to determine if all the lice/eggs are dead immediately following the last treatment, and the two weeks will generally allow time for viable eggs to hatch and product visible lice. Even if no lice are identified at the last treatment visit, remaining eggs may be viable for several days, and evaluation 2 weeks (14 days) after the end-of-treatment will generally reveal live lice if there were viable eggs remaining at the last treatment. Although the problem of “reinfestation” following treatment may also be considered as a reason for the presence of live lice on day 14 following end-of-treatment, the study design described has been used successfully by approved products and continues to be a reasonable approach.

The applicant's initial submission contained datasets that were challenging to review and which appeared to contain some discrepancies when compared to the study reports. These concerns were communicated to the sponsor and the sponsor resubmitted study reports and some data during the review process. Overall, the determination of safety and efficacy conclusions were consistent.

## 2. CMC/Device

The product contains 5% (50mg/g) benzyl alcohol as an active ingredient. The identity, strength, and purity of the drug product were evaluated by the following analytical tests conducted during the process, on the released finished product, and on the stability: description, pH, viscosity, specific gravity, benzyl alcohol ID, assay, and related substances. The drug product specifications were deemed satisfactory by the reviewing chemist.

This application provided adequate information on the raw materials controls, manufacturing process, specification and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during shelf life. However, an "acceptable" recommendation has still not been received from the Office of Compliance for the drug substance manufacturing facility, due to cGMP issues at the manufacturing site.

The NDA should not be approved until the cGMP issues are resolved.

## 3. Nonclinical Pharmacology/Toxicology

Lice breathe through 7 paired "spiracles", one pair on the thorax and 6 pairs on the abdomen. Apparently, these spiracles can be opened/closed in response to wetting and are able to close for up to 12hrs. The purported mechanism of action for this product is a "stunning" of the respiratory spiracles of the louse such that they remain open, leading to blockage and subsequent asphyxiation. The sponsor claims that asphyxiation occurs within minutes in the presence of benzyl alcohol. The mineral oil in the product is purported (b) (4) while the Carbomer 934P provides a (b) (4).

The applicant conducted two in-vitro studies to evaluate the pediculocidal activity of the product. The complete product (b) (4) was compared to the activity of products containing either 5% benzyl alcohol or mineral oil. Virtually complete lice killing was noted for the drug product up to 5 hrs post dose, (b) (4). Scanning electron microscopy demonstrated that when lice were exposed to the drug product their breathing spiracles remain open and allow liquid materials to occlude the breathing apparatus, resulting in death. These studies provide useful insights into the mechanism of action of this product. The applicant is relying upon literature

to satisfy some aspects of the nonclinical toxicology information needed to support the safety of benzyl alcohol, primarily repeat dose toxicology and genetic toxicology.

The pharmacology review summarizes the non-clinical findings. Results from 13-week repeat dose oral rat and mouse toxicology studies conducted by the National Toxicology program suggest that high doses of benzyl alcohol could be neurotoxic. However, it was not anticipated that high systemic doses of benzyl alcohol would be achieved after clinical use of the *Tradename* product. No systemic toxicity was noted in 2 week repeat dose dermal toxicology studies conducted with up to 15% lice asphyxiator product in rats and dogs. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after two weeks of repeat dermal exposure (6 hours/day). However, sporadic systemic levels of benzyl alcohol were observed in the human bioavailability studies (see below) and the applicant should provide information to address this finding.

Benzyl alcohol elicited a positive response in some in vitro genetic toxicology assays and a negative response in other in vitro genetic toxicology assays. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400mg/kg benzyl alcohol) or mice (doses up to 200mg/kg benzyl alcohol) conducted by the NTP. Benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in systemic rat and rabbit embryofetal development studies.

As noted in the pharmacology review, the dermal flux for benzyl alcohol across human skin in vitro was reportedly low. The percentage of the applied dose that penetrated human skin in vitro was less for full term infant skin than adult skin (0.73% vs. 1.42%). The relevance of this information to the in-vivo bioavailability of *Tradename* is unknown. This information should be correlated by the applicant with the information observed in the topical bioavailability studies.

No fertility studies have been conducted with benzyl alcohol.

## **4. Clinical Pharmacology/Biopharmaceutics**

The sponsor requested a waiver of an *in vivo* PK study to determine the systemic exposure under maximal use conditions. This was not granted because, systemic exposure *in vivo*, if feasible, of topical products needs to be determined for purposes of safety assessment. Actual data are needed as the extent of percutaneous absorption depends upon such factors as the formulation and skin conditions. Benzyl alcohol has been associated with “gasping syndrome” in neonates, and the systemic exposure from this product and any implications for “gasping syndrome” in older children should be adequately addressed by the sponsor.

The applicant submitted one study (SU-01-2007) to evaluate the systemic exposure of benzyl alcohol in patients 6 months of age and older with head lice infestation. The study objective

was to assess the systemic exposure of benzyl alcohol in *Tradename* lotion following a single normal 10 minute application or an exaggerated 30 minute application in infested patients 6 months and older (n=45).

The plasma concentrations at 0.5 hr, 1hr, 3hr and 6hrs following 10 minutes exposure in subjects 6 months to 3 yrs (Cohort 1) were all below the quantifiable limit (<1.00 ug/ml) except for a single reading in 7 of the 9 subjects, and these readings were all (b) (4). In the second cohort (4-11 yrs) there were 5 of 9 children with BLQ or readings (b) (4) however, there was 1 subject with 50.8 ug/ml at 1 hr and one subject with 39.9 ug/ml at 1 hrs and 108.3 ug/ml at 3 hrs. Both these subjects had levels BLQ at 6 and 12 hrs. Additionally in this cohort there was one subject with a level of 7.42 at 1 hr and one subject with a level of 13.3 at .5 hrs. In the third cohort (12yrs and older) all levels were BLQ with the exception of one subject with 1.82 ug/ml at .5hrs. The clinical significance of these findings, if any, is unknown.

Information is also provided for 30 minute exposures. For subjects in the 6 months to 3 yrs cohort, the levels were BLQ except for a .5hr level of 2.28 in one subject and levels (b) (4) at .5 and 1 hr in another subject. A third subject had an unexplained level of 324.3 at 6hrs, with BLQ values at preceding time points. This draw was reassayed with similar results, and the applicant offers that this patient had a “difficult draw” that may have affected the result. It is unknown if the area was swabbed with a product containing benzyl alcohol. The second cohort provided results indicating detectable plasma levels in all subjects. Subject 009 demonstrated detectable levels between 0.5 hrs and 6 hrs, with the highest level (131.3) at 6 hrs. Subjects 017 and 023 demonstrated levels at 30 minutes and 1 hr, and subject 039 demonstrated levels at 30 min. All levels in the third cohort were BLQ except for subject 015 with a 0.5hr level at 30.9 and a 1hr level at 2.40, and subject 022 with a 3.18 level at 0.5hrs.

Overall, cohort 2 (4-11 yr old) demonstrated higher plasma concentrations than the other two cohorts. The clinical significance of this is unknown.

These outcomes were discussed with the clinical and biopharm reviewers, to determine the implications, if any, for use of this product. The applicant has not provided information adequate to describe the impact of this bioavailability data. It is unclear why there is such variability in the benzyl alcohol levels in these plasma samples, but there appears to be evidence of systemic absorption and although contamination and sampling error may be reasonable explanations, there is inadequate information provided to establish the degree of systemic bioavailability of benzyl alcohol from application of *Tradename*. The applicant should provide a comprehensive discussion and review of the bioavailability information, including a discussion of implications, if any, for safe use of the product.

My recommendation is that this product not be approved until the applicant has provided sufficient and adequate information regarding the systemic bioavailability of benzyl alcohol from their drug product. The applicant concludes in the study report for SU-01-2007 that “benzyl alcohol concentrations were sporadically observed at 0.5 to 3 hrs post-treatment in various subjects for all three age cohorts in both the 10 and 30 minute treatment groups”. The



applicant has not provided an adequate analysis of the positive samples obtained in this study, and has not provided an adequate safety analysis of this exposure.

## 5. Clinical Microbiology

N/A

## 6. Clinical/Statistical-Efficacy

Two randomized, double blind, vehicle -controlled trials were conducted to support the safety and efficacy of *Tradename* lotion in the treatment of head lice. Studies SU-01-2005 and SU-02-2005 were multi-center, randomized, double blind, vehicle controlled studies. Study 01 was conducted in 5 centers across the US and enrolled 306 (125 index) subjects. Study 02 was also conducted in 5 centers and enrolled 309 subjects (125 index)

The trials included two cohorts: the primary cohort consisted of the youngest child in a household with at least 3 live lice; the secondary treatment cohort consisted of any other household members who also had an active lice infestation. The trials were identically designed to recruit approximately 120 subjects for the primary treatment cohort who would participate in the trials for approximately 22 days.

Study subjects were instructed to apply *Tradename* to dry hair ensuring complete coverage, such that all hair and the entire scalp were thoroughly saturated with the product to the point where some dripping would likely occur. The study protocol included usage guidelines (amount of test product per treatment) based upon the hair length, with subjects with longer hair using more product. Subjects were provided a towel and instructed to cover their eyes, forehead and neckline during treatment. The product was left in place for 10 minutes then rinsed, shampoo with regular shampoo, and rinsed again. Treatment was repeated in one week (day 8). On day 9, treatment failures in both cohorts were offered enrollment in an open-label study with the test product or an FDA approved treatment for head lice. On day 15 all subjects were examined again and subjects with live lice were considered treatment failures and provided therapy. Lice free subjects returned 14 days later for final examination, with lice free subjects determined a treatment success and subjects having live lice offered an FDA approved therapy. In both trials the test product demonstrated superiority over vehicle for the primary endpoint defined as the percentage of subjects who were lice free 14 days after the second 10 minute application.

Table 12 summarizes the outcomes, demonstrating that approximately 75% of the *Tradename* treated subjects were determined to be treatment successes, compared to 5% of vehicle patients in study 01 and 25% of subjects in study 02. It is unclear why the vehicle success rate was higher in study 02. The outcomes are consistent with the lice eradication results in other

groups, including the per protocol and the secondary cohort, and are consistent with a sensitivity analyses evaluating the effect of patients with missing data.

**Table 12: Lice Eradication Results (Primary Cohort-ITT)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Reviewer's analysis and revised Study Report Table 2.

Statistical Review and Evaluation; Mat Soukup, Ph.D.)

Both hair type and hair texture showed relatively consistent response between groups. In terms of hair length, the data showed a slight trend towards less efficacy in subjects with longer hair though small sample sizes limit the reliability of this conclusion. Labeling should include specific instructions to cover ALL the hair and scalp with the product.

## 7. Safety

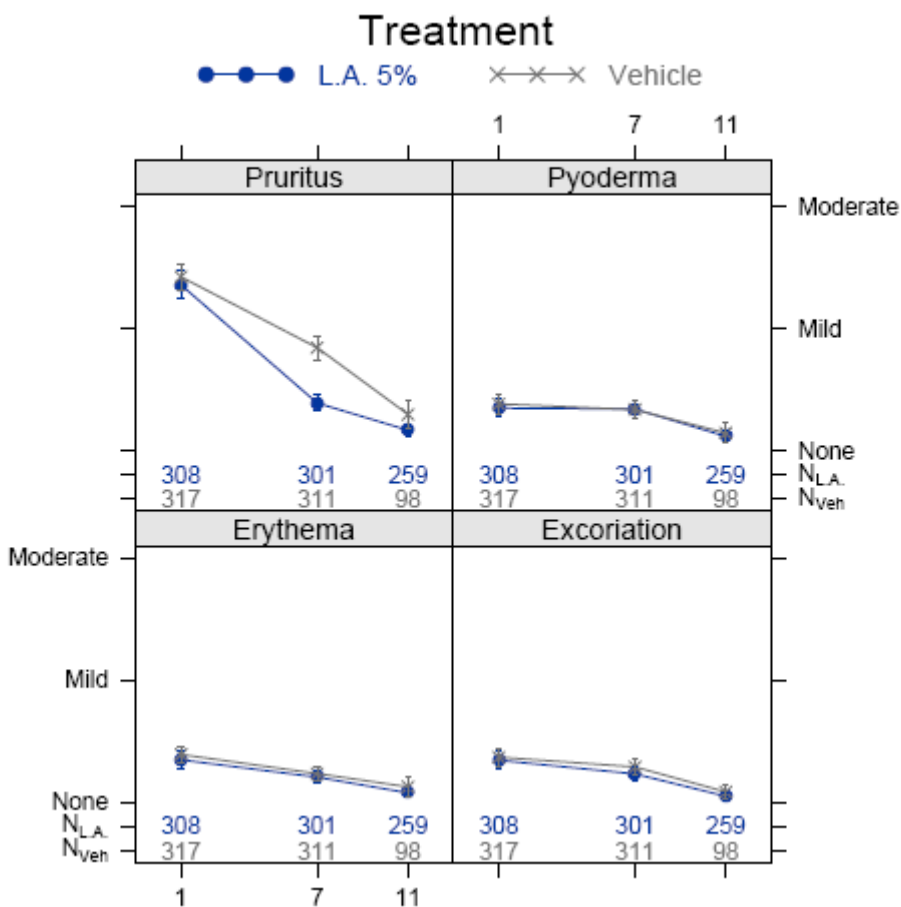
Safety data from eight studies sponsored by the applicant were submitted in the marketing application. The safety of *Tradename* for treatment of head lice (*Pediculus humanis capitis*) was evaluated in two pivotal clinical studies enrolling 628 subjects (SU-01-2005 and SU-02-2005), an open label study enrolling 128 subjects (SU-03-2005), Phase 2 studies enrolling 167 subjects (SU-02-2003, SU-02-2003A and SU-02-2004), Phase 1 single dose bioavailability study enrolling 45 subjects (SU-01-2007), and a special safety study enrolling 244 healthy subjects (SU-01-2006).

A total of 485 subjects were assigned to be treated with two 10 minute treatments, one week apart. There were no study deaths and no serious adverse events. No subjects discontinued from the pivotal trials due to an adverse event and one subject (01-141) withdrew from the topical safety study due to mild nausea.

No deaths and no serious adverse events were reported in the clinical development of *Tradename*. There were no laboratory evaluations completed during the course of this study.

Evaluation of local signs and symptoms specifically included assessment of pruritus, erythema, pyoderma, and excoriation. Treatment with *Tradename* was not demonstrated to worsen or precipitate any of these conditions during the study. Overall, treatment with

*Tradename* appeared to be well tolerated in the clinical studies. The table below from the clinical/biostatistics reviews summarizes the data presented.



There is an outstanding informational need regarding the systemic absorption of benzyl alcohol from *Tradename*, and potential safety implications in children. (See Biopharm section of this review). The safety assessment of *Tradename* should include evaluation of complete and adequate systemic bioavailability information. My recommendation is that *Tradename* not be approved until this informational need has been fulfilled.

## 8. Advisory Committee Meeting

This product was not referred for review to an advisory committee.

## 9. Pediatrics

Pediculosis capitis (head lice infestation) is common in children. The applicant has completed studies and provided sufficient numbers of subjects in the younger pediatric population to establish the efficacy for children 6 months of age and older. Additional information is needed pertaining to the potential systemic absorption of this product and the impact, if any, on safe use in children. The sponsor requested a waiver for pediatric studies in patients less than 6 months, based upon their determination that the studies are impossible or highly impractical because the numbers of patients in this age group (0-8 months) is so small. The applicant provides information that there are no reports in the literature of head lice occurring in children less than 6 months of age and that experts in the field report never having seen a case of head lice in a child younger than 6 months of age.

As discussed at the PeRC, the applicant should be granted a partial waiver for two selected pediatric populations (neonates 0-1 month and children 1-6 months). Final determination of the basis for a waiver will be made with any Approval action letter.

## 10. Other Relevant Regulatory Issues

During a 28Feb08 pre-approval inspection of the manufacturing facility for this application, FDA field investigators conveyed deficiencies to the facility's representative. (b) (4) recommended that the application be placed on a Withhold status due to the deficiencies found during this inspection.

Division of Medication Error Prevention has reviewed the proposed tradename and provided consultative advice. I agree that the applicant's proposed tradename(s) are vulnerable to name confusion that could lead to medication errors. The sponsor should continue to provide tradename for agency review and approval.

## RECOMMENDATIONS

### 11. Labeling

The proprietary name has not been determined. Draft physician's labeling, carton container labeling and patient package insert have been discussed with the sponsor. The draft texts for the package insert and the patient package insert should be revised according to the most recent versions from the review team. The draft texts for the immediate container and carton labels should be revised accordingly. Product labeling should be finalized at the time of any approval action.

## **12. Decision/Action/Risk Benefit Assessment**

I recommend that this product receive an Approvable action in this cycle. Before the application is approved, the applicant should provide clarification of the plasma benzyl alcohol concentrations observed during the study and the potential safety impact, if any, resulting from systemic absorption of benzyl alcohol in children. Additionally, the cGMP issues should be resolved, and draft labeling should be submitted.

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/s/

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Susan Walker  
7/14/2008 10:56:50 AM  
DIRECTOR

## Team Leader Review

<b>Date</b>	July 10, 2008
<b>From</b>	Jill Lindstrom, MD
<b>Subject</b>	Team Leader Review
<b>NDA/BLA #</b>	22-129
<b>Applicant</b>	Sciele Pharma, Inc. (originally submitted by Summers Laboratories, and transferred to Sciele Pharma during review cycle)
<b>Date of Submission</b>	June 15, 2007
<b>PDUFA Goal Date</b>	July 15, 2008
<b>Proprietary Name / Established (USAN) names</b>	TRADENAME (benzyl alcohol) Lotion, 5%
<b>Dosage forms / Strength</b>	Lotion, 5%
<b>Proposed Indication(s)</b>	Topical treatment of head lice infestation in patients 6 months of age and older.
<b>Recommended:</b>	<i>Approvable</i>

### 1. Introduction

TRADENAME (benzyl alcohol) Lotion, 5%, is a topical pediculocide for which the sponsor seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients 6 months of age and older.

### 2. Background

Head lice infestation, pediculosis capitis, is a common and communicable condition in which the human head louse, *Pediculus humanus capitis*, infests the hairy scalp. The most prominent symptom of infestation is pruritus, and signs include lice observed on the scalp, nits attached to hair shafts, and manifestations of excoriation such as crusting and erythema. Excoriation can result in secondary infection due to disruption in the epidermal barrier. Because the infestation is communicable, children diagnosed with the infestation are generally precluded from attending school until they have received effective treatment. The therapeutic armamentarium for the treatment of head lice infestation includes approved and unapproved drug products and mechanical measures such as combing or shaving of the scalp (the latter generally reserved for very young children because of the psychological distress that can result). Approved drug products indicated for the treatment of head lice infestation include lindane shampoo, permethrin cream rinse, pyrethrins with piperonyl butoxide solution and mousse, and malathion lotion; all of these drug products are administered topically and are pesticides which act on the neurologic system of the louse.

Benzyl alcohol is not known to be marketed as a pediculocide in any jurisdiction, and it has not been previously reviewed as a drug substance in a New Drug Application (NDA) for any indication. However, it is monographed for nonprescription use as an anorectal local anesthetic in concentrations of 1% to 4% [21CFR346.10(b)]. It is also referenced in a Tentative Final Monograph published in the Federal Register on January 27, 1988, in which benzyl alcohol was proposed as an over-the-counter oral anesthetic/analgesic for use by patients 2 years of age and older as either a solution or suspension at concentrations from 0.05% to 10% (swish and spit QID) or as a solid oral dosage form containing 100 to 500 mg benzyl alcohol (dissolve in mouth q2hr prn), and in a Tentative Final Monograph published on February 8, 1983, in which benzyl alcohol was proposed as an over-the-counter cutaneous anesthetic for patients 2 years of age and older at concentrations from 10 to 33% to be applied QID. Additionally, it is an excipient (preservative) in multiple approved drug products, including intravenous, oral and topical drug products. For example, benzyl alcohol is present at 5% in Lamisil Dermgel, a topical gel applied once daily for the treatment of tinea pedis, tinea cruris, tinea corporis or tinea versicolor. Benzyl alcohol is also an excipient in the non-prescription products ACT Children's fluoride rinse (for children 6 years and older) and Aveeno Baby sunscreen (for children 6 months and older); this reviewer was not able to ascertain the concentration of benzyl alcohol in the latter two products as neither was reviewed as an NDA.

### 3. CMC/Device

Although the applicant provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product, inspection of the drug substance manufacturing facility did not meet cGMP requirements. Deficiencies include inadequate record keeping, failure to follow established test procedures, failure to qualify testing equipment, inadequate review of the stability monitoring program, failure to obtain approval prior to changing a validated process, and failure to establish written procedures with acceptance and rejection criteria for the drug containers and closures. The CMC reviewer recommended an *Approvable* action pending resolution of these deficiencies.

The applicant proposed that their drug product dosage form be identified as an (b) (4). However, the dosage form has the appearance and flow characteristics of a lotion. The Agency proposed and the applicant agreed that the dosage form will be identified as a lotion.

The applicant initially proposed that their drug product be dispensed in (b) (4). This container and closure system presented a risk for overdosing and ingestion medication errors, respectively. The applicant subsequently proposed a neutral polypropylene bottle with an orifice-reducing plug. Though still opaque, the neutral (b) (4) bottle is sufficiently translucent to allow ascertainment of the amount of drug product remaining in the bottle, which should reduce the risk of over-application (depending on hair length, a patient may need to apply only half of a bottle). Additionally, the incorporation of an orifice-reducing plug into the container closure system, similar to that seen on some shampoo bottles, should reduce the risk of ingestion-type medication errors.



The reviewer is referred to the CMC review by Mr. Tarun Mehta for a full discussion of the CMC issues.

## 4. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical pharmacology/toxicology issues or informational needs. The reader is referred to the comprehensive review by Dr. Barbara Hill for a full discussion of the nonclinical pharmacology/toxicology data.

In brief from her review, two-week repeat dose dermal toxicology studies in rats and dogs showed negligible systemic absorption. In thirteen week oral toxicology studies in rats and mice, both species developed signs of neurotoxicity at in the high dose groups (400 mg/kg and 800 mg/kg, respectively). Oral carcinogenicity studies in rats and mice did not reveal a carcinogenic signal. Reproductive toxicity studies in rats and rabbits did not identify a teratogenic signal.

## 5. Clinical Pharmacology/Biopharmaceutics

Systemic exposure under conditions of maximal use was evaluated in Study SU-01-2007. Forty-five subjects aged 6 months or older with active head lice infestation were treated with either a 10-min application (27 subjects) or an exaggerated 30 minute application (18 subjects) of TRADENAME (benzyl alcohol) Lotion, 5%. Serum samples for benzyl alcohol assay were obtained at baseline and 0.5, 1, 3, and 6 hours after treatment with TRADENAME Lotion (applied for 10 minutes to the scalp). The reader is referred to the review by Dr. Abi Adebawale for a full discussion of the study.

In brief, majority of the samples were below the limit of quantitation. In nine subjects, no benzyl alcohol was detected at any timepoint. Twenty-six (of 45) subjects had detectable serum benzyl alcohol at one or more timepoints. Most subjects with detectable benzyl alcohol had low positive levels at one or both of the first two timepoints, 0.5 and 1.0 hour after treatment. Three subjects had serum levels greater than 100 ug/mL at one or more timepoints, the data from whom are presented in Table 1:

Table 1: Plasma Concentrations (ug/mL) of Benzyl Alcohol in Selected Subjects Following a Single Treatment with TRADENAME Lotion

Time (hr)	Subject ID		
	002	043	009
Pre-dose	BLQ	BLQ	BLQ
0.5	BLQ	BLQ	77.7
1	BLQ	39.9	63.8
3	BLQ	108.3	NR
6	324.3	BLQ	81.5
12	ND	BLQ	131.3

BLQ—below the quantifiable limit, <1.00ug/mL

ND—not done

NR—not reported

Source: adapted from Dr. Abi Adebawale's Clinical Pharmacology and Biopharmaceutics review.

The applicant did not provide a rationale to explain these data. The pattern and timing of the measured levels in these three subjects does not follow expected pharmacokinetics, suggesting contamination or error. However, even if the levels represent true systemic exposure, none of these subjects experienced adverse events. Nonetheless, the applicant should address the findings.

Gershanik et. al. described ten low birth weight neonates who developed Gasping Syndrome following intravenous exposure to benzyl alcohol<sup>1</sup>. These neonates inadvertently received between 99 and 234 mg/kg/day of benzyl alcohol, a preservative in the sterile water and sterile heparin solutions used to flush arterial and venous catheters and in some intravenous mediations. The mean serum benzyl alcohol level, measured in six of the ten neonates, was  $1.01 \pm 0.13$  mmol/L.

Although the mean serum benzyl alcohol level reported by Gershanik, et al, overlaps with the levels measured in the three subjects above, caution needs to be used in extrapolating from the case reports of Gasping Syndrome to the subjects in Study SU-01-2007. In the report by Gershanik, et al, the time of specimen collection is not provided, so it is not clear (and is unlikely) that the mean level reported represents  $C_{max}$ . Additionally, the neonates received repeated intravenous exposures over multiple days, whereas subjects in Study SU-01-2007 received a single topical dose for 10 or 30 minutes duration. Finally, the neonates had immature hepatic, neurologic and respiratory systems, whereas subjects in Study SU-01-2007 were physiologically mature.

Nonetheless, because of the potential for systemic absorption, as well as the possibility of an immature cutaneous barrier in premature infants, it would be prudent to contraindicate the use of TRADENAME (benzyl alcohol) Lotion 5% in children less than 6 months of age.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

The applicant conducted two pivotal trials, Study 01 and Study 02, to investigate the safety and efficacy of their product applied for 10 minutes once a week for two weeks in the treatment of head lice infestation. Both were multi-center, randomized, double blind, vehicle-

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<sup>1</sup> Gershanik J, Boecler B, et. al. The Gasping Syndrome and Benzyl Alcohol Poisoning. New Engl J Med. 1982; 307 (22): 1384-8.

controlled trials and were of identical design. Households were enrolled if one or more member was infested with at least 3 live lice; the youngest infested household member was the index subject (primary efficacy cohort) and other infested household members were enrolled in the secondary cohort. Subjects applied the requisite amount of clinical trial material, depending on hair length, for 10 minutes on day one and for 10 minutes on day seven. Efficacy was assessed 14 days after the second treatment, and success was defined as the absence of live lice. The primary efficacy endpoint is the proportion of subjects with treatment success at 14 days after the last treatment, which is shown in Table 2:

Table 2: Lice Eradication Results (Primary Cohort – ITT)

	Study 01		Study 02	
	TRADENAME Lotion	Vehicle	TRADENAME Lotion	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)
p-value*		<.001		<.001

\*Reported p-values are based on CMH stratified by site

Source: Dr. Mat Soukup's Biostatistics review of NDA 22-129, p12.

In summary, in their pivotal trials Study 01 and Study 02, the applicant demonstrated that TRADENAME Lotion applied for 10 minutes once weekly for two weeks is significantly superior to vehicle in the treatment of head lice infestation. The robustness of the pivotal trial data, detailed in the clinical and biostatistical reviews by Drs. Gordana Diglisic and Mat Soukup, respectively, allow determination of efficacy.

## 8. Safety

During the development of TRADENAME Lotion, 1,212 subjects were evaluated, 752 of whom were exposed to TRADENAME Lotion. Of these, 244 subjects were enrolled in dermal safety studies, for which the dose was not reflective of anticipated labeled use. Five hundred and eight subjects received two applications of TRADENAME Lotion to the scalp and scalp hair, 485 of whom received two applications of 10 minutes duration and 23 of whom received two applications of 30 minutes duration.

There were no deaths or SAEs attributable to TRADENAME Lotion during the development program. The most frequently reported adverse event was nasopharyngitis; the most frequent adverse events considered relevant to treatment were ocular irritation (1), eyelid exfoliation (1), and application site irritation (1), reported in one subject each. Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

The reader is referred to the Clinical Review by Gordana Diglisic, MD, for full discussion.

## **9. Advisory Committee Meeting**

Not applicable, as no Advisory Committee meeting was held.

## **10. Pediatrics**

The applicant conducted their pivotal trials and the systemic exposure study in subjects 6 months of age and older, the relevant population for head lice infestation and the population for whom the applicant seeks labeling.

The applicant requested a pediatric waiver for children less than six months of age based on the rationale that studies are “not feasible.” The application was presented to the PeRC PREA Subcommittee on June 25, 2008. The PeRC concurred with waiving studies in children less than six months. Following further discussion after the meeting, concurrence was obtained that safety considerations, rather than feasibility, should be the basis of the waiver. Thus it is recommended that studies in children six months of age and younger be waived because of safety concerns, specifically that there is an increased risk of systemic absorption in children less than six months of age because of the high ratio of skin surface area to body mass and the potential for an immature skin barrier.

## **11. Other Relevant Regulatory Issues**

Benzyl alcohol is monographed for use as an anorectal analgesic, but there are no products with benzyl alcohol as the active ingredient listed in the Orange Book. At the time of this review, it is not clear whether the applicant would qualify for five years of exclusivity as a new molecular entity, or three years of exclusivity for a new indication. Consultation within the Agency is pending. The issue is not of imminent concern with an approvable action, but will likely need to be addressed eventually.

## **12. Labeling**

The proprietary name has not been established. The applicant submitted four names, but none were found to be acceptable. The product is referred to as TRADENAME (benzyl alcohol) Lotion, 5%, in this review and in the draft labeling.

The applicant submitted proposed labeling in the format that complies with the Physicians’ Labeling Rule. Significant changes incorporated into revised draft labeling, following labeling review, include:

- addition of a contraindication for use in children less than 6 months of age because of the risk for increased systemic absorption
- clarified instructions for use
- incorporation of safety and efficacy data into section 8.4, Pediatric Use; the rationale for the waiver in children less than 6 months of age was also added to this section

- addition of a Patient Package Insert

Labeling negotiations have not concluded at the time of this review.

### **13. Recommendations/Risk Benefit Assessment**

Recommended regulatory action: Approvable

The applicant needs to resolve the manufacturing deficiencies with regard to GMP requirements.

The applicant needs to address the systemic exposure data of the outlier subjects in the systemic exposure study.

Risk Benefit Assessment:

Pending the applicant's successful clarification of the systemic exposure data, the risk-benefit ratio supports approval of this product for the treatment of head lice infestation in patient six months of age and older.

Recommendation for Postmarketing Risk Management Activities:

Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed.

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/s/

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Jill Lindstrom  
7/14/2008 10:51:32 AM  
MEDICAL OFFICER

## Office Memorandum

**RE:** 22-129

**Date:** July 14th, 2008

**From:** Daniel A. Shames MD FACS  
Deputy Director, Office of Drug Evaluation III  
CDER/FDA

**To:** File (DFS)

**Applicant:** Summers Laboratories Inc.

**Therapeutic Class:** Pediculocide

**Established Name:** benzyl alcohol lotion, 5% (BAL 5%)

**Proposed Trade Name:** Undetermined

**Proposed indication:** Indicated for the topical treatment of head lice infestation (*Pediculus humanis capitis*, lice and their ova) of the scalp hair in patients 6 months of age and older.

**Proposed regimen:** Apply sufficient Lotion to dry hair to completely saturate the scalp and hair; leave on for 10 minutes, and then thoroughly rinse off with water. Avoid contact with eyes. Repeat treatment after 7 days.

**Recommended Regulatory Action:** Approvable (AE) because of potential safety issue regarding systemic benzyl alcohol exposure CMC inspection and labeling.

**Attribution:** I primarily consulted and utilized sections of the Reviews from the Division Director of Dermatology and Dental Products (DDP), Susan Walker, the Cross Discipline Team Leader, Jill Lindstrom, the Medical Reviewer, Gordana Diglisic MD the Toxicology Reviewer, Barbara Hill PhD, the Clinical Pharmacology Reviewer, Abimbola Adebowale PhD, and the Chemistry Reviewer, Tarun Mehta PhD for the creation of this Memorandum.

---

### 1.0 Background

#### 1.1 Clinical

Head lice infestation is common in United States among children 3-12 years of age; approximately 6-12 million have infestation each year. <sup>1</sup>Lice are transferred by close contact.

Shames/22-129/AE

contact and possibly by sharing of hats, combs, and brushes. The major complaint of persons infested with head lice is severe pruritus of the scalp. Scratching leads to<sup>2</sup> excoriation and secondary bacterial infection. Therapeutic options include 1% Lindane shampoo/lotion, pyrethrins with piperonyl butoxide solution, 1% permethrin cream rise, and 0.5% malathion lotion.

Lindane requires a prescription. Lindane shampoo should be only used in patients who cannot tolerate or have failed first-line treatment with safer medication for treatment of lice (boxed Warnings, PI). Lindane ( $\gamma$ -benzene hexachloride), an organochloride pesticide, noncompetitively inhibits the  $\gamma$ -amino butyric acid (GABA) receptor, which typically binds GABA, an inhibitory neurotransmitter. Seizures and deaths have been reported following Lindane shampoo use with repeat or prolong application, but also in rare cases following a single application. Infants, children, the elderly, and individuals with other skin condition and those weigh < 110 lbs (50kg) may be at greater risk of serious neurotoxicity.

Permethrin, pyrethrum, pyrethrins, and pyrethroids are over-the-counter (OTC) pediculicides. They affect voltage-gated sodium channels, causing delayed repolarization of the neuron by impeding sodium channel closure. Rare cases of asthma exacerbation and even death have been reported in individuals with ragweed allergy after using pyrethrin-based products.<sup>3</sup> Genetic resistance to pyrethroids is widespread in both the United States and abroad.<sup>4</sup>

Malathion is an organophosphate insecticide that requires a prescription. In the louse, melathion is converted to malaoxion, which irreversibly inhibits acetylcholinesterase. The major concerns are the high flammability of the melathion formulation, and the risk of respiratory depression if accidentally ingested.

In addition, several products are used off label when the above products are not effective or are contraindicated. Two such therapies are oral ivermectin and oral trimethoprim/sulfamethoxazole. Non-pharmacologic approaches involve occlusion therapy (e.g. vinegar, mayonnaise, petroleum jelly, and olive oil), nit combing, and hair removal.

#### References:

<sup>1</sup> American Academy of Pediatrics; Pediatrics; Vol. 110 No. 3, September 2002, pp.638-643

<sup>2</sup> Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, Vol. 2, 2972, 2000

<sup>3</sup> Wax PM, Hoffman RS; Fatality associated with inhalation of pyrethrin shampoo. J. Toxicol Clin Toxicol. 1994; 32:457-460

<sup>4</sup> Therapy for Head lice Based on Life Cycle, Resistance, and Safety Consideration; M. Lebwohl, L Clark and J Levitt; Pediatrics, Vol. 119 No.5 May 2007, pp. 965-974

### 1.2 Product

Benzyl alcohol, 5% lotion (BAL 5%) is a topical, non-pesticide pediculicide. BAL 5% acts by stunning the respiratory spiracles of human head lice open, permitting blockage of the spiracles and asphyxiation.

### 1.3 Regulatory



BAL 5% was developed under one Investigational New Drug application, IND 50, 076, submitted on November 6, 2003.

## 2.0 NDA 22-129

### 2.1 Regulatory

The application, 22 -129 (000) was submitted on June 15<sup>th</sup>, 2007 under 505(b) 2. This is the first drug product to have benzyl alcohol as an active ingredient. It is, therefore, classified as a New Molecular Entity (NME). An amendment to the application (012) related to Product packaging, was sent to the Division on January 25<sup>th</sup>, 2008. This submission was deemed a major amendment and extended the PDUFA Goal Clock until July 15<sup>th</sup> 2008. BAL 5% is not marketed in anywhere.

### 2.2. Chemistry Manufacturing and Controls Analyses and Conclusion

#### 2.21 Drug Substance (DS)

(b) (4) manufactures the benzyl alcohol. The chemistry, manufacturing, and controls information on the drug substance is provided in DMF (b) (4) which is deemed adequate to support this application.

During a recent inspection of the manufacturing facility for the drug substance, the field investigator conveyed deficiencies to the facility's representative. Satisfactory resolution to these deficiencies is required before this application may be approved. The follow-up inspection had not occurred at the time of the PDUGA goal date of the Application.

#### 2.22 Drug Product (DP)

The Drug Product contains 5% (50mg/g) benzyl alcohol as the active ingredient. All the excipients and API of this formulation are compendial (USP/NF).

During manufacturing, (b) (4)



The Drug Product development and the clinical supplies manufacturing were conducted at Contract Pharmaceutical Limited. The Drug Product composition of the clinical supply and the proposed commercial formulation is identical. A commercial size (b) (4) batch was successfully manufactured at the proposed scale-up site, using the proposed commercial manufacturing process and equipment. The manufacturing process controls support the consistent quality of the Drug Product. The identity, strength, and purity of the Drug Product are evaluated by the following analytical tests conducted during the process, on the released finished product and on the stability: Description, pH, viscosity, specific gravity, benzyl alcohol ID, assay, and related substances. The Drug Product specifications are deemed satisfactory.

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the Drug Product. However, the labels do not have adequate information as required. (Appendix 1 for deficiencies in the Approvable Letter).

### 2.3 Animal toxicology

The National Toxicology Program conducted two 13 week oral (gavage) toxicology studies with benzyl alcohol in rats and mice. The results from these 13 week repeat dose oral toxicology studies suggest that high doses of benzyl alcohol could be neurotoxic.

The sponsor conducted 2 week repeat dose dermal toxicology studies with up to 15% BAL Drug Product in rats and dogs. No systemic toxicity was noted in either study. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. BAL 5% caused minor dermal irritation in both rats and dogs after 2 weeks of repeat dermal exposure (6 hours/day). BAL 5% was identified as the dermal NOAEL in both rats and dogs. Both of these studies applied the BAL for 6 hours/day for two weeks. In addition, the rat study was conducted under occlusive conditions. Therefore, the conduct of both the rat and dog studies were under exaggerated use conditions compared to the proposed clinical use. The clinical regimen of the BAL5% will be to apply two ten minute applications of Drug Product separated by at least one week. The duration and extent of dermal exposure to BAL product under conditions of clinical use will be much less than was used in the two week dermal toxicology studies conducted in rats and dogs.

The **systemic NOAEL in both the rat and dog studies** was identified as BAL 15% (**300 mg/kg/day**; 1800 mg/m<sup>2</sup>/day in rats; 6000 mg/m<sup>2</sup>/day in dogs), the maximum dose possible based on maximum feasible concentration. The clinical reviewer, Dr. Gordona Diglisic, informed the Toxicology Reviewer that the maximum amount of BAL 5% that will be applied is six of the eight oz bottles (total 48 oz) to hair that is >22 inches. The 48 oz application is equivalent to a 1440 ml. This would equal a dose of 1200 mg/kg/day {1440 ml x 50ml/Gm (ml) ÷ 60 kg} benzyl alcohol for a 60 kg individual (adult) and a dose of **7200 mg/kg/day** {1440 ml x 50ml/Gm (ml) ÷ 10 kg} benzyl alcohol **for a 10 kg individual (child)**. The multiple of human exposure based on the systemic NOAEL noted in rats and dogs would range from 0.04 – 0.14X in adults and 0.01 – 0.04X in children.

#### **Comment: Nominal maximum dose exposure in child exceeds animal NOAEL**

In the opinion of the Toxicology Review Team “These multiples of human exposure do not accurately represent the safety based on systemic exposure to benzyl alcohol since systemic exposure to benzyl alcohol was minimal after 2 weeks of dermal administration of the BAL Drug Product in rats and dogs. Plasma concentrations of benzyl alcohol were quantifiable in only the one hour post-dose samples (**highest plasma concentration in rats** after 14 days = **3.59 µg/ml**; **highest plasma concentration in dogs** after 14 days = **10.2 µg/ml**). Human use would be a maximum of two 10 minute applications separated by at least 7 days. Therefore, it is anticipated that the multiples of human exposure would be much greater based on actual systemic exposure to benzyl alcohol under conditions of clinical use.”

**Comment: This analysis may not be correct since actual human blood levels from study SU-01-2007 indicate higher blood levels than measured in the animal toxicology study.**

## 2.4 Clinical Pharmacology

The applicant submitted one study (SU-01-2007) to support the clinical pharmacology and biopharmaceutics of BAL 5%. This study evaluated the systemic exposure of benzyl alcohol in patients aged 6 months and older with head lice infestation.

The objective of this study was to assess the systemic exposure of benzyl alcohol in BAL 5% following a single standard 10-minute application or an exaggerated 30-minute application in patients aged 6 months and older (total n=45 patients) with a symptomatic (at least moderate pruritus) and active infestation (at least 3 live lice). All patients were stratified into three age cohorts as follows: 6 months to 3 years, 4 to 11 years, or 12 years and older. For the 10-minute treatment group, 9 subjects were stratified to each of the three age cohorts (n=27) and for the 30-minute treatment group 6 subjects were stratified to each age (n=18).

Benzyl alcohol plasma concentrations ranging from **1.0 mcg/mL to 108.3 mcg/mL** were observed in 15 of the 27 subjects at 0.5 to 3 hours post-treatment for all three age cohorts in the 10 minute treatment group. For the 30-minute treatment group, benzyl alcohol plasma concentrations ranging from **1.2 mcg/mL to 131.3 mcg/mL** were observed in 10 of the 18 subjects at 0.5 to 12 hours post-treatment for all three age cohorts. For other subjects the exposure was below the limits of quantification.

No pharmacokinetic parameters were obtained due to the low levels of exposure and the paucity of the data observed in the study.

**Comment: The subjects in this trial were infested with head lice and therefore may have had inflamed skin which allowed significant systemic absorption of benzyl alcohol. The toxicology studies used animals with normal skin; in addition scalp may absorb benzyl alcohol better than other skin areas.**

Dan

## 2.5 Clinical Efficacy and Safety

### 2.51 Efficacy Analyses and Conclusion

Two pivotal trials (SU-01-2005 and SU-02-2005) were conducted with the objective of establishing the superiority of two 10 minute applications of BAL 5%. (one week apart) to vehicle. These trial were double-blind, placebo (vehicle) controlled, randomized, multi-center studies involving subjects 6 months of age or older with active infestation of the human head lice. Qualified subjects who met the inclusion/exclusion criteria were enrolled into the study. The youngest subject from each household who qualified with at least three live lice was designated as the Primary Treatment Cohort. Any other household members who qualified and resided with the randomized subject were asked to participate and designated the Secondary Treatment Cohort. A total of five visits were scheduled over the course of the study: screening visit (Visit 1, dispensing of clinical test materials), two evaluation visits (Visits 2 and 3, the day after the 1<sup>st</sup> and 2<sup>nd</sup> home treatments) for all subjects, and two follow-up visits for the Primary Cohort subjects for efficacy and safety evaluations (Visits 4 and 5, Day 15 and Day 22).

Study SU-01-2005 was conducted in five centers across the U.S. and enrolled a total of 306 subjects (125 index subjects used for primary efficacy evaluation). Study SU-02-2005 was conducted in five U.S. centers and enrolled a total of 309 subjects (125 index subjects).

The primary endpoint was defined as the percent of subjects who were lice free 14 days after the last treatment (Visit 5, Day 22). The analysis group was pre-specified in the statistical analysis plan to be the intent-to-treat (ITT) population. Results from both studies showed that BAL 5% was statistically superior to vehicle with p-values below 0.001 in both studies.

The Phase 2 studies, SU-02-2003, SU-02-2003A, and SU-02-2004, also provide supportive evidence of efficacy. These Phase 2 studies differed from the pivotal studies in that efficacy was evaluated 15 days after the first treatment, while pivotal studies were evaluate 15 days after the second treatment.

### 2.52 Safety Analysis and Conclusion

The safety data were collected from Phase 3 clinical trials enrolling 628 subjects, an open label study enrolling 128 subjects, Phase 2 studies enrolling 167 subjects, a Phase 1 single dose bioavailability study enrolling 45 subjects, and a special dermal safety study enrolling 244 subjects. The safety measurements were assessment of adverse events and skin/scalp/eye evaluation.

To be included in the safety population, subjects must have had at least one post-baseline assessment. Based upon the above definition, the safety population included 478 subjects exposed to BAL 5% and 336 subjects exposed to vehicle.

A total of 23 (4.8%) subjects, from the 478 subjects treated with BAL 5%, experienced adverse events compared to 6 (1.8%) subjects of the 336 subjects treated with the vehicle control. Four subjects had 5 adverse events that were considered related to the treatment with BAL 5% and one subject had an adverse event that was considered related to vehicle control. Three adverse events in the BAL 5% treated subjects were directly related to treatment with BAL 5%: eye irritation, eye exfoliation, and application site irritation.

The symptom which tended to worsen with BAL 5% treatment compared to vehicle was pruritus. At the first evaluation visit 12% of subjects treated with BAL 5% with no pruritus prior to treatment, had mild pruritus compared to 3% of subjects treated with vehicle control. At second evaluation visit 6% of the subjects treated with BAL 5% with no pruritus prior to treatment, had mild pruritus compared to 0% of subjects treated with vehicle control. The most frequently reported signs/symptoms in the BAL 5% treatment group were "Application site irritation" (11 events, 2.3%), "Application site anesthesia" and "Hypesthesia" combined (10 events, 2.0%), and "Pain" (5 events, 1%).

The most frequently reported sign/symptom in the vehicle treatment group was paresthesia (4 events, 1.2%).

No deaths occurred during the development program of BAL 5%. No serious adverse events were reported during the development program of BAL 5%. One subject was withdrawn from the study due to an adverse event.

## 2.521 Special Safety Issue (benzyl alcohol toxicity)

Sixteen neonatal deaths have been associated with the use of benzyl alcohol as preservative in saline flush solutions. The deaths occurred in pre-term neonates weighing 2500 gms who had central intravascular catheters flushed periodically each day with bacteriostatic normal saline containing **9 mg/ml** benzyl alcohol. Review of the medical records of the affected infants resulted in estimates of daily intake of benzyl alcohol ranging from 99 to 405 mg/kg/day.<sup>1</sup> Sixteen neonatal deaths have been associated with the use of benzyl alcohol as preservative in saline flush solutions. The deaths occurred in pre-term neonates weighing 2500 gms who had central intravascular catheters flushed periodically each day with bacteriostatic normal saline containing 9 mg/ml benzyl alcohol. Review of the medical records of the **affected infants** resulted in estimates of **daily intake of benzyl alcohol ranging from 99 to 405 mg/kg/day.**<sup>1</sup>

The “**gasping syndrome**”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > **99 mg/kg/day in neonates** and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Benzyl alcohol may also cause hypersensitivity reactions. Contact dermatitis, as well as more generalized allergic symptoms including nausea, fatigue, or angioedema may occur following parenteral administration of benzyl alcohol-preserved products.<sup>2</sup>

### References

<sup>1</sup> Neonatal Deaths Associated With Use of Benzyl Alcohol—United States; CDC; MMWR 1982; 31:290-291

<sup>2</sup> “Inactive” Ingredients in Pharmaceutical Products (RE5046); American Academy of Pediatrics, Pediatrics, Policy statement, Vol.76, No.4; October, 1985, p 635-643

**Comment: The potential nominal maximum exposure for children exceeds the NOEL in animals. Dermal animal studies did not reflect significant toxicity but measured blood levels were low despite exaggerated dermal exposure. Human blood levels of benzyl alcohol from the Clinical Pharmacology Trial were considerably higher than blood level from animals in the Dermal Toxicology Trial despite the fact that there was much less dermal exposure in the human study. This apparent discrepancy may be because the animals had intact skin and the humans were lice infested. Therefore, animal toxicology results may not be able to assuage safety concerns regarding dermal applications of BAL 5%.**

**The maximum nominal dose exposure for children (1440 mg/kg/day) exceeds the toxic exposure (99mg/kg/day) in neonates with severe toxic reactions including death. No severe toxic reactions were observed in clinical trials and one would expect that that actual exposure in this dermal product applied only for 10 minutes two times a week apart should not result significant systemic exposure.**

**However, blood benzyl alcohol levels measured in trial SU-01-2007 are remain of concern. Sponsor will be asked to address this concerning finding regarding blood concentrations of some patients in clinical pharmacology trial since high systemic exposure of benzyl alcohol is know to cause severe toxicity even death.**

2.6 labeling (see Appendix 1 for specific labeling deficiencies communicated to Sponsor in Approvable Letter)

### **3.0 Regulatory Conclusion and Action**

I agree with the conclusions and recommendations of the Review Team that this Application (b) (4) is Approvable based on potential safety, CMC and labeling deficiencies. I will communicate these deficiencies in a regulatory letter to the Sponsor. (See Appendix 1 for text of letter)

## **APPENDIX 1**

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Daniel A. Shames  
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MEDICAL OFFICER  
ODE III Memorandum

## CLINICAL REVIEW 22-129

Application Type	NDA 505(b) (2)
Submission Number	22-129
Submission Code	N000
Letter Date	Jun 15, 2007
Stamp Date	Jun 15, 2007
PDUFA Goal Date	July 15, 2008
Reviewer Name	Gordana Diglisic, MD
Review Completion Date	May 13, 2008
Revision Date:	May 20, 2008
Team Leader	Jill Lindstrom
Project Manager	Melinda Bauerlien
Established Name	Lice Asphyxiator (benzyl alcohol), 5% lotion
(Proposed) Trade Name	Undetermined
Therapeutic Class	pediculicide
Applicant	Summers Laboratories Inc.
Priority Designation	S
Formulation	lotion
Dosing Regimen	two 10-minute applications one week apart
Indication	for patients infected with <i>Pediculus humanis capitis</i> (head lice and their ova) of the scalp hair
Intended Population	six months of age and older



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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The applicant submitted a new drug application for a lotion formulation of benzyl alcohol 5% (5% L.A. (b) (4)) proposed for the topical treatment of head lice (*Pediculosis capitis*) infestation in subjects 6 months of age and older. This product is the first drug product to have benzyl alcohol as an active ingredient (NME). The applicant's product is not marketed in any country.

Two well-controlled Phase 3 trials were conducted with objective of establishing the superiority of two 10 minute application of 5% L.A. one week apart to vehicle. In both Phase 3 trials, 5% L.A. demonstrated superiority over vehicle. Safety data included eight 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. However, the drug substance manufacturing facility has not met the cGMP requirements. Therefore, this NDA is recommended for "Approvable" pending resolution of the cGMP issues.

(  
(b) (4)

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

There is no risk management activities recommended at this time.

#### 1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments

#### 1.2.3 Other Phase 4 Requests

There is no other Phase 4 Request

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Lice Asphyxiator (benzyl alcohol) 5% Lotion, is a topical non-pesticide pediculicide. It is indicated for patients infected with *Pediculus humanus capitis* (head lice) of the scalp hair.

The applicant conducted two identical, adequate and well-controlled Phase 3 clinical trials, SU-01-2005 and SU-02-2005, with the objective to evaluate the safety and efficacy of home-use of two 10-minute treatments of 5% L.A. (one week apart) compared to a vehicle control. Phase 3 clinical trials were conducted in ten U.S. centers and enrolled 628 subjects (250 index subjects used for primary efficacy evaluation), 6 months of age or older.

An open label study (SU-03-2005), enrolled 128 subjects, 6 months of age or older, was conducted to provide additional safety information.

Phase 2 studies which investigated two 10-minute applications of 5% L.A. were included in the pooled safety data base (82 subjects 2 years of age or older).

To be included in the safety population, subject must have had at least one post-baseline assessment. Based on above definition, the safety database includes 478 subjects exposed to 5% L.A. and 336 subjects exposed to vehicle in Phase 2 and Phase 3 clinical studies.

The 5% L.A. is not marketed in any country at this time.

### 1.3.2 Efficacy

Two pivotal trials (SU-01-2005 and SU-02-2005) were conducted with the objective of establishing the superiority of two 10 minute applications of 5% L.A. (one week apart) to vehicle. These trials were adequate and well-controlled; randomized, double-blind, vehicle-controlled, and multi-centered.

Study SU-01-2005 was conducted in five centers across the U.S. and enrolled a total of 306 subjects (125 index subjects used for primary efficacy evaluation). Study SU-02-2005 was conducted in five U.S. centers and enrolled a total of 309 subjects (125 index subjects). The youngest subject from each household who qualify for the study was designated for inclusion in the Primary Treatment Cohort. The Primary Treatment Cohort was the population evaluated for the primary efficacy outcome. A total of five visits were scheduled for each primary cohort subject over the course of the study (approximately 22 days).

The primary endpoint is defined as the percent of subjects who are lice free 14 days after the last treatment (Visit 5, Day 22). The analysis group was pre-specified in the statistical analysis plan to be the intent-to-treat (ITT) population. Results from both studies showed that 5% L.A. was statistically superior to vehicle with p-values below 0.001 in both studies.

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 ITT population which finds 5% L.A. to be statistically superior to vehicle.

The secondary efficacy endpoint, the cumulative proportion of subjects determined to be treatment failure at the second evaluation visit (Visit 3, Day 9, the day after the 2<sup>nd</sup> treatment), also showed that 5% L.A. is significantly superior to vehicle for treatment success ( $p < 0.001$ ).

### 1.3.3 Safety

The safety of 5% L.A. for the treatment of head lice was evaluated in 1,199 subjects. The safety data were collected from Phase 3 clinical trials enrolling 628 subjects, an open label study enrolling 128 subjects, Phase 2 studies enrolling 167 subjects, a Phase 1 single dose bioavailability study enrolling 45 subjects, and a special dermal safety study enrolling 244 subjects.

In Phase 2 and Phase 3 trials, four hundred eighty and five (485) subjects were treated for an infestation of head lice with two 10-minute applications of 5 % L.A. one week apart. In the Phase 2 studies, the minimum age for inclusion was 2 years. In the Phase 3 clinical trials, the minimum age was 6 months. Eighty five (85) subjects aged 6 months to 3 years, 233 subjects aged 4 to 11 years, and 167 subjects aged 12 years or older were treated with 5% L.A.

The safety measurements were assessment of adverse events and skin/scalp/eye evaluation.

To be included in the safety population, subjects must have had at least one post-baseline assessment. Base upon above definition, safety population included 478 subjects exposed to 5% L.A. and 336 subjects exposed to vehicle.

A total of 23 (4.8%) subjects, from the 478 subjects treated with 5% L.A., experienced adverse events compared to 6 (1.8%) subjects of the 336 subjects treated with vehicle control. Four subjects had 5 adverse events that were considered related to the treatment with 5% L.A. and one subject had an adverse event that was considered related to vehicle control.

Three adverse events in the 5% L.A. treated subjects were relevant to treatment with 5% L.A.: eye irritation, eye exfoliation, and application site irritation. The most frequent adverse event in group treated wit 5 % L.A. was nasopharyngitis (5 subjects exposed to active, and 1 subject treated with vehicle).

The higher rate of adverse events reported in the 5% L.A group may be been due to the longer duration of follow-up among the subjects treated with 5% L.A. Most subjects treated with vehicle control were treatment failure at the first evaluation visit and discontinued to follow up from the study.

All adverse events in either treatment group occurred at the frequency of less than 2%.

The only signs /symptom which tended to worsen with 5% L.A. treatment compared to vehicle was pruritus. At the first evaluation visit 12% of subjects treated with 5% L.A. with no pruritus prior to treatment, had mild pruritus compared to 3% of subjects treated with vehicle control. At second evaluation visit 6% of the subjects treated with 5% L.A. with no pruritus prior to treatment, had mild pruritus compared to 0% of subjects treated with vehicle control.

The most frequently reported signs/symptoms in the 5% L.A. treatment group were “Application site irritation” (11 events, 2.3%), “Application site anesthesia” and “Hypesthesia” combined (10 events, 2.0%), and “Pain” (5 events, 1%).

The most frequently reported sign/symptom in the vehicle treatment group was paresthesia (4 events, 1.2%).

No deaths occurred during the development program of 5% L.A.

No serious adverse events were reported during the development program of 5% L.A.

One subject was withdrawn from the study due to an adverse event.

Four pregnant subjects were enrolled in Phase3 clinical trials. Two subjects were randomized to vehicle control and two subjects were randomized to 5% L.A. treatment group. No adverse events were reported. No follow-up of these pregnancies was performed. See section 8.3

#### 1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for Lice Asphyxiator 5% lotion is two 10-minute applications one week apart for patient  $\geq 6$  months of age. This is the dosage regimen that was studied in the Phase 2 and Phase 3 safety and efficacy trials.

#### 1.3.5 Drug-Drug Interactions

Not applicable

#### 1.3.6 Special Populations

The only intrinsic factor considered relevant for the studies of 5% L.A. was age of the subjects. 5% L.A. was studied in subjects 6 months of age and older. This is appropriate as head lice (*Pediculus capitis*) infestation is common in the United States among children 3 to 12 years of age<sup>1</sup>. The percent of lice free subjects at Day 22 treated with 5% L.A. does not show any trends with higher efficacy in any of the age subgroups. Subgroup analysis of safety revealed that younger children (age group - 6 month to 3 years) are not at greater risk of developing adverse events. Most adverse events occurred in older children and adults.

Both race and gender were reflective of the U.S. population and disease prevalence. The majority of subjects enrolled in Phase 3 clinical trials were Caucasian and Hispanic females, consistent with the population most frequently identified with lice infestation.

Primary efficacy results were similar between females and males in both pivotal trials. However, both studies showed lower response rates in Hispanic subjects than in other races. Subgroup analysis of safety data did not reveal trends on gender or race (although numbers were too limited for adequate assessment).

Pregnant and/or nursing women were not excluded from Phase 3 trials.

- These demographics are consistent with the epidemiologic data published by U.S. Center for Disease Control (“females are infested more often than males...African-American are rarely infested with head lice”<sup>7</sup>).
- Head lice infestation occurs more common in girls and less common in African American children<sup>2, 3, 4</sup>.
- The lower prevalence rate in African American population is thought to be the result of difference in the structure of the hair shaft, which may be oval shaped and therefore more difficult for louse to grasp.<sup>2, 3, 4</sup>
- Girls are at higher risk of head louse infestation than boys because of social behavior (e.g., social acceptance of close physical contact; sharing of hats, combs, hair ties).<sup>5, 6</sup>

Reference:

- <sup>1</sup> Pediatrics, American Academy of Pediatrics, Vol. 110 No.3 September 2002, pp. 638-643; B.L. Frankowski, MD, MPH, L.B. Weiner, MD
- <sup>2</sup> J Pediatr Health Care, 2005 Nov-Dec; 19(6):369-73; Pediculosis capitis; Leung AK, Fong JH, Pinto-Roias A; Department of Pediatrics, the University of Calgary, Canada
- <sup>3</sup> Rev Saude Publica, 2005 Jun; 39(3):438-43. Epub 2005 Jun 30; Pediculosis capitis infestation according to sex and social factors in Argentina; Catala S et al.
- <sup>4</sup> J Sch Nurs, 2000 Aug; 16(3):32-8; Pediculosis in school population; Estrada JS; San Diego State University, CA, USA
- <sup>5</sup> Recommendations for the treatment of pediculosis capitis (head lice) in children. University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program. 2002. Available at: <http://www.guideline.gov/guidelines/FTNGC-2451.html>. Accessed on June 17, 2004
- <sup>6</sup> Meinking T, Taplin D. Infestations. In: *Pediatric Dermatology*. 3rd ed. Schachner LA, Hansen RC, eds. Edinburgh: Mosby; 2003:1141-1180.
- <sup>7</sup> Center for Disease Control (2005, August 18) Fact sheet: Treating head lice, Department of Parasitic Disease.



## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Lice Asphyxiator (benzyl alcohol), 5% lotion is a topical, non-pesticide pediculicide. The active ingredient in Lice Asphyxiator is benzyl alcohol and it is the first drug product to have benzyl alcohol as an active ingredient (NME).

Lice Asphyxiator act by stunning the respiratory spiracles of human head lice open, permitting blockage of the spiracles and asphyxiation.

The proposed indication for Lice Asphyxiator (benzyl alcohol), 5% Lotion is treatment of patients (6 months of age and older) infected with *Pediculus humanis capitis* (head lice and their ova) of the scalp hair.

The lotion is to be applied to dry hair, to completely cover and wet all hair and the entire scalp, and to remain for 10 minutes. Treatment must be repeated in one week.

The sponsor has proposed the trade names (b) (4) and (b) (4). However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommended the use of the proposed proprietary names from a promotional perspective because the names overstate the efficacy of the drug product.

### 2.2 Currently Available Treatment for Indications

Head lice (*Pediculosis capitis*) infestation is common in United States among children 3-12 years of age; approximately 6-12 million have infestation each year.<sup>1</sup>

Persons from all social and economic background can become infested with head lice, and infestation can reach epidemic proportion, especially among schoolchildren. Lice are transferred by close contact and possibly by sharing of hats, combs, and brushes. The major complaint of person affected with head lice is severe pruritus of the scalp. Scratching leads to excoriation and secondary bacterial infection.<sup>2</sup>

Therapeutic options include 1% Lindane shampoo/lotion, pyrethrins with piperonyl butoxide solution, 1% permethrin cream rise, and 0.5% malathion lotion.

Lindane is the pediculicide that requires a prescription. Lindane shampoo should be only used in patients who cannot tolerate or have failed first-line treatment with safer medication for treatment of lice (boxed Warnings, PI).

Lindane (γ-benzene hexachloride), an organochloride pesticide, noncompetitively inhibits the γ-amino butyric acid (GABA) receptor, which typically binds GABA, an inhibitory neurotransmitter. Seizures and deaths have been reported following Lindane shampoo use with repeat or prolong application, but also in rare cases following a single application according to directions (boxed Neurologic Toxicity, PI). Infants, children, the elderly, and individuals with other skin condition and those weigh < 110 lbs (50kg) may be at greater risk of serious neurotoxicity (Warnings, PI).

Permethrin, pyrethrum, pyrethrins, and pyrethroids are over-the-counter (OTC) pediculicides.

They affect voltage-gated sodium channels, causing delayed repolarization of the neuron by impeding sodium channel closure. Rare cases of asthma exacerbation and even death have been reported in individuals with ragweed allergy after using pyrethrin-based products.<sup>3</sup> Genetic resistance to pyrethroids is widespread in both the United States and abroad.<sup>4</sup>

Malathion is an organophosphate insecticide that requires a prescription. In the louse, malathion is converted to malaoxon, which irreversibly inhibits acetylcholinesterase. The major concerns are the high flammability of the malathion formulation, and the risk of respiratory depression if accidentally ingested.

In addition, several products are used off label when the above products are not effective or contraindicated. Two such therapies are oral ivermectin and oral trimethoprim/sulfamethoxazole. Non-pharmacologic approaches involve occlusion therapy (e.g. vinegar, mayonnaise, petroleum jelly, and olive oil), nit combing, and hair removal.

References:

<sup>1</sup>American Academy of Pediatrics; Pediatrics; Vol. 110 No. 3, September 2002, pp.638-643

<sup>2</sup>Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, Vol. 2, 2972, 2000

<sup>3</sup>Wax PM, Hoffman RS; Fatality associated with inhalation of pyrethrin shampoo. J. Toxicol Clin Toxicol. 1994; 32:457-460

<sup>4</sup>Therapy for Head lice Based on Life Cycle, Resistance, and Safety Consideration; M. Lebwohl, L Clark and J Levitt; Pediatrics, Vol. 119 No.5 May 2007, pp. 965-974

## **2.3 Availability of Proposed Active Ingredient in the United States**

Benzyl alcohol is used as a bacteriostatic preservative and excipient in parenteral (IV) solutions/medication and topical drug products such as Bacteriostatic Water for injection, Solution (0.9% benzyl alcohol), Doxapram IV injection (0.9% benzyl alcohol), Cordarone IV (20.2 mg benzyl alcohol/ml), Somatropin for injection (0.9% benzyl alcohol), Cipro® HC OTIC suspension (9 mg/ml), Cyclocort®, Amcinonide (2% benzyl alcohol).

Benzyl alcohol is also used in wide variety of cosmetic formulations as a fragrance component, preservative, solvent, and viscosity-decreasing agent. Benzyl Alcohol was considered safe up to 10% for use in hair dyes.<sup>1</sup>

References

<sup>1</sup>Nair B. ; Int J Toxicol. 2001; 20 Suppl 3:23-50; Cosmetic Ingredient Review Expert Panel, Washington, DC 20036, USA.

## **2.4 Important Issues with Pharmacologically Related Products**

Sixteen neonatal deaths have been associated with the use of benzyl alcohol as preservative in saline flush solutions. The deaths occurred in pre-term neonates weighing 2500 gms who had central intravascular catheters flushed periodically each day with bacteriostatic normal saline containing 9 mg/ml benzyl alcohol. Review of the medical records of the affected infants resulted in estimates of daily intake of benzyl alcohol ranging from 99 to 405 mg/kg/day.<sup>1</sup>

The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Benzyl alcohol may also cause hypersensitivity reactions. Contact dermatitis, as well as more generalized allergic symptoms including nausea, fatigue, or angioedema may occur following parenteral administration of benzyl alcohol-preserved products<sup>2</sup>.

References

<sup>1</sup>Neonatal Deaths Associated With Use Of Benzyl Alcohol—United States; CDC; MMWR 1982; 31:290-291

<sup>2</sup>“Inactive” Ingredients in Pharmaceutical Products (RE5046); American Academy of Pediatrics, Pediatrics, Policy statement, Vol.76, No.4; October, 1985, p 635-643

## 2.5 Presubmission Regulatory Activity

Lice Asphyxiator (benzyl alcohol), 5% lotion was developed under one Investigational New Drug application, IND 50, 076, submitted on November 6, 2003.

**Table 1: Presubmission Regulatory Activity**

Date of Meeting	Type of Meeting	Meeting Objective
07/22/02	Type B: Pre-IND	Provide the general purpose on the content and format of the proposed new Investigational New Drug Application, pursuant to 21 CFR 312.
09/09/04	Type B: End of Phase 2	The objectives of the meeting were to agree upon the proposed CMC, toxicology, and clinical plans to support an NDA submission for Summers Lice Asphyxiator (L.A.) for the treatment of head lice.

08/08/05	Type A	The objective of the meeting was to agree upon revisions in the study protocols, including changing the design to a superiority trial with placebo control, with rapid evaluation and rescue treatment for defined treatment failures.*
03/12/07	Type B: Pre-NDA	To agree on the chemistry, manufacturing and controls and clinical requirements to support an NDA submission for Lice Asphyxiator (benzyl alcohol), 5% (b) (4) and to agree on the electronic submission proposal.

\* A **Special Protocol Assessment** request was submitted on April 6, 2005. This Type A meeting was held at the Sponsor's request to discuss the Agency's response (from May 18, 2005)

**Pre-IND Meeting:** July 22, 2002

- During the meeting, the sponsor stated that they identified the mineral oil (b) (4)
- Phase 3 trial should be multi-centered, geographically diverse, randomized, and demonstrate superiority to RID, using RID as label.
- Comments on Topical Safety Studies

**End of Phase 2 Meeting:** September 9, 2004

- The sponsor had identified benzyl alcohol as the active ingredient and mineral oil as an excipient.
- The sponsor is advised to conduct an *in vivo* bioavailability study in about 12 patients to monitor exposure of the active ingredient under the maximal usage conditions in the patients using the highest strength of the final 'to-be-marketed' formulation.
- Two independent pivotal trials, that would be representative of the population in the US that would use the drug, will be needed to establish efficacy.
- The sponsor is requested to actively assess for local safety by evaluating cutaneous and ocular irritation within 24 hours of treatment. Safety evaluation for Phase 3 study protocols should include laboratory assessments.
- While it may be reasonable to exclude patients less than two years of age in early studies, these patients may be infested with lice and should not be excluded from Phase 3 trials.

- The primary efficacy variable is the presence of live lice. The primary efficacy endpoint is treatment success, defined as the absence of live lice. The primary time point for efficacy evaluation is 14 days after the second treatment.
- Study procedures in Phase 3 trials should conform as closely as possible to expected real-world use.
- The study objective should be the superiority of Lice Asphyxiator to RID.
- The Division recommended that the ITT population be defined as all randomized patients who are dispensed drug medication, regardless of having any post-baseline outcomes. The proposed missing data handling based on the last observation carried forward (LOCF) is acceptable.
- The regulatory pathway was identified by Agency as a 505(b)(1).

### **Special Protocol Assessment (SPA)**

The design of the two pivotal studies was the subject of a Special Protocol Assessment (SPA) procedure, originally submitted on April 6, 2005 (FDA letter dated May 18, 2005), a Type A meeting August 8, 2005 to discuss the Agency's feedback on the study design, and a second Special Protocol Assessment submitted September 19, 2005 (FDA letter dated November 2, 2005):

- Primary efficacy endpoint is the absence of live lice 14 days after the second treatment.
- Demonstration of a clinically meaningful superiority over vehicle, that is, at least 30 percent difference.
- Study of a geographically diverse study population representative of the population expected to use the product.
- Subjects to be evaluated for efficacy must have at least three live lice.
- For safety analysis, inclusion of at least 80 subjects 6 months to 3 years of age and 100 subjects 4 to 12 years of age.
- No exclusion of pregnant women.
- Evaluation of skin and ocular irritation as a safety measure the day after treatment.

### **Guidance Meeting: August 8, 2005**

- The sponsor stated that their proposed trials would offer rescue therapy within a day of determination of failure of either placebo or Lice Asphyxiator. The Agency then stated that three options exist for establishing efficacy provided that the ethical concerns related to vehicle controlled studies are addressed:
  1. One three arm study with two success criteria; L.A. demonstrates superiority to vehicle as well as non-inferiority to either RID or NIX. The latter comparison is with the product as it is currently labeled. If this option is elected, the data need to be convincing. The sponsor is referred to the FDA Guidance for Industry, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."
  2. Two separate trials; L.A. demonstrates superiority to RID or NIX in both trials.
  3. Two separate trials; L.A. demonstrates superiority to vehicle in both trials.

- The sponsor agreed to study a total of 80 safety-evaluable patients between 6 months to 3 years, and 100 safety-evaluable patients, 3 to 11 years of age. The Agency pointed out that a different safety profile may be seen in infested patients who are symptomatic versus those infested patients who are not symptomatic. The Agency would prefer that the safety database include infested symptomatic patients.
- Primary efficacy endpoint is treatment successes, defined as the absence of live lice at 14 days after final treatment.
- Agency agreed with randomization by household. Members of household who meet enrollment criteria may receive the same treatment as the index patient but should only be included in safety evaluations.
- Safety will be assessed through the monitoring of the adverse events. All subjects who receive at least one dose of study treatment will be included in the safety analysis.
- Subjects will be monitored for skin and eye irritation on Visit 2(Day2) and 4 (Day9), one day after the first and second treatments.
- The sponsor is advised that human pharmacokinetic data will be necessary under maximal use condition.
- The sponsor is requested to complete non-clinical reproductive toxicology studies prior to the initiation of Phase 3 trials.

**Pre-NDA Meeting:** March 12, 2007

- The sponsor is advised that animal study will not suffice as the evidence to permit a biowaiver. An *in vivo* bioavailability study in humans is necessary.
- A complete protocol for the pharmacokinetic (PK) study in patients (with an appropriate number of patients in different age group) should be submitted to the Agency for review no later than 2 months after receipt of Pre-NDA Meeting minutes. The PK study should be initiated no later than 4 months after receipt of Pre-NDA Meeting minutes.
- Case Report Forms (CRFs) should be submitted from the pivotal trials for all Serious AEs, all Severe AEs, and all patients who discontinued for whatever the reason (not just because of adverse events).
- Narrative summaries should be submitted for deaths, dropouts, and serious AEs.

**IND 50,076 Submission 033:**

On April 12, 2007 the sponsor, Summers Laboratories, submitted serial 33 which includes a request for waiver of human bioavailability requirements based on the sponsor's 21CFR Part 320.24 provides alternative methods for evaluating bioavailability for topical products. This issue was discussed with the Clinical Pharmacology Group and the Agency finds that the sponsor's request for waiver of an *in vivo* PK study to determine the systemic exposure under maximal use conditions cannot be granted because although 21CFR Part 320.24 allows different methods for evaluating bioavailability, systemic exposure *in vivo*, if feasible, of topical products needs to be determined for purposes of safety assessment. Actual data is needed since the extent of percutaneous absorption depends upon such factors as the formulation and skin conditions.

**Comments conveyed to sponsor via Fax on May 18, 2007:**

The sponsor's request for waiver of an *in vivo* PK study to determine the systemic exposure under maximal use conditions cannot be granted because of the following reasons:

1. The purpose of determining systemic exposure for a topical drug product is for safety assessment. This is needed for all topical drug products because clinical trials have their limitations in detecting safety signals, especially when the sample size is small. The fact that 21CFR Part 320.24 allows different methods for evaluating bioavailability does not negate the importance of this need, especially in this case when there was no systemic safety monitoring in the Phase 3 trials.
2. The extent of percutaneous absorption depends on the formulation and skin conditions among other factors. In this case, hair follicles may serve as a pathway for percutaneous absorption. For safety assessment, we need actual data and not the best guess.

## **2.6 Other Relevant Background Information**

This is a new formulation of benzyl alcohol and is not approved in any country.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

From the Chemistry review:

"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required. However, the drug substance manufacturing facility has not met the cGMP requirements. Therefore, from a CMC perspective, this NDA is recommended for "Approvable" pending resolution of the cGMP issues."

The following table lists the composition of the drug product:

**Table 2: Composition of the 5% L.A. lotion**

Name of ingredients	% (w/w)	Unit Quantity (g)	Function	Compendial grade
<b>Drug Substance</b> Benzyl Alcohol	5.00	(b) (4)	Active substance	NF
<b>Excipients</b> Purified Water	(b) (4)		(b) (4)	USP
Mineral Oil (b) (4)				NF
Sorbitan Monooleate				NF
Polysorbate 80				NF
Carboxypolymethylene (Carbomer 934P)				NF
Trolamine				NF
<b>Total weight</b>	100.00			

(Chemistry Review; Tarun Mehta, M.Sc.)

### 3.2 Animal Pharmacology/Toxicology

From the pharmacology/toxicology review:

“Results from 13 week repeat dose oral rat and mouse toxicology studies conducted by the National Toxicology Program suggest that high doses of benzyl alcohol could be neurotoxic. However, it is not anticipated that high systemic doses of benzyl alcohol will be achieved after clinical use of the lice asphyxiator drug product. No systemic toxicity was noted in 2 week repeat dose dermal toxicology studies conducted with up to 15% lice asphyxiator drug product in rats and dogs. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after 2 weeks of repeat dermal exposure (6 hours/day).

Benzyl alcohol elicited a positive response in some in vitro genetic toxicology assays and a negative response in other in vitro genetic toxicology assays. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400 mg/kg benzyl alcohol) or mice (doses up to 200 mg/kg benzyl alcohol) conducted by the National Toxicology Program. Benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in systemic rat and rabbit embryofetal development studies.”



## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The Sponsor's NDA submission was the primary source data used in this review.  
Source of the clinical data were trials conducted by the applicant.

### 4.2 Tables of Clinical Studies

**Table 3: Descriptions of Clinical Studies**

Type of Study	Study Identifier	Location of Study Report	Objective Of the Study	Study Design and Type of Control	Test Product, Dosage Regimen, Route of Administration	Number Of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status/ Type of Report
<b>Bioavailability</b>	SU-01-2007	Module 5, Section 5.3.1.4.	Evaluate the bioavailability of benzyl alcohol in final formulation of 5% L.A. in subjects with head lice infestation	Single center, randomized, open label evaluation of the absorption of benzyl alcohol in subjects with head lice infestation.	5% L.A. applied topically in sufficient quantity to fully saturate the hair	45  9 subjects per age cohorts -10 min Tx And 6 subjects per age cohorts- 30 min Tx	Patients infested with <i>Pediculus capitis</i>	A single application of L.A. 5%, randomly assigned to either a 10 minute or 30 minute application	Complete; Full
<b>Efficacy</b>	SU-02-2003	Module 5, Section 5.3.5	Safety and efficacy of two concentrations of L.A.	Single center, randomized, observer blinded, open label, placebo and active controlled	5% L.A., 10% L.A., vehicle, RID shampoo; two 10-minute applications one week apart, topically applied to the hair	81	Patients infested with <i>Pediculus capitis</i>	10-minute treatment, repeated in one week if still infested	Complete; Full
<b>Efficacy</b>	SU-02-2003A	Module 5, Section 5.3.5	Safety and efficacy of two treatment durations, 10-minute or 30-minute	Single center, randomized, evaluator masked	5% L.A., two applications one week apart of 10 minutes or 30 minutes duration, topically applied to the hair	44	Patients infested with <i>Pediculus capitis</i>	10-minute or 30-minute applications, repeated in one week if still infested	Complete; Full

<b>Efficacy</b>	SU-02-2004	Module 5, Section 5.3.5	Establish the minimum effective dose	Single center, randomized, Evaluator controlled	1% L.A., 2.5% L.A., 5% L.A. two applications one week apart, topically applied to the hair	42	Patients infested with <i>Pediculus capitis</i>	10-minute applications one week apart	Complete; Full
<b>Efficacy</b>	SU-01-2005	Module 5, Section 5.3.5	Efficacy and safety of Home-use	Multicenter, double blind, randomized, placebo controlled	5% L.A., or Vehicle, two 10-minute applications one week	Primary Cohort = 125, Secondary Cohort = 189	Patients infested with <i>Pediculus capitis</i>	10-minute applications one week apart	Complete; Full
<b>Efficacy</b>	SU-02-2005	Module 5, Section 5.3.5	Efficacy and safety of home-use	Multicenter, double blind, randomized, placebo controlled	5% L.A. or Vehicle, two 10-minute applications one week apart, topically applied to the hair	Primary Cohort = 125, Secondary Cohort = 189	Patients infested with <i>Pediculus capitis</i>		Complete; Full
<b>Safety</b>	SU-03-2005	Module 5, Section 5.3.5	Safety of Home-use	Multicenter, open label	5% L.A., two 10-minute applications one week apart, topically applied to the hair	128	Patients infested with <i>Pediculus capitis</i>		Complete; Full
<b>Safety</b>	SU-01-2006	Module 5, Section 5.3.5	Combined skin irritation and sensitization	Single center, double blind, placebo controlled, within-subject randomized	5% L.A., vehicle, 0.9% sodium chloride, 0.4% sodium lauryl sulfate	Group 1 = 46 Group 2 = 198	Healthy subjects	<u>Induction:</u> Group 1: 21-daily patch applications; Group 2: 9 patch applications 3 times per week; <u>Challenge:</u> Groups 1 and 2: 1 challenge patch application	Complete; Full

Source: Sponsor's NDA submission: Section 5.2

### 4.3 Review Strategy

The review of efficacy was based primarily on two pivotal Phase 3 trials, SU-01-2005 and SU-02-2005, in 126 subjects, aged 6 months or older. These were double blind, placebo (vehicle) controlled, randomized, multi-center studies. Supportive efficacy data were provided from multi-center, open label study, SU-03-2005, enrolling 128 subjects, aged 6 months and older. The Phase 2 studies, SU-02-2003, SU-02-2003A, and SU-02-2004), also provide supportive evidence of efficacy. These Phase 2 studies differed from the pivotal studies in that efficacy was evaluated 15 days after the first treatment, while pivotal studies were evaluate 15 days after the second treatment.

The review of safety is based on data from two pivotal Phase 3 trials, SU-01-2005 and CU-02-2005, enrolling 615 subjects, aged 6 months or older, an open label study enrolling 128 subjects (SU-03-2005), Phase 2 studies enrolling 167 subjects, aged 2 years and older (SU-02-2003, SU-02-2003A and SU-02-2004), and a special safety study (dermal safety study) enrolling 244 healthy subjects (SU-01-2006).

#### **4.4 Data Quality and Integrity**

Four sites were identified for a DSI inspection. The site and reason for inspection are listed as the following:

- Site 01: Terri Meinking and Heather Woolery Lloyd in Miami, FL.  
Reason: All household members were enrolled on the same date.
- Site 02: Ann Lucky in Cincinnati, OH.  
Reason: This site had nearly 100% response rate for 5% L.A. and 0% for the vehicle control.
- Site 06: Anton Duke in Little Rock, AR.  
Reason: The treatment effect in this site was close to zero which was unlike any other site.
- Site 12: Barry Collins in Pell City, AL.  
Reason: The site has unusually high response in the vehicle control.

The conclusion was as follows: “No significant observations of noncompliance were noted. The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.”

#### **4.5 Compliance with Good Clinical Practices**

The protocol and Informed Consent Forms were reviewed by the Investigational Review Board (IRB) associated with the study site, and approved prior to study initiation. Per the clinical study reports, subjects or subject’s parent or legal guardian signed informed consent form prior to enrollment into the study. The sponsor stated that all studies were conducted in accordance with Good Clinical Practice (GCP) requirements.

#### **4.6 Financial Disclosures**

The applicant certified (Form 3453) that they had not entered into any financial arrangement with any of the clinical investigators.

## 5 CLINICAL PHARMACOLOGY

The applicant submitted one study, SU-01-2007, to support the clinical pharmacology of 5% L.A. lotion.

The objective of this single center, randomized, open label study of 45 patients with head lice infestation, was to assess the systemic exposure of benzyl alcohol in 5% L.A. lotion following a single 10-minute application or single 30-minute application. The patients were stratified into three age cohorts as follows: 6 months to 3 years, 4 to 11 years, or 12 years and older. For the 10-minute treatment group, 9 subjects were stratified to each of the three age cohorts and for the 30-minute treatment group 6 subjects were stratified to each age cohort.

### 5.1 Pharmacokinetics

From the Clinical Pharmacology Review:

“Following the 10-minute-normal application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.00 to 108.3mcg/mL were observed in 15 of the 27 patients between 0.5 hrs and 3 hrs post-treatment across all 3 cohorts. The highest concentration observed was 108.3 mcg/mL at 3 hours post-treatment in an 11 year old male Caucasian patient with short hair (used 4 oz of L.A. 5% (b) (4))

Following the 30-minute exaggerated application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.18 to 131.3 mcg/mL was observed in 10 of the 18 patients between 0.5 hrs and 12 hrs post-treatment across all 3 cohorts. The highest concentration observed was 131.3 mcg/mL at 12 hours post-treatment in a 7 year old female Caucasian patient with short hair (used 8 oz of L.A. 5% (b) (4)) Although one patient (subject 002, 10 month old, male Caucasian patient with short hair (used 4 oz of L.A. % (b) (4)) had a plasma concentration value of 324.3 mcg/mL at 6 hours posttreatment, this value is being interpreted with caution due to poor sampling techniques during the collection of this blood sample.

Plasma concentrations of benzyl alcohol observed following the 10-minute and 30-minute application were generally comparable for the 6 months to 3 year old and 4 to 11 year old patients. Therefore, it does not appear that the longer (3-fold) contact time resulted in a proportional increase in systemic exposure in this patient population. In contrast, the plasma concentrations observed in the 12 years and older cohort was higher (up to ~16 fold) following the 30-minute application compared to the 10-minute application. The number of subjects (N=3) with quantifiable plasma concentrations of benzyl alcohol in the 12 years and older cohort is so small that it is difficult to really draw any definite conclusions from this data.

No pharmacokinetic parameters were obtained due to the low levels of exposure and the paucity of the data observed in the study.

Although the head lice infestation of the patients was consistent with that of the patients included in the phase 3 clinical trials, it was noted that none of the patients included in the PK study had long hair. This indicates that the systemic exposure of benzyl alcohol in patients with long hair was not evaluated in this PK study. However, since the highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair after a 10-minute normal application and an exaggerated 30-minute application, it does not appear that the level of systemic exposure is dependent on the length of the hair.

In addition, in the clinical trials there was only one patient (Caucasian, 5 year old, female, patient with medium length of hair) who was identified as having a possibly drug related systemic effect.

Distribution: No Pharmacokinetic studies evaluating the distribution of benzyl alcohol was conducted.

Metabolism: No pharmacokinetic studies evaluating the metabolism of benzyl alcohol was conducted. However, it is reported in the literature that benzyl alcohol is oxidized by alcohol dehydrogenase in the liver to benzoic acid. Benzoic acid is then conjugated with glycine to form hippuric acid.<sup>1</sup>

Excretion: No pharmacokinetic studies evaluating the excretion of benzyl alcohol was conducted. However, it is reported in the literature that following administration of an oral dose of 1.5 g to humans, 75 % to 85 % was eliminated in the urine as hippuric acid within 6 hours after administration<sup>1</sup>. Benzyl alcohol plasma half-life was reported as 1.5 hours in dogs receiving intravenous doses<sup>2</sup>. No information on the half-life in man was available.

Reference:

<sup>1</sup> Clayton GD & Clayton FE: Patty's Industrial Hygiene and Toxicology, Volume 2D, Toxicology, 4th ed, John Wiley & Sons, New York, NY, 1994, pp 2590-2591;2704-2707.

<sup>2</sup> Kimura ET, Darby TD, & Krause RA: Parenteral toxicity studies with benzyl alcohol. Toxicol Appl Pharmacol 1971; 18:60-68.

## **5.2 Pharmacodynamics**

The applicant did not conduct pharmacodynamic studies.

## **5.3 Exposure-Response Relationships**

The optimal treatment regiment (concentration, duration of application, and number of application) was determined in three Phase 2 studies (SU-02-2003, SU-03-2003A and SU-02-2004).

See section 6 and 7.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The proposed indication for Lice Asphyxiator (benzyl alcohol) 5% lotion is for the treatment of head lice (infestation of *Pediculus humanis capitis* and their ova).

#### 6.1.1 Methods

The primary data used to support the application were from two pivotal Phase 3 clinical studies, SU-01-2005 and SU-02-2005. Supportive efficacy data were provided from open label study, SU-03-2005, and Phase 2 studies, SU-02-2003, SU-02-2003A, and SU-02-2004.

In pivotal Phase 3 clinical trials, open label study and SU-02-2004, subject received two 10-minute treatments one week apart. In Phase 2 studies, SU-02-2003 and SU-02-2003A, subjects received 10-minute treatment, repeated in one week if still infested with live lice.

Phase 2 studies differed from the pivotal studies in that efficacy was evaluated 15 days after the first treatment, while pivotal studies were evaluate 15 days after the second treatment.

**Table 4: Summary of Studies Providing Efficacy Information**

Study Number	Study Objective	Study Design & Type of Control	Test Product(s)	Dosage Regimen	Number of Subjects
<b>Pivotal trials</b>					
SU-01-2005	Evaluate the efficacy and safety of home-use of two-10 minute treatment of 5% L.A. (applied one week apart)	Double blind, randomized, placebo controlled	5% L.A. Vehicle control	Two 10 minute Application one week apart	Primary Cohort N = 125  Secondary N = 189
SU-02-2005	Evaluate the efficacy and safety of home-use of two-10 minute treatment of 5% L.A. (applied one week apart)	Double blind, randomized, placebo controlled	5% L.A. Vehicle control	Two 10 minute Application one week apart	Primary Cohort N = 125  Secondary N = 189
<b>Supporting Studies</b>					
SU-03-2005	Evaluate the efficacy and safety of home-use of two-10 minute treatment of 5% L.A. (applied one week apart)	Open label	5% L.A.	Two 10 minute Application one week apart	N = 128

SU-02-2003	Evaluate the safety and efficacy of two concentration of LA in comparison with vehicle placebo and an active control	Randomized, observer blinded, open label	5% L.A.  10% L.A.  Vehicle  RID shampoo	10 minute application at Visit 1. L.A. and vehicle were applied one week later if live lice were found. RID was applied twice	N = 81
SU-02-2003A	Evaluate the safety and efficacy of 5% L.A. at two duration of application time (10- minute and 30-minute) regiments for the treatment of head lice	Randomized, observer blinded, open label	5% L.A.	Two 10 or 30 minute application one week apart	N = 44
SU-02-2004	Determine the minimum effective dose of L.A. for the treatment of head lice	Randomized, observer blinded, open label	2.5% L.A.  5% L.A.	Two 10 minute application one week apart	N = 42

Source: Sponsor's NDA submission: ISE Section 5.3.5.3.1.2; Summary of Clinical Efficacy 2.7.3 – Table (2.7.3.2)1

### 6.1.2 General Discussion of Endpoints

The applicant was advised at the Pre-IND and End-of Phase 2 meeting that the primary efficacy variable is the presence of live lice, the primary efficacy endpoint is treatment success, defined as the absence of live lice, and the primary time point for efficacy evaluation is 14 days after the second treatment.

Additionally, the applicant was further advised to modify inclusion criteria such that patients must have an active infestation with *Pediculus capitis*, the human head louse, with presence of nits and at least three live lice at baseline (Special Protocol Assessment response letter May 18, 2005).

### 6.1.3 Study Design

**Pivotal Studies:** Protocol Number SU-01-2005 and SU-02-2005

The pivotal studies, SU-01-2005 and SU-02-2005 were identical in design, but were conducted independently at five study sites each.

**Title:** A Multi-center, Randomized, Vehicle Controlled, Double Blind Clinical trial to Evaluate the Efficacy and safety of Summers Non-Pesticide Lice Asphyxiator (L.A.) for the treatment of Head Lice

Investigators

**Table 5: Investigators for Study SU-01-2005**

Site	Investigator	Study site
01	Terri Meinking and Heather Woolery Lloyd, MD	Global Health Associates of Miami 7800 S.W. 57th Avenue - Suite 219E South Miami, FL 33143
02	Anne Lucky, MD	Dermatology Research Associates 7691 Five Mile Road, Suite 312 Cincinnati, OH 45230
03	Jon Thomas, MD	Alegent Health 715 Harmony Street, 2nd Floor Council Bluffs, IA 51503
04	E.A. Clark, MD Anita Scribner, MD, MPH	DCOL Center for Clinical Research 707 Hollybrook Drive, Suite 501 Longview, TX 7560
05	Peter E. Silas	Wee Care Pediatrics 1580 West Antelope Drive, Suite 100 Layton, UT 84041

Source: Sponsor's NDA submission ISE Section 5.3.5.3.1.

**Table 6: Investigators for Study SU-02-2005**

Site	Investigator	Study Sites
06	Anton Duke, MD	Arkansas Pediatric Clinic 500 S. University, Suite 200 Little Rock, AR 72205
07	Brayan M. Harvey, MD	Harvey Pediatrics 623 E. Matthews Ave, #2B Jonesboro, AR 72401-3145
08	Leonard Swinyer, MD	Dermatology Research Center 3920 S. 1100 East, Suite 210 & 310 Salt Lake City, UT 84124
09	Stacy R. Smith, MD	Therapeutics Clinical Research 9025 Balboa Avenue, Suite 105 San Diego, CA 92123
10	Stephan Miller, MD*	8431 Fredericksburg Road, Suite 100 San Antonio, TX 78229
12	Barry Collins, MD	Advanced Clinical Research, LLC 2107 Martin St. South, Suite 103 Pell City, AL 35128

\* Dr Miller did not enroll any subjects

Source: Sponsor's NDA submission ISE Section 5.3.5.3.1.

The Phase 2 studies were conducted at a single center.

**Objective:**

The objective of the studies was to evaluate the efficacy and safety of home-use of two 10-minute treatments of 5% L.A. (applied one week apart) compared to a vehicle control (5% L.A. vehicle without the active ingredient).

**Overall study design:**

Two pivotal clinical studies were double-blind, placebo (vehicle) controlled, randomized, multi-center studies involving subjects 6 months of age or older with active infestation of the human head lice. Qualified subjects who met the inclusion/exclusion criteria were enrolled into the study. The youngest subject from each household who qualified with at least three live lice was



designated as the Primary Treatment Cohort. Any other household members who qualified and resided with the randomized subject were asked to participate and designated the Secondary Treatment Cohort. A total of five visits were scheduled over the course of the study: screening visit (Visit 1, dispensing of clinical test materials), two evaluation visits (Visits 2 and 3, the day after the 1<sup>st</sup> and 2<sup>nd</sup> home treatments) for all subjects, and two follow-up visits for the Primary Cohort subjects for efficacy and safety evaluations (Visits 4 and 5, Day 15 and Day 22).

### **Protocol:**

#### **Inclusion Criteria:**

1. Males and females 6 months of age or older.
2. Primary Treatment Cohort must have an active infestation with *Pediculus capitis*, the human head louse, with at least three live lice at baseline. Secondary Treatment Cohort must have an active infestation with *Pediculus capitis*, the human head louse, with at least one live louse at baseline.
3. Agree not to use any other pediculicides or medicated hair-grooming products during the duration of the study.
4. Be healthy, non-febrile, and not suffering from an infection likely to require antibiotic therapy during the study period.
5. Subject or guardian is able to understand the new HIPAA regulations and sign the HIPAA form.
6. Subject or guardian has read, understood, and signed appropriate informed consent in English. If English is not the primary language, the information about the study must be explained in their language and a copy of the informed consent must be in that language.
7. Subject is willing to participate in the study, and abide by the protocol requirements.

The Phase 2 studies, Protocol # SU-02-2003, SU-02-2003A, SU-02-2004, differed from the pivotal studies in that Inclusion criteria was age of subject from 2 years to 70 years.

#### **Exclusion Criteria:**

1. Participation in any clinical study within the past 30 days
2. Known hypersensitivity to any ingredient in the product formulation

Phase 2 studies, Protocol # SU-02-2003, SU-02-2003A, SU-02-2004, differed from the pivotal studies in that subjects who were pregnant or lactating, have an abnormal scalp condition (not usually associated with head lice infestation, e.g. scalp condition like seborrheic dermatitis, alopecia, tinea capitis, and contact dermatitis), have used hair dyes or who had very short hair (shaved) were excluded from the studies.

#### **Discontinuation from the study:**

Subjects will be discontinued from the study if:

1. The subject is identified as a treatment failure before the final evaluation at Day 22 (Visit 5).
2. The subject has an overt lice infestation (more than 10 head lice at all stages of development) at any point in the study after the first treatment that is considered to represent a high risk of spreading.
3. The subject or subject's legal representative requests that the subject be discontinued from the study
4. Investigator feels that it is not in the best interest of the subject to continue in the study

**Blinding:**

Studies SU-01-2005 and SU-02-2005 were designed as a randomized, double-blind, vehicle-controlled. The investigators and study staff, evaluator and subjects were blinded to whether subjects received active or vehicle treatments. To maintain the study blind, the clinical test materials (5% L.A. and vehicle control) were packaged in randomized order in the boxes and labeled with a sequential randomization number.

Phase 2 studies, Protocol # SU-02-2004, SU-02-2003 and SU-02-2003A, differed from the pivotal studies in that the treatment phase was evaluator-masked. Study SU-03-2005 was open label.

**Study Procedures:**

At the Day 1(Visit 1), subjects were given written instructions on how to use study drug. Subjects were instructed to apply the study drug to dry hair, starting with through saturation of the scalp and than massaging outward until all hair are thoroughly saturated with the product to the point where some dripping will likely occur. They were instructed to use the following amount of study drug based upon their hair length:

**Table 7: Summers 5% L.A. Usage Guideline**

<i><b>Hair Length</b></i>		<i><b>Amount of L.A. per treatment</b></i>
Short	0-2 inches	4-6 oz ( $\frac{1}{2}$ - $\frac{3}{4}$ bottle)
	2-4 inches	6-8 oz ( $\frac{3}{4}$ - 1 bottle)
Medium	4-8 inches	8-12 oz (1-1 $\frac{1}{2}$ bottle)
	8-16 inches	12-24 oz (1 $\frac{1}{2}$ -3 bottles)
Long	16-22 inches	24-32 oz (3-4 bottles)
	Over 22 inches	32-48 oz (4-6 bottles)

Source: Sponsor's NDA submission: 5.3.5.1.3, p13

Subjects were also provided a towel, and instructed to use this or any soft towel to cover and protect their eyes, forehead and neckline during treatment and rinsing procedures. After the scalp and all hair are thoroughly saturated, the timing of 10-minute treatment

should begin. After 10 minutes, subjects are to thoroughly rinse, shampoo with their regular shampoo, and rinse again.

At the First Evaluation (Visit 2), the day after treatment, all CTM containers (used and unused) were returned and weighted (to assess compliance).

All subjects in the Primary and Secondary Treatment Cohorts were examined by the licensed prescriber for local cutaneous and ocular irritation. Subjects in the Primary Treatment Cohort were examined for the presence of live lice. Subjects with any live lice were considered treatment failures and they and other household members were offered enrollment into an open label study with 5% L.A. or offered FDA approved rescue therapy. Subjects with no live lice were given sufficient CTM for the second treatment.

At the Second Evaluation Visit (Visit3, Day 9 – the day after second treatment), the procedure of the First Evaluation Visit was repeated.

At the First Follow Up Visit (Visit 4, day 15), all subject in the Primary Treatment Cohort were examined for lice. Subjects with live lice were considered treatment failures. Any subjects with live lice at Day 15, and other household members were offered an FDA approved treatment. All lice free subjects were follow at the Final Follow Up Visit (Day 22).

At the Final Follow Up Visit (Visit 5, Day 22), all subjects in the Primary Treatment Cohort were examined for lice.

**Table 8: Study Flow Chart**

Activity	Screening/ First treatment	First Evaluation	Second Treatment <sup>1</sup>	Second Evaluation	First Follow Up	Final Follow Up
	Visit1	Visit 2		Visit 3	Visit 4	Visit 5
	Day 1 <sup>2</sup>	The day after Visit 1	Day 8 (± 1 day)	The day after second treatment	Day 15 (± 2 day)	Day 22 (± 3days)
Informed Consent & HIPAA Forms	x					
Inc/Excl Criteria	x					
Demographics	x					
Medical History	x					
Primary Diagnosis	x					
Treatment	x		x			
Efficacy Assessment Safety Assessments <sup>3</sup>		x		x	x	x
Adverse Events		x	x	x	x	x
Medications	x	x		x	x	x
Clinical Summary						x <sup>4</sup>

1. Subjects will be contacted by p-telephone regarding the instructions for the second treatment
2. Screening and the First Treatment will occur on the same day
3. Safety assessment for skin and eye irritation are also made on any treated family members
4. At study completion or premature discontinuation

Source: Sponsor's NDA submission: 5.3.5.1.3, p 12 (Clinical Study Report Protocol # SU-01-2005 and SU-02-2005)

In Phase 2 studies (SU-02-2003 and SU-02-2003A,) subjects were inspected for live lice and nymphs on Day 8(1 week after first treatment with 5% L.A.). If there were no live lice and nymphs present, the second treatment was not performed.

#### Efficacy Endpoints:

- The primary efficacy measurement in the pivotal trials was treatment success (%) at Day 22, 14 days post the last treatment. Treatment success was defined as the absence of live lice.
- The secondary efficacy measurement was treatment failure (%) at the second evaluation visit (one day post the second treatment).

Primary efficacy measurement in Phase 2 studies (SU-02-2003, SU-02-2003A, and SU-02-2004) was treatment success (%) at Day 15( $\pm$ 2), 7 days after the second treatment (two weeks after first treatment). Treatment success was defined as the absence of live lice.

The optimal treatment regiment (concentration, duration of application, and number of treatments) was determined in three Phase 2 studies (SU-02-2003, SU-02-2003A, and SU-02-2004):

- The overall treatment outcome, primary efficacy variable, show no statistically significant difference at the end of study between L.A.5% and L.A. 10% product (study SU-02-2003).
- The results of the SU-02-2004 study determined that the minimum effective dose of L.A. for the treatment of head lice was the 5 % L. A. preparation.
- The results from the study SU-02-2003A show no statistically significant difference in overall treatment outcome between the 10 minute and 30-minute applications of 5 % L.A.
- These studies demonstrated that two treatments one week apart are necessary.

#### 6.1.4 Efficacy Findings

The primary evaluation of efficacy includes data from two adequate and well controlled pivotal trials (SU-01-2005 and SU-02-2005). A total of 628 subjects from 10 sites were randomized to receive treatment with 5% L.A. or vehicle.

#### Patient Disposition

A high proportion of subjects receiving vehicle dropped out of the study early of which the main cause was lack of efficacy. This coincides with the design of the study where subjects who are not lice free at post-treatment follow-up are allowed to discontinue from the trial and enroll in an open-label trial.

**Table 9: Primary cohort - subject disposition for Studies SU-01-2005 and SU-02-2005**  
(Subjects could have more than one reason for study discontinuation)

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
Overall	147	167	161	153
ITT	63	62	64	61
Dropout	13 (20.6%)	57 (91.9%)	16 (25.0%)	45 (73.8%)
Treatment Failure	7 (11.1%)	51 (82.3%)	13 (20.3%)	42 (68.9%)
Overt Lice Infestation	0 (0.0%)	4 (6.5%)	0 (0.0%)	0 (0.0%)
Withdrew Consent	0 (0.0%)	1 (1.6%)	2 (3.1%)	2 (3.3%)
Investigator Decision	2 (3.2%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Other	6 (9.5%)	5 (8.1%)	1 (1.6%)	2 (3.3%)

Source: Reviewer's Analysis and revised Study Reports.

(Statistical Review and Evaluation; Mat Soukup, PhD.)

### Baseline Characteristics

Overall, the demographics and hair characteristics were consistent across studies and treatment groups. However, the demographics most prevalent were females (more than 80% per treatment arm) with race listed as Caucasian (more than 65% per treatment arm). The majority of subjects had straight hair, hair lengths > 8", and average texture.

Results of the baseline comparisons for age, gender, race, hair length, hair texture, and hair curliness are provided in Table 6 and 7.

**Table 10: Baseline factors by Treatment (Study SU-01-2005)**

	L.A. 5% <i>N</i> = 63	Vehicle <i>N</i> = 62
Age of Subject (Years)	4.00 6.00 9.00	4.00 6.00 8.75
Gender : Female	92% (58)	84% (52)
Race : Caucasian	71% (45)	68% (42)
Black	0% ( 0)	2% ( 1)
Hispanic	24% (15)	27% (17)
Other	5% ( 3)	3% ( 2)
Hair Type : Straight	79% (50)	71% (44)
Wavy	16% (10)	19% (12)
Curly	5% ( 3)	10% ( 6)
Hair Length : Short (<2")	5% ( 3)	6% ( 4)
Short (>2" & <4")	17% (11)	13% ( 8)
Medium (>4" & <8")	3% ( 2)	13% ( 8)
Medium (>8" & <16")	35% (22)	44% (27)
Long (>16" & <22")	25% (16)	19% (12)
Long (>22")	14% ( 9)	5% ( 3)
Hair Texture : Fine	32% (20)	32% (20)
Average	65% (41)	60% (37)
Coarse	3% ( 2)	8% ( 5)

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies.

Source: Reviewer's analysis.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

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**Table 11: Baseline factors by Treatment (Study SU-02-2005)**

	L.A. 5%			Vehicle		
	N = 64			N = 61		
Age of Subject(Years)	4.00	7.00	10.25	4.00	7.00	9.00
Gender : Female	88% (56)			85% (52)		
Race : Caucasian	83% (53)			75% (46)		
Black	0% ( 0)			0% ( 0)		
Hispanic	14% ( 9)			16% (10)		
Other	3% ( 2)			8% ( 5)		
Hair Type : Straight	69% (44)			75% (46)		
Wavy	22% (14)			18% (11)		
Curly	9% ( 6)			7% ( 4)		
Hair Length : Short (<2")	9% ( 6)			10% ( 6)		
Short (>2" & <4")	11% ( 7)			15% ( 9)		
Medium (>4" & <8")	14% ( 9)			18% (11)		
Medium (>8" & <16")	41% (26)			41% (25)		
Long (>16" & <22")	14% ( 9)			11% ( 7)		
Long (>22")	11% ( 7)			5% ( 3)		
Hair Texture : Fine	28% (18)			31% (19)		
Average	66% (42)			64% (39)		
Coarse	6% ( 4)			5% ( 3)		

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. Numbers after percents are frequencies.

Source: Reviewer's analysis.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### **Reviewer's comment:**

*See Section 1.3.6: Special population; Reviewer's comments*

#### **Statistical Methodology:**

Efficacy analysis were performed on the intent to-treat (ITT) and the per protocol (PP) populations. PP analysis was used to illustrate consistency of study results with the ITT analysis.

- The intent-to-treat (ITT) population is defined as all subjects in the primary treatment cohort that were randomized and dispensed L.A. 5% or vehicle.
- The per protocol (PP) population is defined as the subset of randomized subjects in the primary treatment cohort that were eligible, received the randomized treatment assignment, had no major protocol violations, and fulfilled all inclusion/exclusion criteria.

All statistical tests were performed at a two-sided alpha level of 0.05. The difference in the two groups' primary endpoint, treatment success rate, was compared using CMH stratified by site for the superiority comparison. The same analysis strategy was used on the secondary cohort.

Due to the design of the study which allows subjects to discontinue for lack of efficacy, it is expected that some subjects will NOT have assessments at Day 22 (Visit 5). It should be noted that in the analysis, such subjects would not be considered missing, but rather as treatment

failures. For subjects that do not withdraw due to lack of efficacy and do not complete the final follow-up visit at day 22, missing day 22 data will be imputed using the last observation carried forward. A sensitivity analysis to this method of data imputation to assess for the robustness of efficacy findings is carried out by the reviewer (See: Statistical Review and Evaluation; Mat Soukup, Ph.D.)

Primary Endpoint Results (Primary Cohort – ITT):

The primary endpoint is defined as the percent of subjects who are lice free 14 days after the last treatment (Visit 5, Day 22). Missing data is imputed by LOCF which by definition imputes missing of those subjects that drop out due to lack of efficacy as failures and all other subjects have the last observation carried forward. Efficacy results for Studies SU-01-2005 and SU-02-2005 are provided in Table 8. Results from both studies show that 5% L.A. is statistically superior to vehicle with p-values below 0.001 in each study.

**Table 12: Lice Eradication Results (Primary Cohort-ITT)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Reviewer's analysis and revised Study Report Table 2.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

Primary Endpoint Results (Primary Cohort – PP):

As a supportive analysis to the ITT population of the primary cohort, Table 9 presents efficacy results for the PP population of the primary cohort. Results from this supportive analysis are consistent with results from the ITT population which finds 5% L.A. to be statistically superior to vehicle.



**Table 13: Lice Eradication Results (Primary Cohort-PP)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	55	53	58	57
Number Lice Free (%)	48 (87.3)	3 (5.7)	45 (77.6)	16 (28.1)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Table 3 of the Study Reports; results reproduced by the reviewer.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### Sensitivity Analysis of the Primary Endpoint:

The following sensitivity analysis assesses the impact missing data has on the efficacy conclusion for the primary cohort (ITT population). The Day 22 assessment of live lice present is considered missing if subjects did have a Day 22 efficacy evaluation and the subject did not discontinue from the trial due to lack of efficacy. An extreme scenario that favors vehicle over L.A. 5% is one in which all missing data for vehicle are imputed as being lice free at Day 22 (success), whereas all missing data for 5% L.A. are imputed as having lice present at Day 22 (failure). Table 9 provides efficacy results under such a scenario. In comparison to the primary cohort analysis of the ITT population, this method of data imputation adds 5 additional successes to vehicle in Study 01 and 3 additional successes to vehicle in Study 02 while no changes are made to the number of successes to L.A. 5% in either study. Due to such a small percentage of missing data, efficacy results are consistent with the protocol-defined primary cohort efficacy analysis of the ITT population (See: Statistical Review and Evaluation; Mat Soukup, Ph.D.)

**Table 14: Sensitivity Analysis of Missing Data**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	9 (14.5)	48 (75.0)	19 (31.1)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Reviewer Analysis.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

### Secondary Endpoint Results:

A total of five visits were scheduled over the course of the study for the Primary Treatment Cohort subjects: screening visit (Visit1), two evaluation visits (Visit 2 and 3, the day after the 1<sup>st</sup> and 2<sup>nd</sup> home treatment), and two follow-up visits (Visit 4 and 5, Day 15 and Day 22). The observed percent of primary ITT population subjects who are lice free is provided for each study visit in Figure 1 along with an unadjusted 95% confidence interval. The figure shows the clear separation of 5% L.A. and vehicle across all time points. Also for both studies, the highest response rate occurs one week after the 1<sup>st</sup> treatment but declines as time progresses. This could indicate a re-infestation or the hatching of eggs which were not subsequently eliminated by the second application although the exact reasoning is not known based upon the data submitted.

**Figure 1: Percent Lice Free Across Study Visits**

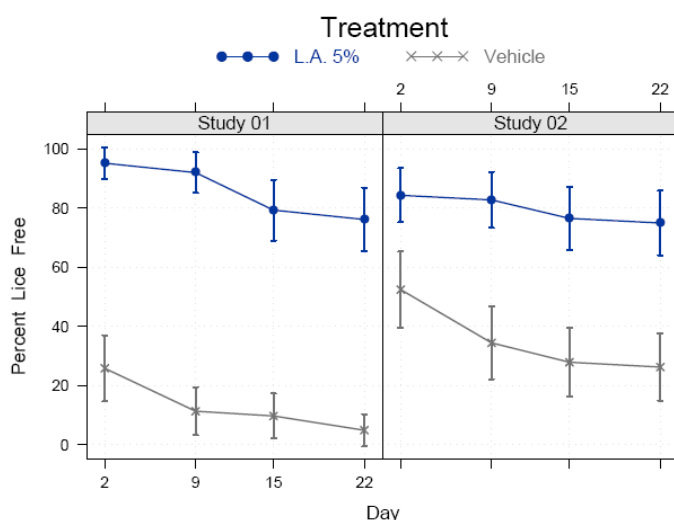


Table provides the efficacy results for the single secondary efficacy endpoint listed in the protocol which is the proportion of subjects determined to be treatment failure at the second evaluation visit (Visit 3, Day 9). As seen in Figure 1 the response rates are higher at Day 9 than the follow-up visits for all treatments arms in which 5% L.A. 5% is significantly superior to vehicle.

**Table 15: Lice Eradication Results (Primary Cohort – ITT Day 9)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	58 (92.1)	7 (11.3)	53 (82.8)	21 (34.4)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Reviewer Analysis.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### Primary endpoint results (Secondary Cohort- ITT)

Subjects in the secondary cohort completed the study following the second evaluation visit (Visit 3/Day 9) which does not include the two follow-up efficacy visits as with the primary cohort. Results are presented in Table 12 which shows efficacy results quite similar to that of the primary cohort evaluation on Day 9.

**Table 16: Lice Eradication Results (Secondary Cohort – ITT)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	84	105	97	92
Number Lice Free (%)	75 (89.3)	22 (21.0)	85 (87.6)	33 (35.9)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site.

Source: Reviewer's analysis and Revised Study Report Table 5.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

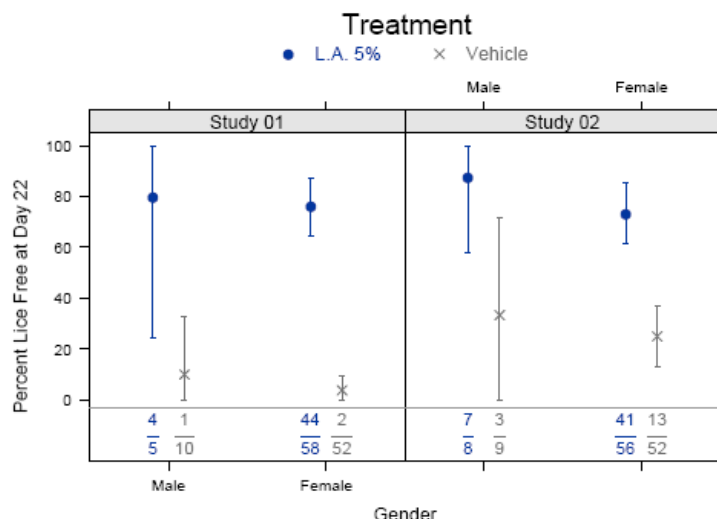
#### **Findings in Special/Subgroup Population:**

##### Primary Efficacy Results by Gender:

Both studies had a higher percentage of female subjects in the primary cohort. However, the percent of primary cohort subjects who were lice free at Day 22 is similar between males and females which are seen in both studies.

Figure 2 depicts efficacy results according to gender along with unadjusted 95% confidence intervals.

**Figure 2: Percent Lice Free by Gender**



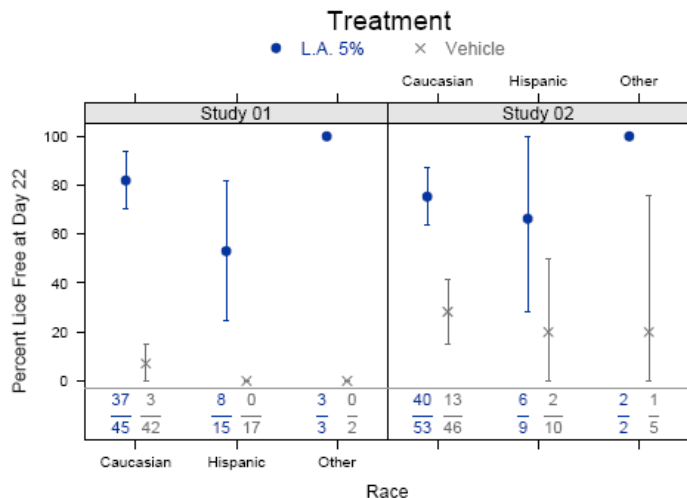
(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### Primary Efficacy Results by Race:

Race was broken into four categories: Caucasian, Black, Hispanic, and Other. However, only one primary cohort subject had race as being recorded as “black”. The recorded race for subjects listed in the “Other” category were: Bi-racial (Black/Caucasian, Hispanic/Caucasian, Asian/Hispanic, and Black/Hispanic), Native American, and Asian. Figure 3 depicts the mean response rates along with unadjusted 95% confidence intervals by race, excluding the category Black. In general, response rates are quite similar for each race, but both studies showed lower response rates in Hispanic subjects than in other races.

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**Figure 3: Percent Lice Free by Race**

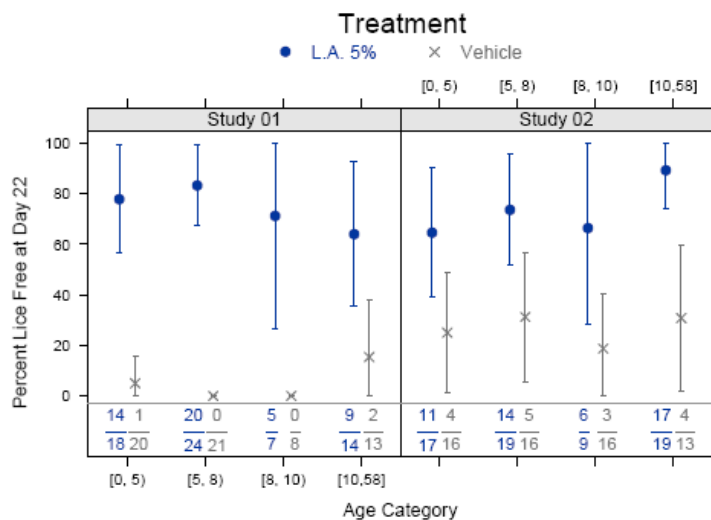


(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### Efficacy by Age Group:

Age was dichotomized into four groups: [0; 5), [5; 8), [8; 10), and [10; 58] where the cut-points are based on the quantiles of age for subjects enrolled in the two pivotal trials. The percent of lice free subjects at Day 22 treated with 5% L.A. does not show any trends with higher efficacy in any of the age subgroups. Overall, a treatment effect favoring 5% L.A. over vehicle is seen in all studies.

**Figure 4: Percent Lice Free by Age Group**

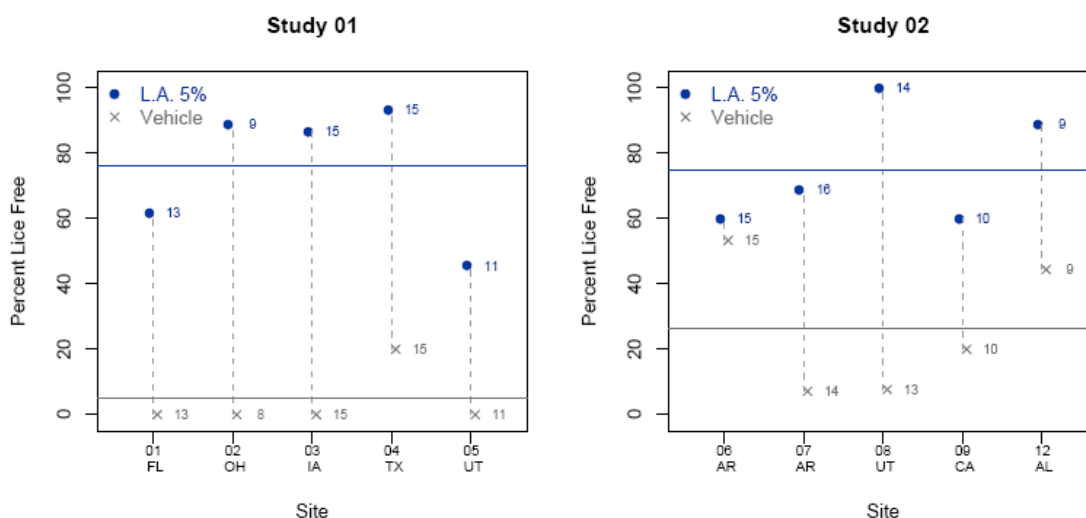


(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

### Primary Efficacy by Site

Figure 5 depicts the treatment effect for each study site (vertical gray dotted lines) as well as the overall percent of lice free subjects at Day 22 (horizontal solid lines). Sample size for a given treatment arm within a site is provided next to the plotting character of each treatment arm. The graph shows results are variable between sites, but with the exception of site 06, all sites had treatment effects of at least 40%.

**Figure 5: Percent Lice Free by Site**



(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

Based on Figure 5 as well as other data submitted in the NDA, four sites were identified for a DSI inspection. See section 4.4

A comparison of the baseline demographics and other baseline factors did not show any difference between Site 06 and the other sites in Study 2. In addition, the amount of drug product dispensed in Site 06 was similar to that in the other sites. Further, the data did not point to any lack of compliance in Site 06 making it difficult to draw any definitive conclusion about why the treatment effect size in site 06 is small in comparison to the other sites.

### Primary Efficacy Results by Hair Characteristics

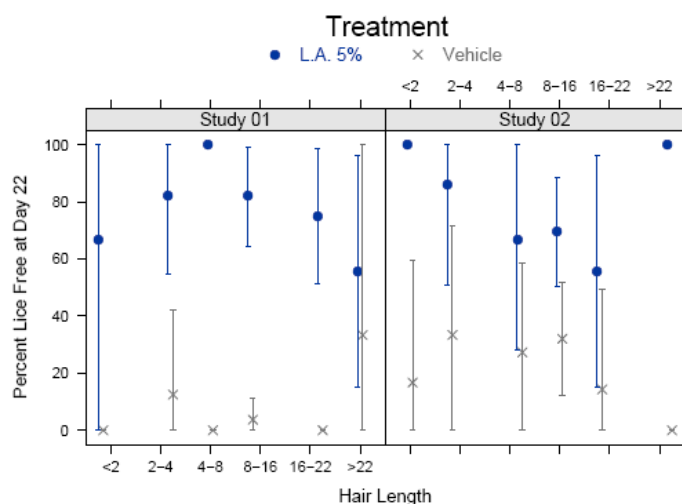
In addition to looking at efficacy by age, gender, and race the characteristics of the subjects' hair were examined for the three hair parameters below (shown with unique values for each parameter).

- Type: straight, wavy, or curly

- Length: short (<2"), short (>2" & <4"), medium (>4" & <8"), medium (>8" & <16"), long (>16" & <22"), or long (>22")
- Texture: fine, average, or coarse

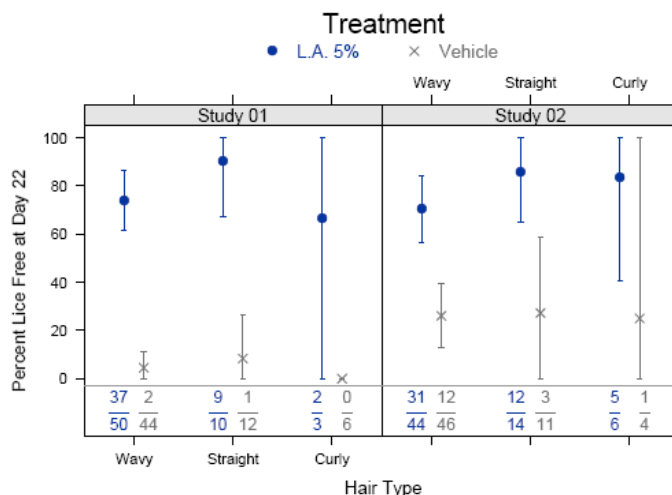
Both hair type and hair texture showed relatively consistent response between groups. In terms of hair length, the data showed a slight trend towards less efficacy in subjects with longer hair though small sample sizes limit the reliability of this conclusion.

**Figure 6: Percent Lice Free by Length**



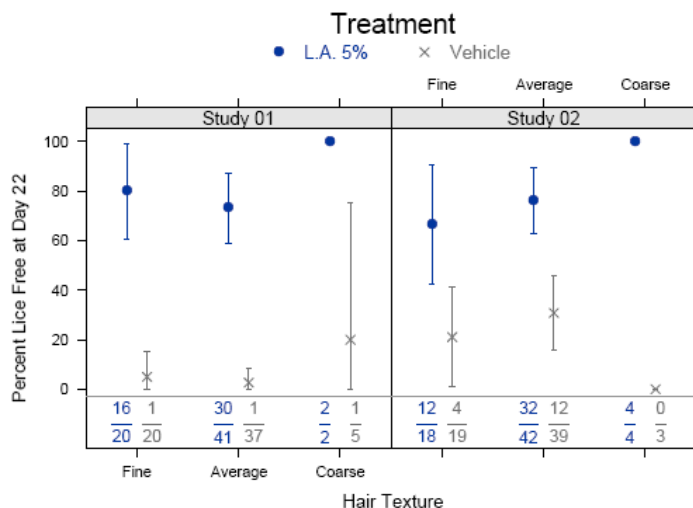
(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

**Figure 7: Percent Lice Free by Type**



(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

**Figure 8: Percent Lice Free by Texture**



(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

## **Supporting Studies**

### **Phase 2 Efficacy Results:**

The optimal treatment regimen; concentration, duration of application, and number of treatments; was determined in Phase 2 studies. These Phase 2 studies differed from the pivotal studies in that efficacy was evaluated 15 days after the 1<sup>st</sup> treatment, while the pivotal studies were evaluated 15 day after the 2<sup>nd</sup> treatment.

- The objective of Study SU-02-2003 (randomized, observer-blinded, open label) was to evaluate the safety and efficacy of two concentration of L.A. in comparison with 5% L.A. vehicle, and active control (RID®). Subjects applied treatment for 10 minutes at baseline and only if lice were present one week latter, subjects in the active arms (5% L.A. and 10% L.A.) received second treatment. The second treatment of RID® shampoo was administrated as per package insert. In subjects treated with vehicle control, 5% L.A. was administrated at Day 8 if live lice were present. The percent of subjects who were lice free at Day 15 for the two doses of L.A. were identical as well as equal to RID®.
- Study SU-02-2003A was an amendment of SU-02-2003. The objectives of this study were to evaluate the safety and efficacy of 5% L.A. for the treatment of head lice after two durations of application time (10—minute and 30-minute) regimens. The 2<sup>nd</sup> treatment was not performed if no live lice and/or nymphs were present at the 1 week follow up visit. Day 15 (14 days after first application) was used as the time point for efficacy evaluation. Both the 10- minute and the 30-minute had 100% of subjects remain lice free at Day 15.



Efficacy results from the Phase 2 dose ranging studies, Studies SU-02-2003 and SU-02-2003A, are presented in Tables 13 and 14.

**Table 17: Efficacy Results for Study SU-02-2003**

	RID <sup>®</sup> (N = 20)	Vehicle (N = 19)	L.A. 5% (N = 20)	L.A. 10% (N = 20)
Lice Free	14 (70.0%)	10 (52.6%)	14 (70.0%)	14 (70.0%)

<sup>†</sup> Sponsor's Results: Study Report of SU-02-2003

**Table 18: Efficacy Results for Study SU-02-2003A**

	L.A. 5% 10 Minutes (N = 21)	L.A. 5% 30 Minutes (N = 22)
Lice Free	21 (100.0%)	22 (100.0%)

<sup>†</sup> Sponsor's Results: Study Report of SU-02-2003A

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

#### 6.1.5 Clinical Microbiology

The applicant did not perform any clinical microbiology studies.

#### 6.1.6 Efficacy Conclusions

The applicant conducted two adequate and well-controlled, pivotal Phase 3 studies, SU-01-2005 and SU-02-2005, in which 5% L.A. was compared to its vehicle in two 10 minute application one week apart treatment of head lice infestation. The primary efficacy measurement was treatment success (%) 14 days post the final (second) treatment. Treatment success was defined as the absence of live lice. The primary efficacy analysis was conducted on intent-to-treat (ITT) population with missing values treated as treatment failure.

In both Phase 3 trials 5% L.A. establishes the superiority over vehicle, based on pre-defined primary endpoint, in the treatment of head lice infestation in subjects 6 months of age and older.

**Table 19: Lice Eradication Results (Primary Cohort – ITT)**

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)
p-value <sup>†</sup>	-	< .001	-	< .001

<sup>†</sup> Reported p-values are based on CMH stratified by site

Source: Reviewer's analysis and revised Study Report Table 2.

(Statistical Review and Evaluation; Mat Soukup, Ph.D.)

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Safety data from eight studies sponsored by the applicant were submitted in the marketing application. The safety of 5% L.A. for treatment of head lice (*Pediculus humanis capitis*) was evaluated in two pivotal clinical studies enrolling 628 subjects (SU-01-2005 and SU-02-2005), an open label study enrolling 128 subjects (SU-03-2005), Phase 2 studies enrolling 167 subjects (SU-02-2003, SU-02-2003A and SU-02-2004), Phase 1 single dose bioavailability study enrolling 45 subjects (SU-01-2007), and a special safety study enrolling 244 healthy subjects (SU-01-2006).

**Table 20: Studies Providing Safety Information**

Study Number	Study Design and Type of Control	Test Product(s)	Dosage Regiment	Number of Subjects Exposed to L.A 5%
<b>Pivotal Studies</b>				
SU-01-2005	Double blind, Randomized Placebo controlled	5% L.A. Vehicle control	Two 10 minute applications one week apart	Primary Cohort N = 63 Secondary Cohort N = 84
SU-02-2005	Double blind, Randomized Placebo controlled	5% L.A. Vehicle control	Two 10 minute applications one week apart	Primary Cohort N = 64 Secondary Cohort

				N = 97
<b>Supporting Studies</b>				
SU-03-2005	Open label	5% L.A.	Two 10 minute applications one week apart	N = 115 (47 new exposure + 68 vehicle TX failure)
SU-02-2003	Randomized, observer blinded, open label	5% L.A. 10% L.A. Vehicle RID shampoo	10 minute application at Visit 1. L.A. was applied one week latter if live lice were found. L.A.5% was applied in vehicle group if live lice were found. RID was applied twice	N = 20
SU-02-2003A	Randomized, observer blinded, open label	5% L.A.	Two 10 or 30 minute application one week apart	N = 44  (only the 21 subject exposed for 10 min are included in the pooled analysis)
SU-02-2004	Randomized, observer blinded, open label	2.4% L.A. 5% L.A.	Two 10 minute application one week apart	N = 21
<b>Phase I Dermal Safety Study</b>				
SU-01-2006	Single center, double-blind, placebo-controlled, within-subject randomized design in which the subject and the trained skin evaluator were blinded to the identity of the test materials	5% L.A.  Vehicle control  0.9% Saline  0.4% sodium lauryl sulfate	<u>Group 1</u> patch test applied daily for 21 consecutive days plus challenge  <u>Group 2</u> patch applied 9 times over 21 days plus challenge	N = 244

Source: Sponsor's NDA submission; 2.7.4 Summary of Clinical safety; Table 2.7.4.1.1.1(1); ISS Table (5.3.5.3.2.1.1.1)1 Summary of Studies Providing Safety Information

The safety measurements were assessment of adverse events and evaluation of the skin, scalp and eyes for irritation.

For the integrated summary of safety, adverse event data in subjects treated with 5% L.A. and vehicle control during the Phase 2 and 3 studies were pooled. Subjects in the open label study, SU-03-2005, who were previously treated with 5% L.A. in one of the double blind studies were counted only once.

Adverse event data from other concentrations of L.A. (10% L.A. in SU-02-2003 and 2.5% L.A. in SU-02-2004) and RID shampoo (SU-02-2003) were not included. In addition, the 30 minute treatment group in Study SU-02-2003A was not included. Studies SU-01-2006 (the dermal safety study in healthy subjects), and SU-01-2007 (bioavailability) were not included in the integrated safety analysis.

In the Phase 2 and 3 studies, a total of 485 subjects were assigned to be treated with 10-minute treatments for an infestation of head lice with L.A. 5% one week apart. The majority of subjects assigned to treatment with L.A. 5% had two treatments while the majority of subjects assigned to treatment with vehicle placebo had only one treatment due to treatment failure and receipt of rescue therapy. In study SU-03-2005, 13 subjects that were treatment failures in one of the double blind studies (SU-01-2005 and SU-02-2005) and had been treated with 5% L.A. were enrolled into this open label study.

#### 7.1.1 Deaths

No deaths occurred in clinical development of L.A. 5%.

#### 7.1.2 Other Serious Adverse Events

No serious adverse events were reported during the clinical development of L.A. 5%.

#### 7.1.3 Dropouts and Other Significant Adverse Events

##### 7.1.3.1 Overall profile of dropouts

In the Phase 3 and Phase 2 studies, a total of 485 subjects were randomized to be treated with 10-minute treatment(s) for an infestation of head lice with L.A. 5% one week apart. None of these subjects discontinued treatment due to an adverse event.

One subject, 01-141, withdrew from the combined skin irritation and sensitization study due to an adverse event of mild nausea.

In the Phase 3 clinical trials, the percentage of dropouts was similar between 5% L.A. Primary and 5% L.A. Secondary Cohort (22.83% and 20.99%, respectively), as well as between vehicle Primary and vehicle Secondary Cohort (82.9% and 78.17%). However, the percentage of dropouts in vehicle controlled group (including Primary and Secondary Cohorts) was higher

(80%) then in group treated with 5% L.A. (21.75%). The most common reason for premature study drug discontinuation in either treatment group was treatment failure.

The following tables (Table 17 and Table 18) present the summary of subjects who discontinued from the phase 3 clinical trials.

**Table 21: Disposition of Subjects: Study SU-01-2005**

Parameter		5% L.A. Primary Cohort	5% L.A. Secondary Cohort	Vehicle Primary Cohort	Vehicle Secondary Cohort
<b>Randomized</b>		63 (100.0%)	84 (100.0%)	62 (100.0%)	105 (100.0%)
<b>Completed the study</b>		50 (79.4%)	67 (79.8%)	5 (8.1%)	20 (19.0%)
<b>Discontinued from the study</b>		13 (20.6%)	17 (20.2%)	57 (91.9%)	85 (81.0%)
Reason for premature termination	Treatment failure	7 (53.8%)	5 (29.4%)	51 (89.5%)	73 (85.9%)
	Overt lice infestation	0 (0.0%)	0 (0.0%)	4 (7.0%)	7 (8.2%)
	Withdrew consent	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
	Investigator's clinical/admin. decision	2 (15.4%)	2 (11.8%)	1 (1.8%)	6 (7.1%)
	Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	6 (46.2%)	13 (76.5%)	5 (8.8%)	9 (10.6%)
<b>Deviate from the protocol</b>		3 (4.8%)	6 (7.1%)	6 (9.7%)	5 (4.8%)

Source: Sponsor's NDA submission; Clinical Study Report; Statistical Table 1.1.1. and Statistical Table 1.1.2. :  
Disposition of the Subjects

Note:

- There could be more than one reason for premature termination
- "Other" included: lost to follow up, the site did not have enough CMT to dispense, or they did not return for scheduled visit.

**Table 22: Disposition of Subjects: Study SU-02-2005**

Parameter		5% L.A. Primary Cohort	5% L.A. Secondary Cohort	Vehicle Primary Cohort	Vehicle Secondary Cohort
<b>Randomized</b>		64 (100.0%)	97 (100.0%)	61 (100.0%)	92 (100.0%)
<b>Completed the study</b>		48 (75%)	76 (78.4%)	16 (26.2%)	23 (25%)
<b>Discontinued from the study</b>		16 (25%)	21 (21.6%)	45 (73.8)	69 (75%)
Reason for premature termination	Treatment failure	13 (81.3%)	13 (61.9%)	42 (93.3%)	60 (87.0%)
	Overt lice infestation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrew consent	2 (12.5%)	0 (0.0%)	2 (4.4%)	2 (2.9%)

	Investigator's clinical/admin. Decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	1 (6.3%)	8 (38.1%)	2 (4.4%)	7 (10.1%)
<b>Deviate from the protocol</b>		3 (4.7%)	0 (0.0%)	2 (3.3%)	4 (4.3%)

Source: Sponsor's NDA submission; Clinical Study Report, Disposition of the Subjects; revision 12/02/2007;  
Statistical Table 1.1.1, Data listing 18

Note:

- There could be more than one reason for premature termination
- "Other" included: had lice at Visit 5, lost to follow up, and family member had lice causing treatment failure

In the Phase 3, open label study, 128 subjects were treated with 5% L.A. and 27 subjects discontinued from the study (21.1%) with the treatment failure as the most common cause for discontinuation (81.5%). The percentage of dropouts was similar between open label study and two pivotal Phase 3 clinical trials for the 5% L.A. treatment group (21.1% and 21.75%).

The following table presents the summary of subjects who discontinued from the open label study SU-03-2005

**Table 23: Disposition of Subjects: Open Label study (SU-03-2005)**

<b>5% L.A.</b>					
		<b>5% L.A. N = 13</b>	<b>Vehicle N = 68</b>	<b>New Subjects N = 47</b>	<b>Overall N = 128</b>
<b>Discontinued from the study</b>		2 (15.4%)	16 (23.5%)	9 (19.1%)	27 (21.1%)
<b>Completed the study</b>		11 (84.6%)	52 (76.5%)	38 (80.9%)	101 (78.9%)
Reason for premature termination	Treatment failure	2 (100.0%)	14 (87.5%)	6 (66.7%)	22 (81.5%)
	Overt lice infestation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Investigator's clinical/admin. decision	0 (0.0%)	2 (12.5%)	0 (0.0%)	2 (7.4%)
	Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Lost to follow up/other	0 (0.0%)	1 (6.3%)	3 (33.3%)	4 (14.8%)
<b>Deviate from the protocol</b>		0 (0.0%)	8 (11.8%)	10 (21.3%)	18 (14.1%)

Source: Sponsor's NDA submission; Clinical Study Report, Disposition of the Subjects; revision 12/04 /2007;  
Statistical Table 1.1., Data listing 17

In the Phase 2 clinical studies 62 subjects received treatment with 5% L.A. and three subjects (4.83%) discontinued due to "lost to follow-up". None of these subjects discontinued treatment due to an adverse event.

The following table presents the summary of subjects who discontinued from the phase 2 clinical trials.

**Table 24: Study termination: Phase 2 clinical trials**  
(SU-02-2004, SU-20-2003, and SU-02-2003A)

Parameter		SU-02-2004 5% L.A.	SU-02-2003A 5%L.A. 10min	SU-02-003 5% L.A. Vehicle	
<b>Randomized</b>		21 (100.0%)	21 (100.0%)	20 (100.0%)	20 (100.0%)
<b>Study completion</b>		18 (85.7%)	21 (100%)	20 (100.0%)	19 (95.0%)
<b>Discontinued from the study</b>		3 (14.3%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Reason for premature termination	Lack of product efficacy	0 (0.0%)			
	Withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Investigator's clinical/admin. decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Adverse event				
	Lost to follow up/other	0 (0.0%)		0 (0.0%)	
		3 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
<b>Deviate from the protocol</b>		8 (38.1%)	3 (14.3%)	1 (5.0%)	1 (5.0%)

Source: Sponsor's NDA submission: Clinical Study Report, Statistical Table 6

#### 7.1.3.2 Adverse events associated with dropouts

None of the subjects were discontinued from Phase 2 and Phase 3 studies due to adverse event. In study SU-01-2006, "A combined skin irritation and sensitization study of Summer's lice asphyxiator in healthy adult subjects", one subject, 01-141, withdrew from the study due to an adverse event of mild nausea.

- **Subject 01-141:** A 43-year-old Caucasian male consented to join study on October 26, 2006; he experienced mild nausea on November 03, 2006 which was treated with Pepto-Bismol and resolved the same day without sequelae; event was not related to the study drug.

#### 7.1.3.3 Other significant adverse events

None identified.

#### 7.1.4 Other Search Strategies

The dermal safety studies are discussed in Section 7.1.12.

None of the adverse events reported in subjects treated with 5% L.A. or vehicle control were considered severe by investigator. However, by active assessment (evaluation visits) of skin/scalp and eye for irritation, one subject (12y/o) experienced eye irritation (burning) and one subject (11 y/o) experienced scalp numbness that was rated severe.

##### Local Safety:

In the pivotal studies, SU-01-2005, SU-02-2005, and SU-03-2005, investigators actively assessed for signs (erythema, pyoderma, and excoriation) and symptoms (pruritus) of the effects of lice infestation and/or irritation from application of 5% L.A.

#### **A. THE SCALP AND SKIN EVALUATION**

##### **SU-01-2005 and SU-02-2005**

In two pivotal clinical trials (SU-01-2005 and SU-02-2005), 308 subjects received 5% L.A and 320 subjects received the vehicle treatment. The scalp and skin evaluation were performed pretreatment (Day1), First Evaluation Visit (Day 2, one day post first treatment), and Second Evaluation Visit (Day 8, one day post second treatment). The evaluations were rated on scale of 1 (none), 2 (mild), 3 (moderate), and 4 (severe) for five categories: pruritus, erythema, pyoderma, and excoriation. In addition, a category of “other” was specified on the CRF, which allowed for description of other signs and/or symptoms.

The only sign/symptom which tended to worsen with treatment of 5 % L.A. compared with vehicle control was scalp pruritus in subjects with no pruritus prior to treatment.

##### Pruritus:

Prior to treatment, the majority of subjects had pruritus. Both treatment groups showed improvement in severity of skin and scalp pruritus throughout studies. (See Table 25)

- In the 5% L.A. treatment group 75.3% of subjects had pruritus prior to treatment, 33.5% had pruritus at the 1<sup>st</sup> evaluation visit, and 15.8% had pruritus at the 2<sup>nd</sup> evaluation visit.
- In the vehicle treatment group, prior to treatment pruritus was present in 77.8% of the subjects, at the 1<sup>st</sup> evaluation visit 56.9% and at the 2<sup>nd</sup> evaluation visit 25.5%.

However, presence of pruritus was observed post-treatment in some subjects without pruritus prior to either treatment.

- At the 1<sup>st</sup> evaluation visit, 10 of 75 (13.3%) of subjects treated with 5% L.A., with no pruritus prior to treatment, had mild/moderate pruritus, compared to 3 of 67 (4.5%) of subjects treated with vehicle control.
- At the 2<sup>nd</sup> evaluation visit, 4 of 63 (6.3%) of subjects treated with 5% L.A., with no pruritus prior to treatment, had mild pruritus compared to 0 of 29 (0.0%) subjects treated with vehicle control.



Children (age 6 months to 11 years of age) treated with 5% L.A. are not at greater risk of developing scalp pruritus than the older subjects.

- At the 1<sup>st</sup> evaluation visit, 6 of 50 (12.0%) subjects age 6 months to 11 years treated with 5% L.A. with no pruritus prior to treatment, had mild/moderate pruritus compared to 4 of 25 (16.0 %) of subjects in the > 12 years age group.
- At the 2<sup>nd</sup> evaluation visit, 2 of 41 (4.9%) subjects from the age 6 months to 11 years group, with no pruritus prior to treatment, had mild pruritus compared to 2 of 22 (9.1%) subjects from the group > 12 years of age.

**Table 25: Presence of Pruritus Pre-treatment and Post-treatment**

Pruritus	6 months- 3 years		4-11 years		> 12 years	
	5%L.A.	Vehicle	5%L.A.	Vehicle	5%L.A.	Vehicle
<i>Pre-treatment</i>	26/35 (72.3%)	28/35 (80.0%)	113/155 (72.9%)	133/168 (79.2%)	93/118 (78.8%)	88/114 (77.2%)
<i>1<sup>st</sup> evaluation visit</i>	9/34 (26.5%)	23/35 (65.7%)	50/151 (33.1%)	88/165 (53.3%)	42/116 (36.2%)	66/111 (59.4%)
<i>2<sup>nd</sup> evaluation visit</i>	4/28 (14.3%)	3/ 7 (42.8%)	16/129 (12.4)	9/ 54 (16.7%)	21/102 (20.6%)	13/37 (35.1%)

Source: Sponsor's NDA submission: 12/28/07, Table 3.1.3 Skin and Scalp evaluation, Protocol SU-01-2005 and SU-02-2005

Overall, both treatment groups showed continuous improvement in the severity of the pruritus. The pruritus was statistically significantly improved in the 5% L.A. treatment group compared to the vehicle treatment group at the first evaluation visit (SU-01-2005 and SU-02-2005) and the second evaluation visit (SU-01-2005).

### Erythema

In the majority of subjects, erythema of the skin and scalp was not present prior to treatment.

- In the 5% L.A. treatment group, erythema of skin and scalp was not observed in 225 of 308 (73%) subjects prior to treatment, 248 of 301 (82.3%) subjects at the 1<sup>st</sup> evaluation visit, and 242 of 259 (93.4%) subjects at the second evaluation visit.
- In the vehicle treatment group, 221 of 317 (69.7%) subjects prior to treatment, 253 of 311 (81.3%) subjects at the 1<sup>st</sup> evaluation visit and 88 of 98 (89.7%) subjects at the 2<sup>nd</sup> evaluation visit did not have erythema.

Similar findings were observed between children (6months to 11 years of age group) and older subjects (> 12 years age group).

- In the 6 months to 11 years age group treated with 5% L.A, 51 of 190 (26.8%) subjects had erythema prior to treatment. At the 1<sup>st</sup> evaluation visit, erythema was present in 37 of 185 (20.0%) subjects and at 2<sup>nd</sup> evaluation visit in 12 of 151 (7.9%) subjects.
- In the >12 years age group, erythema was present in 32 of 118 (27.1%) subjects prior to treatment, 16 of 116 (13.8%) subjects at the 1<sup>st</sup> and in 5 of 102 (4.9%) subjects at the 2<sup>nd</sup> evaluation visit.

**Table 26: Presence of Erythema Pre-treatment and Post-treatment**

<b>Erythema</b>	<b>6 months- 3 years</b>		<b>4-11 years</b>		<b>&gt; 12 years</b>	
	<b>5%L.A.</b>	<b>Vehicle</b>	<b>5%L.A.</b>	<b>Vehicle</b>	<b>5%L.A.</b>	<b>Vehicle</b>
<i>Pre-treatment</i>	10/35 (28.6%)	11/35 (31.4%)	31/155 (20.0%)	49/168 (29.2%)	32/118 (27.1%)	36/114 (31.6%)
<i>1<sup>st</sup> evaluation visit</i>	6/34 (17.6%)	10/35 (28.6%)	31/151 (20.5%)	29/165 (17.6%)	16/116 (13.8%)	19/111 (17.1%)
<i>2<sup>nd</sup> evaluation visit</i>	2/28 (7.1%)	2/7 (28.6%)	10/129 (7.7%)	4/ 54 (7.4%)	5/102 (4.9%)	4/37 (10.8%)

Source: Sponsor's NDA submission: 12/28/07, Table 3.1.3 Skin and Scalp evaluation, Protocol SU-01-2005 and SU-02-2005

Although, both treatment groups showed continuous improvement in the severity of the erythema, presence of skin and scalp erythema was observed at 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit in subjects without erythema prior to either treatment.

- At the 1<sup>st</sup> evaluation visit, 18 of 223 (8.1%) of subjects treated with 5% L.A., with no erythema prior to treatment, had mild/moderate erythema, compared to 13 of 217 (5.9%) subjects treated with vehicle control. Fifteen of these 18 subjects were from the 6 months to 11 years group (15/138; 10.9%).
- At the 2<sup>nd</sup> evaluation visit, 8 of 189 (4.2%) subjects treated with 5 % L.A, with no erythema prior to treatment, developed mild erythema compared to 7 of 68 (10.3%) subjects treated with vehicle control. Six of these 8 subjects (5% L.A treatment group) were from the 6 months to 11 years group (6/115; 5.2%).

### Pyoderma

Majority of the subjects did not have skin and scalp pyoderma prior to treatment. Both treatment groups showed improvement in severity of skin and scalp pyoderma throughout studies.

- In the 5% L.A. treatment group, pyoderma was present in 79 of 308 (25.6%) subjects prior to treatment, 74 of 301 (24.6%) at the 1<sup>st</sup>, and in 29 of 259 (11.2%) subjects at the 2<sup>nd</sup> evaluation visit.
- In the vehicle controlled group, pyoderma was present in 83 of 320 (25.9%) subjects prior to treatment, 75 of 301 (24.1%) at the 1<sup>st</sup>, and 12 of 98 (12.2%) subjects at the 2<sup>nd</sup> evaluation visit.

Similar findings were observed between children (6 months to 11 years of age group) and older subjects.

- In the 6 months to 11 years age group, 53 of 190 (27.9%) subjects had pyoderma of the scalp present prior to treatment with 5% L.A. compare to 26 of 118 (22.0%) subjects in the > 12 years age group.
- At the 1<sup>st</sup> evaluation visit, pyoderma was present in 51 of 185 (27.6%) subjects in the 6 months to 11 years age group, and in 23 of 116 (19.8%) subjects from the > 12 years age group.
- At the 2<sup>nd</sup> evaluation visit, 20 of 157 (12.7%) and 9 of 102 (8.8%) subjects had pyoderma present in the 6 months to 11 years age group and the > 12 years age group, retrospectively.

**Table 27: Presence of Pyoderma Pre-treatment and Post-treatment**

Pyoderma	6 months- 3 years		4-11 years		> 12 years	
	5% L.A.	Vehicle	5% L.A.	Vehicle	5% L.A.	Vehicle
<i>Pre-treatment</i>	7/35(20.0%)	10/35(28.6%)	46/155(29.7%)	46/168(27.4%)	26/118(22.0%)	27/114(23.7%)
<i>1<sup>st</sup> evaluation visit</i>	6/34(17.6%)	7/35(20.0%)	45/151(29.8%)	40/165(24.2%)	23/116(19.8%)	28/111(25.2%)
<i>2<sup>nd</sup> evaluation visit</i>	1/28( 3.6%)	3/7(42.8%)	19/129(14.7%)	5/54( 9.2%)	9/102( 8.8%)	4/37(10.8%)

Source: Sponsor's NDA submission: 12/28/07, Table 3.1.3 Skin and Scalp evaluation, Protocol SU-01-2005 and SU-02-2005

Although, both treatment groups showed continuous improvement in the severity of pyoderma, the presence of skin and scalp pyoderma was observed at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit in subjects without pyoderma prior to either treatment.

- At the 1<sup>st</sup> evaluation visit, 16 of 223 (7.2%) subjects treated with 5 % L.A. with no pyoderma prior to treatment developed mild/moderate pyoderma, compared to 8 of 230 (3.5%) subjects treated with vehicle control. Three of subjects (5% L.A. treatment group) were from the 6 months to 3 years age group, 7 were from the 4-11 years age group, and 6 were from the > 12 years age group.
- At the 2<sup>nd</sup> evaluation visit, 6 of 186 (3.2%) subjects treated with 5 % L.A. with no pyoderma prior to treatment developed mild pyoderma compared to 2 of 75 (2.7%) subjects treated with vehicle control. None of 6 subjects (5% L/A. treatment group) was from the 6 mounts to 3 years age group, 4 were from the 4-11 years age group, and 2 were from the > 12 years age group.

Overall, continuous improvement in the severity of pyoderma was observed in both treatment groups (5% L.A. and vehicle control), and in all three age groups. Children 6 months to 3 years treated with 5 % L.A. are not at grater risk of developing pyoderma of the skin and scalp, than older subjects.

### Excoriation

The majority of the subjects did not have excoriation prior to treatment. Both treatment groups showed improvement in severity of skin and scalp excoriation throughout studies.

- In the 5% L.A. treatment group, excoriation of the scalp was present in 82 of 308 (26.6%) subjects prior to treatment, in 56 of 301 (18.6%) subjects at the 1<sup>st</sup> evaluation visit, and in 12 of 259 (4.6%) subjects at the 2<sup>nd</sup> evaluation visit.
- In the vehicle treatment group, excoriation was present prior to treatment in 88 of 320 (27.5%), at 1<sup>st</sup> evaluation visit in 71 of 311 (22.8%), and at the 2<sup>nd</sup> evaluation visit in 7 of 98 (7.1%) subjects.

Similar findings were observed between children (6 months to 11 years of age group) and older subjects.

- In the 6 months to 11 years age group, 53 of 190 (27.9%) subjects had excoriation of the scalp present prior to treatment with 5% L.A. compare to 29 of 118 (24.6%) subjects in the > 12 years age group.
- At the 1<sup>st</sup> evaluation visit, pyoderma was present in 38 of 185 (20.5%) subjects in the 6 months to 11 years age group, and in 18 of 116 (15.5%) subjects from the > 12 years age group.
- At the 2<sup>nd</sup> evaluation visit, 8 of 157 (6.2%) and 4 of 102 (3.9%) subjects had pyoderma present in the 6 months to 11 years age group and the > 12 years age group, retrospectively.

**Table 28: Presence of Excoriation Pre-treatment and Post-treatment**

<b>Excoriation</b>	<b>6 months- 3 years</b>		<b>4-11 years</b>		<b>&gt; 12 years</b>	
	<b>5%L.A.</b>	<b>Vehicle</b>	<b>5%L.A.</b>	<b>Vehicle</b>	<b>5%L.A.</b>	<b>Vehicle</b>
<i>Pre-treatment</i>	9/35 (25.7%)	9/35 (25.7%)	44/155 (28.4%)	49/168 (29.2%)	29/118 (24.6%)	9/114 (25.4%)
<i>1<sup>st</sup> evaluation visit</i>	6/34 (17.6%)	8/35 (22.8%)	32/151 (21.2%)	35/165 (21.2%)	18/116 (15.5%)	28/111 (25.2%)
<i>2<sup>nd</sup> evaluation visit</i>	2/28 (7.1%)	2/ 7 (28.6%)	6/129 ( 4.6%)	2/ 54 ( 3.7)	4/102 (3.9%)	3/ 37 ( 8.1%)

Source: Sponsor's NDA submission: 12/28/07, Table 3.1.3 Skin and Scalp evaluation, Protocol SU-01-2005 and SU-02-2005

Although, overall both treatment groups showed continuous improvement in the severity of excoriation, presence of skin and scalp excoriation was observed at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit in subjects without excoriation prior to either treatment.

- At the 1<sup>st</sup> evaluation visit, 11 of 219 (5.0%) subjects treated with 5 % L.A. with no excoriation prior to treatment developed mild excoriation, compared to 15 of 225 (6.7%) subjects treated with vehicle control. One of 11 subjects (5% L.A. treatment group) were from the 6 months to 3 years age group, 5 were from the 4-11 years age group, and 5 were from the > 12 years age group.

- At the 2<sup>nd</sup> evaluation visit, 2 of 182 (1.1%) subjects treated with 5 % L.A. with no excoriation prior to treatment developed mild excoriation compared to 3 of 73 (4.1%) subjects treated with vehicle control. One of two subjects (5% L/A. treatment group) was from the 6 months to 3 years age group, one was from the 4-11 years age group, and none were from the > 12 years age group.

Overall, continuous improvement in the severity of excoriation was observed in both treatment groups (5% L.A. and vehicle control), and in all three age groups. Children 6 months to 3 years treated with 5 % L.A. are not at greater risk of developing excoriation of the skin and scalp, than older subjects.

**Table 29: Frequency of Shifts from Baseline in Severity of Scalp Signs/Symptoms**

	5% L.A			Vehicle		
	SU-01-2005	SU-02-2005	Total	SU-01-2005	SU-02-2005	Total
	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)
<b>Pruritus</b>						
<i>First Evaluation</i>						
Moderate to severe	0/42 (0%)	2/45(4%)	2/87 (2%)	2/55 (4%)	0/40 (0%)	2/95 (2%)
Mild to moderate	0/53 (0%)	0/39 (0%)	0/92 (0%)	0/57 (0%)	3/38 (8%)	3/95 (3%)
None to Mild	4/24 (17%)	5/51 (10%)	9/75 (12%)	2/17 (12%)	1/50 (2%)	3/67 (4%)
None to Moderate	0/24 (0%)	1/51 (2%)	1/75 (1%)	0/17 (0%)	0/50 (0%)	0/67 (0%)
<i>Second Evaluation</i>						
Moderate to severe	0/41 (0%)	0/37 (0%)	0/78 (0%)	0/15 (0%)	0/10 (0%)	0/25 (0%)
Mild to moderate	0/47 (0%)	0/31 (0%)	0/78 (0%)	0/12 (0%)	0/17 (0%)	0/29 (0%)
None to Mild	4/22 (18%)	0/41 (0%)	4/63 (6%)	0/5 (0%)	0/24 (0%)	0/29 (0%)
None to Moderate	0/22 (0%)	0/41 (0%)	0/63 (0%)	0/5 (0%)	0/24 (0%)	0/29 (0%)
<b>Erythema</b>						
<i>First Evaluation</i>						
Moderate to severe	0/11 (0%)	0/7 (0%)	0/18 (0%)	0/14 (0%)	0/10 (0%)	0/24 (0%)
Mild to moderate	0/26 (0%)	1/32 (3%)	1/58 (2%)	2/29 (7%)	0/37 (0%)	2/66 (3%)
None to Mild	6/104 (6%)	10/119 (8%)	16/223 (7%)	10/116(9%)	2/101 (2%)	12/217 (6%)
None to Moderate	1/104(1%)	1/119 (1%)	2/223 (1%)	1/116 (1%)	0/101 (0%)	1/217 (0.5%)
<i>Second Evaluation</i>						
Moderate to severe	0/11 (0%)	0/5 (0%)	0/16 (0%)	0/7 (0%)	0/6 (0%)	0/13 (0%)
Mild to moderate	1/23 (4%)	0/29 (0%)	1/52 (2%)	0/5 (0%)	0/12 (0%)	0/17 (0%)
None to Mild	4/96 (4%)	3/93 (3%)	7/189 (4%)	1/26 (4%)	4/42 (10 %)	5/68 (7%)
None to Moderate	1/96 (1%)	0/93 (0%)	1/189 (1%)	2/26 (8%)	0/42 (0%)	2/68 (3%)
<b>Pyoderma</b>						
<i>First Evaluation</i>						
Moderate to severe	0/13 (0%)	0/7 (0%)	0/20 (0%)	0/23 (0%)	0/5 (0%)	0/28 (0%)
Mild to moderate	1/32 (3%)	1/22 (5%)	2/54 (4%)	3/24 (13%)	1/21 (5%)	4/45 (9%)
None to Mild	2/93 (2%)	12/130 (9%)	14/223 (6%)	3/108 (3%)	5/122 (4%)	8/230 (3%)
None to Moderate	0/93 (0%)	2/130 (2%)	2/223 (1%)	0/108 (0%)	0/119 (0%)	0/227 (0%)
<i>Second Evaluation</i>						

Moderate to severe	0/13 (0%)	0/5 (0%)	0/18 (0%)	0/9 (0%)	0/3 (0%)	0/12 (0%)
Mild to moderate	0/32 (0%)	0/19 (0%)	0/51 (0%)	0/5 (0%)	0/5 (0%)	0/10 (0%)
None to Mild	3/82 (4%)	3/104 (3%)	6/186 (3%)	2/23 (8%)	0/52 (0%)	2/75 (3%)
None to Moderate	0/82 (0%)	0/104 (0%)	0/186 (0%)	0/23 (0%)	0/52 (0%)	0/75 (0%)
<b>Excoriation</b>						
<i>First Evaluation</i>						
Moderate to severe	0/10 (0%)	0/9 (0%)	0/19 (0%)	0/17 (0%)	0/4 (0%)	0/21 (0%)
Mild to moderate	1/31 (3%)	0/30 (0%)	1/61 (2%)	0/28 (0%)	0/31 (0%)	0/59 (0%)
None to Mild	3/99 (3%)	8/120 (7%)	11/219 (5%)	7/112 (6%)	7/113 (6%)	14/225 (6%)
None to Moderate	0/99 (0%)	0/120 (0%)	0/219 (0%)	1/112 (1%)	0/113 (0%)	1/225 (0%)
<i>Second Evaluation</i>						
Moderate to severe	0/10 (0%)	0/8 (0%)	0/18 (0%)	0/6 (0%)	0/1 (0%)	0/7 (0%)
Mild to moderate	0/31 (0%)	0/26 (0%)	0/57 (0%)	0/6 (0%)	0/10 (0%)	0/16 (0%)
None to Mild	0/88 (0%)	2/94 (2%)	2/182 (1%)	2/24 (8%)	0/49 (0%)	2/73 (3%)
None to Moderate	0/88 (0%)	0/94 (0%)	0/182 (0%)	1/24 (4%)	0/49 (0%)	1/73 (1%)

Source: Sponsor's NDA submission: 12/28/07, 2.7.4 Summary of Clinical Safety, Table 2.7.4.4.1(1) Frequency of Shift from Baseline in Severity of Scalp Signs/Symptoms

### **SU-03-2005**

In the open label study, SU-03-2005, 128 subjects received treatment with 5% L.A. of whom 13 were treatment failures from two pivotal trials.

The 5% L.A. treatment showed improvement in pruritus, erythema, pyoderma and excoriation in all three age groups.

#### **Pruritus:**

The majority of the subjects (81/128; 63.3%) had pruritus prior to treatment. Twenty-eight of 128 (21.9%) subjects, and 12 of 121 (9.9%) subjects had pruritus at the 1<sup>st</sup> and the 2<sup>nd</sup> evaluation visit, respectively. One of 47 subjects (2.1%) without pruritus prior to treatment developed mild pruritus at the 1<sup>st</sup> evaluation visit and 3 of 46 (6.5%) without pruritus developed pruritus at the 2<sup>nd</sup> evaluation visit. Worsening of the pruritus was observed in 1 of 45 (2.2%) subjects with mild pruritus prior to treatment. This subject developed moderate pruritus at the 1<sup>st</sup> evaluation visit. In the 6 months to 3 years age group, 51 subjects received treatment with 5% L.A. One of 22 subjects (4.5%) without pruritus prior to treatment, develop mild pruritus at the 1<sup>st</sup> evaluation visit and 1 of 21 (4.8%) subjects without pruritus developed pruritus at the 2<sup>nd</sup> evaluation visit. Forty seven subjects in the age 4 to 11 years group received treatment with 5 % L.A. None of 15 subjects without pruritus prior to treatment developed pruritus at the 1<sup>st</sup> evaluation visit, and 1 of 15 subjects without pruritus developed pruritus at the 2<sup>nd</sup> evaluation visit. In the >12 years age group, 30 subjects received treatment with 5% L.A. None of 10 subjects without pruritus prior to treatment developed pruritus at the 1<sup>st</sup> evaluation visit, and 1 of 10 (10%) subjects developed pruritus at the 2<sup>nd</sup> evaluation visit.

Overall in all three age groups, treatment with 5% L.A. showed continuous improvement in severity of the pruritus throughout the study.

**Table 30: Presence of Pruritus Pre-treatment and Post-treatment**

<b>Pruritus</b>		Double blind Tx failure: 5% L.A. N = 13	Double blind Tx failure: Vehicle N = 68	New subjects N = 47	Overall N = 128
<i>Pre-treatment</i>	N	13	68	47	128
	None	6 (46.2%)	15 (22.1%)	26 (55.3%)	47 (36.7%)
	Mild	5 (38.5%)	33 (48.5%)	7 (14.9%)	45 (35.2%)
	Moderate	0 (0.0%)	12 (17.6%)	12 (25.5%)	24 (18.8%)
	Severe	2 (15.4%)	8 (11.8%)	2 (4.3%)	12 (9.4%)
<i>1<sup>st</sup> evaluation visit</i>	N	13	68	47	128
	None	10 (76.9%)	48 (70.6)	42 (89.4%)	100 (78.1%)
	Mild	2 (15.4%)	12 (11.3%)	3 (6.4%)	17 (13.3%)
	Moderate	1 (7.7%)	7(10.3%)	1 (2.1%)	9 (7.0%)
	Severe	0 (0.0%)	1 (1.5%)	1 (2.1%)	2 (1.6%)
<i>2<sup>nd</sup> evaluation visit</i>	N	13	62	46	121
	None	10 (76.9%)	55 (88.7%)	44 (95.7%)	109 (90.1%)
	Mild	3 (23.1%)	7 (11.3%)	2 (4.3%)	12 (9.9%)
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's NDA submission: 03/09/2007, Clinical Study Report, Table 3.1 Skin and scalp evaluation

### Erythema

In the majority of subjects (93/128; 72.7%), erythema of the skin and scalp was not present prior to treatment with 5% L.A. Twenty one of 128 (16.4%) and 7 of 121 (5.8%) subjects experienced erythema at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, retrospectively.

**Table 31: Presence of Erythema Pre-treatment and Post-treatment**

<b>Erythema</b>		Double blind Tx failure: 5% L.A. N = 13	Double blind Tx failure: Vehicle N = 68	New subjects N = 47	Overall N = 128
<i>Pre-treatment</i>	N	13	68	47	128
	None	7 (53.8%)	48 (69.1%)	39 (83.0%)	93 (72.7%)
	Mild	5 (38.5%)	19 (27.9%)	5 (10.6%)	29 (22.7%)
	Moderate	1 ( 7.7%)	2 ( 2.9%)	3 (6.4%)	6 (4.7%)
	Severe	0 ( 0.0%)	0 ( 0.0%)	0 (0.0%)	0 (0.0%)
<i>1<sup>st</sup> evaluation visit</i>	N	13	68	47	128
	None	11 (84.6%)	56 (82.4%)	40 (85.1%)	107 (83.6%)
	Mild	2 (15.4%)	9 (13.2%)	4 (8.5%)	15 (11.7%)
	Moderate	0 ( 0.0%)	3(4.4%)	3 (6.4%)	6 (4.7%)
	Severe	0 ( 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>2<sup>nd</sup> evaluation visit</i>	N	13	62	46	121
	None	12 (92.3%)	58 (93.5%)	44 (95.7%)	114 (94.2%)
	Mild	1 ( 7.7%)	4 ( 6.5%)	2 ( 4.3%)	7 (5.8%)
	Moderate	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's NDA submission: 03/09/2007, Clinical Study Report, Table 3.1 Skin and scalp evaluation

Similar improvement in severity of scalp erythema was observed between different age groups.

**Table 32: Presence of Erythema Pre-treatment and Post-treatment per age group**

<b>Erythema</b>	<b>6m -3y age group</b>	<b>4y- 12 y age group</b>	<b>&gt; 12 y age group</b>
<i>Pre-treatment</i>	12/51 (23.5%)	14/47 (29.8%)	9/30 (30.0%)
<i>1<sup>st</sup> evaluation visit</i>	10/51 (19.6%)	7/47 (14.9%)	4/30 (13.1%)
<i>2<sup>nd</sup> evaluation visit</i>	4/47 (6.4%)	0/45 (0.0%)	4/30 (13.1%)

Five of 93 subjects (5.4%) without erythema prior to treatment developed mild (4)/ moderate (1) erythema at the 1<sup>st</sup> evaluation visit and 3 of 87 (3.4%) subjects developed mild erythema at the 2<sup>nd</sup> evaluation visit. Worsening of erythema was observed in 3 of 29 (10.3%) subjects with mild erythema prior to treatment. These subjects developed moderate erythema at the 1<sup>st</sup> evaluation visit.

In the 6 months to 3 years age group, 3 of 39 (7.7%) without erythema prior to treatment developed mild erythema at the 1<sup>st</sup> evaluation visit and one of 36 (2.8%) developed erythema at the 2<sup>nd</sup> evaluation visit. In the 4 to 11 years age group, one of 3 (3.0%) subjects without erythema developed moderate erythema at the 1<sup>st</sup> evaluation visit and none of 31 (0.0%) subjects developed erythema at the 2<sup>nd</sup> evaluation visit. In the > 12 years age group, one of 21 (4.8%) subjects without erythema prior to treatment developed erythema at the 1<sup>st</sup> evaluation visit and 2 of 20 (10%) subjects developed erythema at the 2<sup>nd</sup> evaluation visit.

Worsening of erythema was observed in 3 of 29 subjects with mild erythema prior to treatment. These subjects developed moderate erythema at the 1<sup>st</sup> evaluation visit. Two of these three subjects were from the 6m-3 years age group and one subject was from 4-11 years age group.

Overall, in all three age groups treatment with 5%L.A. showed continuous improvement in severity of erythema throughout the study.

### Pyoderma

Mild to severe pyoderma of the skin and scalp was present in 32 of 128 (25%) subjects prior to treatment with 5 % L.A. Twenty seven of 128 (21.1%) and 9 of 121 (7.4%) subjects had pyoderma of the scalp at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, retrospectively.

**Table 33: Presence of Pyoderma Pre-treatment and Post-treatment**

<b>Pyoderma</b>		Double blind Tx failure: 5% L.A. N = 13	Double blind Tx failure: Vehicle N = 68	New subjects N = 47	Overall N = 128
<i>Pre-treatment</i>	N	13	68	47	128
	None	11 (84.6%)	52 (76.5%)	33 (70.2%)	96 (75.0%)
	Mild	1 ( 7.7%)	9 (13.2%)	9 (19.1%)	19 (14.8%)
	Moderate	1 ( 7.7%)	6 ( 8.8%)	2 ( 4.3%)	9 ( 7.0%)
	Severe	0 ( 0.0%)	1 ( 1.5%)	3 ( 6.4%)	4 ( 3.1%)



<i>1<sup>st</sup> evaluation visit</i>	N	13	68	47	128
	None	12 (92.3%)	56 (82.4%)	33 (70.2%)	101 (78.9%)
	Mild	1 ( 7.7%)	7 ( 10.3%)	9 (19.1%)	17 ( 13.3%)
	Moderate	0 ( 0.0%)	4 ( 5.9%)	5 (10.6%)	9 ( 7.0%)
	Severe	0 ( 0.0%)	1 ( 1.5%)	0 ( 0.0%)	1 ( 0.8%)
<i>2<sup>nd</sup> evaluation visit</i>	N	13	62	46	121
	None	13 (100.0%)	57 (91.9%)	42 (91.3%)	112 (92.6%)
	Mild	0 ( 0.0%)	5 ( 8.1%)	4 ( 8.7%)	9 ( 7.4%)
	Moderate	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
	Severe	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)

One of 96 (1.0%) subjects without pyoderma of the skin and scalp developed mild pyoderma at the 1<sup>st</sup> evaluation visit. This subject was from the 4-11 years age group.

Worsening of the pyoderma was observed in one of 19 (5.3%) subjects with mild pyoderma prior to treatment. This subject (> 12 y age group) developed moderate pyoderma at the 1<sup>st</sup> evaluation visit.

In the 6 months to 3 years age group, 12 of 51 (23.5%) subjects had pyoderma prior to treatment, 11 of 51 (21.6%) at the 1<sup>st</sup> evaluation visit, and 4 of 47 (8.5%) at the 2<sup>nd</sup> evaluation visit.

In the 4-11 years age group, 12 of 47 (25.5%) subjects had had pyoderma prior to treatment, 12 of 47 (25.5%) at the 1<sup>st</sup> evaluation visit, and 4 of 45 (8.9%) at the 2<sup>nd</sup> evaluation visit.

In the >12 years age group, 8 of 30 (26.7%) subjects had had pyoderma prior to treatment, 4 of 30 (13.3%) at the 1<sup>st</sup> evaluation visit, and 1 of 29 (3.4%) at the 2<sup>nd</sup> evaluation visit.

Overall, in all three age groups treatment with 5% L.A. showed continuous improvement in severity of scalp and skin pyoderma throughout the study.

### Excoriation

Majority of the subjects did not have excoriation of the skin and scalp prior to treatment.

Mild to severe excoriation of the skin and scalp was present in 38 of 128 (29.7%) subjects prior to treatment with 5 % L.A. Fourteen of 128 (10.9%) and 8 of 121 (6.6%) subjects had excoriation of the scalp at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, retrospectively.

**Table 34: Presence of Excoriation Pre-treatment and Post-treatment**

<b>Excoriation</b>		Double blind Tx failure: 5% L.A. N = 13	Double blind Tx failure: Vehicle N = 68	New subjects N = 47	Overall N = 128
<i>Pre-treatment</i>	N	13	68	47	128
	None	10 (76.9%)	52 (76.5%)	28 (59.6%)	90 (70.3%)
	Mild	3 (23.1%)	11 (16.2%)	15 (31.9%)	29 (22.7%)
	Moderate	0 ( 0.0%)	4 ( 5.9%)	2 ( 4.3%)	6 ( 4.7%)
	Severe	0 ( 0.0%)	1 ( 1.5%)	2 ( 4.3%)	3 ( 2.3%)
<i>1<sup>st</sup> evaluation visit</i>	N	13	68	47	128
	None	12 (92.3%)	61 (89.7%)	41 (87.2%)	114 (89.1%)
	Mild	1 ( 7.7%)	4 ( 5.9%)	2 ( 4.3%)	7 ( 5.5%)

	Moderate	0 ( 0.0%)	2 ( 2.9%)	4 ( 8.5%)	6 ( 4.7%)
	Severe	0 ( 0.0%)	1 ( 1.5%)	0 ( 0.0%)	1 ( 0.8%)
<i>2<sup>nd</sup> evaluation visit</i>	N	13	62	46	121
	None	12 (92.3%)	57 (91.9%)	44 (95.7%)	113 (93.4%)
	Mild	0 ( 0.0%)	5 ( 8.1%)	2 (4.3%)	7 ( 5.8%)
	Moderate	1 ( 7.7%)	0 ( 0.0%)	0 (0.0%)	1 ( 0.8%)
	Severe	0 ( 0.0%)	0 ( 0.0%)	0 (0.0%)	0 ( 0.0%)

Source: Sponsor's NDA submission: 12/28/07, Clinical Study Report, Table 3.1. Skin and scalp evaluation by visit

Two of 90 (2.2%) subjects without excoriation of the skin and scalp developed mild excoriation at the 1<sup>st</sup> evaluation visit. One subject who developed mild excoriation was from the 6 months to 3 years age group and one was from the > 12 years age group.

Three of 83 (3.6%) subjects without excoriation of the skin and scalp developed mild/moderate excoriation at the 2<sup>nd</sup> evaluation visit. These subjects were from the 6 months to 3 years age group.

In all three age groups treatment with 5% L.A. showed continuous improvement in severity of scalp and skin excoriation throughout the study.

- In the 6 months to 3 years age group, 14 of 51 (27.4%) subjects had mild to moderate scalp excoriation prior to treatment, 6 of 51 (11.8%) at the 1<sup>st</sup> evaluation visit, and 4 of 47 (8.5%) at the 2<sup>nd</sup> evaluation visit.
- In the 4-11 years age group, 16 of 47 (34.0%) subjects had had excoriation prior to treatment, 5 of 47 (10.6%) at the 1<sup>st</sup> evaluation visit, and 3 of 45 (6.7%) at the 2<sup>nd</sup> evaluation visit.
- In the >12 years age group, 8 of 30 (26.7%) subjects had had excoriation prior to treatment, 3 of 30 (10.0%) at the 1<sup>st</sup> evaluation visit, and 1 of 29 (3.4%) at the 2<sup>nd</sup> evaluation visit.

### **Phase 2 studies:**

In the Phase 2 clinical studies (SU-02-2004, SU-02-2003A, SU-02-2003), investigators actively assessed for signs (erythema, pyoderma) and symptoms (pruritus) of the effects of lice infestation and/or irritation from application of 5% L.A. Sixty two subjects (age 2-70 years of age) received 10 minutes treatment with 5% L.A. one week apart.

The majority of the subjects (55/62; 88.7%) had pruritus prior to treatment. Treatment with 5% L.A. showed continuous improvement in severity of the pruritus throughout the studies [39 of 62 (62.9%) and 25 of 59 (42.4%) subjects had pruritus at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, retrospectively]. One subject (43 01S-43- study SU-02-2003A) without pruritus prior to treatment developed pruritus after the second treatment and one subjects (01-032, Study SU-02-2994) with moderate pruritus prior to treatment developed severe pruritus after the second treatment with 5% L.A.

Erythema of the scalp was present in one of 62 subjects (01-107, Study SU-02-2004) prior to treatment and none of subjects had erythema at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit.

In the Phase 2 studies, none of subjects had pyoderma of scalp and skin present.

### **“OTHER” signs and symptoms**

In addition to the four local skin/scalp reactions as described above, the CRF also contained a category “other” with the same scoring scale as described above to capture additional local skin/scalp irritation. For “other” signs and symptoms, a pooled analysis of all Phase 2 and Phase 3 studies was performed. (See Table 35)

- Thirty-three (6.9%) of the 478 subjects treated with 10- minute application of 5% L.A. were reported to have 52 “other” signs and/or symptoms of the scalp.  
The most frequently reported signs and symptoms were:
  - “Application site irritation” (11 subjects: two subjects from the 6 months to 3 years age group; six subjects from the 4-11 years, and three subjects from the >12 years age group; mild “burning” lasted from few seconds to 5 minutes)
  - “Application site anesthesia” and “Hypoesthesia” combined (10 subjects: four from the 4-11 years age group and six from the >12 years age group); “numbness” lasted from 1 minute to 2 hours). One subject (SU-02-2005; 08-205-0304; 11y/o F, “numbness”) reported severe hypoesthesia at the 2<sup>nd</sup> evaluation visit.
  - “Pain” (5 subjects: one subject was 3 years old, two subjects were from the 4-11 years age group and two from the > 12 years age group); mild “sting” lasted from 10 seconds to 1-2 minutes).
  - One subject (SU 01-2005; 02-111-0409, 34y/o F ), reported an adverse event of application site irritation associated with application of 5 % L.A. (“ burning of scalp” mild, probably related, action taken : none; recovery within 24h)
- Fifteen (4.5%) of 336 subjects treated with vehicle for 10 minutes were reported 19 “other” signs and/or symptoms of the scalp.  
The most frequently reported signs and symptoms was paraesthesia (4; mild “tingling”)

Severe events were reported by two subjects:

- 9y/o F (SU 01-2005; 03-126-0226): reported skin ulcer that was considered “moderate” at baseline, and “severe” at the 1<sup>st</sup> evaluation visit
- 45y/o F (SU 01-2005; 04-101-0201): reported paraesthesia (“tingling”) that was considered “moderate” at baseline, “mild” at the 1<sup>st</sup> evaluation visit, and “severe” at the 2<sup>nd</sup> evaluation visit

**Table 35: Skin and Scalp Evaluation (“OTHER” Signs and Symptoms) MedRa System**  
**Organ Class/Preferred Term (number of subjects)**

System organ class/preferred term	5% L.A. (N= 478)	Vehicle (N=336)
General disorders		
<b>Administration Application site condition</b>		
Application site anesthesia	6 (1.2%)	0 (0.0%)
Application site bleeding	0 (0.0%)	1 (0.3%)
Application site dermatitis	1 (0.2%)	0 (0.0%)

Application site dryness	3 (0.6%)	0 (0.0%)
Application site excoriation	2 (0.4%)	0 (0.0%)
Application site irritation	11 (2.3%)	2 (0.6%)
Application site pain	0 (0.0%)	1 (0.3%)
Application site papules	0 (0.0%)	1 (0.3%)
Application site pruritus	0 (0.0%)	1 (0.3%)
Application site reaction	1 (0.2%)	2 (0.6%)
Pain	5 (1.0%)	1 (0.3%)
<b>Injury, poisoning and procedural complication</b>		
Excoriation	1 (0.2%)	0 (0.0%)
Thermal burn	1 (0.2%)	0 (0.0%)
<b>Nervous System disorder</b>		
Dizziness	0 (0.0%)	1 (0.3%)
Hypoanesthesia	4 (0.8%)	0 (0.0%)
paraesthesia	2 (0.4%)	4 (1.2%)
<b>Skin and subcutaneous tissue disorder</b>		
Dandruff	1 (0.2%)	0 (0.0%)
Erythema	1 (0.2%)	0 (0.0%)
Rash	1 (0.2%)	0 (0.0%)
Seborrheic dermatitis	0 (0.0%)	2 (0.6%)
Skin exfoliation	1 (0.2%)	1 (0.3%)
Skin ulcer	0 (0.0%)	1 (0.3%)

\*Same event is counted once for each subject

\* Among the total 71 events, 59 unique events are counted

Source: Sponsor's NDA submission: 12/28/07, ISS; Skin and scalp evaluation (OTHER) MedRA System Organ Class/ Preferred Term (number of subjects), Table 5

- Benzyl alcohol at low concentration (in saline solution; 0.9%) injected intradermally has been reported in the literature to be useful as a local anesthetic for brief superficial skin procedures.<sup>1</sup>
- Adverse reaction such as pain and paresthesia, have been reported with use of Lindane Lotion and Shampoo (see labeling, ADVERSE REACTION).
- Burning, stinging, tingling and numbness are described as possible side effects with the use of permethrins ( Nix Cream Rinse, PI)

**Reference:**

<sup>1</sup> Ann Emerg Med. 1999 May; 33(5):495-9; Wilson L., Martin S.; Benzyl alcohol as an alternative local anesthetic

**B. OCULAR IRRITATION**

In Phase 3 clinical trials (SU-01-2005, SU-02-2005, and open label SU-03-2005), ocular irritation was evaluated on Day 2 (one day post 1<sup>st</sup> treatment), and Day 9 (one day post 2<sup>nd</sup> treatment) using the same four-category scale as for skin and scalp evaluation. Evaluations of ocular irritation were collected on separate case report form. Time of onset, time of resolution, therapy, and outcome were not collected for ocular irritation. A review of concomitant medication listing for the three studies does not reveal any use of medication to treat ocular

irritation. Ocular irritation was describe as itching, burning, redness, redness of upper and lower eye lids, stinging, and burning around eyes.

Subjects were instructed to protect their eyes during treatment with the provided towel.

### **SU-01-2005 and SU-02-2005**

During the studies SU-01-2005 and SU-02-2005, 22 subjects had ocular irritation (19 subjects in the 5% L.A. treatment group and 3 subjects in the vehicle treatment group). 13 subjects (13/300, 4.3%) treated with 5% L.A. experienced ocular irritation at the 1<sup>st</sup> evaluation visit, and 7 (7/259, 2.7%) at the 2<sup>nd</sup> evaluation visit. In the vehicle treatment group one subject (1/313, 0.3%) had ocular irritation at the 1<sup>st</sup> evaluation visit and two (2/98, 2.0%) subjects at the 2<sup>nd</sup> evaluation visit. At the 1<sup>st</sup> evaluation visit, 4 of 185 (2.16%) subjects age 6 months to 11 years treated with 5% L.A. had ocular irritation compare to 9 of 115 (7.8%) subjects from the > 12 years age group. At the 2<sup>nd</sup> evaluation visit, 3 of 157 (1.9%) subjects age 6 months to 11 years treated with 5% L.A. had ocular irritation compare to 4 of 102 (3.9%) subjects from the > 12 years age group. Young children were not at grater risk of ocular irritation than older children and adults.

- During the study SU-01-2005, 8 subjects treated with 5% L.A. experienced ocular irritation. Five subjects were in the >12 years of age group (4/52, 7.69% at 1<sup>st</sup> evaluation visit; 1/48, 2.1% at 2<sup>nd</sup> evaluation visit), 3 in the 4-11 years group (3/75, 4.0% at 1<sup>st</sup> evaluation visit, 0/69, 0.0% at 2<sup>nd</sup> evaluation visit), and none (0/14, 0.0% at 1<sup>st</sup> evaluation visit, 0/13, 0.0% at 2<sup>nd</sup> evaluation visit) in the 6 months to 3 years group. Seven subjects (5%) experienced ocular irritation at the first evaluation visit. Of these, 6 subjects had mild ocular irritation, and one subject (01-118-0418; 12y/o Hispanic female; long hair, amount used 610g – 1<sup>st</sup> and 615g-2<sup>nd</sup> treatment) experienced eye irritation (burning) that was rated severe. None of these subjects had ocular irritation on second evaluation visit. One subject (0.8%) had mild ocular irritation at the second evaluation visit (for the first time). No ocular irritation occurred in the vehicle group.
- During the study SU-02-2005, 11 subjects treated with 5% L.A. experienced ocular irritation (redness, inching, burning). Five subjects experienced ocular irritation at the first evaluation visit, five at the second evaluation visit and one subject had ocular irritation at both evaluation visits. From 6 subjects who experienced ocular irritation at the first evaluation visit, one (1/76, 1.3%) subject was in 4-11 years group, and 5 (5/63, 7.9%) were from the >12 years of age group. None (0/20, 0.0%) in the 6 months to 3 years age group had ocular irritation at the first evaluation visit. At second evaluation visit, one subject (1/15, 6.7%) was from 6 month to 3 years of age group, 2 (2/60, 3.3%) in 4-11 years group and 3 (3/54, 5.5%) in the > 12 years of age group. All ocular irritations were mild except for two subjects who experienced moderate ocular irritation (stinging and burning around eyes) at the second evaluation visit (>12 years old age group). Three subjects treated with the vehicle experienced ocular irritation. One subject had ocular irritation at the first evaluation visit (1/153, 0.7%) and 2 (2/60, 3.3%) at second

evaluation visit. In the 6 months to 3 years age group, none experienced ocular irritation on either visits (0/17, 0.0%; 0/3, 0.0%). At first evaluation visit, one (1/79, 1.3%) subject in the 4-11 years group and none (0/57, 0.0%) in the > 12 years age group had ocular irritation. At second evaluation visit none (0/38, 0.0%) in the 4-11 years group, and 2 (2/19, 10.5%) in the > 12 years group had ocular irritation. All ocular irritations were mild.

Table below summarized the frequency of the ocular irritation in the two pivotal studies.

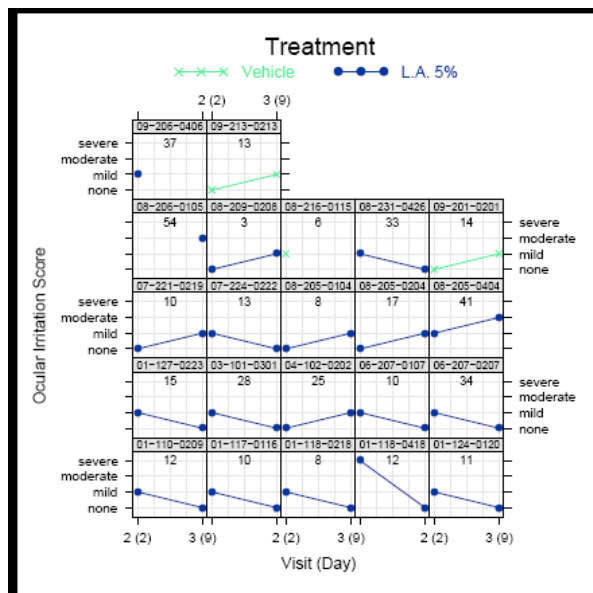
**Table 36: Frequency of Ocular Irritation by Severity**

	<b>5% L.A.</b>			<b>Vehicle Control</b>		
	<b>SU-01-2005</b>	<b>SU-02-2005</b>	<b>Total</b>	<b>SU-01-2005</b>	<b>SU-02-2005</b>	<b>Total</b>
<i>First Evaluation</i>						
None	134/141 (95%)	153/159 (96.2%)	287/300 (95.6%)	160/160 (100.0%)	152/153 (99.3%)	312/313 (99.6%)
Mild	6/141 (4.3%)	6/159 (3.8%)	12/300 (4.0%)	0/160 (0.0%)	1/153 (0.7%)	1/313 (0.3%)
Moderate	0/141 (0.0%)	0/159 (0.0%)	0/300 (0.0%)	0/160 (0.0%)	0/153 (0.0%)	0/313 (0.0%)
Severe	1/141 (0.7%)	0/159 (0.0%)	1/300 (0.3%)	0/160 (0.0%)	0/153 (0.0%)	0/313 (0.0%)
<i>Second Evaluation</i>						
None	129/130 (99.2%)	123/129 (95.3%)	252/259 (97.2%)	38/38 (100.0%)	58/60 (96.7%)	96/98 (97.9%)
Mild	1/130 (0.8%)	4/129 (3.1%)	5/259 (1.9%)	0/38 (0.0%)	2/60 (3.3%)	2/98 (2.0%)
Moderate	0/130 (0.0%)	2/129 (1.6%)	2/259 (0.7%)	0/38 (0.0%)	0/60 (0.0%)	0/98 (0.0%)
Severe	0/130 (0.0%)	0/129 (0.0%)	0/259 (0.0%)	0/38 (0.0%)	0/60 (0.0%)	0/98 (0.0%)

Source: Sponsor's NDA submission: 12/28/07, 2.7.4 Summary of Clinical Safety, Table 2.7.4.4.2(1) Frequency of Ocular Irritation by Severity; Table 4.1

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**Figure 9: Ocular irritation/Visit**



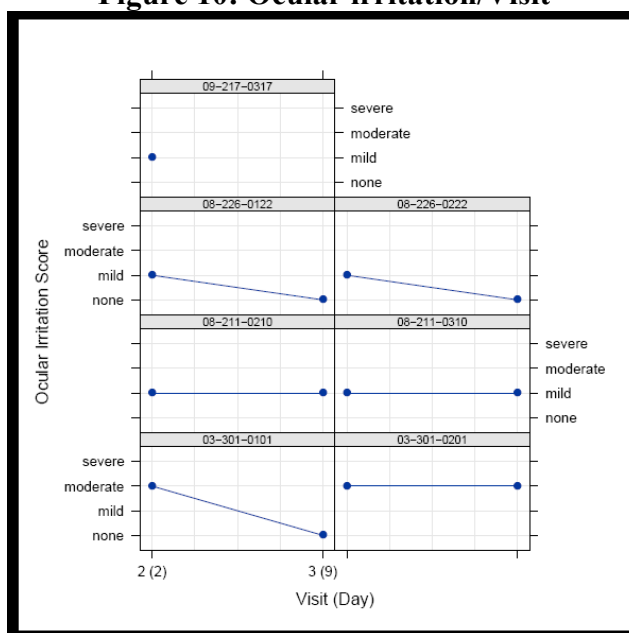
### **SU-03-2005**

During the open label study, SU- 03-2005, 7 subjects (5.5%) experienced ocular irritation (redness of eye lids, burning 1-2 minutes), three of which were reported at both the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visits.

At the 1<sup>st</sup> evaluation visit 7 of 128 (5.5%) subjects had ocular irritation (5 mild and 2 moderate irritations). Three of 121 (2.5%) subjects experienced ocular irritation (2 mild and 1 moderate) at the 2<sup>nd</sup> evaluation visit.

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**Figure 10: Ocular irritation/Visit**



In the 6 months to 3 years age group, 2 of 51 (3.9%) subjects developed ocular irritation (1 of them had mild and 1 moderate irritation) at the 1<sup>st</sup> evaluation visit, and none of 47 (0.0%) subjects had ocular irritation at the 2<sup>nd</sup> evaluation visit.

In the 4-11 years age group, 4 of 47 (8.9%) and 3 of 45 (6.6%) subjects developed ocular irritation at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, respectively.

In the > 12 years age group, 1 of 30 (3.3%) subjects at 1<sup>st</sup> evaluation visit and none of 29 (0.0%) subjects experienced mild ocular irritation.

During the two pivotal trials and open label study, at the 1<sup>st</sup> evaluation visit, 10 of 271 (3.7%) subjects age 6 months to 11 years treated with 5% L.A. had ocular irritation compare to 10 of 145 (6.9%) subjects from the > 12 years age group. At the 2<sup>nd</sup> evaluation visit, 6 of 237(2.5%) subjects age 6 months to 11 years treated with 5% L.A. had ocular irritation compare to 4 of 130 (3.1%) subjects from the > 12 years age group. Based on these data young children were not at grater risk of ocular irritation than older children and adults.

During the two pivotal trials and open label study, at the 1<sup>st</sup> evaluation visit 17 of 416 (4.1%) subjects had mild, 2 of 416 (0.5%) moderate, and 1 of 416 (0.2%) severe ocular irritations. At the 2<sup>nd</sup> evaluation visit 7 of 367 (1.9%) had mild, 3 of 367 (0.8%) moderate, and none of 367 (0.0%) severe ocular irritation. Four subjects had ocular irritation at both evaluation visits (1 mild /moderate; 1 moderate/ moderate, 2 mild/ mild). Four subjects in the 5% L. A. treatment group and 2 subjects in the vehicle treatment group without ocular irritation at the 1<sup>st</sup> evaluation visit developed mild ocular irritation at 2<sup>nd</sup> evaluation visit.



Additionally, two subjects treated with 5% L.A. reported adverse events (AEs), eye irritation and eye exfoliation:

- 03-101-0301, study SU-01-2005, 28 y/o Caucasian male, medium/straight hair; AE: eye irritation (redness and stinging), mild, recovered within 24h, no action taken, probably related
- 07-216-0114, study SU-02-2005, 14 y/o Caucasian female, medium/straight hair; AE: eye exfoliation (peeling of skin on upper eyelids), mild, recovered in 7 days, no action taken, possibly related

These results are consistent with 5% L.A. being a mild irritant to the eyes, and eye contact should be avoided.

The dermal safety studies are discussed in Section 7.1.12.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

The primary safety measurement was assessment of adverse events. Adverse events were monitored at all visits.

In the vehicle controlled Phase 3 studies (SU-01-2005 and SU-02-2005), and open label study (SU-03-2005), adverse event data were collected at Day 2 (First Evaluation Visit - the day after First Treatment), Day 8 (Second Treatment), Second Evaluation Visit (the day after Second Treatment), Day 15 (First Follow-up Visit) and Day 22 (Final Follow-up Visit). At Day 2 and Day 9 subjects were examined by licensed prescriber for presence of local cutaneous and ocular irritation.

Adverse events resulting from concurrent illnesses or reaction to concurrent medication were also recorded.

Each adverse event was evaluated for severity, duration, and whether the event may be associated with the study drug. All adverse events were followed to resolution.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified by body system using the Medical Dictionary of Regulatory Affairs (MedDRA) classification, and summarized by incidence, severity, and causality to study medication.

### 7.1.5.3 Incidence of common adverse events

In the Phase 2 and Phase 3 clinical studies, 485 subjects were assigned to be treated with two 10-minute treatments for an infestation of head lice with 5% L.A. one week apart. To be included in the safety population, subjects must have at least one post-baseline assessment. Therefore, 478 subjects were exposed to 5% L.A., and 336 subjects were exposed to vehicle. The proportion of subjects who reported an adverse event was higher among subjects treated with 5% L.A. (4.8%) compare to vehicle (1.8%). Younger subjects (6month to 3 years) are not at greater risk for developing adverse event than older subjects. The incidence of adverse events was low for both the active and vehicle arms, none of which were considered serious.

- A total of 23 subjects (23/478; 4.8%) treated with 5% L.A. reported 26 adverse events. The majority of subjects (11/23; 47.8%) who experienced adverse events were from the 4-11 years age group. Two subjects were from the 6 months to 3 years age group and 10 subjects were from the > 12 years age group. Four subjects (0.8%) had events (5) that were considered related to treatment with 5% L.A. One subject was from the 4-11 years age group, and 3 were from the > 12 years age group. (See Table 37 and Table 38)
- In the subjects treated with vehicle control, 6 of 336 (1.8%) subjects reported 6 adverse events. One subject was from the 6 month to 3 years age group, one from the 4-11 years age group and 4 subjects were from the > 12 years age group. One subject (0.3%) had an event (1) that was considered related to vehicle control. This subject was from the > 12 years age group. (See Table 37 and Table 38)

**Table 37: Number of Subjects with Adverse Events (AE)**

Parameter	6month-3years		4-11 years		> 12 years	
	5% L.A. N= 84	Vehicle N=37	5% L.A. N=229	Vehicle N=177	5% L.A. N=165	Vehicle N=122
With at least one AE	2 (2.4%)	1 (2.7%)	11 (4.8%)	1 (0.6%)	10 (6.1%)	4 (3.3%)
Mild/ moderate AE	2 (2.4%)	1 (2.7%)	11 (4.8%)	1 (0.6%)	10 (6.1%)	4 (3.3%)
Severe AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
With at least one probably or definitely not related AE	2 (2.4%)	1 (2.7%)	10 (4.4%)	1 (0.6%)	7 (4.2%)	3 (3.3%)
With at least one definitely, probably, or possibly related AE	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	3 (1.8%)	1 (0.8%)

Source: Sponsor's NDA submission: 12/28/07, ISS, Table: 1.1; 1.2; 1.3 Number of Subjects with AE and Table 1 02/27/2008

**Table 38: Number of Adverse Events (AE)**

Parameter	6month-3years		4-11 years		> 12 years	
	5% L.A.	Vehicle	5% L.A.	Vehicle	5% L.A.	Vehicle
Adverse Events	2	1	13	1	11	4
Mild or Moderate AE	2	1	13	1	11	4
Severe AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE probably or definitely not related to treatment	2	1	11	1	8	3
AE definitely, probably, or possibly related to treatment	0 (0.0%)	0 (0.0%)	2	0 (0.0%)	3	1

Source: Sponsor's NDA submission: 12/28/07, ISS, Table: 2.1; 2.2; 2.3 Number of AE

None of the subjects were discontinued from Phase 2 and Phase 3 studies due to adverse event. In study SU-01-2006, "A combined skin irritation and sensitization study of Summer's lice asphyxiator in healthy adult subjects", one subject, 01-141, withdrew from the study due to an adverse event of mild nausea.

- **Subject 01-141:** A 43-year-old Caucasian male consented to join study on October 26, 2006; he experienced mild nausea on November 03, 2006 which was treated with Pepto-Bismol and resolved the same day without sequelae; event was not related to the study drug.

#### 7.1.5.4 Common adverse event tables

All adverse events in either treatment group occurred at a frequency of less than 2 %.

The largest number of adverse events occurred in the system organ class "infectious and infestations". The most common adverse event was nasopharyngitis, which occurred in five subjects treated with 5% L.A. (1.0%). However, if combined nasopharyngitis, pharyngitis and URI occurred in 8 subjects (1.7%). Five of them were from the 4-11 years age group and 3 were from the > 12 years age group. These AEs were classified as "definitely not" related to study drug and severity were rated as mild (6) or moderate (2). (See Table 39 )

**Table 39: Number of Subjects with AE by MedRA System organ class/preferred term**

System organ class/ preferred term	5% L.A. N= 478	Vehicle N= 336
Eye disorder		
Conjunctivitis	0 (0.0%)	1 (0.3%)
Eye irritation	1 (0.2%)	0 (0.0%)
Eyelid exfoliation	1 (0.2%)	0 (0.0%)
Gastrointestinal disorder		
Diarrhea	0 (0.0%)	1 (0.3%)
Vomiting	3 (0.6%)	0 (0.0%)
General disorders and administration Site condition		
Application site irritation	1 (0.2%)	0 (0.0%)
Influenza like illness	1 (0.2%)	0 (0.0%)
Pyrexia	3 (0.6%)	0 (0.0%)
Infections and infestation		
Bronchitis	1 (0.2%)	0 (0.0%)
Gastroenteritis viral	1 (0.2%)	0 (0.0%)
Nasopharyngitis	5 (1.0%)	1 (0.3%)
Pharyngitis	2 (0.4%)	0 (0.0%)
URI	1 (0.2%)	0 (0.0%)
Injury, poisoning and procedural complication		
Arthropod sting	0 (0.0%)	1 (0.3%)
Skin laceration	1 (0.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders		
Costochondritis	1 (0.2%)	0 (0.0%)
Nervous system disorders		
Headache	1 (0.2%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorder		
Bronchospasm	1 (0.2%)	0 (0.0%)
Cough	1 (0.2%)	0 (0.0%)
Skin and subcutaneous tissue disorder		
Alopecia	0 (0.0%)	1 (0.3%)

Source: Sponsor's NDA submission: 12/28/07, ISS, Table 3 Number of Subjects with AE by MedRA System organ class/preferred term

- Although nasopharyngitis/pharyngitis/URI were more reported in the 5% L.A. treatment group compare to vehicle control treatment group, upper respiratory tract infections are the most common types of infectious diseases among children and adults. It is estimated that each adult in the United States experiences two to four respiratory infections annually and young children may have as many as six to eight episodes.<sup>1,2</sup>

**Reference:**

- <sup>1</sup> Am. J. Med. 1985 Jun 28;78 (6B):32-7; Garibaldi RA; Epidemiology of community-acquired respiratory tract infections in adults. Incidence, etiology, and impact.
- <sup>2</sup> Am. Fam. Physician; 2007 February 15; Vol. 75 No4; M Simasek, D. Blandino; Treatment of the common cold

7.1.5.5 Identifying common and drug-related adverse events

5% L.A. Treatment Group:

- From 478 subjects treated with 5% L.A., 23 (4.8%) subjects reported 26 adverse events.
- Four subjects reported five events that were considered related (probably/possibly) to treatment with 5% L.A.:

1. 02-111-0409, 34 y/o Caucasian female: Application site irritation; General disorders and administration site condition

AE	Intensity	Serious	Date of Onset	Date recovered	Action taken	Outcome	Relationship
Burning of scalp	Mild	No	08/13/2006 2 <sup>nd</sup> treatment	08/13/06	None	Recovered	Probably
Dose: 1 <sup>st</sup> = 172 g; 2 <sup>nd</sup> = 505g							

Source: Sponsor's NDA submission: CRF

2. 03-101-0301, 28 y/o Caucasian male : Eye irritation; Eye disorders

AE	Intensity	Serious	Date of Onset	Date recovered	Action taken	Outcome	Relationship
Eye irritation	Mild	No	03/23/06 1 <sup>st</sup> treatment	03/24/06	None	Recovered	Probably
Dose: 1 <sup>st</sup> = 314g; 2 <sup>nd</sup> = 312g							

Source: Sponsor's NDA submission: CRF

Also, recorded in CRF: ocular irritation 1<sup>st</sup> evaluation visit assessment: "mild redness and stinging".

3. 03-111-0111, 5 y/o Caucasian female: Vomiting; Gastrointestinal disorders

AE	Intensity	Serious	Date of Onset	Date recovered	Action taken	Outcome	Relationship
Vomiting	Moderate	No	04/21/06 (2 <sup>nd</sup> treatment 04/19/06)	04/22/06	None	Recovered	Possibly
Vomiting	Moderate	No	04/13/06 (1 <sup>st</sup> treatment 04/12/06)	04/14/06	None	Recovered	Possibly
Dose: 1 <sup>st</sup> = 313g; 2 <sup>nd</sup> 392g							

Source: Sponsor's NDA submission: CRF

4. 07-216-0114, 14 y/o Caucasian female: Eyelid exfoliation; Eye disorders

AE	Intensity	Serious	Date of Onset	Date recovered	Action taken	Outcome	Relationship
Peeling of skin on upper eyelids	Mild	No	08/22/06 (1 <sup>st</sup> treatment 08/21/06)	08/29/06	None	Recovered	Possibly
Dose: 1 <sup>st</sup> = 283g; 2 <sup>nd</sup> 316g							

Source: Sponsor's NDA submission: CRF

Vehicle Control Treatment Group:

- Six (1.8%) from 336 subjects treated with vehicle control reported 6 adverse events.
- One event was considered related (possibly) to vehicle control.

1. 05-116-0417, 31 y/o Hispanic female, Alopecia, Skin and subcutaneous tissue disorders

AE	Intensity	Serious	Date of Onset	Date recovered	Action taken	Outcome	Relationship
Hair loss after treatment	Moderate	No	08/16/06 (1 <sup>st</sup> treatment 08/15/06)		None	Continuing	Possibly
Dose: 1 <sup>st</sup> = 438g							

Source: Sponsor's NDA submission: CRF

**Table 40: Summary of AEs Related to Study Drug, Safety population**

System organ class/ preferred term	5% L.A. N= 478	Vehicle N= 336
<b>Eye disorder</b>		
Eye irritation	1 (0.2%)	0 (0.0%)
Eyelid exfoliation	1 (0.2%)	0 (0.0%)
<b>Gastrointestinal disorder</b>		
Vomiting	2 (0.4%)	0 (0.0%)
<b>General disorders and administration Site condition</b>		
Application site irritation	1 (0.2%)	0 (0.0%)
<b>Skin and subcutaneous tissue disorder</b>		
Alopecia	0 (0.0%)	1 (0.3%)

Source: Sponsor's NDA submission: 12/28/07, ISS, Table 3 Number of Subjects with AE by MedDRA System organ class/preferred term

None of the adverse events in either treatment group were considered severe in intensity by investigator. However, one subject (01-118-0418, 12 y/o female) in study SU-01-2005 experienced eye irritation ("burning") at the 1<sup>st</sup> evaluation visit that was rated severe.

#### 7.1.5.6 Additional analyses and explorations

The only intrinsic factor considered relevant for the studies of 5% L.A. was age of the subject.

##### The 6 month to 3 years age group:

- 2 of the 84 (2.4%) subjects treated with 5% L.A. experienced adverse events compare to 1 of 37 (2.7%) subjects treated with vehicle control.
- In subjects treated with 5 % L.A., 2 adverse events reported were viral gastroenteritis and cough, both of which were mild and not considered to be related to treatment with 5% L.A.
- In the subjects treated with vehicle control, one adverse event reported was “arthropod sting” (moderate, definitely not related to treatment).

##### The 4-11 years age group:

- 11 of 229 (4.8%) subjects treated with 5% L.A. reported 13 adverse events: vomiting (3), pyrexia (3), nasopharyngitis (3), pharyngitis (2), and skin laceration (1).  
One subject developed moderate nausea and vomiting at the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visit, “possibly” related to treatment. This subject recovered within 24 hours, no action was taken. All other adverse events were mild/moderate and not considered to be related to treatment with 5% L.A.
- In the vehicle treatment group one subject (1/177; 0.6%) reported 1 adverse event (“diarrhea”, mild, definitely not related to treatment).

##### The 12 years and older age group:

- 10 of 165 (6.1%) subjects treated with 5% L.A. reported 11 adverse events: nasopharyngitis (2), eye irritation (1), eyelid exfoliation (1), application site irritation (1), influenza like illness (1), bronchitis (1), upper respiratory infection (1), costochondritis (1) and bronchospasm (1). Three events, eye irritation, eyelid exfoliation and application site irritation were considered related to treatment with 5% L.A.
- In the subjects treated with vehicle control, 4 of 122 (3.8%) subjects reported 4 adverse events: conjunctivitis (1), headache (1), nasopharyngitis (1), and alopecia (1).  
One event, alopecia, was considered related to treatment with vehicle control.

“Vomiting” was the only drug-related adverse event reported after the first and second drug application (5% L.A.). Five year old female, developed nausea and vomiting one day after first treatment and two days after second treatment with 5% L.A.  
Date of onset for all other drug-related adverse events was reported as the day of treatment (first or second).

- One subject (01-117-0116; 10 y/o Hispanic female) developed vomiting 4 days after the 1<sup>st</sup> treatment- dose 400g, but not after the 2<sup>nd</sup> treatment-dose 425g with 5% L.A. (AE: mild, recovered within 24 hours, no action taken, definitely not related).

- None of subjects from the vehicle control group reported vomiting as an adverse event.
- According to Material Data Safety Sheet: “High vapor concentration, ingestion and skin absorption may cause headache, sore throat, coughing, difficulty breathing, low blood pressure, fatigue, nausea, vomiting, diarrhea and abdominal pain”.

#### 7.1.6 Less Common Adverse Events

See Section 7.1.5.4 Table

#### 7.1.7 Laboratory Findings

Clinical laboratory evaluations were not performed.

##### 7.1.7.1 Overview of laboratory testing in the development program

##### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

##### 7.1.7.3 Standard analyses and explorations of laboratory data

###### 7.1.7.3.1 *Analyses focused on measures of central tendency*

###### 7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

###### 7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

##### 7.1.7.4 Additional analyses and explorations

##### 7.1.7.5 Special assessments

#### 7.1.8 Vital Signs

Vital signs and physical examinations were not performed in the clinical studies of L.A.5%.



7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

*7.1.8.3.1 Analyses focused on measures of central tendencies*

*7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal*

*7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities*

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed during any of the studies of 5% L.A.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

*7.1.9.3.1 Analyses focused on measures of central tendency*

*7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

*7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities*

#### 7.1.9.4 Additional analyses and explorations

#### 7.1.10 Immunogenicity

Not applicable, as the drug is not a therapeutic protein.

Assessment for allergenicity (type IV delayed hypersensitivity) is discussed in section 7.1.12, Special Safety Studies.

#### 7.1.11 Human Carcinogenicity

Controlled trials were not sufficient duration to permit assessment of carcinogenicity.

#### 7.1.12 Special Safety Studies

##### **Combined skin irritation and sensitization study**

A special safety study, SU-01-2006, a combined skin irritation and sensitization study, was done in population of healthy adult subjects. This was a Phase 1, single center, double-blind, placebo-controlled, within-subjects randomized study.

The primary study objectives were:

- to assess the cumulative skin irritation potential of the 5% L.A. using 21-day cumulative irritation study design, and
- to evaluate the contact sensitization potential of the 5% L.A. using Jordan-King repeat insult patch study design.

The secondary study objective was to evaluate safety profile of the 5% L.A. by collection of product related adverse events.

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

Two hundred forty four subjects (244; 59 males and 185 females) 18 to 65 years of ages, who met the study criteria, were enrolled in the study. Test products are 5% L.A., 5% L.A. vehicle (placebo), 0.9% sodium chloride (negative control,) and 0.4% sodium lauryl sulfate (positive control). Subject received 0.2 ml of test products on each patch (approximately 3.25cm<sup>2</sup>). The test products were tested under semi-open patching condition.

Subjects were assigned to Group 1 (the cumulative irritation endpoint) and Group 2 (the sensitization endpoint).

- **Group 1** (46 subjects were enrolled, and 37 subjects completed) received two controls and two test articles (5% L.A. and placebo L.A.) for 21 consecutive days during the induction phase. The patches were worn for 24 (±1) hours each day.
- **Group 2** (198 subjects were enrolled and 173 subjects completed) received negative control and two test articles (5% L.A. and placebo L.A.) 3 times a week for total 9 applications during the induction phase.

During the induction phase, skin evaluation was performed at least 15 minutes after supervised patch removal. After induction phase, all subjects entered a 2- week rest phase. During the challenge phase, both groups received one 48-hour application of the 5% L.A., placebo L.A. test article and the negative control to naïve sites. Skin evaluations were done at least 15 minutes and at approximately 24, 48, and 72 hours following supervised patch removal. A trained and blinded evaluator performed the skin evaluation during the induction and challenge phases using Hill Top Scoring System.

### Irritation Scale

The Berger and Brown scale were utilized for Group 1 subjects during the induction phase only. Each of the scores represents the presence of a clinically significant effect (e.g. erythema occupies  $\geq 25\%$  of the patch site).

#### Numeric grades

- 0 = no evidence of irritation
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible; or minimal edema; or minimal response
- 3 = erythema and papules
- 4 = definite edema
- 5 = erythema, edema, and papules
- 6 = vascular eruption
- 7 = strong reaction, spreading beyond test site

#### Letter Grades:

- A = slight glazed appearance
- B = marked glazing
- C = glazing with peeling and cracking
- F = glazing with fissures
- G = film of dried serous exudates covering all portion of the patch site
- H = small petechial erosions and/or scabs

### Sensitization Scale

For Group 1 challenge phase and Group 2 both induction and challenge phase, the HTR sensitization scale were utilized. Each of the scores represents the presence of a clinically significant effect that is localized at the patch area (e.g. erythema occupies  $\geq 25\%$  of the patch site). Questionable reactions as well as the + designation were considered to be inconclusive.

#### Skin Inflammatory Response – Numeric Grades:

- 0 = no visible reaction and/or erythema
- + = slight, confluent or patchy erythema
- 1 = mild erythema (faint, but definite pink)

2 = moderate erythema (definite redness)  
3 = strong erythema (very intense redness)

*Skin Inflammatory Response – Letter Grades:*

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 patch area  
W = weeping – result of a vesicular or bulla reaction – serous exudate  
I = induration – solid, elevated, hardened, thickened skin

*Skin Superficial Effects – Letter Grades:*

g = glazing  
y = peeling  
c = scab, dried film of serous exudate 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

- **Irritation Population** (N=38): To be considered an evaluable subject for irritation assessment, Group 1 subjects had to complete the induction portion of the study or have been withdrawn due to an exceeding tolerability score of 3 or higher.
- **Sensitization Population** (N = 210): To be considered evaluable subject for sensitization assessment, a subject must have received sufficient induction patches, worn the challenge patch, and participated in at least 3 challenge evaluations during the challenge phase.
- **Safety population** (N = 244): all randomized subjects who received at least one dose of study patches.

Cumulative Irritation results:

The primary comparative endpoint was the cumulative irritation score derived from 21 applications of assigned patch during induction.

The statistical analysis of cumulative irritancy is summarized in Table 41.

**Table 41: Converted Cumulative Irritation Scores**

<b>Converted Cumulative Irritation Scores- Group 1</b>				
	Treatment			
	HTR Code A (5% L.A.)	HTR Code B (Placebo L.A.)	HTR Code C (0.9% sodium chloride)	HTR Code D (0.4% sodium lauryl sulfate)
Num	38	38	38	38
Mean	0.44	0.22	0.02	0.71
STD	0.58	0.55	0.03	0.83
Median	0.26	0.1	0.00	0.33
Minimum	0.00	0.00	0.00	0.00
Maximum	2.52	2.62	0.10	2.62
Friedman Rank sum p -value	< 0.0001			
Significant comparison	C vs. ABD vs. AD			

Source: Sponsor's NDA submission: Section 5.3.5.4.3, Table 11.4.1.1.1-1, p 29

The results indicated that 5% L.A. and Placebo L.A are more irritating than 0.9% sodium chloride (negative control), but less irritating than sodium lauryl sulfate (positive control). The results also indicate that the Placebo L.A. was less irritating than the active (5% L.A.).

Sensitization results:

Two hundred and ten subjects completed the challenge phase of the study.

Two subjects (0.82%) were considered sensitized to the 5% L.A.

No subjects were considered sensitized to the Placebo L.A.

Table 38 summarizes the frequencies of challenge patch scores for each test article and the control.

**Table 42: Challenge Patch Scoring/Skin Inflammatory Response**

<b>Challenge Patch Scoring Scale</b>	<b>15 min</b>	<b>24 hr</b>	<b>48 hr</b>	<b>72 hr</b>
Evaluable Population for Sensitization Evaluation (N = 210)	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<b>HTR Code A (5% L.A.)</b>				
0 = no visible reaction, and/or erythema	184 (87.2)	189 (89.6)	195 (92.9)	206 (98.1)
+ = slight, confluent or patchy erythema	16 (7.6)	11 (5.2)	9 (4.3)	3 (1.4)
1 = mild erythema (faint, but definite pink)	9 (4.3)	9 (4.3)	4 (1.9)	0 (0.0)
2 = moderate erythema (definite redness)	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)
3 = string erythema (very intense redness)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
<b>HTR Code B (Placebo L.A.)</b>				
0 = no visible reaction, and/or erythema	188 (89.1)	199 (94.3)	202 (96.2)	207 (98.6)

+ = slight, confluent or patchy erythema	17 (8.1)	6 (2.8)	5 (2.4)	3 (1.4)
1 = mild erythema (faint, but definite pink)	5 (2.4)	5 (2.4)	3 (1.4)	0 (0.0)
2 = moderate erythema (definite redness)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
3 = string erythema (very intense redness)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>HTR Code C (0.9% sodium chloride)</b>				
0 = no visible reaction, and/or erythema	204 (96.7)	209 (99.1)	208 (99.1)	210 (100)
+ = slight, confluent or patchy erythema	6 (2.8)	1 (0.5)	2 (1.0)	0 (0.0)
1 = mild erythema (faint, but definite pink)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
2 = moderate erythema (definite redness)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 = string erythema (very intense redness)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Sponsor's NDA submission: Section 5.3.5.4.3, Table 11.4.1.2-2; 11.4.1.2-3; 11.2.1.2-4, p 32, Protocol SU-01-2006

**Table 43: Presence of edema in Skin Sensitivity**

Presence of edema in Skin Sensitivity		15 min	24 hr	48 hr	72 hr
		N (%)	N (%)	N (%)	N (%)
<b>HTR Code A (5% L.A.)</b>	NO	210 (99.5)	210 (99.5)	209 (99.5)	210 (100.0)
	YES	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)
<b>HTR Code B (Placebo L.A.)</b>	NO	210 (99.5)	211 (100.0)	210 (100.0)	210 (100.0)
	YES	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
<b>HTR Code C (0.9% sodium chloride)</b>	NO	210 (99.5)	211 (100.0)	210 (100.0)	210 (100.0)
	YES	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Sponsor's NDA submission: Section 5.3.5.4.3, Table 11.4.1.2-5; p 33, Protocol SU-01-2006

#### Safety Results:

The assessment of the safety was based on the frequency of adverse events. At each visit subjects were asked generalized questions about their well being.

Two hundred forty-four (244) subjects were enrolled in the study and received at least one patch application.

- 38 subjects in Group 1 were exposed to all 21 induction phase applications, 37 subjects were exposed to one additional challenge application.
- 173 subjects were exposed to all 9 induction applications and one challenge application.

16 non-serious adverse events (13 mild, 2 moderate, 1 severe) were reported for 15 subjects (6.1%) during the course of the study.

All adverse events were considered unrelated to the test articles.

One subject, 01-141, withdrew from the study due to an adverse event of mild nausea.

#### Conclusion:

These findings are consistent with 5% L.A. being a mild irritant and potential sensitizer, but with rare occurrence, particularly under the conditions studied for treatment of head lice infestations. Under condition of the study, 5% L.A. was judge by investigator as "appeared to be well tolerated by subjects".

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Benzyl alcohol is not in the class with a history of abuse or withdrawal phenomena. There would appear to be limited potential for abuse of this product and no apparent withdrawal symptoms.

#### 7.1.14 Human Reproduction and Pregnancy Data

Four pregnant subjects were enrolled in the Phase 3 clinical trials:

- 05-102-0304: 27 y/o Caucasian female , in third trimester of pregnancy, randomized to vehicle control, treatment failure at the first evaluation visit; no adverse events
- 08-201-0201: 30 y/o Caucasian female, in third trimester of pregnancy, randomized to vehicle control, treatment failure at the first evaluation visit, no adverse event
- 12-202-0201: 16 y/o, Caucasian female, in third trimester of pregnancy, randomized to 5% L.A.; completed second evaluation visit with no lice found, no adverse events
- 01-110-0309: 20 y/o Hispanic female, in third trimester of pregnancy, randomized to 5% L.A.; treatment failure after first treatment; no adverse events
- As subjects were allowed to be pregnant during the study, no follow up on the pregnant subjects was done.

#### 7.1.15 Assessment of Effect on Growth

The protocol for the pivotal Phase 3 studies allowed for enrollment of subject 6 months of age and older. Assessment of the effect of the product on growth was not done because of short study duration.

#### 7.1.16 Overdose Experience

There has been no experience of overdose with 5% L.A. lotion reported in the Phase 2 or Phase 3 trials. No incidents of accidental ingestion have been reported.

#### 7.1.17 Postmarketing Experience

The applicant's drug product, 5% L.A. (benzyl alcohol) lotion, is not marketed in any country at this time.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety sources are characterized in the following table:

**Table 44: Subject Exposure to 5% L.A. (Safety Population)**

Study	5% L.A.	Vehicle	Total
<b>Pivotal studies</b>			
SU-01-2005	141	164	305
SU-02-2005	160	153	313
<b>Supporting studies ( Phase 3 and Phase 2)</b>			
SU-03-2005*	115	**	115
SU-02-2003	20	19	39
SU-02-2003A	21	**	21
SU-02-2004	21	**	21
<b>Total</b>	<b>478</b>	<b>336</b>	<b>814</b>

Safety Population: Patients who were randomized and made at least one evaluation visit post-treatment

\*subjects in SU-03-2005 who were treated with 5% L.A. in SU-01-2005 and SU-02-2005 excluded

Source: Sponsor's NDA submission: February 27, 2008, Table 1: Distribution of Safety Population by age

#### 7.2.1.1 Study type and design/patient enumeration

See Table : Tables of Clinical Studies in Section 4.2 and Table : Studies Providing Safety Information in Section 7.1

#### 7.2.1.2 Demographics

The following tables provide overall demographic information for the development program.

**Table 45: Phase 2 studies and Open-label Phase 3 Study - Safety population**

Parameter	SU-02-2003		SU-02-2003A	SU-02-2004	SU-03-2005
	5% L.A. 20	Vehicle 19	5% L.A. 21	5% L.A. 21	5% L.A. 115
<b>Gender</b>					
Male	0 (0.0%)	0 (0.0%)	2(9.5%)	1(4.8%)	17(14.8%)
Female	20(100%)	19(100%)	19(90.5%)	20(95.2%)	98(85.2%)
<b>Age</b>	Years:	Years:	Years:	Years:	Month:



Mean	7.4	17.6	8.8	9.8	119
Median	11.5	10.0	7.0	9.0	66
Range	5 to 36	2 to 54	2 to 29	4 to 24	6 to 581
<b>Race</b>					
Caucasian	0 (0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	66(57.4)
Black	0 (0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hispanic	20(100%)	18(94.7%)	20(95.2%)	21(100%)	45(39.1%)
Other	0 (0.0%)	1(5.3%)	1(4.8%)	0(0.0%)	4(3.5%)

Source: Sponsor's NDA submission: Tables: 1a, 1b, 1c, 1f; Submission: March 31, 2008

**Table 46: Phase 3 pivotal trials - Safety population**

Parameter	SU-01-2005		SU-02-2005	
N	5% L.A. 141	Vehicle 164	5% L.A. 160	Vehicle
<b>Gender</b>				
Male	16(11.3%)	29(17.7%)	23(14.4%)	19(12.4%)
Female	125(88.7%)	135(82.3%)	137(85.6%)	134(87.6%)
<b>Age</b>	Month	Month	Month	Month
Mean	159	166	183	184
Median	116	114	126	116
Range	13 to 666	15 to 702	15 to 762	12 to 777
<b>Race</b>				
Caucasian	99(70.2%)	102(62.2%)	118(73.8%)	109(71.2%)
Black	0(0.0%)	2(1.2%)	3(1.9%)	1(0.7%)
Hispanic	37(26.2%)	55(33.5%)	28(17.5%)	34(22.2%)
Other	5 (3.5%)	5(3.0%)	11(6.9%)	9(5.9%)

Source: Sponsor's NDA submission: Tables: 1d, 1e; Submission March 31, 2008/April 14, 2008

**Table 47: Phase 3 pivotal trials and open-label Phase 3 study, 5% L.A treatment group; Safety population**

Study	Parameter	6months to 3years N=14	4-11 years N=75	12 years or older N=52
SU-01-2005 5%L.A.	<b>Gender</b>			
	Male	4 (28.6%)	7 (9.3%)	5 (9.6%)
	Female	10 (71.4%)	68 (90.7%)	47 (90.4%)
	<b>Age(month)</b>			
	Mean	30.2	96.0	385
	Median	31.5	93.0	297
	Range	13-46	48to 142	145 to 666
	<b>Race</b>			
	Caucasian	10 (71.4%)	53 (70.7%)	36 (69.2%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hispanic	1 (7.1%)	20 (26.7%)	16 (30.8%)
	Other	3 (21.4%)	2 (2.7%)	0 (0.0%)

<b>SU-02-2005 5%L.A.</b>	<b>Gender</b>	<b>N= 20</b>	<b>N=76</b>	<b>N=64</b>
	Male	4 (20.0%)	10 (13.2%)	9 (14.1%)
	Female	16 (80.0%)	66 (86.8%)	55 (85.9%)
	<b>Age</b>			
	Mean	34.8	97.4	332
	Median	38.5	94.0	300
	Range	15 to 48	52 to 141	146 to 762
	<b>Race</b>			
	Caucasian	13 (65.0%)	53 (69.7%)	52 (81.3%)
	Black	0 (0.0%)	2 (2.6%)	1 (1.6%)
<b>SU-03-2005 5%L.A.</b>	Hispanic	5 (25.0%)	15 (19.7%)	8 (12.5%)
	Other	2 (10.0%)	6 (7.9%)	3 (4.7%)
	<b>Gender</b>	<b>N=47</b>	<b>N=39</b>	<b>N=29</b>
	Male	7 (14.9%)	8 (20.5%)	2 (6.9%)
	Female	40 (85.1%)	31 (79.5%)	27 (93.1%)
	<b>Age</b>			
	Mean	29.2	86.3	308
	Median	32.0	85.0	289
	Range	6 to 46	51 to 142	145 to 581
	<b>Race</b>			
	Caucasian	24 (51.1%)	22 (56.4%)	20 (69.0%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hispanic	20 (42.6%)	16 (41.0%)	9 (31.0%)
	Other	3 (6.4%)	1 (2.6%)	0 (0.0%)

Source: Sponsor's NDA submission: Tables 1a, 1b, 1c, 1d, 1e; March 31, 2008/April 14, 2008

Within the Phase 3 studies the treatment groups are similar with regard to age, sex and race. See Section 1.3.6; Reviewer's comment.

#### 7.2.1.3 Extent of exposure (dose/duration)

The majority of the subjects assigned to treatment with 5% L.A. had two treatments while the majority of subjects assigned to treatment with vehicle had only one treatment due to treatment failure and receipt of rescue therapy.

- In the two vehicle - controlled Phase 3 studies (SU-01-2005 and SU-02-2005), 41 subjects (13.7%) received only 1<sup>st</sup> 10-minute treatment with 5 % L.A. and 258 subjects (86.3%) received two (1<sup>st</sup> and 2<sup>nd</sup>) 10-minute treatments with 5% L.A. one week a part.
- In the Phase 3 open-label study (SU-03-2005), 6 subjects (5.4%) received only 1<sup>st</sup> 10-minute treatment, while 106 subjects (94.6%) received 1<sup>st</sup> and 2<sup>nd</sup> 10-minute treatment with 5% L.A. one week a part.

**Table 48: Number of 5% L.A. treatments received (Safety population) per age group**

<b>5% L.A. treatment /age</b>	<b>6months - 3 years</b>	<b>4 to 11 years</b>	<b>12 years or older</b>
<b>SU-01-2005</b>			
140	14	75	51
1 <sup>st</sup> treatment only 10 (7.1%)	1 (7.1%)	6 (8.0%)	3 (5.9%)
1 <sup>st</sup> and 2 <sup>nd</sup> treatments 130 (92.9%)	13 (92.9%)	69 (92.0%)	48 (94.1%)
<b>SU-02-2005</b>			
159	20	75	64
1 <sup>st</sup> treatment only 31 (19.5%)	5 (25.0%)	15 (20.0%)	11 (17.2%)
1 <sup>st</sup> and 2 <sup>nd</sup> treatments 128 (80.5%)	15 (75.0%)	60 (80.0%)	53 (82.8%)
<b>SU-03-2005</b>			
112	46	39	27
1 <sup>st</sup> treatment only 6 (5.4%)	4 (8.7%)	2 (5.1%)	0 (0.0%)
1 <sup>st</sup> and 2 <sup>nd</sup> treatments 106 (94.6%)	42 (91.3%)	37 (94.9%)	27 (100.0%)

Source: Sponsor's NDA submission: Tables 3a, 3b, 3c; March 31, 2008/April 14, 2008

The amount of study drug given to subject was based upon subject's hair length. In addition, subjects were instructed to completely saturate their hair and scalp to the point where dripping was likely to occur.

The total amount of study medication used was found by summing up the difference between the dispensing weight and the return weight of the individual bottles (done on Visit 2 and 3, day after the 1<sup>st</sup> and 2<sup>nd</sup> treatment). Overall, in the Phase 3 clinical studies (SU-01-2005, SU-02-2005 and SU-03-2005), the mean amount used of 5% L.A. range from 385g to 493g, and the mean percentage used from 59.4 to 66%. (See Table 49)

**Table 49: Weight of bottles dispensed, returned, and amount and percentage used (Safety population), per application**

	<b>SU-01-2005</b>	<b>SU-02-2005</b>	<b>SU-03-2005</b>
	<b>Overall N=141</b>	<b>Overall N=160</b>	<b>Overall N=115</b>
	<b>short medium long</b>	<b>short medium long</b>	<b>short medium long</b>
<b>Wt of bottles dispensed</b>			
V2 N 135	19	34	25
Mean 780	257	271	281
Median 771	256	257	255
V3 N 121	16	28	27
Mean 774	256	274	281
Median 769	256	257	254
<b>Wt of bottles returned</b>			
V2	125	102	111
Mean 308	126	83	55
Median 200	332	234	256
V3	304	212	258
Mean 281	211	129	111
Median 174	182	251	55
<b>Amount used</b>			
V2	132	169	170
Mean 472	403	417	381
Median 410	379	423	372
V3	424	448	349
Mean 493	658	751	171
Median 429	637	836	201

% used	V2				V2				V2			
	Mean 60	52	55	66	Mean 63	61	64	62	Mean 62	62	60	64
	Median 62	51	50	81	Median 80	73	81	77	Median 74	78	75	72
	V3				V3				V3			
	Mean 64	60	59	69	Mean 66	65	68	64	Mean 59	62	55	64
	Median 80	69	62	82	Median 81	83	82	80	Median 69	78	65	72

Source: Sponsor's NDA submission: Tables 2a, 2b, 2c; March 31, 2008/April 14, 2008

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.2.1 Other studies

All studies used in the review of safety were submitted in the marketing application.

### 7.2.2.2 Postmarketing experience

There has been no postmarketing experience with applicant's drug product, as 5% L.A. is not approved in any country at the time of this review.

### 7.2.2.3 Literature

The sponsor submitted literature regarding treatment options for head lice infestation, reports on the safety assessment of benzyl alcohol, benzoic acid and sodium benzoate (the Cosmetic Ingredient Review Expert Panel report). The literature review is acceptable.

## 7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug to characterize its safety in the short-term (14 days post 2<sup>nd</sup> treatment). In Phase 2 and 3 trials, 478 subjects (safety population) received 5% L.A. and had at least one post treatment evaluation visit. The majority of subjects received two 10 - minute treatment with 5% L.A. one week apart. Doses and duration of exposure were adequate to assess the safety of the product for its intended use.

The design of vehicle-controlled and open-label studies is acceptable to assess safety and efficacy.

Topical safety was adequately assessed in the development program in the Phase 3 efficacy and/or safety studies and the Phase 1 dermal safety studies.

There was adequate experience with the drug in regard to overall number of subjects exposed and duration of exposure.

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Per the pharmacology/toxicology review (reviewer: Barbara Hill, Ph.D.):

- “This NDA submission is a 505(b)(2) application because the applicant is relying on literature references to satisfy some aspects of nonclinical toxicology information needed to support the safety of benzyl alcohol (primary systemic repeat dose toxicity and genetic toxicity).
- The applicant completed a 14-day dermal toxicity study in rats, a 14-day dermal toxicity study in dogs, a study for effects of benzyl alcohol on embryofetal development in rats, and a study for effects of benzyl alcohol on embryofetal development in rabbits. oxikokineticc analysis for benzyl alcohol was incorporated into 2 week dermal toxicology studies conducted in rats and dogs with the lice asphyxiator product.
- No nonclinical safety pharmacology studies were conducted with benzyl alcohol. Based on the toxicity profile established for benzyl alcohol in the literature and the results of the 2 week dermal toxicology studies conducted in rats and dogs with the lice asphyxiator drug product, the need for safety pharmacology studies was waived for the lice asphyxiator drug product. No treatment related effects were noted on the electrocardiographic parameters evaluated in the 2 week dermal dog toxicology study.”

The pharmacology/toxicology reviewer found preclinical testing to be adequate and no non-clinical safety issues that were relevant to clinical use.

#### 7.2.5 Adequacy of Routine Clinical Testing

Vital signs and ECGs were not performed during any of the studies of 5% L.A.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant did not conduct drug-drug interaction assessment

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has conducted an adequate repeat insult patch test study to assess for cutaneous irritancy and allergenicity, as standard for topical medication.

The applicant actively solicited for complains of burning/stinging, pain, numbness, and tingling. Also, subjects were encouraged to report any adverse event.

There are no recommendations for further study.

#### 7.2.8 Assessment of Quality and Completeness of Data

The initial study reports did not accurately capture the data of several subjects in the reporting of the safety and efficacy data from the two pivotal trials. After multiple communications, the applicant re-submitted (12/28/07) revised study reports of the two pivotal trials which appear to be consistent with results based upon the electronic data records.

Although initial study reports were not 100% accurate the overall determination of efficacy and safety conclusions was consistent.

See Appendix A (Statistical Review and Evaluation, Mat Soukup, Ph.D.)

Deficiencies in the quality/completeness of efficacy/safety data:

- Data for Efficacy evaluation:  
Study SU-01-2005 Electronic Data Inconsistency  
Study SU-02-2005 Electronic Data Inconsistency
- Data for Safety Evaluation

#### 7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted letter on October 12, 2007 regarding the 120 Day Safety Update. The sponsor stated that “no new studies have been conducted and there are no new safety data to report”.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

#### 1. Adverse events:

In the Phase 2 and Phase 3 clinical studies, a total of 23 subjects (23/478; 4.8%) in the 5% L.A. treatment group experienced adverse events compared to 6 subjects (6/336; 1.8%) in the vehicle group. Four (4/23; 17.4%) subjects reported five adverse events that were considered related to treatment with 5% L.A. One subject (1/6; 16.7%) reported one adverse event that was considered related to vehicle control.

- AE related to 5% L.A. treatment:
  1. General disorder and administration site condition:
    - Application site irritation (1)
  2. Eye disorders:
    - Eye irritation (1)

- Eye exfoliation (1)
- 3. Gastrointestinal disorders:
  - Vomiting (2)
- AE related to Vehicle control treatment:
  - 1. Skin and subcutaneous tissue disorders:
    - Alopecia (1)

See Section 7.1.5.5

## 2. “OTHER” signs and/or symptoms:

In addition to reported adverse events, the CRF also contain a category “OTHER” signs and/or symptoms to assure that all, adverse events (change from baseline) would be captured.

- Thirty three subjects (33/478; 6.9%) treated with 5% L.A. reported to have 52 “other signs and/or symptoms of the scalp.  
The most common reported 5% L.A. treatment- related “other” signs and/or symptoms was listed under “General disorder and administration site condition” system organ class and were related to the application site. Eleven (11/478; 2.3%) subjects reported “Application site irritation” as mild scalp burning lasted from few seconds to 5 minutes. “Application site anesthesia” and “Hypoesthesia” was reported by 10 (10/478, 2.1%) subjects, as “numbness” lasted from 1 minute to 2 hours. Five subjects (5/478; 1.0%) reported mild “sting (“Pain”) lasted from 10 seconds to 1-2 minutes.
- Fifteen subjects (15/336; 4.5%) treated with vehicle reported 19 “other” signs and/or symptoms of the scalp. The most common reported vehicle treatment- related “other” signs and/or symptom was listed under “Nervous System disorder” system organ class (Paraesthesia).

See Section 7.1.4; Table “Other” signs and symptoms

## 3. Ocular irritation:

During the Phase 3 clinical trials subject were evaluated for ocular irritation (after the first and second treatment). Ocular irritation was present in 26 (26/416; 6.2%) subjects treated wit 5% L.A compare to 3 (3/317; 0.9%) subjects treated with vehicle. The majority of the subjects had ocular irritation only at the 1<sup>st</sup> evaluation visit. Four subjects in the 5% L.A. treatment group reported ocular irritation at both the 1<sup>st</sup> and 2<sup>nd</sup> evaluation visits. Ocular irritation that was rated severe was reported from one subject (12 y/o). Ocular irritation was described as itching, burning, redness, redness of upper and lover eyelids, stinging, and burning around eyes. Additionally, two subjects treated with 5% L.A. reported adverse events, eye irritation and eye exfoliation.

See section 7.1.4 Ocular irritation

#### 4. Pruritus of the skin and scalp:

The majority of subjects had pruritus prior to treatment. Both treatment groups showed improvement in severity of skin and scalp pruritus throughout studies. However, pruritus was observed post-treatment in some subjects without pruritus prior to treatment. (See Table 50)

**Table 50: Developed Pruritus Post-treatment  
(For subjects without pruritus pre-treatment) - Safety population, Phase 3 studies**

Study	SU-01-2005 and SU-02-2005				SU-03-2005			
5% L.A.								
1 <sup>st</sup> evaluation visit	N 10/75 (13.3%)	6m-3y 1/9 (11.1%)	4-11y 5/41 (12.2%)	≥12y 4/25 (16.0%)	N 1/41 (2.4%)	6m-3y 1/19 (5.3%)	4-11y 0/12 (0.0%)	≥12y 0/10 (0.0%)
2 <sup>nd</sup> evaluation visit	4/63 (6.3%)	1/7 (14.3%)	1/34 (2.9%)	2/22 (9.1%)	1/39 (2.5%)	0/18 (0.0%)	0/12 (0.0%)	1/10 (10.0%)
Vehicle								
1 <sup>st</sup> evaluation visit	3/67 (4.5%)	0/7 (0.0%)	2/35 (5.7%)	1/25 (4.0%)				
2 <sup>nd</sup> evaluation visit	0/29 (0.0%)	0/3 (0.0%)	0/18 (0.0%)	0/8 (0.0%)				

Source: Sponsor's NDA submission, Tables 2a 1-4, 2b1-4, 2c1-4; amendment 4/14/08

- In the 5% L.A. treatment group (studies SU-01-2005, SU-02-2005, and SU-03-2005), 14 of 116 (12.1%) subjects without pruritus developed pruritus post-treatment.
- In the vehicle treatment group (studies SU-01-2005 and SU-02-2005), 3 of 67 (4.5%) subjects without pruritus developed pruritus post-treatment.

#### 5. Erythema of the skin and scalp:

Although, both treatment groups showed continuous improvement in the severity of the erythema, presence of skin and scalp erythema was observed in some subjects without erythema prior to either treatment. (See Table 51)

**Table 51: Developed Erythema Post-treatment  
(For subjects without erythema pre-treatment) - Safety population, Phase 3 studies**

Study	SU-01-2005 and SU-02-2005				SU-03-2005			
5% L.A.								
1 <sup>st</sup> evaluation visit	N 18/223 (8.1%)	6m-3y 1/25 (4.0%)	4-11y 14/113 (12.4%)	≥12y 3/85 (3.5%)	N 5/86 (5.8%)	6m-3y 3/36 (8.3%)	4-11y 1/29 (3.5%)	≥12y 1/21 (4.8%)
2 <sup>nd</sup> evaluation visit	8/189 (4.2%)	2/20 (10.0%)	4/95 (4.2%)	2/74 (2.7%)	2/80 (2.5%)	0/33 (0.0%)	0/27 (0.0%)	2 /20 (10.0%)
Vehicle								
1 <sup>st</sup> evaluation visit	13/217 (5.9%)	3/24 (12.5%)	6/117 (5.1%)	4/76 (5.3%)				
2 <sup>nd</sup> evaluation visit	7/68 (10.3%)	1/5 (20.0%)	2/39 (5.1%)	4/24 (16.7%)				

Source: Sponsor's NDA submission, Tables 2a 1-4, 2b1-4, 2c1-4; amendment 4/14/08



- In the 5% L.A. treatment group (studies SU-01-2005, SU-02-2005, and SU-03-2005), 32 of 309 (10.3%) subjects without erythema developed erythema post-treatment.
- In the vehicle treatment group, (studies SU-01-2005 and SU-02-2005), 19 of 217 (8.7%) subjects without erythema developed erythema post-treatment.

#### 6. Pyoderma of the skin and scalp:

Both treatment groups showed continuous improvement in the severity of the pyoderma. However, presence of skin and scalp pyoderma was observed in some subjects without pyoderma prior to either treatment.

**Table 52: Developed Pyoderma Post-treatment**  
**(For subjects without pyoderma pre-treatment) - Safety population, Phase 3 studies**

Study	SU-01-2005 and SU-02-2005				SU-03-2005			
5% L.A.								
1 <sup>st</sup> evaluation visit	N 16/223 (7.2%)	6m-3y 3/27 (11.1%)	4-11y 7/106 (6.6%)	≥12y 6/89 (6.7%)	N 1/85 (1.2%)	6m-3y 0/36 (0.0%)	4-11y 1/28 (3.6%)	≥12y 0/21 (0.0%)
2 <sup>nd</sup> evaluation visit	6/186 (3.2%)	0/21 (0.0%)	4/85 (4.7%)	2/77 (2.6%)	0/78 (0.0%)	0/32 (0.0%)	0/26 (0.0%)	0/20 (0.0%)
Vehicle								
1 <sup>st</sup> evaluation visit	8/230 (3.5%)	0/25 (0.0%)	3/120 (2.5%)	5/85 (5.9%)				
2 <sup>nd</sup> evaluation visit	2/75 (2.7%)	0/3 (0.0%)	1/43 (2.3%)	1/29 (3.4%)				

Source: Sponsor's NDA submission, Tables 2a 1-4, 2b1-4, 2c1-4; amendment 4/14/08

- In the 5% L.A. treatment group (studies SU-01-2005, SU-02-2005, and SU-03-2005), 22 of 308 (7.1%) subjects without pyoderma developed pyoderma post-treatment.
- In the vehicle treatment group, (studies SU-01-2005 and SU-02-2005), 10 of 230 (4.3%) subjects without pyoderma developed pyoderma post-treatment.

#### 7. Excoriation of the skin and scalp:

Although, both treatment groups showed continuous improvement in the severity of the excoriation, presence of skin and scalp excoriation was observed in some subjects without excoriation prior to either treatment.

**Table 53: Developed Excoriation Post-treatment**  
**(For subjects without pyoderma pre-treatment) - Safety population, Phase 3 studies**

Study	SU-01-2005 and SU-02-2005				SU-03-2005			
5% L.A.								
1 <sup>st</sup> evaluation visit	N 11/219 (5.0%)	6m-3y 1/25 (4.0%)	4-11y 5/107 (4.7%)	≥12y 5/87 (5.7%)	N 2/80 (2.5%)	6m-3y 1/34 (2.9%)	4-11y 0/25 (0.0%)	≥12y 1/21 (4.8%)
2 <sup>nd</sup> evaluation visit	2/182 (1.1%)	1/20 (5.0%)	1/88 (1.1%)	0/74 (0.0%)	2/73 (2.7%)	2/30 (6.7%)	0/23 (0.0%)	0/20 (0.0%)
Vehicle								

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1 <sup>st</sup> evaluation visit	15/225 (6.7%)	2/26 (7.7%)	5/116 (4.3%)	8/83 (9.6%)
2 <sup>nd</sup> evaluation visit	3/73 (4.1%)	1/4 (25%)	1/43 (2.3%)	1/26 (3.8%)

Source: Sponsor's NDA submission, Tables 2a 1-4, 2b1-4, 2c1-4; amendment 4/14/08

- In the 5% L.A. treatment group (studies SU-01-2005, SU-02-2005, and SU-03-2005), 16 of 299 (5.3%) subjects without excoriation developed excoriation post-treatment.
- In the vehicle treatment group, (studies SU-01-2005 and SU-02-2005), 17 of 225 (7.5%) subjects without excoriation developed excoriation post-treatment.

See Section 7.1.4. The scalp and skin evaluation

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The pooling was accomplished by combining of the numerator events and denominators for selected studies because of similar elements of study design, including study populations and treatment regimens. The applicant's approach was acceptable.

#### 7.4.1.1 Pooled data vs. individual study data

The applicant integrated the safety data from the Phase 2 and Phase 3 studies. The combined safety data were reviewed above. See Section 7.1 (and subsections) of this review

#### 7.4.1.2 Combining data

The pooling was accomplished by combining of the numerator events and denominator for the selected studies. The combine safety data were reviewed above. See Section 7.1 of this review.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

The quantity of 5% L.A. to be applied to each subject was based on the length of the subject's hair. Investigators were given the latitude to increase or decrease the quantity of product to provide the subjects based on the coarseness or fineness of the hair. It was emphasized to the subjects the importance of completely saturating the hair for effective treatment.

The total amount of study medication used was found by summing up the difference between the dispensing weight and the return weight of the individual bottles (done on Visit 2 and 3, the day after the 1<sup>st</sup> and 2<sup>nd</sup> treatment). Overall, in the Phase 3 clinical studies (SU-01-2005, SU-02-2005 and SU-03-2005) the mean amount of 5% L.A. used range from 385g to 493g (mean percentage used: 59.4 to 66%).

None of the subjects were discontinued from the Phase 2 and Phase 3 studies due to adverse events. Four subjects reported five adverse events that were considered related (probably/possibly) to treatment with 5% L.A. The amount of 5% L.A. used per treatment range from 172g to 505g. See Section 7.1.5.5

#### Explorations for time dependency for adverse findings

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

#### 7.4.2.2 Explorations for drug-demographic interactions

Adverse event profile did not appear to vary with the age. The numbers of male and non-Caucasian subjects were too low to adequately explore adverse event rates in these groups.

#### 7.4.2.3 Explorations for drug-disease interactions

Scalp and skin evaluation post treatment allowed for capture of disease exacerbation during therapy.

See Section 7.1, 7.3, 7.2.8

#### 7.4.2.4 Explorations for drug-drug interactions

These explorations were not done.

#### 7.4.3 Causality Determination

Although reported in both the active and vehicle groups, application site reaction such as irritation, burning, numbness, pain, and pruritus and ocular irritation were more common in subjects who received treatment with 5% L.A. The known potential of 5% L.A. and vehicle for irritancy (cumulative irritancy scores greater than the score for the negative control, 0.9% sodium chloride, in the cutaneous safety study - SU-01-2006), support the causality of 5% L.A. and vehicle in application site reactions.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The dosing regiment for 5% L.A. is two 10-minute applications to the hair and scalp (to be completely saturated) one week apart.

This is the dosing regiment that was used in Phase 2 and Phase 3 clinical studies.

The optimal concentration of Lice Asphyxiator, the treatment duration and frequency were determinate in Phase 2 clinical studies, SU-02-20003, SU-02-2003A and SU-02-2004.

These studies demonstrated that:

- two treatments one week apart are necessary,
- thoroughly saturating the hair with the product during treatment is important,
- 10 minute application was effective as 30 minute application, and
- 5% benzyl alcohol in the formulation was effective <sup>(b) (4)</sup>

### **8.2 Drug-Drug Interactions**

The applicant did not conduct drug interaction studies.

### **8.3 Special Populations**

5% L.A. has not been studied in children younger than 6 months of age. Head lice infestation is not prevalent in that population.

There are no special dosing recommendations for demographics based on clinical trial data.

Women of childbearing potential were not excluded from the Phase 3 clinical trials. Four pregnant subjects were enrolled in the Phase 3 clinical trials:

- 05-102-0304: 27 y/o Caucasian female, in the third trimester of pregnancy randomized to vehicle control, treatment failure at the first evaluation visit, amount used: 1135g (70%); no adverse events
- 08-201-0201: 30 y/o Caucasian female, in the third trimester of pregnancy, randomized to vehicle control, treatment failure at the first evaluation visit, amount used: 487g (49%); no adverse events
- 12-202-0201: 16 y/o Caucasian female, in the third trimester of pregnancy, randomized to 5% L.A.; completed second evaluation visit with no lice found, had no adverse events; amount used: 288g (58%) and 318g (64%);
- 01-110-0309: 20 y/o Hispanic female, in the third trimester of pregnancy, randomized to 5% L.A.; treatment failure after first treatment; amount used: 620g (83%); no adverse events

No follow-up of these pregnancies was performed.

## **8.4 Pediatrics**

The sponsor requested waiver for pediatric studies for the treatment of head lice infestation in children less than 6 months of age. The partial pediatric waiver was granted because product does not represent a meaningful therapeutic benefit over existing therapeutic approach (“head shaving”). Additionally, head lice infestation is not prevalent in the population younger than 6 months of age and is unlikely to be used in a substantial number of this pediatric subpopulation. The pivotal studies (SU-01-2005 and SU-02-2005) and open label (SU-03-2005) included sufficient number of younger pediatric population to make a determination of safety and efficacy for pediatric subjects 6 months of age and older. The sponsor appears to have complied with the requirements of PREA.

## **8.5 Advisory Committee Meeting**

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

## **8.6 Literature Review**

See Section 7.2.2.3

## **8.7 Postmarketing Risk Management Plan**

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.

## **8.8 Other Relevant Materials**

### A. Tradenames:

The applicant submitted two tradenames, (b) (4) and (b) (4).

The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed proprietary names (b) (4) and (b) (4) from a promotional perspective because the names overstate the efficacy of the drug product.

### B. Dosage form:

The proposed product dosage form was (b) (4). However, upon examining the clinical supply samples submitted in proposed marketing container, CMC and clinical reviewers recommend the dosage form should be a lotion (b) (4) (See Chemistry Review).

The Division of Medication Errors and Technical Support (DMETS) evaluated dosage form “lotion” (b) (4) for its potential for error and did not have objections to the use of term “lotion” in the established name of 5% L.A.

### C. Product Labels and Packaging:

DMETS reviewed the product packaging, labels and labeling and “identified design issues that may result in failures in the medication use process leading to error”.

The followings are safety concerns:

- 1) the packaging resembles that of an oral medication
- 2) the size of the bottle – 8oz (minimum amount that would needed by patients with short hair is 4 oz)
- 3) the bottle is opaque (inability to provide correct dosing)

In response to the first safety issue, the applicant proposed (b) (4) design changes to the container closure system (December 7, 2007). The (b) (4) proposal: an orifice reducing plug (b) (4) and current cap was considered to be the most beneficial at reducing the risk for oral ingestion (recommended by DMETS).

Results from USP <661> study (submitted in CMC amendment 0012, January 25, 2008) and 14days stability data (submitted in CMC amendment 0014, March 4, 2008) met the USP requirements and stability specification (See Chemistry review).

In response to third issue the applicant changed the proposed marketing container to natural polypropylene bottles. The natural PP bottle found to be translucent enough to see through the drug product level. The translucent bottle is identical to the (b) (4) bottle originally proposed for to-be-marketed container (b) (4). This change made bottle transparent, which may exposed the product to the light. However, 48 hours open dish UV light degradation study of the drug product and the drug substance (exposed in the clear quartz cell) shows no degradation. Analysis of the exposed drug product and the drug substance met the specification. (See Chemistry review).

In addition, DMETS recommended revising the labels and labeling as follows:

- Relocate the dosage form statemen (b) (4) so that it immediately follows the established name (since it is part of the established name).
- Delete the (b) (4) designation or consider using an (b) (4) numerical strength and note the meaning of the term lower down on the label (e.g., 5%<sub>w</sub>).
- Relocate the wording (b) (4) from the side panel to the principal display panel and increase the size of the wording to make it more prominent on the label. Please consider rewording the statement to (b) (4) in order to make the warning more specific. Additionally, consider adding the warning “Harmful if swallowed” and “Keep out of reach of children” to help prevent accidental oral ingestion of the product.
- The instructions for use in the Dosage and Administration, as presented on the side panel, are incomplete. Please print a complete set of instructions for use of the product.
- Delete the distributor’s name logo or decrease its size.
- Please clarify whether the dosing chart presented in the draft text description of the Outer Box is to be included in the actual carton and insert labeling.
- Increase the size of the statement of strength “8 oz. (227 g)”, slightly, in order to increase its visibility on the label.

- We recommend limiting (b) (4) .
- The Division of Anti-Infective and Ophthalmology Products review of NDA 22-129 is not available at the time of completion of this review. (consult issued 02/13/2008)

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

Lice Asphyxiator (benzyl alcohol) , 5% lotion is a topical non-pesticide pediculocide intended for two 10-minutes application one week apart for the treatment of head lice (*Pediculus capitis*) infestation in patients 6 months of age and older.

In NDA 22-129, the applicant demonstrated in two vehicle controlled clinical trials that 5% L.A. was superior to vehicle for the primary endpoint defined as percentage of subjects who were lice free 14 days after the second 10-minute application. The incidence of the adverse events was low in both the active and vehicle arms. Four subjects reported five adverse events [eye irritation (1), eye exfoliation (1), vomiting (2) and application site irritation (1)] that were considers (probably/possibly) related to treatment with 5% L.A compared to one subject who reported one adverse event (alopecia) that was considered (possibly) related to vehicle treatment. Both treatment groups showed continuous improvement (post-treatment) in the severity of the pruritus, erythema, pyoderma and excoriation of the skin and scalp. However, 33 of 478 (6.9%) subjects treated with 5% L.A. were reported to have “other” signs / symptoms of the scalp. The most frequently reported signs/symptoms were “Application site irritation” (11 subjects), “Application site anesthesia”, “Hypoesthesia” and “Pain”. Fifteen (4.5%) of 336 subjects treated with vehicle reported “other” signs / symptoms of the scalp. The most frequently reported sign/symptom was paraesthesia (4). Younger subjects (6months to 3 years) are not at greater risk for developing adverse events than older subjects.

Most treatment related adverse events occurred during the treatment period. None of adverse events were severe enough to require treatment interruption or discontinuation. No deaths occurred during the development program for 5% L.A, and no serious adverse events were attributed to drug use.

### 9.2 Recommendation on Regulatory Action

The applicant provided sufficient clinical data to establish safety and efficacy of Lice Asphyxiator (benzyl alcohol) 5% lotion for topical application (two 10- minute applications one week apart) for the treatment of head lice infestation in subjects 6 months of age and older.

However, the drug substance manufacturing facility has not met the cGMP requirements. Therefore, this NDA is recommended for “Approvable” pending resolution of the cGMP issues.

Lice Asphyxiator (benzyl alcohol) 5% lotion is a topical, non-pesticide pediculicide. In both Phase 3 trials, 5% L.A. demonstrated superiority over vehicle. Safety data included eight studies conducted under the clinical development program. The incidence of adverse events was low in both the active and vehicle arms and none were considered serious.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

Prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug product at this time.

#### **9.3.2 Required Phase 4 Commitments**

There are no required Phase 4 commitments

#### **9.3.3 Other Phase 4 Requests**

There is no other Phase 4 Request.

### **9.4 Labeling Review**

Changes to the proposed label supplied by applicant were based on evaluation of chemistry information, preclinical and clinical studies for the NDA and DEMETS and DDMAC review. A patient Package Insert (PPI) has been included and reviewed by the Division and appropriate consults.

See Section 8.8

Refer to the appendix for line-by-line review.

### **9.5 Comments to Applicant**

None



## 10 APPENDICES

### Appendix A

#### **Study SU-01-2005 Electronic Data Inconsistencies**

The errors highlighted in Table 3 led to the differences in efficacy results based upon the primary cohort ITT population defined as the youngest household member randomized and dispensed drug product as presented in the initial study reports versus the reviewer analysis. In addition, this also impacts the secondary ITT population defined as all household members other than the youngest member randomized and dispensed drug product.

Table 3: Electronic Data Set Inconsistencies in Study 01

Data Set Name	No. Subjects	Summary of Error
SUBJECTS	314	Households 02-110 and 05-112 do not contain a member with the variables primary and itt set to 1 <sup>†</sup> . For secondary household members in households 03-119, 05-109, and 05-112 the value of the second variable is not recorded as 1 <sup>†</sup> .
LICE	305	This data set excludes the following subjects: 02-110-0108, 04-104-0104, 04-104-0204, 04-104-0304, 05-112-0113, 05-112-0213, 05-112-0313, 05-112-0413, 05-112-0513

<sup>†</sup> The value of 1 is used as an indicator variable to denote that the subject should be included in the analysis population.

#### **Study SU-02-2005 Electronic Data Inconsistencies**

The errors in the electronic data sets submitted in Study 02 are highlighted in Table 4. These errors led to the differences in efficacy results based upon the primary ITT population as well as secondary ITT population as presented in the initial study reports in comparison to the reviewer analysis.

**Table 4: Electronic Data Set Inconsistencies in Study 02**

Data Set Name	No. Subjects	Summary of Error
SUBJECTS	314	Households 07-233 and 07-236 do not contain a member with the variables primary and itt set to 1 <sup>†</sup> . For secondary household members in households 08-224 the value of the second variable is not recorded as 1 <sup>†</sup> .
LICE	313	This data set excludes the following subject: 07-233-0128.

<sup>†</sup> The value of 1 is used as an indicator variable to denote that the subject should be included in the analysis population.

### Data for Safety Evaluation

In the initial submission, several deficiencies were identified in the derived safety data sets and the Agency requested the sponsor to submit new data sets for ISS evaluation. The following is a summary of the deficiencies of the original safety data sets.

1. The evaluation of the scalp recorded values of none (1) to severe (4) for erythema, pruritus, pyoderma, and excoriation. However, other local adverse events such as burning, numbness, stinging, etc. may have occurred. The electronic data capture may list more than one of these events on the same row of the data set rather than as separate events. In a addition, they are recorded in a verbatim like fashion without converting them to a common terminology. Thus, as currently structured, tabulation of events based on a common terminology which were recorded under the other category cannot be performed.
2. The ISS analysis data set, AE CODED, lacks data to designate the time of AE occurrence, time of resolution, time of study enrollment, and time of study completion.

From Statistical Review and Evaluation, Mat Sukup, Ph.D.

### 10.1 Review of Individual Study Reports

Non applicable

### 10.2 Line-by-Line Labeling Review

The label will be entered separately into DFS.

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