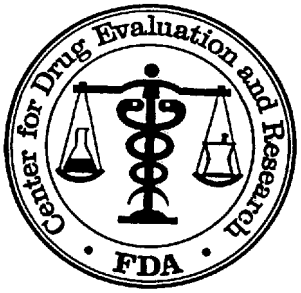
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

STATISTICAL REVIEW(S)



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

New Drug Application

Clinical Studies

NDA/Serial Number:	22-129/SN000
Drug Name:	Lice Asphyxiator (benzyl alcohol), 5%
Indication(s):	Head Lice
Applicant:	Summer's Laboratories
Dates:	Submitted: 06/15/2007
	PDUFA: 04/15/2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Mat Soukup, Ph.D.
Concurring Reviewer:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	Reviewer: Gordana Diglisic, M.D. (DDDP)
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Keywords:	superiority, vehicle-control

Contents

1 Executive Summary

1.1 Conclusions and Recommendations

Lice Asphyxiator (L.A., tradename not approved prior to review completion) contains 5% benzyl alcohol which Summers Labs is seeking approval for the treatment of head lice. Two Phase 3 trials were conducted with the objective of establishing the superiority of two 10 minute applications of L.A. 5% one week apart to vehicle. In both Phase 3 trials, L.A. 5% 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. The incidence of adverse events was low for both the active and vehicle arms, none of which were considered serious.

1.2 Brief Overview of Clinical Studies

Two identical Phase 3 safety and efficacy trials, Study 01 and Study 02, were conducted to compare L.A. 5% to vehicle with the objective of establishing the superiority of L.A. 5% over vehicle. Treatment consisted of two 10 minute applications of topical product to the scalp separated by one week. Study 01 was conducted in 5 centers across the U.S. enrolling a total of 306 subjects (125 index subjects used for primary efficacy evaluation). Study 02 was conducted in 5 U.S. centers enrolling a total of 309 subjects (125 index subjects). The primary efficacy objective was to demonstrate the superiority of L.A. 5% to vehicle where the primary endpoint was defined as the percent of subjects lice free 14 days after the second application of drug product.

1.3 Statistical Issues and Findings

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 studies. The discrepancies between the electronic data sets and the initial study reports were communicated to the sponsor on 08/13/2007, 09/17/2007, and 11/05/2007. On 12/28/2007 the sponsor resubmitted the study reports which appear to be consistent with results based upon the electronic data records. While some of the reported results from the initial study reports were not 100% accurate, it should be noted that the overall determination of efficacy and safety conclusions were consistent.

For the primary endpoint, percent of subjects lice free 14 days after the second application, both studies establish the statistical superiority of L.A. 5% to vehicle for the primary cohort which is defined as the youngest household member; results provided in Table 1. The safety evaluation uses the MedDRA nomenclature and no single preferred term is reported for more than 2.0% of subjects treated with L.A. 5%.

Table 1: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site

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

2 Introduction

2.1 Overview

The sponsor conducted two Phase 2 trials which led to the selection of L.A. 5% applied in two 10-minute applications one week apart as the dosing and treatment regimen. Two confirmatory trials, Study SU-01-2005 (Study 01) and Study SU-02-2005 (Study 02), were conducted to assess the safety and efficacy of L.A. 5%. In addition, Study SU-03-2005 was an open-label study to assess the safety of L.A. 5%.

Table 2: Efficacy and Safety Studies Overview

Study	Development Objective	Drug Products	Number[†] Subjects	Treatment Duration	Date[*]
SU-02-2003	Phase 2 Dose Ranging	L.A. 5% L.A. 10% Vehicle RID®	20 21 20 20	10-min application repeat in one week if still lice infestation	01/2004 – 01/2004
SU-02-2003A	Phase 2 Dose Ranging	L.A. 5% (10m) L.A. 5% (30m)	21 23	Two 10- or 30-min applications one week apart	04/2004 – 05/2004
SU-01-2005	Phase 3 Superiority	L.A. 5% Vehicle	140 166	Two 10-min applications one week apart	03/2006 – 10/2006
SU-02-2005	Phase 3 Superiority	L.A. 5% Vehicle	159 150	Two 10-min applications one week apart	06/2006 – 11/2006
SU-03-2005	Phase 3 Safety	L.A. 5%	128	Two 10-min applications one week apart	03/2006 11/2006

[†] Sample sizes report the total sample size which includes the primary and secondary cohorts for the two pivotal Phase 3 trials.

[*] Dates correspond to the start and end of the study.

The review provides a summary of the Phase 2 efficacy results and relies primarily on Study

01 and Study 02 to establish the efficacy of L.A. 5% versus vehicle. The review of safety incorporates data from subjects that received two 10-minute applications of L.A. 5% one week apart in comparison to subjects receiving vehicle.

2.2 Data Sources

In addition to the electronic data sets submitted as data listings, the electronic resources provided in this submission contain data definition files and an annotated CRF. Several problems existed with both the safety and efficacy electronic data sets which are described in the following sections. The original data sets submitted in the NDA can be found at `//cdsesub1/evsprod/NDA022129/0000/m5/datasets`. These data sets are used in the evaluation of efficacy. The revised safety data sets based on the Agency request can be found at `//cdsesub1/evsprod/NDA022129/0004/m5/datasets/iss/analysis`.

2.2.1 Data for Efficacy Evaluation

In the original submission the sponsor did not submit analysis data sets, submitting only data listings for all clinical trials. Consequently, several data listing data sets needed to be merged to form the efficacy data sets used for the evaluation of efficacy. The following data sets were used to create an analysis data set for efficacy assessment.

- `SUBJECTS.XPT`: data listing which includes analysis population flags.
- `LICE.XPT`: data listing providing efficacy results.

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. However, after merging of the above two data sets, several households which were randomized and dispensed medication did not list the youngest member of the household as being a member of the primary cohort ITT population. The initial study reports also failed to account for some subjects. The following two sections describe the errors in the sponsor's electronic data sets submitted in the original NDA. It should be noted that due to these errors in the electronic data sets, results in the sponsor's initial study reports are not consistent with those of the statistical review. The sponsor was made aware of the inconsistencies on 08/13/2007, 09/17/2007, and 11/05/2007 as the inconsistencies were discovered by the review team. Revised study reports of the two pivotal trials addressing these inconsistencies was submitted on 12/28/2007.[1]

[1]The revised study reports for Study 01 and Study 02 submitted on 12/28/2007 are consistent with those of the statistical review.

2.2.1.1 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†. For secondary household members in households 03-119, 05-109, and 05-112 the value of the second variable is not recorded as 1†.
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

† The value of 1 is used as an indicator variable to denote that the subject should be included in the analysis population.

2.2.1.2 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†. For secondary household members in households 08-224 the value of the second variable is not recorded as 1†.
LICE	313	This data set excludes the following subject: 07-233-0128.

† The value of 1 is used as an indicator variable to denote that the subject should be included in the analysis population.

2.2.2 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.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The evaluation of efficacy includes data from Study 01 and Study 02. Efficacy results from the Phase 2 dose ranging trials, Studies SU-02-2003 and SU-02-2003A, are provided in the Appendix Section A.3 on page 27.

3.1.1 Study Design

3.1.1.1 Studies SU-01-2005 and SU-02-2005 Studies 01 and 02 were multi-center, randomized, double blind, vehicle-controlled trials. The trials were identically designed to recruit approximately 120 subjects for the primary treatment cohort who would participate in the trial for approximately 22 days. A total of five visits were scheduled for each primary cohort subject over the course of the study.

Households who satisfied the inclusion criteria and did not meet any exclusion criteria were randomized in a 1:1 ratio to L.A. 5% or vehicle. The youngest subject from each household with at least three live lice was enrolled for efficacy and safety evaluation in the primary treatment cohort. Any other household member who resided with the randomized subject and had an active lice infestations was asked to participate in this trial in the secondary treatment cohort. If household members agreed, after giving informed consent they were treated with the same clinical test material (CTM) as the primary treatment cohort. Household members who did not qualify were not included in these studies.

Randomized subjects were given sufficient CTM to treat all participating household members for Day 1 application and written instructions on how to use it. At the Day 1 visit, subjects or care givers were given written instructions to administer the treatment at home on that same day. They were instructed to use the following amount of product based upon their hair length:

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

Hair Length		Amount of L.A. 5% per treatment
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 Protocol

At the first evaluation visit (Visit 2) which is to occur the day after treatment, subjects were to return all CTM containers (used or unused) to the study site and a staff member weighed them on a standardized scale to assess compliance. All subjects in the primary and secondary treatment cohorts were examined by a 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 L.A. 5% or offered an FDA approved rescue therapy. Subjects with no live lice were dispensed sufficient CTM for a second treatment.

Prior to the second treatment (Day 8), a staff member contacted each subject or care giver to confirm their appointment for the second evaluation visit (Visit 3). On Day 8 subjects again treated themselves or had their care givers administer a 10-minute treatment at home as directed.

On Day 9 at the second evaluation visit (Visit 3), the procedures of the first evaluation visit were repeated. Primary cohort treatment failures and other household members were offered enrollment into an open label study with L.A. 5% or offered an FDA approved rescue therapy.

On Day 15 at the first follow-up visit (Visit 4), all subjects in the primary treatment cohort were visually examined for lice.[2] Subjects with live lice at Visit 4 were considered treatment failures. Any subject having live lice at Day 15 was offered an FDA approved treatment. All lice-free subjects were to return for follow up at the final follow-up visit (Day 22).

[2]Note that subjects in the secondary efficacy cohort did not have efficacy evaluations at any visits beyond Day 9.

At the final follow-up visit (Visit 5), all subjects in the primary treatment cohort were visually examined for lice. Subjects without live lice were determined a treatment success. Any subject having live lice at Day 22 was offered an FDA approved treatment.

3.1.2 Endpoints

The primary efficacy variable is the treatment success rate 14 days after last treatment (second follow-up visit, Visit 5, Day 22). Treatment success is defined as the absence of live lice. Note that subjects who are identified as treatment failures prior to Visit 5 are considered treatment failures.

The protocol lists a single secondary efficacy endpoint as the cumulative proportion of subjects determined to be treatment failure at the second evaluation visit (Visit 3, Day 9).

3.1.3 Patient Disposition and Baseline Characteristics

3.1.3.1 *Patient Disposition* Table 6 depicts the primary subject disposition for Studies 01 and 02 (subjects could have more than one reason for study discontinuation). 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 6: Primary Subject Disposition

	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.

The disposition of the supportive secondary cohort analysis population is similar to that of the primary cohort and provided in the Appendix Section A.1.

3.1.3.2 *Baseline Characteristics*

3.1.3.2.1 Demographics Results of the baseline comparisons for age, gender, race, hair length, hair texture, and hair curliness are provided in Tables 17 and 18 in Appendix Section A.2 on page 24. 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). Of the two Phase 3 trials only one primary cohort subject had race recorded as 'Black'. Note that these demographics are somewhat consistent with the epidemiologic data published by the U.S. Center for Disease Control[1] which states that females are more likely than males to be infested and in the U.S., "African Americans rarely get head lice."

3.1.4 Statistical Methodology

The following details pertain to the statistical analysis plan as written in the protocol; any deviations from the protocol are explicitly stated.

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. Efficacy analysis will be performed on the ITT and PP populations. PP analysis will be used to illustrate consistency of study results with the ITT analysis.

All statistical tests will be performed at a two-sided alpha level of 0.05. The difference in the two groups' primary endpoint, treatment success rate, will be compared using CMH stratified by site for the superiority comparison. The same analysis strategy is 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 in Section 3.1.7.1.

3.1.5 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 01 and 02 are provided in Table 7. Results from both studies show that L.A. 5% is statistically superior to vehicle with p-values below 0.001 in each study.

Table 7: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site

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

3.1.6 Primary Endpoint Results (Primary Cohort - PP)

As a supportive analysis to the ITT population of the primary cohort, Table 8 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 L.A. 5% to be statistically superior to vehicle.

Table 8: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site

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

3.1.7 Sensitivity Analysis of the Primary Endpoint

3.1.7.1 Sensitivity to Method of Data Imputation 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 not

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 L.A. 5% 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, efficacy results are consistent with the protocol-defined primary cohort efficacy analysis of the ITT population.

Table 9: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site

Source: Reviewer Analysis.

3.1.8 Secondary Endpoint Results

The study included four post treatment visits. These occurred on day 2 (1 day from first treatment), day 9 (1 day after second treatment), day 15 (one week from last treatment), and day 22 (two weeks from last treatment). 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 L.A. 5% and vehicle across all time points. Also for both studies, the highest response rate occurs one week after the first 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.

Table 10 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 then the follow-up visits for all treatments arms in which L.A. 5% is significantly superior to vehicle.

Figure 1: Percent Lice Free Across Study Visits

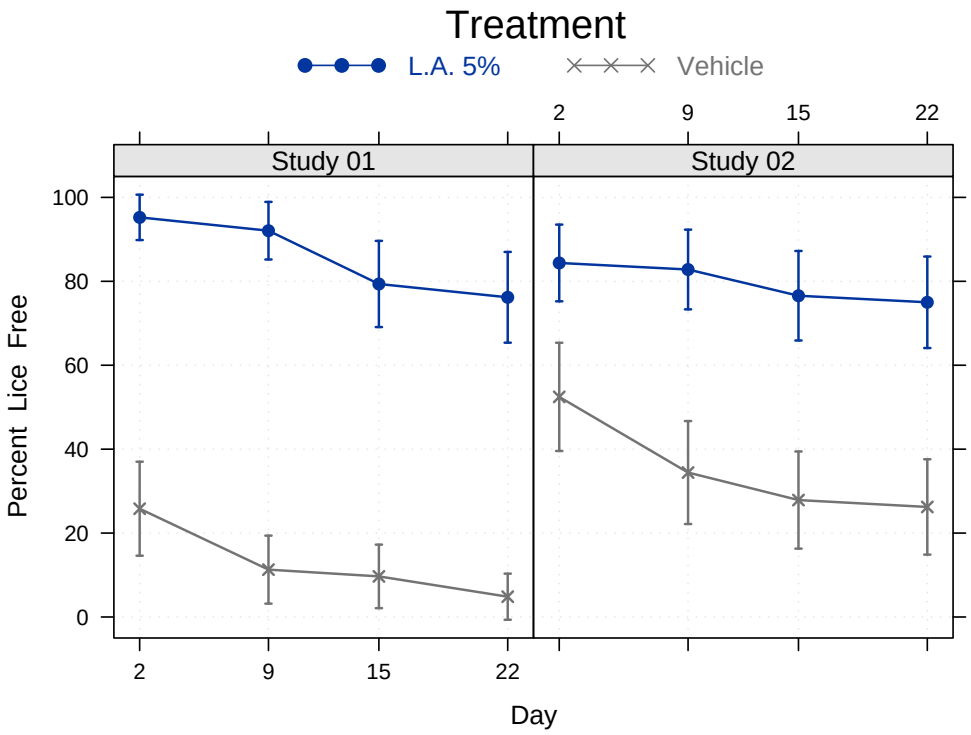


Table 10: Lice Eradication Results (Primary Cohort - ITT Day 9)

	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†	-	$< .001$	-	$< .001$

† Reported p-values are based on CMH stratified by site

Source: Reviewer Analysis.

3.1.9 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. Subjects with missing data are handled in the same way as with the primary cohort. Results are presented in Table 11 which show efficacy results quite similar to that of the primary cohort evaluation on Day 9 (Table 10).

Table 11: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site.

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

3.2 Evaluation of Safety

In addition to the two Phase 3 trials, the evaluation of safety also incorporates data from Study SU-03-2005 (Study 03) which was a multi-center, open label study designed to evaluate the efficacy and safety of home-use of two 10-minute treatments of L.A. 5% (applied one week apart). The study enrolled a total of 128 subjects. The visit schedule which included evaluation and follow-up visits was similar to that of the pivotal Phase 3 trials. In addition to the Phase 3 trials, the Phase 2 studies which investigated two 10 minute applications of L.A. 5% were included in the pooled safety data base which included an additional 81 subjects to the safety data base (62 treated with L.A. 5% and 19 treated with vehicle).

3.2.1 Treatment Emergent Adverse Events

To be included in the safety population, subjects must have at least one post-baseline assessment. In addition, subjects treated with L.A. 5% in either Study 01 or 02 and who subsequently enrolled in Study 03 are not counted twice in the denominator though adverse events occurring during Study 03 were eligible to be counted[3]. In addition, to be considered as treatment emergent, adverse events had to occur the day randomized and before the last study visit (up to 14 days after last application).

Based upon the above definitions, 478 subjects were exposed to L.A. 5% and 336 subjects were exposed to vehicle. Table 12 depicts the MedDRA preferred term and system organ classification for preferred terms that were reported in more than one subject treated with either L.A. 5% or vehicle. This table shows that very few subjects experienced any single general adverse event while on treatment.

3.2.2 Serious Adverse events

No serious adverse events were reported either related or unrelated to L.A. 5% or vehicle.

[3]Of the 128 subjects enrolled in Study 03, 13 were treated with L.A. 5% in Study 01 or Study 02.

Table 12: Adverse Events by Preferred Term

	L.A. 5% ($N = 478$)	Vehicle ($N = 336$)
Gastrointestinal disorders		
Vomiting	3 (0.6)	0 (0.0)
General disorders and administration site conditions		
Pyrexia	3 (0.6)	0 (0.0)
Infections and infestations		
Nasopharyngitis	5 (1.0)	0 (0.0)
Pharyngitis	2 (0.4)	0 (0.0)
Nervous system disorders		
Headache	1 (0.2)	1 (0.3)

Source: Reviewer's analysis.

3.2.3 Local Skin Reactions

For the two pivotal studies, the CRF contained a section where local skin reactions were to be recorded as being not present (1), mild (2), moderate (3), or severe (4) for the following four signs: pruritus, erythema, pyoderma, and excoriation. Figure 2 provides the mean estimate along with an unadjusted 95% confidence interval for each of the visits (the number of subjects with local skin evaluations is provided on the bottom of each graph panel). This figure demonstrates that the local skin reaction ratings tend to decrease with time is expected with the eradication of the lice.

In addition to the four local skin reactions as described above, the CRF also contained a category called 'Other' with the same scoring scale as described above to capture additional local skin and scalp irritation in the two Phase 3 trials. These other terms were defined according to the MedDRA nomenclature by the sponsor and presented in Table 13. This table includes all terms, occurring in at least 0.5% of subjects treated with L.A. 5%, which emerged after treatment in the safety population for the two Phase 3 trials. Only a small percentage of subjects reported any adverse events which were captured in the 'Other' category of the local skin reactions.

Figure 2: Local Scalp and Skin Assessment

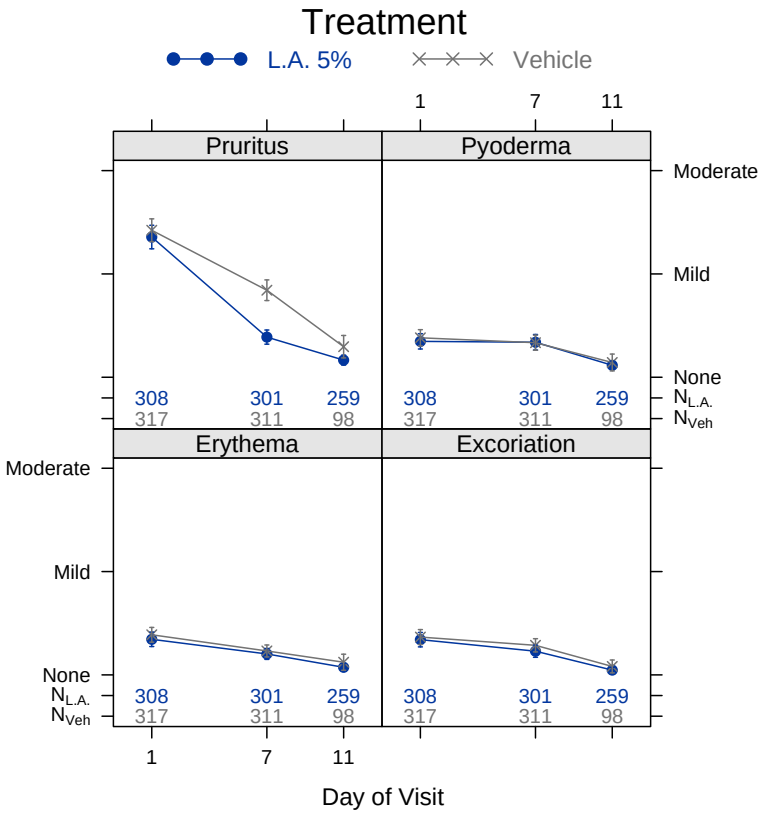


Table 13: Other Local Adverse Events by SOC and PT

	L.A. ($N = 301$)	Vehicle ($N = 317$)
General disorders and administration site conditions		
Application site irritation	7 (2.3)	1 (0.3)
Application site anaesthesia	6 (2.0)	0 (0.0)
Pain	5 (1.7)	0 (0.0)
Skin and subcutaneous tissue disorders		
Skin exfoliation	2 (0.7)	0 (0.0)
Skin lesion	2 (0.7)	0 (0.0)

Source: Reviewer's analysis using `SSEVAL-C.XPT` submitted on 09/21/2007.

4 Findings in Special/Subgroup Populations

Section 4.1 provides a graphical assessment of efficacy by subgroup as well tabular information listed in the lower section of each graph. The efficacy summaries by gender, race, and age

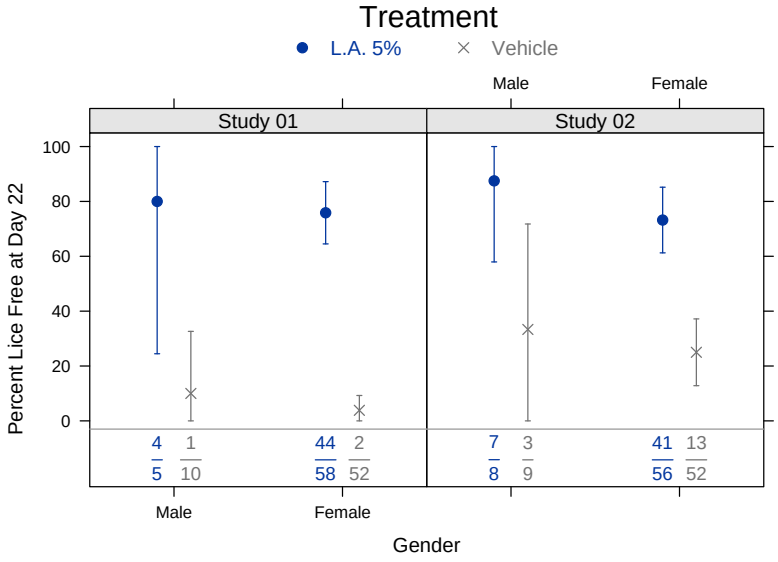
are reported for the ITT population of the primary cohort. Note that the protocol did not pre-specify any subgroup analysis which controlled the overall Type I error rate.

4.1 Gender, Race, and Age

4.1.1 Primary Efficacy Results by Gender

Figure 3 depicts efficacy results according to gender along with unadjusted 95% confidence intervals. 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 is seen in both studies.

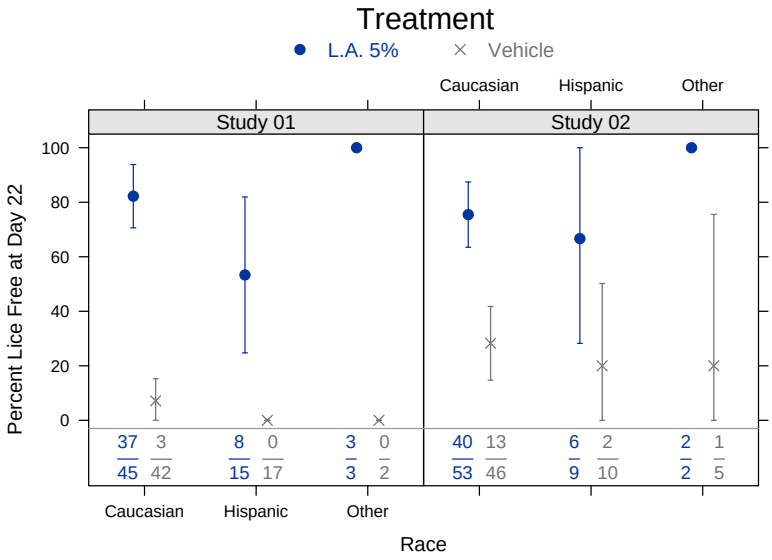
Figure 3: Percent Lice Free by Gender



4.1.2 Primary Efficacy Results by Race

Race was broken into four categories: Caucasian, Black, Hispanic, and Other. However, as noted in Section 3.1.3.2 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 4 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.

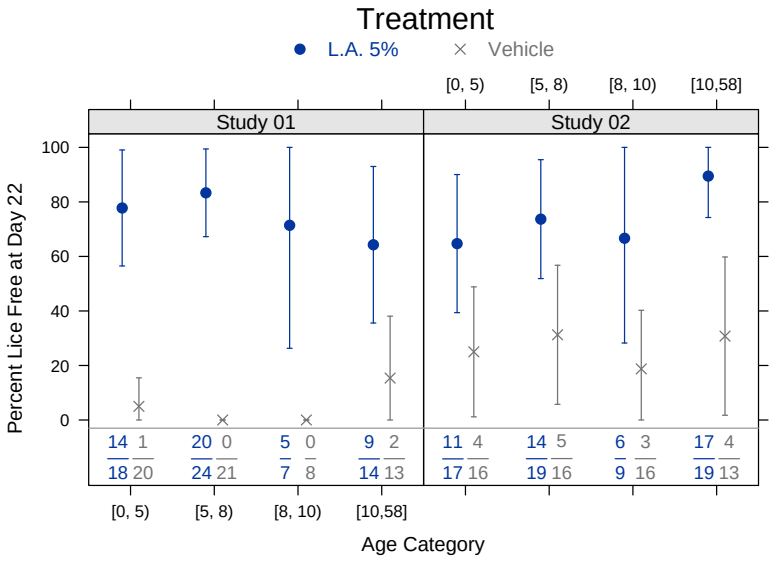
Figure 4: Percent Lice Free by Race



4.1.3 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 L.A. 5% does not show any trends with higher efficacy in any of the age subgroups. Overall, a treatment effect favoring L.A. 5% over vehicle is seen in all studies.

Figure 5: Percent Lice Free by Age Group

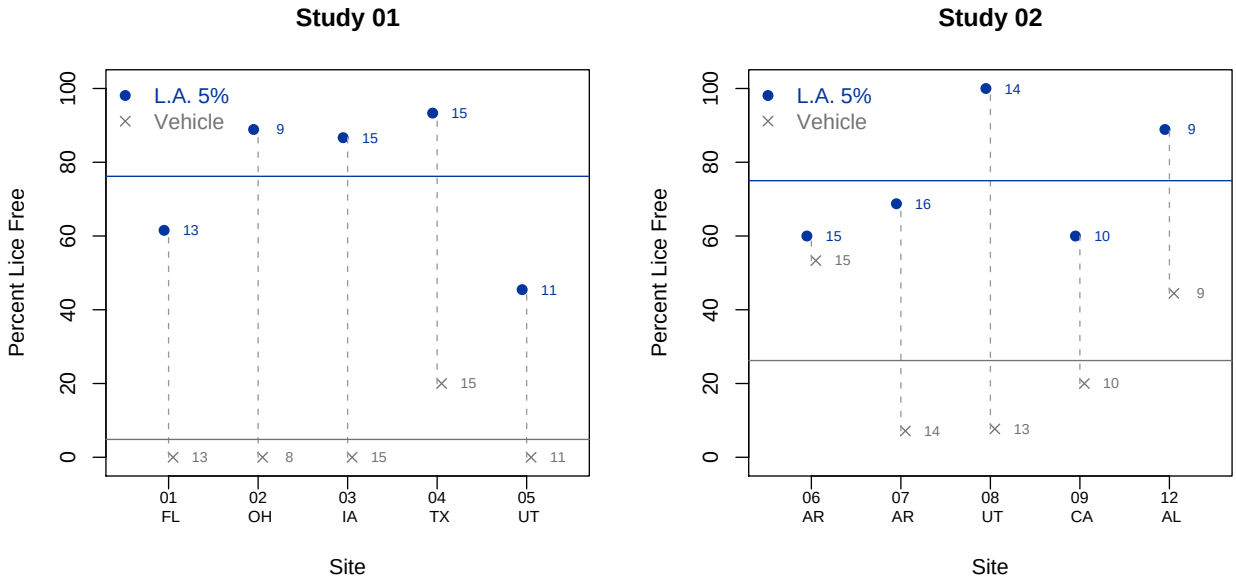


4.2 Other Special/Subgroup Populations

4.2.1 Primary Efficacy Results by Site

Figure 6 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 6: Percent Lice Free by Site



Based on Figure 6 as well as other data submitted in the NDA, 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 L.A. 5% 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.

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.

4.2.2 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

Results are provided as graphical summaries in the Appendix Section A.4. 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.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

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 studies. The discrepancies between the electronic data sets and the initial study reports were communicated to the sponsor on 08/13/2007, 09/17/2007, and 11/05/2007. On 12/28/2007 the sponsor resubmitted the study reports which appear to be consistent with results based upon the electronic data records. While some of the reported results from the initial study reports were not 100% accurate, it should be noted that the overall determination of efficacy and safety conclusions were consistent.

For the primary endpoint, percent of subjects lice free 14 days after the second application, both studies establish the statistical superiority of L.A. 5% to vehicle for the primary cohort which is defined as the youngest household member; results provided in Table 15. The safety evaluation uses the MedDRA nomenclature and no single preferred term is reported for more than 2.0% of subjects treated with L.A. 5%.

Table 14: 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[†]	-	$< .001$	-	$< .001$

[†] Reported p-values are based on CMH stratified by site

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

5.2 Conclusions and Recommendations

In the two Phase 3 trials L.A. 5% establishes the superiority of two 10 minute applications of L.A. 5% one week apart over vehicle based on the pre-defined primary endpoint defined as the percentage of subjects who were lice free 14 days after the second 10 minute application. Overall the incidence of adverse events was low for both the active and vehicle arms, none of which were considered serious.

In the sponsor's originally proposed label, the subjects who were the cause of the discrepancies in the initial study reports and the electronic data sets (i.e. the total number of primary cohort subjects) are not included in the proposed label. As these subjects meet the pre-specified definition of the ITT population which was pre-specified to be the primary analysis population, this reviewer recommends such subjects be included in the label. The proposed label also lists multiple analysis populations and multiple imputation strategies. For clarity, this reviewer suggests the table of efficacy results focus on the individual studies and only include a single analysis population and imputation technique which would be the pre-specified primary analysis defined as the ITT population imputing the missing data using LOCF when the subject was lost to follow-up.[4] Using such a definition the following table might be included in the label.

Table 15: Percent of Subjects Lice Free

	L.A. 5%	Vehicle
Study 1	48/63 (76.2%)	3/62 (4.8%)
Study 2	48/64 (75.0%)	16/61 (26.2%)

[4]Note that regardless of the analysis population or method of data imputation, efficacy conclusions are much alike only with slightly varying point estimates.

References

[1] Center for Disease Control (2005, August 18) Fact sheet: Treating head lice, Department of Parasitic Disease. http://www.cdc.gov/ncidod/dpd/parasites/lice/factsht_head_lice_treating.htm

[2] Statistical Analysis and Graphics produced with R software. R Development Core Team (2007). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

Appendix

A.1 Disposition of the Secondary ITT Population

Table 16 contains information about the disposition of subjects in the secondary cohort ITT population. Efficacy evaluations of this population of subjects are used as supportive to the primary cohort ITT population.

Table 16: Secondary Subject Disposition

	Study 01		**Study 02**	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
Overall	147	167	161	153
Secondary Efficacy	84	105	97	92
Dropout	17 (20.2%)	85 (81.0%)	21 (21.6%)	69 (75.0%)
Treatment Failure	5 (6.0%)	73 (69.5%)	13 (13.4%)	60 (65.2%)
Overt Lice Infestation	0 (0.0%)	7 (6.7%)	0 (0.0%)	0 (0.0%)
Withdrew Consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Investigator Decision	2 (2.4%)	6 (5.7%)	0 (0.0%)	0 (0.0%)
Other	13 (15.5%)	9 (8.6%)	8 (8.2%)	7 (7.6%)

Source: Reviewer's analysis.

A.2 Baseline Demographic Tables

The following tables for baseline demographics are for the ITT population only which consists of the youngest household member with at least one live lice present at baseline. Dominant demographics were females and Caucasians which appeared to be balanced between the two treatment groups. Looking at the characteristics of the hair the majority of subjects had straight hair, hair lengths > 8", and average texture which was consistent across treatment groups and studies.

Table 17: Baseline Factors by Treatment (Study 01)

	L.A. 5% $N = 63$	Vehicle $N = 62$
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.

Table 18: Baseline Factors by Treatment (Study 02)

	L.A. 5% $N = 64$	Vehicle $N = 61$
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.

A.3 Phase 2 Efficacy Results

Study SU-02-2003 incorporated two doses of L.A., 5% and 10%, as well as an active-control (RID®) and a vehicle-control. Subjects applied treatment for 10 minutes at baseline and if lice were present one week later, subjects in the active arms received second application as that received at baseline. Day 15 (14 days after first application) was used as the time point for efficacy evaluation. Efficacy results are presented in Table 19. 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®.

Table 19: Efficacy Results for Study SU-02-2003†

	RID® ($N = 20$)	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%)

† Sponsor's Results: Study Report of SU-02-2003

Study SU-02-2003A incorporated two application durations L.A. 5%. Subjects enrolled applied treatment two times for either 10 or 30 minutes with one week between treatments. Day 15 (14 days after first application) was used as the time point for efficacy evaluation. Efficacy results are presented in Table 20. Both the 10-minute and the 30-minute had 100% of subjects remain lice free at day 15.

Table 20: 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%)

† Sponsor's Results: Study Report of SU-02-2003A

Based on the Phase 2 clinical program the sponsor's rationale to select L.A. 5% for two 10 minute applications one week apart is supported by the dose levels and regimens explored.

A.4 Efficacy Results by Hair Characteristics

The following figures contain efficacy results based upon the subjects hair characteristics as measured by the hair length, type of hair, and the hair texture. Tables below the figures depict the number of successes for a given subgroup with the exception of Figure 7 as the multiple levels made it difficult to interpret the tabular. For sample size for each length, refer to Tables

17 and 18 on pages 25 and 26 in the Appendix. Note that results are based upon the primary cohort using the ITT population.

Figure 7: Percent Lice Free by Length

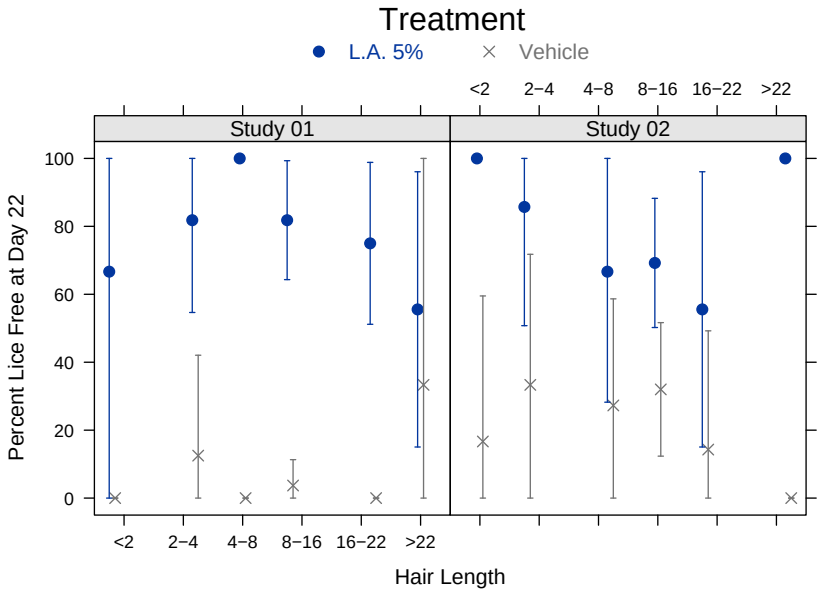


Figure 8: Percent Lice Free by Type

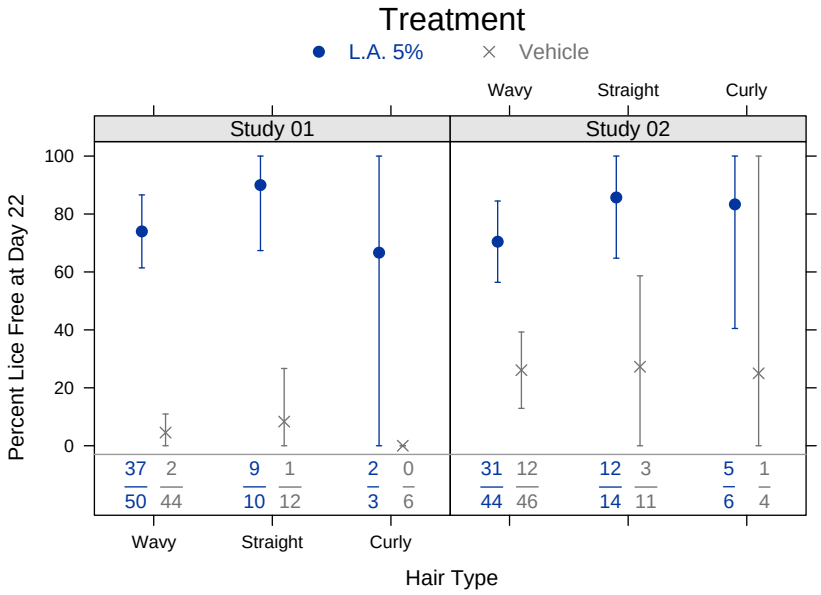
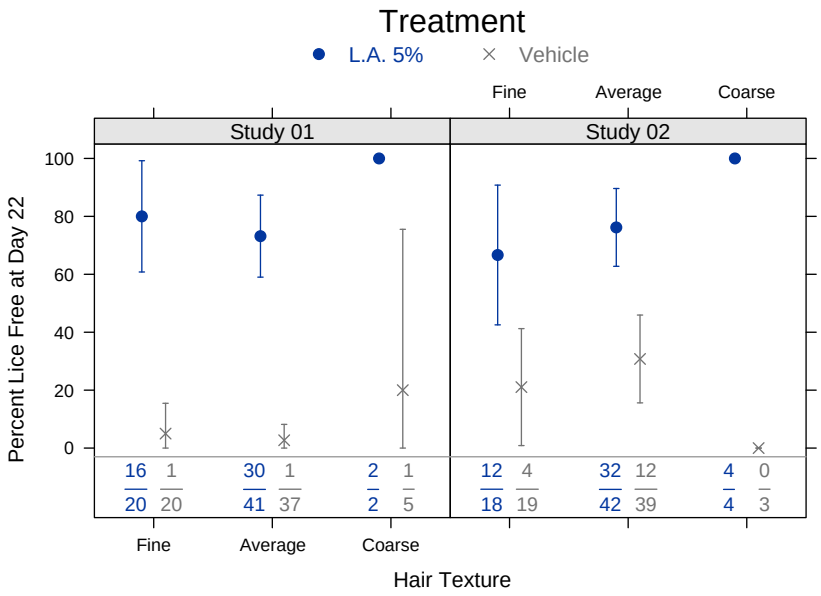


Figure 9: Percent Lice Free by Texture



Signatures/Distribution List

Primary Statistical Reviewer: Mat Soukup, Ph.D.
Date: March 20, 2008

Statistical Team Leader: Mohamed Alosh, Ph.D.

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Archival NDA
DDDP/Walker
DDDP/Lindstrom
DDDP/Diglisic
DDDP/Bauerlien
OBIO/Patrician
DB3/Wilson
DB3/Alosh
DB3/Soukup

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/s/

Matt Soukup
3/31/2008 10:39:24 AM
BIOMETRICS

Mohamed Alosh
3/31/2008 12:14:58 PM
BIOMETRICS

Statistical Review and Evaluation
Fileability Review

NDA Number:	22-129
Drug Name:	Lice Asphyxiator 5%
Applicant:	Summer Laboratories
Indication:	Head Lice
Fileability Meeting Date:	07/31/2007
User Fee Date:	12/15/2007
Received for Stat Review:	07/12/2007
Statistical Reviewer:	Mat Soukup, Ph.D., DBIII
Medical Officer:	Gordana Diglisic, M.D., DDDP
Project Manager:	Melinda Bauerlien, M.S., DDDP

1 Introduction

Summer Laboratories has submitted NDA 21-129 for Lice Asphyxiator 5% for the treatment of head lice. Two randomized, vehicle-controlled studies were conducted to assess the efficacy and safety of two 10 minute applications (one week apart) of Lice Asphyxiator 5%. This is a filing review to address the adequacy of the NDA to support statistical review.

2 Organization and Data Representation

1. Is there a comprehensive table of contents with adequate indexing and pagination?
   Yes - the structure follows eCTD specifications and contains a properly functioning XML backbone file.

2. Are the original protocols, protocol amendments, and proposed label provided?
   Yes, protocols and amendments are submitted (Section 16.1). The label is submitted in module 1 which includes a MS Word version.

3. Are the following tables/listings provided in each study report?

   (a) Patient profile listings by center for all enrolled subjects.
   Results by center can be ascertained by electronic data sets.

   (b) Discontinued subject tables by center (includes reason and time of loss).
   The table is not provided by center, however, this is possible with the electronic data.

   (c) Subgroup analysis summary tables (gender, race, age, etc.).
   No subgroup results are presented in the study reports. The report for the ISE states that no efficacy results by sub-populations were performed. The efficacy data set, `LICE.XPT`*, does contain variables for age, race, and sex.*

(d) Adverse event listings by center and time of occurrence.
No adverse events by center or time of occurrence are presented in the study reports. The AE_CODED data set in the ISS lacks a variable to designate the time of occurrence. A revised data set is requested to capture the time of onset in days from first treatment.

4. Have the data been submitted electronically?

   (a) Has adequate documentation of the data sets been provided?
   For the most part. Further information is requested for Study SU-01-2005.

   (b) Do the data appear to accurately represent the data described in the study reports?
   The data base is not structured to capture local adverse events of the scalp which were not pre-specified on the CRF. A revised data set to assess local skin and scalp adverse events is requested below.

   (c) Can the data be easily merged across studies and indications?
   For the most part, the variable PID is the unique patient ID which can be used to merge data sets.

3 Statistical Methodology

1. Are all primary efficacy studies of appropriate design to meet basic approvability requirements within current Division policy or to the extent agreed upon previously with the sponsor by the Division?
   Yes, the design is consistent with the Agency's comments on the protocol submitted for Special Protocol Asssessment.

2. For each study, is there a comprehensive statistical summary of the efficacy which covers the intent-to-treat population and per protocol population?
   The study reports for the two pivotal trials, SU-01-2005 and SU-02-2005, appear to have adequate documentation of the efficacy.

3. Based on the summary analyses of each study:

   (a) Are the analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims)?
   Analysis of the percent with no live lice 14 days from the last day of treatment is analyzed using CMH stratified by site which is in a agreement with the Agency.

   (b) Are the intent-to-treat and per protocol patient analyses properly performed?
   The definitions of ITT and PP appear to be consistent with the protocol definitions submitted to the SPA. However, 3 subjects in Study SU-01-2005 require further input from the sponsor. See below for sponsor clarification.

(c) Has missing data been appropriately handled?
Many subjects have missing data and this is due to the design of the trial which allowed subjects to drop out early from the trial if live lice were present at any of the treatment visits. These subjects are handled as failures in the analysis for the primary method of data imputation with LOCF presented as a sensitivity analysis.

(d) Have multiplicity issues (regarding endpoints, timepoints, or dose groups) been adequately addressed?
NA

(e) If interim analyses were performed, were they planned in the protocol and appropriate significance level adjustments made?
NA

4. Were sufficient and appropriate references included for novel statistical approaches?
NA

5. Are all pivotal studies complete?
Yes.

6. Has the safety data been comprehensively and adequately summarized?
No. 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. A summary or discussion of these other events do not appear in the sponsor's study report and the electronic data capture may list multiple such events on the same row of the data set rather than as separate events. In a addition, the are recorded in a verbatim like fashion without converting them to a common terminology. A revised data set for assessing skin and scalp events is requested.

4 Fileability Conclusions

From a statistical perspective this submission, or indications therein, *is* reviewable with moderate further input from the sponsor.

5 74-Day Letter Comments

The following comments were requested to be sent as information requests to the sponsor, not as filing issues.

1. In Study SU-01-2005 three households (Household ID: 02-110, 05-112, and 04-104) appear to randomize subjects to treatment based upon the CRF's of each of the youngest member for the household. However, only household 04-104 (randomized to vehicle) is included in the ITT population, whereas the two households randomized to L.A. 5% were

NOT included in the ITT population. As the definition of the ITT population is all subjects randomized and dispensed medication, based on the subject's CRF's it is unclear why households 02-110 and 05-112 are not included in the ITT analysis. Please provide clarification as to why households 02-110 and 05-112 are not included in the ITT analysis.

2. 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. A summary or discussion of these other events do not appear in the sponsor's study report and the electronic data capture may list multiple 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. To facilitate the review of all adverse events of the scalp evaluation the sponsor is requested to submit an ISS data set for the skin and scalp evaluation. The following are specifications that the sponsor should use in order to construct the data set.

   - When more than one term is recorded in a row of the SSEVAL data sets (e.g. numbness, burning/stinging as reported for PID 08-205-0204) then each of the terms should be recorded on separate rows.
   - For terms that are currently listed in the OTHER variable of the SSEVAL data sets, these verbatim-like terms should be coded to a lower-level MedDRA term or other common terminology in order to create a nomenclature for similar adverse events. The variable to capture these other terms should be defined as TERM_OT in the ISS data set.
   - The structure of the data set should contain the following information which is similar to the analysis data set AE_CODED; variable names are suggested in parentheses.
     - Unique Subject ID (PID)
     - Unique Study ID (STUDY)
     - Treatment Group (TRTGRP)
     - Age of Patient (AGE)
     - Race of Patient (RACE)
     - Sex of Patient (SEX)
     - Date of Onset (ONSET)
     - Stage of Onset (STAGE)
     - Pruritus Severity: 1-4 (PRURIT)
     - Erythema Severity: 1-4 (ERYTHEM)
     - Excoriation Severity: 1-4 (EXCORT)
     - Pyoderma Severity: 1-4 (PYODERM)
     - Term for Other Events (TERM_OT)
     - Other Severity: 1-4 (OTHER)

3. No adverse events by time of occurrence are presented in the study reports. In addition, the AE_CODED analysis data set in the ISS lacks a variable to designate the time of occurrence. The analysis data set submitted in the ISS should contain a variable to denote the date of onset of the adverse event. In addition it should contain the date of enrollment as well as the date of study completion. A revised AE_CODED ISS data set should be submitted to contain these additional variables.

Mat Soukup, Ph.D.
Mathematical Statistician, Biometrics 3

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics 3

Cc:
Orig. NDA 22,129/SN000
DDDP/Walker
DDDP/Lindstrom
DDDP/Diglisic
DDDP/Bauerlien
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Soukup

August 3, 2007

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/s/

Matt Soukup
8/3/2007 12:29:47 PM
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Mohamed Alosh
8/13/2007 10:43:35 AM
BIOMETRICS