CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. 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

CLINICAL STUDIES

NDA Serial Number:	202-736/N0001
Drug Name:	Sklice (Ivermectin), topical cream, 0.5%, (b) (4)
Indication(s):	Treatment of head lice infestations
Applicant:	Topaz Pharmaceuticals, Inc
Date(s):	Submission Date: 04-07-2011
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Biometrics Division:	Division of Biometrics 3
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Keywords: clinical studies, NDA review, logistic regression, Cochran-Mantel-Haenszel

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1. EXECUTIVE SUMMARY

Statistical results from two phase-3 studies demonstrate that Sklice (0.5% Ivermectin Cream) statistically significantly increased the proportion of lice-free subjects on Day 15 compared with the vehicle. Efficacy results are summarized in Table 1. In Study Top11, the treatment difference is 59.8% with a 95% confidence interval (CI) of 45.5% to 74.2%. While in Study Top12, the treatment difference is 52.5% with a 95% CI of 37.3% to 67.7%. The treatment differences from both studies are positive and of similar magnitude.

Though no major concerns seriously affecting this overall conclusion were found, statistical review issues evaluated and described in this review include: the effects of an operational discrepancy in the sponsor's pre-planned randomization procedures and study conduct noted prior to the filing meeting; re-adjudication of imputed missing values; and the appropriateness of pre-specified analytical methodology in the presence of sparse data:

- The errors in the randomization identified at the filing meeting on May 18, 2011 do not appear to significantly influence the p-values reported for the treatment differences as shown in Table 13.
- The sponsor imputed "lice free" (positive response) for ITT subjects without a post-baseline efficacy assessment (3 Sklice and 1 vehicle in Study Top12). We do not agree that this is the appropriate imputation for these missing data. Instead, for the subjects without post-baseline efficacy data, we impute their baseline values as "lice present" (negative response). This re-adjudication reduces the point estimate for the treatment difference for Study Top12 from 55.4% to 52.5%.
- Due to the errors in the randomization and sparse data per treatment group per study site, the overall Chi-square Test without stratification by site is considered as the most appropriate method for the primary analysis. We report the efficacy results based on the overall Chi-square.

From a statistical perspective, the submitted efficacy results for the two phase-3 studies, displayed in Table 1, are adequate to support the efficacy of Sklice in the treatment of head lice infestations.

Table 1. Proportion of Head Lice Free Subjects on Day 2 through Day 15

Study	Vehicle	Sklice	Difference
	% (n/N)	% (n/N)	(95% CI)
Top11	16.2% (12/74)	76.1% (54/71)	59.8% (45.5%, 74.2%)
Top12	18.9% (14/74)	71.4% (50/70)	52.5% (37.3%, 67.7%) *

*: Based on the reviewer's reanalysis (See Section 3.2.1.2.3)

2. INTRODUCTION

2.1 Overview

The applicant, Topaz Pharmaceuticals, Inc. is seeking approval of Sklice, ivermectin topical cream 0.5%, for the treatment of head lice infestations under Section 505(b)(2). Oral ivermectin 3 mg was approved for the treatment of strongyloidiasis of the intestinal tract and onchocerciasis in 1996. No other indications have been approved by the Agency for ivermectin.

The sponsor conducted a dose selection phase-2 study (Top03) with 3 doses of ivermectin (0.15%, 0.25%, and 0.5%) followed by two pivotal phase-3 studies (Top11 and Top12). The Division requested this dose finding study in three communications under IND 73,134: at a pre-IND meeting on July 24, 2006 (letter dated Aug. 23, 2006), in a correspondence to the sponsor's draft phase-3 protocol dated Oct. 16, 2008, and at a type-A End-of-Phase 2 meeting on Nov. 14, 2008 (letter dated Dec. 22, 2008). Following this study, the highest dose of 0.5% ivermectin was selected for the phase-3 trials.

In responding to a proposed special protocol on Dec. 23, 2009, the division noted that there was a disagreement with the sponsor concerning the definition of the ITT population. The Division preferred that the ITT population include all index subjects who were randomized and dispensed study medication, regardless whether or not they were treated. The sponsor addressed this disagreement in the design of the Phase-3 protocols submitted on Jan. 20, 2010 for Studies Top11 and Top12.

As these two trials were being conducted (the studies were run simultaneously), an error was discovered in the implementation of the planned randomization procedures during a routine sponsor's team teleconference on April 15, 2010. The sponsor realized that the initial randomization for the two studies had been performed centrally at the trial level, rather than using the protocol-specified by-site methodology. Following this discovery, the sponsor used the protocol-specified by-site methodology for the treatment selection of all subjects who entered the trial on or after April 19, 2010 and amended the Statistical Analysis Plan (SAP) to include logistic regression modeling to investigate potential site effects (in addition to the original proposed CMH test). The Agency was not told of this randomization error and of the corrective action taken by the sponsor prior to the submission of the NDA. The potential effects of this procedural randomization issue are discussed in this review.

This review will focus on the evidence supporting the efficacy of Sklice based on clinical data from the two randomized, vehicle-controlled, double-blind and multicenter phase-3 studies (Top11 and Top12) noted above. While the review of safety will include data from a phase-2 doses selection study (Top03) and a phase-2 safety study (Top10). All of the four studies are summarized in Table 2.

2.2 Data Sources

The study report and additional information were submitted electronically. The data quality of the submission is within the acceptable limits. Analysis datasets and associated definition files are listed in Table 3.

Table 2: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Number of Subjects per Arm	Study Country (Number of Sites)	Study Population
Top03	*Phase 2, Dose-selection, Randomized, Double-blind, Vehicle-controlled*	*1 time on Day 1*	*Planned:* *0.15% ivermectin 18, 0.25% ivermectin 18, 0.5% ivermectin 18, Vehicle 18* *Enrolled:* *0.15% ivermectin 18, 0.25% ivermectin 18, 0.5% ivermectin 19, Vehicle 23*	*US (1)*	*Head lice infected subjects aged >=6 months*
Top10	*Phase 2, Safety Randomized, Double-blind, Vehicle-controlled Multicenter*	*1 time on Day 1*	*Planned:* *0.5% ivermectin 200, Vehicle 50* *Enrolled:* *0.5% ivermectin 206, Vehicle 58*	*US (12)*	*At least 1 live louse infected subjects*
Top11	*Phase 3, Randomized, Double-blind, Vehicle-controlled Multicenter*	*1 time on Day 1*	*Planned:* *Sklice 66 index subjects (150 total)* *Vehicle 66 index subjects (150 total)* *Enrolled:* *Sklice 71 index subjects (211 total)* *Vehicle 74 index subjects (199 total)*	*US (8)*	*Head lice infected subjects aged >=6 months*
Top12	*Phase 3, Randomized, Double-blind, Vehicle-controlled Multicenter*	*1 time on Day 1*	*Planned:* *Sklice 66 index subjects (150 total)* *Vehicle 66 index subjects (150 total)* *Enrolled:* *Sklice 70 index subjects (169 total)* *Vehicle 74 index subjects (202 total)*	*US (8)*	*Head lice infected subjects aged >=6 months*

Table 3. Data Sources

Study	File	Location
Top03	Datasets	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-003\analysis\datasets\
	Definition	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-003\analysis\datasets\define.pdf
Top10	Datasets	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-010\analysis\datasets\
	Definition	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-010\analysis\datasets\define.pdf
Top11	Datasets	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-011\analysis\datasets\
	Definition	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-011\analysis\datasets\define.pdf
Top12	Datasets	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-012\analysis\datasets\
	Definition	\\CDSESUB1\EVSPROD\NDA202736\0001\m5\datasets\top-012\analysis\datasets\define.pdf

2.3 Indication

Sklice is indicated for the treatment of head lice infestations. There have been three approved drugs by the Agency for the treatment of head lice: Nix, Natroba (spinosad) and Ulesfia. Clinical studies for Natroba and Ulesfia showed that the point estimate for active treatment effect ranged from about 75.0% to 86.7% and the point estimate for the vehicle effect ranged from 4.8% to 26.2% -- similar to the efficacy results reported for the two Phase-3 Sklice studies.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The primary and secondary analysis variables in EFFDATA analysis dataset can be derived from the tabulation dataset FA. Some improper LOCF imputation was found and corrected in Section 3.2.1.2.3.

3.2 Evaluation of Efficacy

3.2.1 Overview of Studies Top11 and Top12

Studies Top11 and Top12 are identical independent trials. Therefore, this reviewer will review the two studies together.

3.2.1.1 Design, Objectives and Endpoints

Design and Objective: Both studies Top11 and Top12 were randomized, double-blind, vehicle-controlled, and multicenter phase-3 trials conducted in the United States as shown in Table 1. Both studies had a targeted enrollment of 132 households, 66 index subjects per treatment group. An index subject was defined as the youngest member of the enrolled household who had at least 3 live head lice and met all of the inclusion/exclusion criteria. All eligible index subjects aged 6 months or older were randomized in a ratio of 1:1 to receive one of the following two treatments:

- 0.5% Ivermectin Cream (Sklice)
- Vehicle control cream

Eligible non-index subjects enrolled in the index subject's household with an active head lice infestation present on the scalp and/or hair received the same treatment as that of the index subject. The randomization was planned to be stratified by study sites. After randomization, subjects living in the same household were instructed to apply the same 1-time treatment on their hair and scalp for 10 minutes at home on Day 1. All subjects were scheduled for follow-up visits on Days 2, 8 and 15 post dosing. If live lice were present on Days 2, 8 or 15, the subject was to receive an FDA-approved over-the-counter (OTC) rescue treatment and their study participation was considered complete.

The primary objective of both studies was to establish the efficacy of a single application of Sklice in the treatment of head lice under at-home use conditions compared with the vehicle. The secondary objective of both studies was to demonstrate the safety and local tolerability of 0.5% Ivermectin Cream compared with the vehicle.

Primary Efficacy Endpoint: The primary efficacy endpoint was the number and percentage of index subjects who were lice-free by Day 2 and maintained lice-free through Day 8 and Day 15.

Secondary Efficacy Endpoint: The secondary efficacy endpoint was the number and percentage of all subjects who were lice-free by Day 2 and maintained this lice-free status through Day 8 and Day 15.

Determination of Sample Size: The sample size was calculated based on the following assumptions:

- A treatment difference of 45% between Sklice and the vehicle in the proportion of eradication by Day 15

It was estimated that a total of 132 index subjects, 66 index subjects per treatment group, would provide at least 90% power to detect the above treatment difference with a 2-sided alpha of 0.05, and provide a lower bound of the 95% CI greater than 30%. Based on an average of 2.5 individuals per household, approximately 330 total subjects (including index subjects and the eligible household members) were to be enrolled.

Determination of Analysis Sets: Three analysis populations were defined for efficacy analysis. The intent-to-treat (ITT) population included all index subjects who were randomized and dispensed study medication (but not necessarily treated). The index subject was the youngest person within each household who had at least 3 live lice present at Screening (Day 1). The intent-to-treat-2 (ITT2) population included all subjects who were randomized or enrolled and dispensed study medication (but not necessarily treated). The per-protocol (PP) population included all ITT subjects who had no major protocol deviations or violations.

Handling of Missing Data: The missing data were to be imputed by the last observation carried forward (LOCF) method. The treatment failure imputation was to be used as a sensitivity analysis, in which a subject with a missing measurement on Day 15 was considered treatment failure regardless whether there was a post-baseline measurement or not before Day 15. No imputation was planned to be performed for the analysis on the ITT2 and PP populations.

Multiplicity Adjustment: There were no planned multiplicity adjustments.

Statistical Methods: The site-adjusted Cochran-Mantel-Haenszel test was employed for the overall comparison of the primary endpoint. A chi-square test was also used to compare Sklice with the vehicle, and a 95% CI for the treatment difference was calculated based on this test. The results of chi-square tests were also provided for each study site.

As noted above, with the discovery of the procedural error in the randomization, logistic regression modeling was employed to assess possible study site effects and treatment-by-site interactions. The model contained success/failure as the dependent variable and fixed effect of treatment, site, and treatment-by-site interaction as the independent variables. The sponsor stated that if in using this method, a treatment-by-site interaction was found to be statistically significant, then the sites with smaller numbers of subjects and similar success rates would be pooled into one or two sites of at least 14 subjects each. The model was to be reduced in a stepwise manner until only statistically significant ($p \leq 0.05$) terms and treatment remained.

If not all of the success rates for each study site were in favor of the active treatment group, an exploratory analysis was to be conducted to investigate possible influential factors, such as hair characteristics.

Reviewer's Comments on the Design: *Studies Top11 and Top12 appear to have been adequately designed to detect a non-zero treatment difference in the proportion of subjects free of head lice. We do not agree with the sponsor's method of pooling sites. The sponsor should pool the similar sites first before using statistical modeling. The impact of missing values was addressed by the LOCF imputation and the failure imputation, which is acceptable for this indication.*

3.2.1.2 Results: Studies Top11 and Top12

3.2.1.2.1 Subject Disposition

At 16 US sites (8 for each study), a total of 145 and 144 index subjects (ITT) were randomized into Studies Top11 and Top12, respectively. The lice-infected household members for each index subject were also enrolled and were treated the same drug as the index subject. Consequently, the total intent-to-treat subjects (ITT2) were 410 and 371 in Study Top11 and Top12, respectively. No single site was predominant in terms of enrollment. The discontinuation rates are 1.0% in Study Top11 and 3.2% in Study Top12. The major reason for discontinuation was the lost to follow-up (1.9%) in Study Top12. The numbers of ITT subjects and the per-protocol subjects in both studies were well over the planned 132 index subjects.

Table 4. Subject Disposition for Studies Top11 and Top12 (All Randomized Subjects)

Category	Study Top11			Study Top12		
	Sklice N=211	Vehicle N=199	Total N=410	Sklice N=169	Vehicle N=202	Total N=371
To-be-Treated Subjects	211 (100.0%)	199 (100.0%)	410 (100.0%)	169 (100.0%)	202 (100.0%)	371 (100.0%)
Randomized Index Subject	71 (33.6%)	74 (37.2%)	145 (35.4%)	70 (41.4%)	74 (36.6%)	144 (38.8%)
Completed (index subjects)	71 (33.6%)	73 (36.7%)	144 (35.1%)	65 (38.5%)	72 (35.6%)	137 (36.9%)
Completed (all subjects)	210 (99.5%)	196 (98.5%)	406 (99.0%)	161 (95.3%)	198 (98.0%))	359 (96.8%)
Discontinued (all subjects)	1 (0.5%)	3 (1.5%)	4 (1.0%)	8 (4.7%))	4 (2.1%)	12 (3.2%)
Reason of Discontinuation						
Protocol Deviation	1 (0.5%)	0 (0.0%)	1 (0.2%)	--	--	--
Subject Withdrawal	0 (0.0%)	3 (1.5%)	3 (0.7%)	1 (0.6%)	2 (1%)	3 (0.8%)
Lost to Follow-Up	--	--	--	7 (4.1%)	0 (0.0%)	7 (1.9%)
Non-compliance	--	--	--	0 (0.0%)	2 (1.0%)	2 (0.5%)
ITT Population	71 (33.6%)	74 (37.2%)	145 (35.4%)	70 (41.4%)	74 (36.6%)	144 (38.8%)
ITT2 Population	211 (100.0%)	199 (100.0%)	410 (100.0%)	169 (100.0%)	202 (100.0%)	371 (100.0%)
Per Protocol Population	70 (33.2%)	73 (36.7%)	143 (34.9%)	64 (37.9%)	72 (35.6%)	136 (36.7%)

3.2.1.2.2 Subject demographic and baseline characteristics

Subject baseline characteristics such as age, race, sex and hair factors were similar for the two treatment groups in both studies as shown in Table 5 and Table 6. Body mass index is not summarized here as the study drug was only applied externally to the head of a subject.

Table 5. Subject Demographic and Baseline Characteristics for Study Top11

Parameters	ITT			ITT2		
	Sklice N=71	Vehicle N=74	Total N=145	Sklice N=211	Vehicle N=199	Total N=410
Mean Age (SD)	7.2 (4.94)	7.8 (6.35)	7.5 (5.69)	14.0 (11.97)	15.1 (13.46)	14.5 (12.71)
Race: n (%)						
Black	0 (0.0)	1 (1.4)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.2)
Indian/Alaskan Native	1 (1.4)	0 (0.0)	1 (0.7)	2 (1.0)	1 (0.5)	3 (0.7)
Multi-Racial: White/Black	1 (1.4)	2 (2.7)	3 (2.1)	1 (0.5)	5 (2.5)	6 (1.5)
White	69 (97.2)	71 (95.9)	140 (96.6)	208 (98.6)	192 (96.5)	400 (97.6)
Sex: n (%)						
Male	11 (15.5)	13 (17.6)	24 (16.6)	39 (18.5)	35 (17.6)	74 (18.1)
Hair Shape: n (%)						
Curly	10 (14.1)	9 (12.2)	19 (13.1)	21 (10.0)	18 (9.0)	39 (9.5)
Wavy	23 (32.4)	18 (24.3)	41 (28.3)	60 (28.4)	53 (26.6)	113 (27.6)
Straight	38 (53.5)	47 (63.5)	85 (58.6)	130 (61.6)	128 (64.3)	258 (62.9)
Hair Length: n (%)						
Short	18 (25.4)	15 (20.3)	33 (22.8)	44 (20.9)	37 (18.6)	81 (19.8)
Medium	22 (31.0)	30 (40.5)	52 (35.9)	55 (26.1)	63 (31.7)	118 (28.8)
Long	24 (33.8)	21 (28.4)	45 (31.0)	83 (39.3)	71 (35.7)	154 (37.6)
Very Long	7 (9.9)	8 (10.8)	15 (10.3)	29 (13.7)	28 (14.1)	57 (13.9)
Hair Texture: n (%)						
Coarse	13 (18.3)	13 (17.6)	26 (17.9)	36 (17.1)	34 (17.1)	70 (17.1)
Medium	39 (54.9)	39 (52.7)	78 (53.8)	132 (62.6)	116 (58.3)	248 (60.5)
Fine	19 (26.8)	22 (29.7)	41 (28.3)	43 (20.4)	49 (24.6)	92 (22.4)
Hair Volume: n (%)						
Thick	23 (32.4)	24 (32.4)	47 (32.4)	67 (31.8)	63 (31.7)	130 (31.7)
Medium	26 (36.6)	31 (41.9)	57 (39.3)	95 (45.0)	95 (47.7)	190 (46.3)
Thin	22 (31.0)	19 (25.7)	41 (28.3)	49 (23.2)	41 (20.6)	90 (22.0)
Live Lice: n (%)						
≥ 3	71 (100)	74 (100)	145 (100)	150 (71.1)	139 (69.8)	289 (70.5)
Viable Nits: n (%)						
Yes	71 (100)	74 (100)	145 (100)	208 (98.6)	199 (100)	407 (99.3)

Table 6. Subject Demographic and Baseline Characteristics for Study Top12

Parameters	ITT			ITT2		
	Sklice N=70	Vehicle N=74	Total N=144	Sklice N=169	Vehicle N=202	Total N= 371
Mean Age (SD)	8.5 (7.69)	9.1 (9.71)	8.8 (8.77)	14.5 (13.20)	15.2 (13.82)	14.9 (13.53)
Race: n (%)						
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Indian/Alaskan Native	0 (0.0)	2 (2.7)	2 (1.4)	0 (0.0)	5 (2.5)	5 (1.4)
Multi-Racial: White/Black	4 (5.7)	1 (1.4)	5 (3.5)	12 (7.1)	2 (1.0)	14 (3.8)
White	66 (94.3)	71 (96.0)	137 (95.1)	157 (92.9)	195 (96.5)	352 (94.9)
Sex: n (%)						
Male	13 (18.6)	20 (27.0)	33 (22.9)	33 (19.5)	51 (25.3)	84 (22.6)
Hair Shape: n (%)						
Curly	8 (11.4)	9 (12.2)	17 (11.8)	14 (8.3)	25 (12.4)	39 (10.5)
Wavy	26 (37.1)	24 (32.4)	50 (34.8)	61 (36.1)	72 (35.6)	133 (35.8)
Straight	36 (51.4)	41 (55.4)	77 (53.5)	94 (55.6)	105 (52.0)	199 (53.6)
Hair Length: n (%)						
Short	14 (20.0)	26 (35.1)	40 (27.8)	40 (23.7)	64 (31.7)	104 (28.0)
Medium	23 (32.9)	21 (28.4)	44 (30.6)	43 (25.4)	52 (25.7)	95 (25.6)
Long	28 (40.0)	19 (25.7)	47 (32.6)	68 (40.2)	63 (32.2)	131 (35.3)
Very Long	5 (7.1)	8 (10.8)	13 (9.0)	18 (10.7)	23 (11.4)	41 (11.1)
Hair Texture: n (%)						
Coarse	6 (8.6)	5 (6.8)	11 (7.6)	21 (12.4)	28 (13.9)	49 (13.2)
Medium	30 (42.9)	37 (50.0)	67 (46.5)	83 (49.1)	109 (54.0)	192 (51.8)
Fine	34 (48.6)	32 (43.2)	66 (45.8)	65 (38.5)	65 (38.5)	130 (35.0)
Hair Volume: n (%)						
Thick	15 (21.4)	19 (25.7)	34 (23.6)	39 (23.1)	65 (32.2)	104 (28.0)
Medium	38 (54.3)	30 (40.5)	68 (47.2)	91 (53.8)	86 (42.6)	177 (47.7)
Thin	17 (24.3)	25 (33.8)	42 (29.2)	39 (23.1)	51 (25.2)	90 (24.3)
Live Lice: n (%)						
≥ 3	70 (100.0)	74 (100.0)	144 (100.0)	109 (64.5)	116 (57.4)	225 (60.6)
Viable Nits: n (%)						
Yes	69 (98.6)	72 (97.3)	141 (97.9)	167 (98.8)	194 (96.0)	361 (97.3)

3.2.1.2.3 Efficacy Evaluation

The primary efficacy population was the ITT population defined in Section 3.2.1.1. In reviewing the submitted data, this reviewer noted that a total of six ITT subjects (three in each study) did not have "exposure date" of study drug recorded. However, their efficacy data were included in the primary analysis and it did not appear that the inclusion of these data had a significant impact on the statistical inference for efficacy.

In addition, during the review of the data from Top12, it was discovered that the treatment results for the four ITT subjects (TOP012-01-308-01, TOP012-02-314-01, TOP012-02-321-01, and TOP012-07-301-01) had been improperly imputed by the sponsor (using the pre-specified LOCF methodology). Specifically, three of these subjects were in the Sklice treatment group and one subject (TOP012-01-308-01) received the vehicle control. All four of these subjects did not have a

post-baseline measurement, yet the sponsor recorded that they were successes. This imputation potentially biases the results in favor of the new treatment. For this reason, this reviewer chose to take the approach of re-adjudicating these missing values to "Lice Present" for the primary efficacy analysis. With these changes, the observed difference between Sklice and the vehicle control was reduced from 55.4% to 52.5%. These results are reflected in Table 7.

Sparse site-specific data were observed in both studies. In Study Top11 (8 sites), Site 02 and 04 had 1 and 2 subjects in the vehicle group, respectively. In Study Top12 (8 sites), Site 03, 06, and 08 had 3, 5, and 3 subjects in the vehicle group, respectively. In the presence of these levels of sparse data, the CMH test adjusted by site and the logistics regression model including a treatment-by-site interaction effect are not appropriate analytical approaches. Instead, we chose to perform the overall Chi-square test without adjustment by study site. We first examined the efficacy results for each site and found all sites, in both studies, demonstrated a positive treatment effect favoring Sklice (Figure 1). Here, we have reported the overall Chi-square test for a non-zero treatment difference in the proportion of lice-free subjects between Sklice and the vehicle on Day 15 and provided a 95% CI for the treatment difference from this test (Table 7).

Table 7 shows the primary efficacy results based on overall Chi-square tests after the correction of the LOCF imputations described above. In Study Top11, the proportions of head lice-free subjects are 16.2% and 76.1% in the vehicle and Sklice, respectively. The treatment difference is 59.8% with the 95% CI of 45.5% to 74.2%. In Study Top12, the proportions of head lice-free subjects are 18.9% and 71.4% in the vehicle and Sklice, respectively. The treatment difference is 52.5% with the 95% CI of 37.3% to 67.7%. Results by failure imputation are comparable to those by LOCF.

Table 7. Proportion of Head Lice Free ITT Subjects on Day 2, Maintained through Day 15 (ITT)

Study	Imputation Method	Vehicle		Sklice		Difference % (95% CI) [a]	P-value [a]
		n/N	%	n/N	%		
Top11	LOCF	12/74	16.2	54/71	76.1	59.8 (45.5, 74.2)	<.001
	Failure Imputation	11/74	14.9	54/71	76.1	61.2 (47.0, 75.4)	<.001
Top12	LOCF	14/74	18.9	50/70	71.4	52.5 (37.3, 67.7) [b]	<.001
	Failure Imputation	13/74	17.6	48/70	68.6	51.0 (35.7, 66.3)	<.001

a: Results were from the overall Chi-Square Test without stratification by study site.
b: The sponsor reported as 55.4 (40.5, 70.4) due to the LOCF imputation based on a positive response assumption for the subjects without a post-baseline efficacy measurement.

The impact of errors in the randomization identified at the filing meeting on May 18, 2011 will be discussed and addressed in a subgroup analysis in Section 4.2.

3.2.1.2.4 Secondary Efficacy

The secondary efficacy population is the ITT2 population defined in Section 3.2.1.1. A total of 13 ITT2 subjects (8 in Study Top11 and 5 in Study Top12) did not have exposure date of study drug recorded. Their efficacy data were included in the secondary analysis and do not appear to have a significant impact on the statistical inference for efficacy. One ITT2 subject (TOP011-03-208-07) in Study Top11 and Five ITT2 subjects (TOP012-01-308-01, TOP012-01-308-02, TOP012-02-314-01, TOP012-02-321-01, and TOP012-07-301-01) in Study Top12 had improper LOCF imputation. Subjects TOP011-03-208-07, TOP012-01-308-01 and TOP012-01-308-02 received the vehicle control and subjects TOP012-02-314-01, TOP012-02-321-01, and TOP012-07-301-01 received

Sklice. They did not have a post-baseline measurement and their efficacy endpoint was reset to "Lice Present" in reviewing the results for the secondary efficacy analyses.

Table 8 shows the secondary efficacy results on overall Chi-square tests after the correction of the LOCF imputations. In Study Top11, the proportions of head lice-free subjects are 22.1% and 81.0% in the vehicle and Sklice, respectively. The treatment difference is 58.9% with the 95% CI of 50.6% to 67.2%. In Study Top12, the proportions of head lice-free subjects are 75.7% and 22.3% in the vehicle and Sklice, respectively. The treatment difference is 53.5% with the 95% CI of 44.3% to 62.6%. Results by failure imputation are comparable to those by LOCF and very similar to the results obtained in the primary analysis of the index subjects (display in Table 7).

Table 8. Proportion of Head Lice Free ITT2 Subjects on Day 2, Maintained through Day 15 (ITT2)

Study	Imputation Method	Vehicle		Sklice		Difference	P-value
		n/N	%	n/N	%	% (95% CI) [a]	
Top11	LOCF	44/199	22.1	171/211	81.0	58.9 (50.6, 67.2) [b]	<.001
	Failure Imputation	41/199	20.6	171/211	81.0	60.4 (52.2, 68.6)	<.001
Top12	LOCF	45/202	22.3	128/169	75.7	53.5 (44.3, 62.6) [c]	<.001
	Failure Imputation	43/202	21.3	122/169	72.2	50.9 (41.6, 60.2)	<.001

a: Results were from the overall Chi-Square Test without stratification by study site.
b: The sponsor reported as 59.4 (51.1, 67.7) due to the LOCF imputation based on a positive response assumption for the subjects without a post-baseline efficacy measurement.
c: The sponsor reported as 54.2 (45.1, 63.4) due to the same reason as that in b.

3.2.1.2.5 Adjustment for Multiple Comparisons

There is no multiplicity adjustment needed for the primary efficacy analysis. There is no pre-specified multiplicity adjustment for the secondary efficacy analysis.

3.2.1.2.6 Reviewer's Comment on the Efficacy Results

Even with the review criticisms noted above, it can be concluded that Sklice is highly effective in the treatment of head-lice infestations. Compared with the vehicle, Sklice statistically significantly increased the proportion of head lice-free subjects in both studies Top11 and Top12 on Day 15.

3.3 Evaluation of Safety

This review of safety includes data from four studies: Study Top10 (phase-2 safety), Study Top03 (phase-2 dose selection), Studies Top11 (phase-3 efficacy) and Top12 (phase-3 efficacy). As studies Top03 and Top10 were designed for the same duration and similar dosing as the two phase-3 trials, data from these two phase-2 studies were included into this safety review in order to gain more power in observing low-rate treatment emergent adverse events (TEAE).

In general, this safety population includes all subjects who were randomized into a study and treated with the study medication (either Sklice or the vehicle). The evaluation of safety is based on the descriptive statistics of the TEAE which were counted as follow:

- For occurrence: only first event was counted
- For severity: the most severe event was counted
- For relationship: the most closely related to treatment was counted.

Our review will focus on the frequency and percentage of the TEAE based on two sets of data: (1) the combined data from the two phase-3 studies (Top11 and Top12), and (2) the combined data from all four similar-duration studies (Top03, Top10, Top11, and Top12).

3.3.1 Treatment Emergent Adverse Events

Table 9 depicts the frequency and percentage of TEAE in terms of MedDRA preferred term and system organ classification based on the integrated data from two phase-3 studies: Top11 and Top12. In the Sklice treatment group, none of the TEAE has a rate of ≥1.0%. The most frequently TEAE is Pruritus (0.8% in Sklice, 1.5% in the vehicle) followed by Erythema (0.5% in Sklice, 1.2% in the vehicle) and Excoriation (0.3% in Sklice, 1.2% in the vehicle).

Table 10 depicts the frequency and percentage of TEAE in terms of MedDRA preferred term and system organ classification based on combined data from four studies: Top03, Top10, Top11 and Top12. In the Sklice treatment group, the TEAEs with a rate of ≥1.0% are Pruritus (1.9%) followed by Excoriation (1.5%). In the vehicle group, the TEAEs with a rate of ≥1.0% are Excoriation (1.9%) and Erythema (1.9%) followed by Pruritus (1.5%).

In general, Sklice was well tolerated by the study subjects.

3.3.2 Serious Adverse Events

There were no deaths and no TEAEs classified as serious adverse events in the four studies.

Table 9: Integrated Treat-emergent Adverse Events: Safety Population (Studies Top11 + Top12)

Body System	Preferred Term	Sklice (N=379*)	Vehicle (N=401#)	Total (N=780)
Blood and lymphatic system disorders				
	Lymphadenopathy	0 (0.0%)	1 (0.2%)	1 (0.1%)
Eye disorders				
	Conjunctivitis	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Eye irritation	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Ocular hyperaemia	1 (0.3%)	1 (0.2%)	2 (0.3%)
Gastrointestinal disorders				
	Toothache	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Vomiting	0 (0.0%)	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions				
	Pyrexia	0 (0.0%)	1 (0.2%)	1 (0.1%)
Infections and infestations				
	Impetigo	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Otitis media	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Pharyngitis streptococcal	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Tonsillitis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Injury, poisoning & procedural complications				
	Excoriation	1 (0.3%)	5 (1.2%)	6 (0.8%)
	Injury	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Scratch	0 (0.0%)	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders				
	Musculoskeletal pain	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Pain in extremity	0 (0.0%)	1 (0.2%)	1 (0.1%)
Respiratory, thoracic & mediastinal disorders				
	Cough	2 (0.5%)	0 (0.0%)	2 (0.3%)
Skin and subcutaneous tissue disorders				
	Dandruff	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Dry skin	1 (0.3%)	0 (0.0%)	1 (0.1%)
	Erythema	2 (0.5%)	5 (1.2%)	7 (0.9%)
	Pruritus	3 (0.8%)	6 (1.5%)	9 (1.2%)
	Skin burning sensation	1 (0.3%)	0 (0.0%)	1 (0.1%)

*: Study Top11 has 210 subjects for safety population, which excluded one subject who did not apply Sklice to her. Study Top12 has 169 subjects for safety population.
#: Study Top11 has 199 subjects for safety population and. Study Top12 has 202 subjects for safety population.

Table 10: Integrated Treat-emergent Adverse Events: Safety Population (Studies Top03+Top10+Top11+Top12)

Body System	Preferred Term	Sklice (N=590*)	Vehicle (N=479#)	Total (N=1069)
Blood and lymphatic system disorders				
	Lymphadenopathy	0 (0.0%)	1 (0.2%)	1 (0.1%)
Eye disorders				
	Conjunctivitis	3 (0.5%)	0 (0.0%)	3 (0.3%)
	Eye irritation	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Ocular hyperaemia	1 (0.2%)	1 (0.2%)	2 (0.2%)
Gastrointestinal disorders				
	Toothache	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Vomiting	0 (0.0%)	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions				
	Pyrexia	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Application site pruritus	1 (0.2%)	1 (0.2%)	2 (0.2%)
Infections and infestations				
	Impetigo	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Influenza	2 (0.3%)	0 (0.0%)	2 (0.2%)
	Nail bed infection	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Otitis media	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Pharyngitis	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Pharyngitis streptococcal	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Pyoderma	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Swine influenza	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Tonsillitis	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Upper respiratory tract infection	5 (0.8%)	0 (0.0%)	5 (0.5%)
Injury, poisoning & procedural complications				
	Contusion	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Excoriation	9 (1.5%)	9 (1.9%)	18 (1.7%)
	Injury	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Scratch	1 (0.2%)	1 (0.2%)	2 (0.2%)
Musculoskeletal and connective tissue disorders				
	Musculoskeletal pain	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Pain in extremity	0 (0.0%)	1 (0.2%)	1 (0.1%)
Nervous system disorders				
	Headache	1 (0.2%)	0 (0.0%)	1 (0.1%)
Respiratory, thoracic & mediastinal disorders				
	Asthma	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Cough	2 (0.3%)	0 (0.0%)	2 (0.2%)
	Dyspnoea	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Oropharyngeal pain	2 (0.3%)	0 (0.0%)	2 (0.2%)
Skin and subcutaneous tissue disorders				
	Erythema	5 (0.8%)	9 (1.9%)	14 (1.3%)
	Folliculitis	0 (0.0%)	1 (0.2%)	1 (0.1%)
	Dandruff	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Dry skin	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Pruritus	11 (1.9%)	7 (1.5%)	18 (1.7%)
	Rash maculo-papular	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Skin burning sensation	1 (0.2%)	0 (0.0%)	1 (0.1%)
	Skin irritation	0 (0.0%)	1 (0.2%)	1 (0.1%)

*: Study Top11 has 210 subjects for safety population, which excluded one subject who did not apply Sklice to her. There are 19, 192, and 169 subjects for safety population in Studies Top03, Top10 and Top12, respectively.
#: There are 23, 55, 199, 202 subjects for safety population in Studies Top03, Top10, Top11 and Top12, respectively.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor did not perform efficacy analyses for subgroups. We do not disagree with the sponsor's decision, but rather look for consistent efficacy results in subgroups. Due to the small sample sizes in the subgroups, all subgroup analyses are considered as exploratory in our review.

4.1 Gender, Race, Age, and Geographic Region

Table 11 displays the efficacy results for Sklice and the vehicle comparator by gender subgroup. In both studies, there were large majorities of female subjects (83.4% in Study Top11 and 77.1% in Studies Top12). The results were similar for the males and females in the studies and there is no evidence to suspect that there is a true treatment difference by gender.

Table 11: Gender Impact on Proportion of Head Lice Free Subject on Day 15 (ITT)

Gender (LOCF)	Study Top11			Study Top12		
	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)
Female	76.7 (46/60)	16.4 (10/61)	60.3 (44.5, 76.1)	73.7 (42/57)	18.5 (10/54)	55.2 (37.9, 72.4)
Male	72.7 (8/11)	15.4 (1/13)	57.3 (16.1, 98.6)	61.5 (8/13)	20.0 (4/20)	41.5 (3.5, 79.6)

As shown in Table 5 and Table 6 (above in Section 3.2.1.2.2), almost all of the subjects in both studies were white (96.6% in Study Top11, and 95.1% in Study Top12). Therefore, with so few non-white subjects in the two primary efficacy studies, race subgroup analyses were not performed.

Table 12 shows the efficacy of Sklice by age subgroup. Age was broken into three groups: 6 month to < 4 years old denoted as [0.5, 4), 4 to <12 years old denoted as [4, 12), and ≥12 years old. Majority subjects were in age of 4 to <12 years old (67.6% in Study Top11 and 56.9 % in Study Top12). From these results there does not appear to be an indication that the treatment's effect varied substantially by age subgroup.

Table 12: Age Impact on Proportion of Head Lice Free Subject on Day 15 (ITT)

Age group (LOCF)	Study Top11			Study Top12		
	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)
[0.5, 4)	66.7 (10/15)	16.7 (2/12)	50 (10.7, 89.3)	83.3 (15/18)	12.5 (2/16)	70.8 (41.3, 100.0)
[4, 12)	80.4 (37/46)	19.2 (10/52)	61.2 (43.5, 78.9)	74.3 (26/35)	17.0 (8/47)	57.3 (36.7, 77.8)
≥12	70.0 (7/10)	0.0 (0/10)	70.0 (31.6, 100.0)	52.9 (9/17)	36.4 (4/11)	16.6 (-27.9%, 61.1%)

The impact of geographic region is not performed since both studies were conducted in US. Treatment effect by study site is illustrated in Figure 1. All sites demonstrated a positive treatment difference in the proportion of head lice-free ITT subjects on Day 15.

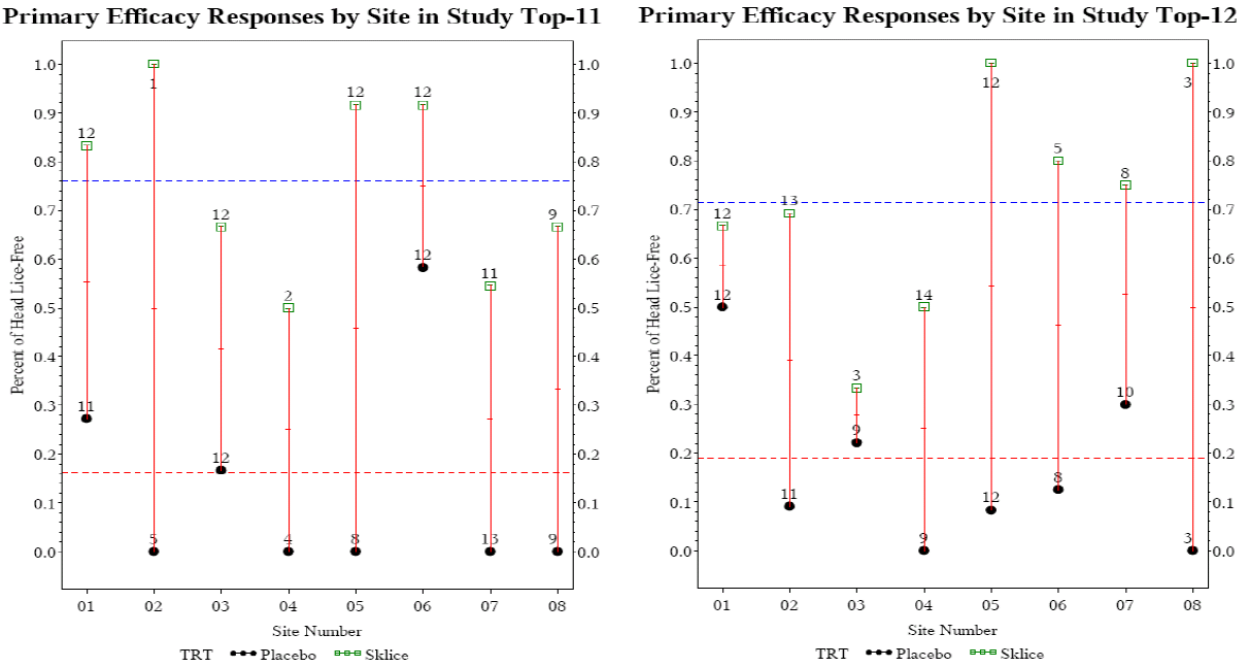

Figure 1: Treatment Effect by Study Site

4.2 Other Subgroups (Date/Method of Randomization and Hair Type)

Table 13 presents the efficacy results by subject enrollment date (before or on/after April 19th). The sponsor noted in the NDA submission that a randomization error had occurred and was discovered on April 15th, 2010, which affected the treatment selection for all patients who enrolled in the studies conducted simultaneously and received treatment prior to April 19th, 2010. While the protocol called for randomization by site, the actual enrollment prior to April 19th was done on a by-study basis. After April 19th the protocol-specified, site-stratified randomization was implemented for all subsequent treatment assignments. It was observed during the initial review of this submission that the early randomization by study led to treatment imbalances in some sites. To investigate the impact of this error in the randomization we compared the efficacy results for subjects enrolled prior to April 19th with those for subjects enrolled on and after April 19th. The efficacy results shown in this table are comparable for the two enrollment periods; thus indicating that no bias in findings due to the change in the randomization.

Table 13: Proportion of Head Lice Free ITT Subjects by Subgroup Resulted by Randomization Method (LOCF)

Study	Stratification Method	Vehicle % (n/N)	Sklice % (n/N)	Difference (95% CI)	P-value
Top11	Pre-4/19*	17.1 (7/41)	74.4 (29/39)	57.3 (36.9, 77.7)	<.001
	Post-4/19**	15.2 (5/33)	78.1 (25/32)	63.0 (41.1, 84.9)	<.001
Top12	Pre-4/19*	15.2 (5/33)	66.7 (22/33)	51.5 (28.3, 74.8)	<.001
	Post-4/19**	22.0 (9/41)	75.7 (28/37)	53.7 (32.4, 75.0)	<.001

* Study-wide randomization (not according to the protocol).
** Protocol-specified, site-specific randomization.

Table 14 presents efficacy results by hair subgroup. Four hair characteristics are identified as: hair shape, length, texture and volume. Hair subgroups are determined within each of the four

characteristics. Generally the results are fairly consistent across hair types. There is little evidence to suggest that there were substantial differences in treatment due to hair type (Table 14)

Table 14: Hair Impact on Proportion of Head Lice Free Subject on Day 15 (ITT)

Hair group (LOCF)	Study Top11			Study Top12		
	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)	Sklice % (n/N)	Vehicle % (n/N)	Difference (95% CI)
Hair Shape:						
Curly	80.0 (8/10)	11.1 (1/9)	68.9 (26.1, 100.0)	100.0 (8/8)	11.1 (1/9)	88.9 (56.6, 100.0)
Wavy	78.3 (18/23)	16.7 (3/18)	61.6 (32.6, 90.6)	65.4 (17/26)	16.7 (4/24)	48.7 (21.1, 76.3)
Straight	73.7 (28/38)	17.0 (8/47)	56.7 (36.6, 76.7)	69.4 (25/36)	22.0 (9/41)	47.5 (25.2, 69.8)
Hair Length:						
Short	77.8 (14/18)	20.0 (3/15)	57.8 (23.8, 91.8)	78.6 (11/14)	26.9 (7/26)	51.7 (18.7, 84.6)
Medium	72.7 (16/22)	13.3 (4/30)	59.4 (33.2, 85.6)	78.3 (18/23)	4.8 (1/21)	73.5 (49.8, 97.2)
Long	79..2 (19/24)	19.1 (4/21)	60.1 (32.3, 88.0)	67.9 (19/28)	21.1 (4/19)	46.8 (17.2, 76.4)
Very Long	71.4 (5/7)	12.5 (1/8)	58.9 (5.0, 100.0)	40.0 (2/5)	25.0 (2/8)	15.0 (-53.6, 83.6)
Hair Texture:						
Coarse	92.3 (12/13)	30.8 (4/13)	61.5 (24.9, 98.2)	83.3 (5/6)	40.0 (2/5)	43.3 (-27.3, 100.0)
Medium	71.8 (28/39)	7.7 (3/39)	64.1 (45.1, 83.1)	73.3 (22/30)	21.6 (8/37)	51.7 (28.1, 75.4)
Fine	73.7 (14/19)	22.7 (5/22)	51.0 (19.6, 82.3)	67.7 (23/34)	12.5 (4/32)	55.2 (32.7, 77.6)
Hair Volume:						
Thick	78.3 (18/23)	16.7 (4/24)	61.6 (34.8, 88.4)	73.3 (11/15)	31.6 (6/19)	41.8 (5.2, 78.3)
Medium	76.9 (20/26)	12.9 (4/31)	64.0 (40.5, 87.6)	68.4 (26/38)	20.0 (6/30)	48.4 (24.9,72.0)
Thin	72.7 (16/22)	21.1 (4/19)	51.7 (20.7, 82.7)	76.5 (13/17)	8.0 (2/25)	68.5 (40.7, 96.2)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major statistical issues affecting the overall conclusion were found. The errors in the randomization identified at the filing meeting on May 18, 2011 did not appear to have significantly influenced the p-values reported for the treatment differences as shown in Table 13. Due to the errors in the randomization and sparse data per treatment group per study site, the overall Chi-square test without stratification by site is considered to be the appropriate primary analysis method and we therefore report efficacy results based on overall Chi-square tests. The sponsor imputed "lice-free" for ITT subjects (3 Sklice and 1 vehicle in Study Top12) without any post-baseline efficacy assessment. We do not agree on the sponsor's imputation. Instead, for subjects without post-baseline efficacy data, we imputed their baseline values as "lice present" (negative response).

5.2 Conclusions and Recommendations

Data from both phase-3 studies show that Sklice statistically significantly increase the proportion of lice-free subjects on Day 15 compared with the vehicle. In Study Top11, the treatment difference is 59.8% with the 95% CI of 45.5% to 74.2%. In Study Top12, the treatment difference is 52.5% with the 95% CI of 37.3% to 67.7%. Both studies provide strong positive statistical results.

From a statistical perspective, the data provided in this application support the efficacy of Sklice for the treatment of head lice infestations.

SIGNATURES/DISTRIBUTION LIST

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/s/

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