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/BLA #:	NDA 206966
Drug Name:	Abametapir Lotion 0.74%
Indication(s):	Treatment of head lice infestation in subjects 6 months of age and older
Applicant:	Dr. Reddy's Laboratories, Inc.
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1. EXECUTIVE SUMMARY

Abametapir lotion 0.74% was superior to vehicle lotion in two identical Phase 3 trials in subjects with head lice. The trials enrolled subjects aged 6 months and older with at least 3 live lice for index subjects defined as the youngest member in the household, and at least 1 live louse for other household members.

The SPA-agreed upon primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14 (i.e., Days 1, 7, 14). The SAP stated that subjects who have been treated with investigational product (IP) and have any live lice detected at any clinic visit post-treatment (i.e., Day 1, 7, 14 or an unscheduled visit) were considered as treatment failures. Efficacy results for the primary endpoint were significant for both trials (p-value<0.001). See Table 1 for the results of the primary efficacy endpoint analysis.

Table 1. Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint)

	Trial 001			Trial 002		
	Abametapir N=53	Vehicle N=55	p-value	Abametapir N=55	Vehicle N=53	p-value
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001	45 (82%)	25 (47%)	<0.001

Source: P-value from CMH test stratified by pooled sites; the protocol-specified imputation method was to impute missing data at Day 14 as treatment failure.

In addition to the two pivotal trials, the applicant submitted results for an in-vitro study (Ha03-008 from hereon referred to as Study 008) whose primary objective was to evaluate the ovicidal efficacy of a single application of abametapir lotion 0.74%. For this study, a minimum of 5 undamaged eggs located on hair shafts less than 1 cm from the scalp were randomly selected and removed from each subject's head by clipping the hairs to which the eggs were attached. Eggs deemed viable from the microscope examination were then incubated and were examined after the 14 days of incubation. However, the Agency previously commented at the Pre-NDA meeting (1/21/2015) that the "ovicidal activity observed ex-vivo may not predict the ovicidal activity observed in-vivo", and given the differences in conditions (ex-vivo vs. in-vivo), interpretation of the results is challenging.

For the two Phase 3 trials (Trials 001 and 002), there were no major statistical issues affecting the overall conclusions.

2. INTRODUCTION

2.1 Overview

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The applicant submitted results from two identical randomized, double-blind, multicenter, vehicle-controlled Phase 3 trials (Ha03-001 and Ha03-002 from hereon referred to as Trials 001 and 002, respectively) to support the efficacy and safety of abametapir lotion 0.74% for the treatment of head lice infestation in subjects 6 months of age and older. Table 2 provides an overview of the applicant's pivotal Phase 3 trials.

Table 2. Clinical Study Overview for the Pivotal Trials

Study	Study Sites	Study Population	Treatment Arms	N	Dates
001 (N=108 index subjects)	7 U.S. centers	• Age ≥6 months, • At least 3 live lice for index subject defined as the youngest member in the household, and at least 1 live louse for other household members.	Abemetapir	53	2/12/2014 - 6/26/2014
			Vehicle	55	
002 (N=108 index subjects)	7 U.S. centers		Abemetapir	55	2/18/2014 - 6/27/2014
			Vehicle	53	

Source: Reviewer table.

2.2 Regulatory History

The clinical development program for abametapir lotion 0.74% for the treatment of head lice was under IND 77510. A Pre-IND meeting between the Agency and the sponsor was held on June 20, 2007 and the original IND was opened on 12/20/2007. On August 1, 2012, there was an End of Phase 2 (EOP2) meeting between the Agency and the sponsor, and on October 23, 2013, the sponsor submitted a single Phase 3 study protocol (Ha03-001) for a Special Protocol Assessment (SPA). A "Special Protocol – Agreement" letter was sent to the sponsor on December 4, 2013, and the letter specified that the Agency agreed to the following:

- general design of the proposed Phase 3 trial
- proposal to conduct two identical, well-controlled Phase 3 trials
- study population of males or females 6 months of age or older with active head lice defined as at least 3 live lice for the index subject, and 1 live louse for the other household members
- dosing regimen of single application for 10 minutes
- primary endpoint of the proportion of index subjects who are lice free at all follow-up visits though Day 14
- definition of Intent to Treat (ITT) as all index subjects who were randomized to treatment
- primary analysis method of using the Cochran Mantel-Haenszel (CMH) test stratified by site.

In the SPA letter, there were two non-agreement items concerning the sponsor's imputation method (Non-Agreement #1) and the secondary endpoints:

> "You proposed to impute missing data using the last observation carried forward (LOCF), "except for the subjects without follow up lice-evaluation at the Day 14 visit who will be considered as treatment failures". It is not clear whether your

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imputation method is intended for the primary as well as the secondary endpoints. You should propose an imputation method that is consistent for handling both the primary and the secondary endpoints so that the study findings can be reasonably interpreted. Note that your proposed approach might inflate the success rate of the secondary endpoint at Day 7 (i.e., lice-free index subjects at Day 7) if a subject was a success at Day 1 and missed the Day 7 visit".

"Your proposed secondary endpoints are:

- Proportion of all index subjects who are lice free at visit Day 1
- Proportion of all index subjects who are lice free at visit Day 7

Based on the life cycle of the louse, an evaluation of the proportion of index subjects who are lice free on Day 1 or Day 7 may not be clinically meaningful. As you proposed two secondary endpoints, testing each endpoint at α=0.05 would inflate the Type I error rate. The protocol needs to include a method of controlling multiplicity among the secondary endpoints. Secondary endpoints should be clinically relevant".

In response to the SPA letter, the sponsor submitted an amended Phase 3 protocol along with its Statistical Analysis Plan (SAP) which included a multiplicity adjustment plan for controlling the Type I error rate for the analysis of the two secondary endpoints. In an advice letter dated: October 20, 2014, the Agency reiterated its previous comments (dated: December 4, 2013; March 10, 2014) that the sponsor consider a method of handling missing data consistent for the primary as well as for the secondary endpoints so that results of the clinical trial can be reasonably interpreted.

On October 31, 2014, the sponsor stated that "FDA provided additional clarity around their request for consistent missing data imputation across Day 1, Day 7, and Day 14 visits". According to the cover letter, the sponsor stated that the Phase 3 trials were "clinically complete, the data were unblinded, and the clinical study reports were being prepared at the time Hatchtech received FDA's October 20, 2014 letter and clarification". They then referenced a part in the ICH E9 Statistical Principles for Clinical Trials that reads that "redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess". Therefore, the sponsor's final study reports for the two Phase 3 trials would be prepared in accordance with the analyses specified in the final protocols and SAPs, then the sponsor added that "to address the issues that FDA has raised around the imputation methods used for missing data, Hatchtech intends on providing a discussion and additional analysis on the pooled efficacy data from these studies in 2.7.3. Summary of Clinical Efficacy in the NDA using the LOCF sensitivity analysis as defined in the SAP for imputing missing data".

On January 21, 2015, there was a Pre-NDA meeting to discuss the dataset contents and format for the NDA submission, and this application was submitted for review on September 14, 2015. On December 29, 2015, the Agency received a notification

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regarding a "Change in Ownership of an Application" from HatchTech to Dr. Reddy's Laboratories, S.A.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets in this review are archived at the following location: \\cdsesub1\evsprod\nda206966\0000\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Each of the Phase 3 trials was entitled a "randomized, double-blind, multi-center, vehicle-controlled study of the efficacy and safety of Abametapir Lotion 0.74% administered for the treatment of head lice infestation".

The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application of abametapir lotion 0.74% w/v for the treatment of head lice. The secondary objective of each trial was to evaluate the safety and tolerability of at-home administration of a single application of abametapir lotion, 0.74%.

Each trial consisted of the following two treatment groups:

- Group A: Abametapir lotion 0.74%
- Group B: Vehicle lotion

Randomization of subjects to treatment group was stratified by site.

For enrollment criteria of the clinical trials, refer to Table 2. Eligible subjects from each household were provided the same IP for a single 10-minute, self-application, at-home treatment on Day 0, and had study visits on Days 1, 7, and 14.

The SPA-agreed upon primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14 (i.e., Days 1, 7, 14). The SAP stated that subjects who have been treated with IP and have any live lice detected at any clinic visit post-treatment (i.e., Day 1, 7, 14 or an unscheduled visit) were considered as treatment

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failures. The protocol stated that subjects with treatment failure (i.e., any live lice detected at any follow-up visit) were provided with an application of NIX at no cost.

The protocol-specified secondary endpoints were:

- Proportion of index subjects who are lice free at Day 1 visit
- Proportion of index subjects who are lice free at Day 7 visit.

Note that these secondary endpoints were one of the two non-agreements per the SPA letter (dated: December 4, 2013).

3.2.2 Statistical Methodologies

The primary analysis population was the Intent-to-Treat (ITT) index subjects where ITT was defined as all index subjects who were randomized. A supportive analysis using the Per Protocol (PP) population was done and the PP was defined as all subjects in the ITT population without a significant protocol deviation.

For the SPA-agreed upon primary efficacy analysis, the Cochran Mantel-Haenszel (CMH) test stratified by pooled sites was used. For the analysis of the secondary endpoints, the protocol specified using the "stepdown Bonferroni method" to which, the SAS program referenced the Bonferroni-Holm (1979) correction. For the Bonferroni-Holm correction for two comparisons, the smallest p-value of the two is first compared at $\alpha/2$, and if statistically significant, the other p-value is compared at a full α level (0.05).

According to the protocol, sites with <8 index subjects per treatment arm was pooled within geographical region starting from the smallest site, until each pooled site had at least 8 subjects per treatment arm. For Trial 001, sites were pooled within the following regions for the sites that did not enroll at least 8 subjects per treatment arm: (i) Ohio and Tennessee, (ii) Florida and Texas, and (iii) California and Nevada. For Trial 002, sites were pooled within the following regions for the sites that did not enroll at least 8 subjects per treatment arm: (i) North Carolina and Tennessee, (ii) Florida and Mississippi, and (iii) California, Utah, and Arizona.

For handling of missing data, the protocol specified that last observation carried forward (LOCF) would be used except for those subjects with missing Day 14 visit that would be considered as treatment failures. The LOCF was then used as a sensitivity analysis for handling missing data for the primary endpoint.

3.2.3 In-Vitro Study (Study 008)

The applicant called this study a "double-blind, randomized, vehicle-controlled, parallel-group study in subjects 3 years of age and older with an active head lice infestation". This study utilized an ex-vivo method where prior to the application of the abametapir or vehicle lotion, a minimum of 5 undamaged eggs located on hair shafts less than 1 cm from the scalp were randomly selected and to serve as a control sample and were removed from each subjects' head. Then the abametapir lotion or vehicle was applied for

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10 minutes, and an additional minimum of 5 undamaged eggs located on hair shafts less than 1 cm from the scalp were randomly selected to serve as the "treated sample" and removed from the hair by clipping the hairs to which the eggs were attached. Eggs deemed viable from the microscope examination were then incubated at 30 ±1 °C and approximately 60% relative humidity (RH) for 14 days. All eggs were examined to determine if they were hatched, partially hatched, or unhatched after the 14 days of incubation. Table 3 presents the applicant's study results of hatched eggs (%) pre- and post-treatment.

Table 3. Summary of Hatched Eggs by Treatment Group

	Study 008	
Hatched Eggs %; 95% CI	Abametapir N=25	Vehicle N=25
Pre-treatment	93 (83, 98)	79 (69, 87)
Post-treatment	0.3 (0.3, 0.4)	37 (28, 47)

Source: applicant's study report

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Each pivotal Phase 3 trial enrolled and randomized a total of 108 index ITT subjects from 7 U.S. centers (53 to Abametapir, 55 to Vehicle and 55 to Abametapir and 53 to Vehicle in Trials 001 and 002, respectively). Table 4 presents the disposition of subjects for each trial. While the discontinuation rates were similar across the treatment arms within each trial, the discontinuation rates were slightly higher in Trial 001 compared to those in Trial 002.

Table 4. Subject Disposition (Index ITT)

	Trial 001		**Trial 002**	
	Abametapir	Vehicle	Abametapir	Vehicle
Randomized	53	55	55	53
Discontinued	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Adverse Events	0	0	0	0
Withdrew consent	0	3	0	0
Loss to Followup	3	0	1	1
Protocol violation	0	0	0	0
Other	0	0	0	0

Source: Applicant's Study Report Table 14.1.1.1

The demographics and baseline presence of live lice and nits are displayed in Tables 5 and 6, respectively. The majority of the enrolled index ITT subjects were female (85%), and Caucasians (95%). Approximately 95% of the index subjects were between the ages of 6 months and less than 18 years of age, and there were no index subjects ≥65 years of age. The demographics and baseline live lice and nits presence were generally balanced across treatment arms.

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Table 5. Baseline demographic characteristics (Index ITT)

	Trial 001		Trial 002	
	Abametapir N=53	Vehicle N=55	Abametapir N=55	Vehicle N=53
Sex				
Female	48 (91%)	45 (82%)	48 (87%)	43 (81%)
Male	5 (9%)	10 (18%)	7 (13%)	10 (19%)
Race				
White	50 (94%)	55 (100%)	51 (93%)	49 (92%)
Black	2 (4%)	0 (0%)	0 (0%)	2 (4%)
Other	1 (2%)	0 (0%)	4 (7%)	2 (4%)
Age				
Mean (SD)	7.5 (4.2)	7.4 (6.7)	9.8 (10.5)	7.8 (7.7)
Median	6.8	6.0	7.0	6.5
Range	0.5-19.2	1.2-49.1	1.6-58.5	1.1-56.9
by age groups				
6 months – 4 years	11 (21%)	11 (20%)	7 (13%)	11 (21%)
4-12	36 (68%)	39 (71%)	41 (93%)	36 (57%)
12-18	4 (8%)	3 (5%)	2 (4%)	4 (8%)
>=18, <65	2 (4%)	2 (4%)	5 (9%)	2 (4%)
≥ 65	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer Table

All index subjects except for 1 subject in Trial 001 had ≥3 live lice at baseline. In Trial 001, there was 1 vehicle subject (b) (6)) that was reported to have <3 live lice at baseline. The applicant's study report (page 44) specified that this was an error that occurred at the site during allocation of index and non-index subjects. In error, the subject's twin sister (b) (6) was reported to have 3 or more lice instead. The applicant stated that this entry error was not corrected as this subject and their whole family withdrew consent and failed to return to the study site after the baseline visit. This subject was included in the primary efficacy analysis, and was considered as a treatment failure.

Table 6. Baseline Presence of Live Lice and Nits (Index ITT)

	Trial 001		Trial 002	
	Abametapir N=53	Vehicle N=55	Abametapir N=55	Vehicle N=53
Baseline Live Lice				
≥3	53 (100%)	54 (98%)	55 (100%)	53 (100%)
<3	0 (0%)	1(1) (2%)	0	0
Baseline Nits Presence				
Yes	53 (100%)	55 (100%)	55 (100%)	53 (100%)
No	0	0	0	0

Source: Reviewer Table; (1) Per the applicant's study report, this was an entry error between subjects (b) (6) (twin sisters).

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3.2.5 Efficacy Results

Table 7 presents results for the primary efficacy endpoint at Day 14 as well as the secondary endpoints at Days 1 and 7 for both Trials in the index ITT population. In both trials, Abametapir lotion was statistically superior to vehicle lotion ($p<0.001$) for the primary endpoint of the proportion of lice-free subjects at Day 14. For the secondary endpoints of the proportion of lice-free subjects at Day 1 and at Day 7, while the results were not statistically significant at Day 1, they were at Day 7. Although the results for the secondary endpoint at Day 7 were statistically significant, these secondary endpoints were not agreed upon with the Agency per the SPA agreement letter (12/4/2013),.

Table 7. Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint), and at Days 1, 7 (Secondary Endpoints)

	Trial 001			Trial 002		
	Abametapir N=53	Vehicle N=55	p-value	Abametapir N=55	Vehicle N=53	p-value
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001	45 (82%)	25 (47%)	<0.001
Secondary endpoints						
Day 1	49 (93%)	46[(1)] (84%)	0.10	48 (87%)	44 (83%)	0.45
Day 7	48 (91%)	34 (62%)	0.001	47 (86%)	36 (68%)	0.025

Source: P-value from CMH test stratified by pooled sites; the protocol-specified imputation method was to impute missing as last observation carried forward (LOCF), except for missing data at Day 14 that was imputed as treatment failure.

(1) Subject (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

As a supportive analysis, the primary and the secondary efficacy results were analyzed using the Per Protocol (PP) population. The results from the PP analysis yielded very similar results to those of the index ITT population as 105 of the 108 index ITT subjects in Trial 001, and 106 of the 108 index ITT subjects were included in the PP population. Table 8 presents the efficacy analyses using the PP population.

Table 8. Proportion of Lice-free Per Protocol (PP) Subjects at Day 14 (Primary Endpoint), and at Days 1, 7 (Secondary Endpoints)

	Trial 001		Trial 002	
	Abametapir N=52	Vehicle N=53	Abametapir N=53	Vehicle N=53
Primary Endpoint (Day 14)	43 (83%)	28 (53%)	43 (81%)	25 (47%)
Secondary endpoints				
Day 1	49 (94%)	45 (85%)	46 (88%)	44 (83%)
Day 7	48 (92%)	33 (62%)	45 (85%)	36 (68%)

Source: Reviewer table

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As an exploratory analysis per the protocol, the following Table 9 presents the results for the primary endpoint at Day 14 as well as the secondary endpoints at Days 1 and 7 for both trials in all randomized subjects (all ITT) which included all subjects in the household with at least 1 live louse. The response rates were slightly higher than those of the index ITT population.

Table 9. Proportion of Lice-free Intent to Treat (all ITT) Subjects at Day 14 (Primary Endpoint), and at Days 1, 7 (Secondary Endpoints)

	Trial 001		Trial 002	
	Abametapir N=187	Vehicle N=191	Abametapir N=163	Vehicle N=162
Primary Endpoint (Day 14)	165 (88%)	119 (62%)	132 (81%)	98 (60%)
Secondary endpoints				
Day 1	175 (94%)	167 (87%)	148 (91%)	143 (88%)
Day 7	175 (94%)	138 (72%)	142 (87%)	123 (76%)

Source: Reviewer table.

Table 10 presents the sensitivity analysis results for the primary efficacy endpoint at Day 14 by using the last observation carried forward (LOCF) for Trials 001 and 002. The results were similar to those of the primary imputation method of imputing missing value as treatment failure. It should be noted that the amount of missing data in each trial was minimal.

Table 10. Results for the Primary Efficacy Endpoint at Day 14 with Last Observation Carried Forward (index ITT)

	Trial 001			Trial 002		
	Abametapir N=53	Vehicle N=55	p-value	Abametapir N=55	Vehicle N=53	p-value
MVTF (1)	43 (81%)	28(1) (51%)	0.001	45 (82%)	25 (47%)	<0.001
LOCF (2)	45 (85%)	29 (53%)	0.001	46 (84%)	26 (49%)	<0.001

Source: Reviewer analysis; p-value based on a CMH test stratified by pooled sites.
(1) MVTF: Missing value treated as failure – primary imputation method; (2) LOCF: last observation carried forward.

3.4 Evaluation of Safety

Table 11 presents an overview of the adverse events reported in Trials 001 and 002. The adverse reactions reported in both trials by system organ class are presented in Table 12.

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Table 11. Overall Summary of Treatment Emergent Adverse Events (TEAEs)

	Trial 001		Trial 002	
	Abametapir N=186	Vehicle N=188	Abametapir N=163	Vehicle N=162
At least one TEAE	37 (20%)	32 (17%)	48 (29%)	33 (20%)
At least one Severe TEAE	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
At least one drug-related TEAE	17 (9%)	19 (10%)	33 (20%)	22 (14%)
At least one Serious TEAE	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

Source: applicant's study reports

Table 12. Summary of the TEAEs by System Organ Class

	Trial 001		Trial 002	
	Abametapir N=186	Vehicle N=188	Abametapir N=163	Vehicle N=162
Skin and subcutaneous tissue disorders	17 (9%)	14 (7%)	32 (20%)	23 (14%)
Infections and infestations	7 (4%)	3 (2%)	1 (<1%)	4 (3%)
Respiratory, thoracic, and mediastinal disorders	5 (3%)	5 (3%)	8 (5%)	0 (0%)
Eye disorders	5 (3%)	8 (4%)	1 (<1%)	0 (0%)
Gastrointestinal disorders	2 (1%)	1 (<1%)	4 (3%)	3 (2%)
General disorders and administration site conditions	2 (1%)	4 (2%)	3 (2%)	2 (1%)
Investigations	1 (<1%)	4 (2%)	4 (3%)	1 (<1%)
Nervous system disorders	1 (<1%)	2 (1%)	3 (2%)	4 (3%)
Vascular disorders	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
Blood and lymphatic system disorders	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Psychiatric disorders	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Renal and urinary disorders	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)
Injury, poisoning, and procedural complications	0 (0%)	0 (%)	1 (<1%)	5 (3%)
Ear and labyrinth disorders	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Metabolism and nutrition disorders	0 (0%)	0 (0%)	1 (<1%)	0 (0%)

Source: applicant's study reports

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Efficacy by Gender, Race, and Age

The majority of the enrolled index ITT subjects were female (85%), and Caucasians (95%), therefore, any differences in efficacy for the male subjects, and non-Caucasians would be difficult to detect. Furthermore, approximately 89% of the index subjects were

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between the ages of 6 months and less than 12 years of age. Therefore, any differences in efficacy for those subjects ≥12 years of age would be difficult to detect. Table 13 presents the results for the primary efficacy endpoint at Day 14 by age groups, gender, race (white vs. non-white) for Trials 001 and 002.

Table 13. Baseline demographic characteristics (Index ITT)

	Trial 001		**Trial 002**	
	Abametapir N=53	Vehicle N=55	Abametapir N=55	Vehicle N=53
Sex				
Female	38/48 (79%)	22/45 (49%)	41/48 (85%)	19/43 (44%)
Male	5/5 (100%)	6/10 (6%)	4/7 (57%)	6/10 (60%)
Race				
White	41/50 (82%)	28/55 (51%)	44/51 (86%)	23/49 (47%)
Black	1/2 (50%)	-	-	1/2 (50%)
Other	1/1 (100%)	-	1/4 (25%)	1/2 (50%)
Age				
6 months – 4 years	10/11 (91%)	7/11 (64%)	5/7 (71%)	4/11 (36%)
4-12	28/36 (78%)	18/39 (46%)	33/41 (80%)	15/36 (42%)
12-18	3/4 (75%)	1/3 (33%)	2/2 (100%)	4/4 (100%)
>=18, <65	2/2 (100%)	2/2 (100%)	5/5 (100%)	2/2 (100%)
≥ 65	-	-	-	-

Source: Reviewer table.

4.2 Efficacy by Center

Each Phase 3 trial enrolled subjects from 7 U.S. centers. Table 14 below presents the results for the primary efficacy endpoint at Day 14 by the original center. For Site #106 in Trial 001, while the response rate for the vehicle was higher than that of abametapir lotion, this could occur due to chance alone. Note that given the number of subjects in each center was relatively small, the findings from centers were expected to have large variability due to chance.

Table 14. Primary Efficacy by Center at Day 14 by Original Center (Index ITT)

Trial 001			**Trial 002**		
Site	Abametapir N=53	Vehicle N=55	Site	Abametapir N=53	Vehicle N=55
101	7/8 (88%)	4/8 (50%)	201	9/12 (75%)	7/12 (58%)
102	2/3 (67%)	3/4 (75%)	202	7/7 (100%)	3/7 (43%)
103	6/8 (75%)	5/8 (63%)	203	2/2 (100%)	0 (0%)
104	10/12 (83%)	4/12 (33%)	204	4/4 (100%)	3/4 (75%)
105	6/7 (86%)	1/8 (13%)	205	8/8 (100%)	2/8 (25%)
106	1/3 (33%)	2/3 (67%)	206	2/6 (50%)	4/12 (33%)
107	11/12 (92%)	9/12 (75%)	207	9/10 (90%)	6/10 (60%)

Source: Reviewer table

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant submitted results from two identical randomized, double-blind, multicenter, vehicle-controlled Phase 3 trials (Trials 001 and 002) to support the efficacy and safety of abametapir lotion 0.74% for the treatment of head lice infestation in subjects 6 months of age and older. The trials enrolled subjects with at least 3 live lice for index subjects defined as the youngest member in the household, and at least 1 live louse for other household members. For the two Phase 3 trials (Trial 001 and 002), there were no major statistical issues affecting the overall conclusions.

In addition to the two pivotal trials, the applicant submitted results for an in-vitro study (Ha03-008 from hereon referred to as Study 008) whose primary objective was to evaluate the ovicidal efficacy of a single application of abametapir lotion 0.74%. For this study, a minimum of 5 undamaged eggs located on hair shafts less than 1 cm from the scalp were randomly selected and removed from each subjects' head by clipping the hairs to which the eggs were attached. Eggs deemed viable from the microscope examination were then incubated and were examined after the 14 days of incubation. However, the Agency previously commented at the Pre-NDA meeting (1/21/2015) that the "ovicidal activity observed ex-vivo may not predict the ovicidal activity observed in-vivo", and given the differences in conditions (ex-vivo vs. in-vivo), interpretation of the results is challenging.

5.2 Conclusions and Recommendations

The SPA-agreed upon primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14 (i.e., Days 1, 7, 14). The SAP stated that subjects who have been treated with IP and have any live lice detected at any clinic visit post-treatment (i.e., Day 1, 7, 14 or an unscheduled visit) were considered as treatment failures. Efficacy results for the primary endpoint were significant for both trials (p-value<0.001). See Table 1 (page 3) for the results of the primary efficacy endpoint analysis.

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