Statistical Analysis Plan

Study Title:	A Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® Ivermectin 0.5% Lotion in the Treatment of Head Lice
Phase:	Phase 3
Protocol No.:	MAP-7189
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Prepared By:	Jon Roth VP Data Sciences and Biometrics Biorasi, LLC
Prepared For:	MAYNE PHARMA, LLC. 1240 Sugg Parkway, Greenville, NC 27858 USA Phone: +1 (252) 717-1382 Fax: +1 (252) 758-8522

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

Jon Roth, VP Data Sciences and Biometrics
Biorasi, LLC.

16 Jan 2018
Date

Statistical Review:

Yuliya Yurova, PhD Statistics
Biorasi, LLC.

14-JAN 2018
Date

Sponsor Review:

Chandra Vattikonda

Chandra Vattikonda, M.Pharm., Ph.D.
Senior Director, Clinical Pharmacology
Mayne Pharma, Inc.

09-JAN-2018
Date

Contents

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol MAP-7189. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

1.1. Study Overview

Clinical protocol MAP-7189 is a Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® Ivermectin 0.5% Lotion in the Treatment of Head Lice. The primary objective of the study is to establish the efficacy of a single application of Ivermectin 0.5% lotion in the treatment of head lice under at-home use conditions compared with Sklice® 0.5% lotion, and to demonstrate that both active lotions have superior efficacy compared to Placebo.

The study also assesses comparative safety of Ivermectin 0.5% Lotion (Mayne Pharma, LLC) and Sklice® Ivermectin 0.5% Lotion and local tolerability of Ivermectin 0.5% Lotion.

The subject population includes healthy male and female subjects aged 6 months to 18 years who are infested with Pediculus humanus capitis. The youngest infested household member will be considered the index subject. Household members, up to a maximum of 3 members, infested with an active head lice infestation defined as at least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator will receive treatment with an over-the-counter head lice treatment product at baseline.

The study is comprised of three phases: Screening, Treatment, and Follow-Up. The duration of this study is 15 days (+/- 3). The Screening Phase is Day -1-0. The Treatment Phase is Day 1. Preferably, screening and treatment will occur on the same day. The Final Study Visit is on day 15 (+/- 3 days) following administration of the study product.

Potential subjects will be screened and the index subject will be eligible for enrollment into the study. During the baseline visit (Day 1), which can occur on the same day as screening (Day 0), the Investigator will record subject's demographics, medical history, review concomitant medication, identifying any prohibited therapies the subject may receive, perform physical examination, collect vital signs and perform urine pregnancy test.

Eligible subjects will be randomized in a ratio of 3:3:1 to receive either the Mayne Pharma's Ivermectin 0.5% lotion, Sklice® 0.5% lotion, or placebo lotion treatment and will be trained on the application of the study drug and subject's diary completion. Infested household members, up to 3 members per household, will be treated with an over-the-counter head lice treatment product on-site.

The study drug will be applied as a single, at-home dose. Subjects will be instructed to apply a full tube amount (4 oz.) of Ivermectin 0.5% lotion to fully coat dry hair and scalp, avoiding the

eyes and mucus membranes. The lotion will be left on the hair and scalp for 10 minutes, then rinsed off with warm water. The tube is intended for a single use; all used tubes should be returned at the second visit (first follow-up visit) to the clinical site for product accountability. In addition to receiving the study drug, the index subjects and household members will be instructed on an overall lice management program, which includes:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash (in hot water) personal care items such as combs, brushes and hair clips.
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits after treatment.

Index subjects will return for post-baseline visits assessments at Days 2, 8, and 15, returning used tubes of the study drug at Day 2, which will be accounted for along with diary cards, which will be reviewed by the site personnel for completeness. The Investigator will perform a visual assessment for the presence or absence of head lice, record local application site reactions, and perform an ocular irritation assessment. The site will provide a Subject Self-Assessment worksheet to record tolerability of treatment. Urine pregnancy testing will be performed at the Screening Visit and the Final Study Visit, with interim visits confirming pregnancy has not occurred through questioning of the index subject.

Final efficacy, safety and tolerability assessments will occur at visit 5 (Day 15±3). Subjects will be encouraged to report any complications or adverse effects during their participation.

1.2. Time and Events Schedule

TABLE 1.2 Study Procedures and Assessments.

Visit Number	Visit 1 Screening[1]	Visit 2 Baseline[2]	Visit 3 Follow-up	Visit 4 Follow-up	Visit 5 EOS/ET[3]
Visit Day	**Day -1 to 0**	**Day 1**	**Day 2[4]**	**Day 8 (±2)**	**Day 15 (±3)**
Informed Consent	X				
Eligibility Criteria	X				
Subject Demographics	X				
Medical History	X				
Physical Examination	X[5]				
Investigational Product Dispensation/Randomization		X[6]			
Vital Signs[7]		X			X
Urine Pregnancy Test[8]	X				X
Head Lice Visual Assessment	X[9]	X[9]	X	X	X
Household Members Standard of Care Treatment		X			
Local Skin/Scalp Irritation Assessment			X	X	X
Ocular Irritation Assessment			X	X	X
Subject Self-Assessment		X	X	X	X
Investigational Product Accountability			X		
Subject Diary Dispensation		X			
Subject Diary Collection and Compliance Review			X		
Concomitant and Prohibited Medication Review	X	X	X	X	X
Adverse Events Assessment			X[10]	X	X

[1] Rescreening will be permitted for out of window index subjects and those subjects whose household members cannot accompany them at their initial screening visit.
[2] visit 2 (baseline) may be completed on the same day as visit 1 (screening). If screening and baseline are completed on the same day, assessments performed on both screening and baseline need only be performed once. Refer to section 7. Study procedures and schedule of events for details and restrictions.
[3] index subjects identified as treatment failures will be terminate early from the study and be provided the standard of care rescue treatment.
[4] must be within 24 hours of treatment.
[5] physical examinations are to be performed if inclusion/exclusion criteria are satisfied at screening.
[6] prior to randomization, the investigator must confirm the subject still meets all inclusion/exclusion criteria.
[7] vital signs will include body temperature, heart rate and blood pressure (systolic and diastolic). Blood pressure and heart rate will be measured after the subject has been sitting restfully for at least 5 minutes.
[8] for female index subjects of child-bearing potential.
[9] for both index subjects and infested household members.
[10] AE reporting period for this study begins upon receiving the first application of investigational product and ends at the final protocol required visit.

1.3. Glossary of Terms

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Forms
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMV	Interim Monitoring Visit
IRB	Investigational Review Board
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
Mayne	Mayne Pharma, LLC/ Mayne Pharma International Pty Ltd
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRT	Mean Residence Time
OTC	Over the Counter
PI	Principal Investigator
PMH	Past Medical History
PP	Per-Protocol
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
US	United States

2. OBJECTIVES

The primary objective of this study is:

- To establish the efficacy of a single application of Ivermectin 0.5% lotion in the treatment of head lice (Pediculus humanus capitis) under at-home conditions compared with Sklice® 0.5% lotion
- To demonstrate that both active lotions have superior efficacy compared to Placebo

The secondary objective of this study is:

- To demonstrate comparative safety and local tolerability of Ivermectin 0.5% lotion (Mayne Pharma, LLC) vs Sklice® 0.5% lotion.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Sample Size Estimation

Under the assumption that the Test and Reference treatments are equally efficacious with a true cure rate of at least 67%, and that the placebo has a true cure rate no greater than 27%, computer simulations were performed to determine the probability (power) of study success for different sample sizes. Study success in a simulated trial was defined as having the 90% continuity-corrected confidence interval in the PP population for the Test-to-Reference difference in cure proportions be contained in the bioequivalence interval [-0.20, +0.20] at the same time that both active treatments were demonstrated in the mITT population to have cure rates that were greater than, and statistically different ($p<0.05$) from, that of the placebo. It was assumed that approximately 90% of the mITT subjects would qualify as PP ones.

It was determined that for at least an 80% probability of study success, 280 mITT index subjects would be needed (120:120:40; Test: Reference: Placebo) to obtain 252 PP ones (108:108:36; Test: Reference: Placebo).

3.2. Randomization

This is a double-blind study, thus all site staff, study monitor, and subjects will be blinded to the randomization scheme except for the Unblinded Site Personnel/ designee and Unblinded Monitor. Furthermore, the randomization scheme will be retained by the Drug Depot and will only be shared with Unblinded Site Personnel or designee.

The actual treatment given to individual subjects is determined by a computerized block randomization scheme prepared by an independent third party. The independent third party will prepare the randomization list and hold it throughout the conduct of the study. Subjects are randomized on a 3:3:1 basis (test drug: active comparator: placebo) and stratified by clinical site.

After signing the Informed Consent, each subject will be assigned a unique subject number. Subjects are identified using subject initials, subject number, and date of birth. The subject numbers will be generated by the EDC and assigned sequentially in the order in which subjects are consented at each center.

If a subject discontinues from the study, the subject number and randomization number are not to be reused, and the subject is not allowed to re-enter the study.

The randomization scheme for treatment allocation will be used for statistical and reporting purposes. A copy of the randomization assignment will be retained at each clinical site by unblinded personnel and will be available to FDA or other regulatory agency investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

3.3. Blinding and Procedures for Unblinding the Study

This is a double-blind study, thus Sponsor, CRO, assessor site staff, study monitors, and subjects will be blinded to the randomization scheme. The packaging of the study drug products will be similar in appearance to make difference in treatment less obvious to the subjects. Blank, opaque diaper labels will be applied to each study tube for maintenance of study blinding. Each tube will be packaged in individualized cartons. Neither the Investigator nor the subject should be able to identify the received treatment. The dispensed investigational product will NOT be opened by the index subject and their family members at the study center.

The blinding code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator to complete a serious adverse event report. In such situations, the Medical Monitor or the Investigator will use the Unblinded Treatment List in order to unblind the treatment for the individual subject. Unblinded information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded.

The Medical Monitor must be contacted by telephone prior to unblinding but no later than 24 hours after unblinding. As the study is blinded, the Investigator should promptly document and explain to the Sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s). Every effort should be made to avoid unblinding extra study personnel.

3.4. Handling of Data

3.4.1. Examination of Subject Subsets

The primary and secondary efficacy endpoints will be summarized separately using descriptive statistics by treatment group and study day, where appropriate. No formal statistical testing will be utilized.

3.4.2. Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized. In situations where it is not possible to obtain all safety data, imputation of missing data will not be conducted. A Last-Observation-Carried-Forward imputation method for missing efficacy data will be used for the mITT population.

3.4.3. Definitions and Terminology

Treatment Day 1 (Baseline)

Treatment Day 1 is the day that study treatment is first initiated.

Study Day

Study Day is defined relative to study treatment initiation (Study Day 1). Thus, the study day of an event is calculated as:

Study Day = event date – date of Study Day 1 +1.

Days on Study

Days on Study is the number of days from Study Day 1 to the date of study completion or early termination as recorded on the study termination eCRF.

End of Treatment

For efficacy assessments, end of treatment is defined as the last non-missing assessment taken prior to discontinuation of study treatment.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study treatment. This definition includes prescription and all over-the-counter (OTC) medications and all dietary supplements.

Previous Medications

Previous medications are those medications taken within the 30 days and stopped prior to the initiation of study therapy.

Treatment-Emergent Adverse Event

A treatment-emergent adverse event is defined as any adverse event occurring on or after the initiation of study treatment. For the purpose of defining treatment-emergent adverse events, it is assumed that an adverse event which was reported to have started on Treatment Day 1 without an associated onset time may have occurred after the initiation of study treatment. Hence, adverse events occurring on Treatment Day 1 are assumed to be treatment-emergent.

3.5. Planned Analyses

A final analysis is planned after the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

4. ANALYSIS POPULATIONS

The populations defined for analysis will include the modified intent-to-treat (mITT), per-protocol (PP), and the safety population.

Safety Population includes all subjects who were randomized and dispensed treatment. This is the population that will be used for the safety assessments.

Modified Intent-to-Treat (mITT) Population includes all Index subjects who met all inclusion/exclusion criteria, were randomized, dispensed treatment, and had at least one post-treatment efficacy evaluation. This is the primary population for determination of the superiority of the active treatments over placebo.

Per-Protocol (PP) Population includes all mITT subjects who applied their dispensed treatment, had no protocol deviations which could have interfered with the accurate assessment of treatment efficacy, and returned for the Day 15 visit within the allowed window. This is the primary population for the efficacy comparisons between the two active treatment groups.

Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of head lice during the study will be discontinued, included in both the mITT and PP population analyses as treatment failures. Subjects who discontinue early for reasons other than treatment failure will be excluded from the PP population, but included in the mITT population. Last Observation Carried Forward (LOCF) will be used to impute any missing endpoints.

Efficacy analyses will be performed on both the per-protocol population and the mITT population. Safety analyses will be performed using the Safety population as defined.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with confidence intervals calculated for the primary and secondary efficacy endpoints. The term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term "treatment group" refers to randomized treatment assignment: active-test, active-reference, and placebo. All data collected during the study will be included in data listings. The data will be sorted first by subject number, and then by date within each subject number. Unless specified otherwise, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher within a validated statistical computing environment.

5.1. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, including the number of subjects who completed the study, discontinued from the study, reasons for early discontinuation, and the number of days on study will also be provided and presented for all subjects randomized. Subject disposition will be summarized by treatment group.

Demographic data and baseline characteristics including age, ethnicity, race, gender, severity of itching and stinging/burning sensations, and skin/scalp irritation assessment will be summarized using appropriate descriptive statistics by treatment group for the mITT and PP populations. Descriptive statistics will be generated for continuous variables (e.g. age). The number and percentage of subjects in each class of categorical demographic and Baseline variables (e.g. gender, ethnicity, race, severity of itching and stinging/burning sensation; skin/scalp irritation assessment) will be tabulated by treatment group and population (mITT and PP) for Baseline (Visit 1). Individual subject demographic and Baseline characteristics data will be listed. No inferential testing will be performed.

5.2. Efficacy Analyses

5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of index subjects who are lice free (defined as no live lice, adults or nymphs) 14 days (Day 15) after treatment.

Descriptive statistics (number of subjects, number of subjects cured, and proportion of cured) for the primary efficacy variable will be tabulated by treatment group and population (mITT and PP).

5.2.2. Primary Efficacy Analyses

Bioequivalence assessment will be evaluated by comparing proportions of patients successfully cured in the test and the reference treatment groups. Bioequivalence between the test and the reference product will be established if the continuity-corrected 90% confidence interval for the difference in cure proportions between test and reference treatment is contained between the equivalence limits [-0.20, +0.20]. The hypothesis testing for the two, one-sided tests will be conducted using a 5% level of significance.

In this case, the compound two, one-sided tests hypothesis is:

H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$ (meaning test product is not bioequivalent to the reference);

H_A: $-0.20 \leq p_T - p_R \leq 0.20$ (supporting bioequivalence);

where p_T = cure rate of test treatment, p_R = cure rate of reference treatment.

Let n_T = sample size of test treatment group, n_R = sample size of reference treatment group and se = $(\widehat{p_T}(1-\widehat{p_T})/n_T + \widehat{p_R}(1-\widehat{p_R})/n_R)^{\frac{1}{2}}$.

The 90% confidence interval will be estimated as follows, using Yates correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645 \times se - (\frac{1}{n_T} + \frac{1}{n_R})/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645 \times se + (\frac{1}{n_T} + \frac{1}{n_R})/2$$

H_0 is rejected if $L \geq -0.20$ and $U \leq 0.20$ resulting in accepting H_A and concluding bioequivalence of the two products.

The primary endpoint is the evaluation at Day 15. The bioequivalence results in the PP population will be considered definitive, with those in the mITT population as supportive.

The following SAS code will be used for testing bioequivalence:

```
proc freq data = dataset;
      weight count;
      tables treat*outcome/ riskdiffc (equiv);
run;
```

The efficacy assessments for each active treatment vs. the Placebo will be conducted using two-sided, continuity corrected Z-tests based on the following hypotheses:

Ho: $\pi_T = \pi_P$

Ha: $\pi_T \neq \pi_P$

where,

π_T, π_R, and π_P = the true cure proportions for Test, Reference, and Placebo treatments, respectively.

If both null hypotheses are rejected ($p<0.05$) and the observed cure proportions for the Test and Reference treatments are greater than that for the Placebo, then Superiority will be considered to have been demonstrated.

The superiority results in the mITT population will be considered definitive, with those in the PP population considered supportive.

5.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoint is the number and percentage of all index subjects who are lice-free at Day 2. Descriptive statistics (number of subjects, number of subjects cured, and proportion cured) for the secondary efficacy variable will be tabulated by treatment group and population (mITT and PP).

5.2.4. Secondary Efficacy Analyses

As a secondary endpoint evaluation, patients' clinical progress at Visit 4 (Day 14) will be assessed and proportion of cured patients in treatment arms will be compared using the procedures described in the analysis of the primary efficacy endpoint.

5.3. Tolerability Assessment

Subjects' self-assessment of itching and stinging/ burning sensations during screening and treatment periods (Visits 2 through 5), skin/scalp irritation assessment by clinical site personnel (Visits 2 through 5), and ocular irritation assessment (Visits 3 through 5) by clinical site personnel will used to assess tolerability to the study treatments. Itching is defined as intense, distracting irritation or tickling sensation in the last 24 hours and is evaluated on a scale from 0 (No Itching) to 3 (Severe Itch). Stinging/ burning is defined as sensation of the skin is painfully hot or noticeable tingling sensation in the last 24 hours and is evaluated on a scale from 0 (Absent) to 3 (Severe). Skin/Scalp irritation is evaluated on a scale from 0 (None) to 3 (Severe) for four types of irritation including Pruritus= Itching, Erythema= Redness of the scalp, Excoriation= Breaking of the skin, usually caused by scratching, Pyoderma= Sores filled with clear fluid, pus or crusting. Each type of irritation is evaluated separately and its total score is recorded. Ocular irritation is evaluated for the presence of eye irritation, Conjunctivitis, and Ocular Hyperemia on a scale from 0 (No) to 1 (Yes).

Descriptive statistics using categorical methods will be used to compare tolerability measures between the test and reference treatment groups and various study days (e.g. Baseline (Visit 2), Visit 3, Visit 4, and Visit 5). Tolerability analyses will be presented for mITT and PP populations.

5.4. Safety Assessment

The reporting of safety data is descriptive, and will include all subjects in the Safety population. The variables for safety endpoints are AEs. AEs will be summarized based on their frequency and their severity. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to study drug will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study drug.

Summaries of treatment-emergent AEs will include any AEs reported beginning with the first dose of study drug on Day 1. The occurrence of treatment-emergent adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study drug will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. These data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

5.4.1. Adverse Events

Analysis of adverse events as safety variables will be based on all adverse event (AE) capture measuring severity and frequency utilizing MedDRA terminology for consistency. AEs will be mapped to a MedDRA-preferred term and system organ classification. If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to study drug will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study drug.

Summaries of treatment-emergent AEs will include any AEs reported beginning with the first dose of study drug on Day 1. The occurrence of treatment-emergent adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events (SAEs), treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study drug will be generated.

All AEs will be listed for individual subjects showing both verbatim and preferred terms.

5.4.2. Vital Signs

Vital signs will be collected at the Screening visit; on the Baseline, and at Visit 5 (or upon subject discontinuation). Vital signs will include body temperature (oral), heart rate and blood pressure (systolic and diastolic). Any abnormal characteristics will be evaluated by the Investigator based on their clinical significance. Abnormal vital signs will be considered AEs if they require therapeutic medical intervention, and/or if the Investigator considers them to be AEs due to the clinical judgement.

5.4.3. Previous and Concomitant Medications

All medications (both prescription and nonprescription, and including vitamins, herbals, topical, inhaled, and intranasal) taken within 30 days prior to the start of the Study Drug and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand names, if known) with the corresponding indication, start and stop dates. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed) medication use.

Previous treatment of head lice must be recorded irrespective of the term it was given. Corresponding condition shall be captured in the subject's Medical History.

6. CHANGES IN THE PLANNED ANALYSES

No deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. PROGRAMMING CONVENTIONS

Statistical programs will be developed using SAS® version 9.4 or higher. Programs will be documented, produced, and validated. Additionally, the following conventions should be incorporated:

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of at least 8. Titles may be printed using a larger font (e.g., Arial point size 10).

- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the treatment group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects summarized within any given summary module; some subjects in the analysis population may have missing values and, thus, may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented to indicate clearly to a reviewer the method of calculation. Missing data will not contribute to the calculation of percentages.
- Sorting: Listings will be sorted by treatment group, subject identification number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically on the eCRFs.
    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
    - Means will be reported to the same number of significant digits as the parameter, unless the parameter is an integer, then 1 decimal place will be reported.
    - Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
- Time will be presented according to the 24-hour clock (HHMM).

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APPENDIX A: ITCHING SENSATION SCALE

Itching – Intense, distracting irritation or tickling sensation in the last 24 hours

Score	Grade	Definition
0	None	The scalp does not itch.
1	Mild	Occasional episodes of itching, not bothersome.
2	Moderate	Frequent, several times a day, bothersome.
3	Severe	Nearly constant, frequent, very bothersome.

APPENDIX B: STINGING/ BURNING SENSATION SCALE

Stinging/Burning – Sensation of the skin is painfully hot or noticeable tingling sensation in the last 24 hours

Score	Grade	Definition
0	None	Absent
1	Mild	Slight, barely present
2	Moderate	Distinct presence
3	Severe	Marked, intense

APPENDIX C: Skin/Scalp Irritation Assessment (include forehead, neck and ears):

Rating	Type of Irritation			
	Pruritus= Itching	Erythema= Redness of the scalp	Excoriation= Breaking of the skin, usually caused by scratching	Pyoderma= Sores filled with clear fluid, pus or crusting
None = 0	The scalp does not itch.	No redness of the scalp.	No broken skin on the scalp.	No lesions visible on the scalp.
Mild = 1	Occasional episodes of itching, not bothersome.	Faint, barely perceptible erythema with limited distribution.	One or two areas on the scalp on which skin is broken.	One or two lesions visible with crusting or other evidence of infection.

Moderate = 2	Frequent, several times a day, bothersome.	Diffuse pink areas of scalp are readily visible.	More than two separate areas of the scalp with broken skin but not generalized across the scalp.	Presence of more than two lesions with crusting or other evidence of infection, but not generalized across the scalp.
Severe = 3	Nearly constant, frequent scratching, very bothersome.	Large areas of the scalp are red.	Widespread breaking of the skin involving most of the scalp.	Lesions with crusting or other evidence of infection, involving most of the scalp.

APPENDIX D. Ocular Irritation Assessment:

Eye irritation present: ☐ Yes ☐ No

Conjunctivitis present: ☐ Yes ☐ No

Ocular Hyperemia present: ☐ Yes ☐ No