Statistical Analysis Plan

Study Title:	A multi-center, double-blind, randomized, parallel-group study comparing Permethrin 5% cream (Mayne Pharma, Inc.) with Elimite™ in patients with active scabies
Phase:	Phase 3
Protocol No.:	MAP-8184
Original Protocol Version 1.0	18 March 2016
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Analysis Plan Version and Date	Version 1: 14 April 2017
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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

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Sponsor Review:

Mayne Pharma, Inc.	Date
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Prepared by:

Jon Roth, VP Data Sciences and Biometrics — 05 Jun 2017 Date

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Sponsor Review:

Mayne Pharma, Inc. — 09 Jun 2017 Date

Mayne Pharma, Inc. — Date — N/A PH 09 Jun 2017

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol MAP-8184. 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-8184 is a multicenter, randomized (1:1), double blind, two-arm parallel group study to compare the treatment success of the test product, Permethrin Cream, 5% (Mayne Pharma, Inc.), and the Reference product, Elimite™ (marketed by Prestium Pharma, Inc.) on scabies infestations.

This study assesses the comparative efficacy of Permethrin Cream, 5% (Mayne Pharma, Inc.) and Elimite™ in patients with scabies infestation at the end of the treatment period (28±4 days).

The study also assesses comparative safety of Permethrin Cream, 5% (Mayne Pharma, Inc.) and Elimite™ and tolerability of Permethrin Cream, 5%.

This study is comprised of two phases: screening and treatment. The screening period will be up to 5 days in duration and treatment will be 28±4 days in duration. Please refer Table 1.2 below for a more detailed presentation of the study visits and assessments. After signing informed consent during screening (Visit 1), subjects, at least 12 years of age, male or female, of any race, will be evaluated to determine if they meet inclusion/exclusion criteria. Any subject under the age of 18 must sign the Assent Form and have the signature by a parent or legal guardian on informed consent form prior to enrollment in this study. Eligible patients will be enrolled and randomized in a 1:1 ratio for Test and Reference, and will be stratified by site. Following the receipt of informed consent, the subject's medical history will be recorded along with concomitant medications and prohibited treatments will be assessed as they should be discontinued. A physical examination will be performed for all subjects and a urine pregnancy test will be performed for women of childbearing potential. The subject's scabies infestation will be evaluated for papules and burrows during the visual examination. Presence of acarids, feces, or ova will be assessed via microscopic exam of skin lesion scraping. Subjects who meet all inclusion/exclusion criteria will return to the office for visit 2 within 5 days.

At Visit 2 (Baseline, Day 1), the subject's concomitant medications will be updated and any changes to medical history will be recorded. If subjects meet the randomization criteria, they will be assigned to one of the two treatment arms (Test or Reference) and the respective investigational product will be dispensed to subjects along with detailed instructions of drug application. The subjects also will be instructed on completion of subject diaries. Visits 1 and 2 can be combined, if subject's eligibility can be confirmed at the Screening visit and conducted on the same day,

which then is Day 1. All regular bedmates of the subject and individuals with prolonged physical contact with the subject will undergo an assessment by the Investigator and receive one 60 g tube of the standard of care generic Permethrin Cream, 5% at the Baseline visit, sufficient for two applications to prevent cross-infestation within the household.

Subject will return at visit 3 (Day 7±1) with the used investigational product tube and subject diaries. Compliance with investigational product applications will be assessed. Safety and tolerability assessments will be conducted.

At visit 4 (Day 14±2), subjects will return for efficacy, safety and tolerability assessments. If signs of active scabies infection are present at this visit, the subject will be treated with a second application of their assigned investigational product.

Final efficacy, safety and tolerability assessments will occur at visit 5 (Day 28±4). If the subject was retreated, the used tube of the investigational product will be returned at this visit. The duration of each subject's participation in the study will be a maximum of 37 days.

Subjects will be encouraged to report any complications or adverse effects during their participation. Investigator may evaluate the subject at an unscheduled visit, if subject's condition will be considered as worsening. If the Investigator assesses the subject's condition at any time and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as treatment failure. Visit 5 Early Termination procedures will be performed, and a standard of care treatment may be advised at the Investigator's discretion.

1.2. Time and Events Schedule

TABLE 1.2 Study Procedures and Assessments.

Visit Number	Visit 1 Screening	Visit 2 Baseline[1]	Visit 3 Interim	Visit 4 Interim	Visit 5 EOS/ET[2]
Visit Day	Day -5 to 1	Day 1	Day 7 (±1)	Day 14 (±2)	Day 28 (±4)
Informed Consent	X				
Eligibility Criteria	X				
Subject Demographics	X				
Medical History	X				
Physical Exam	X[3]				
Randomization		X[4]			
Vital Signs	X	X			X
Urine Pregnancy Test[5]	X				X
Visual Examination of Lesions	X	X	X	X	X
Microscopic Examination of Skin Scraping[6]	X				
Patient Self-Assessment		X	X	X	X
Investigational Product Dispensation		X		X[7]	
Treatment with Investigational Product		X		X[7]	
Investigational Product Accountability			X		X[8]
Subject Diary Compliance Review			X		X[8]
Concomitant and Prohibited Medication Review	X	X	X	X	X
Adverse Events Assessment		X[8]	X	X	X

1. 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.
2. End of Study/Early Termination
3. Physical examinations are to be performed if Inclusion/Exclusion Criteria are satisfied at Screening
4. Prior to Randomization, the Investigator must confirm the subject still meets all Inclusion/Exclusion Criteria.
5. For females of child-bearing potential
6. Any new lesions identified at Visits 3, 4, or 5 will be confirmed by microscopic evaluation of skin scraping
7. Applicable for subjects requiring second application of the investigational product
8. AE reporting period for this study begins from the time of application of the investigational product and ends at the final protocol required visit

1.3. Glossary of Terms

AE	Adverse Event
CRA	Clinical Research Associate
CRF	Case Report Form
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference On Harmonization
IEC	Independent Ethics Committee
IGE	Investigator's Global Evaluation
IP	Investigation Product
IRB	Institutional Review Board
ISF	Investigator Site File
LOCF	Last Observation Carried Forward
mITT	Modified Intent-To-Treat
PP	Per-Protocol
PD	Protocol Deviation
PDRR	Protocol Deviation Review Request
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions

2. OBJECTIVES

The primary objective of this study is:

- To demonstrate bioequivalence between Permethrin Cream, 5% (Mayne Pharma, Inc.) and Elimite™ in patients with active scabies.

The secondary objective of this study is:

- To demonstrate comparative safety of Permethrin Cream, 5% (Mayne Pharma, Inc.) vs Elimite™ and tolerability of 5% Permethrin cream.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Sample Size Estimation

Under the assumption that the Reference product has a cure rate of at least 88%, sample size evaluations were conducted, via computer simulation, to determine the probability (power) of the calculated 90% continuity-corrected confidence interval on the Test-to-Reference difference in cure proportions to be contained in the bioequivalence interval [-0.20, +0.20]. When the Test product was assumed to have the same 88% cure rate, the required number of PP subjects in each treatment group was determined to be 56 (112 total) for a power ≥0.80. Assuming 20% of drop-out rate, 70 subjects in each treatment group (140 total) would be needed.

If it is assumed that the Test product cure rate might deviate from that of the Reference by as much as 2% (e.g. 86% instead of 88%) and if a higher power, ≥0.95, was desired, then 91 PP subjects in each treatment group (182 total) would be needed. Assuming 20% drop-out rate, 114 subjects in each treatment group (228 total) would need to be enrolled.

3.2. Randomization

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. The content of the randomization list will not be available to either clinical sites or sponsor up until the database is locked. Subjects are randomized on a 1:1 basis (test drug: active comparator) in blocks of two and stratified by clinical site. The subject randomization number corresponds to either one of the active drugs treatment allocation.

Clinical sites will contact the independent third party responsible for the randomization scheme at the time subject has met all inclusion criteria and is ready for enrollment. Blocks of two (2) tubes will be supplied to the sites. Site's dispensing pharmacist will randomly select a tube with an

investigational product from the block for the study subject. Next enrolled subject will receive the remaining investigational product from the same block until the block is entirely used. Subject eligibility is established before treatment randomization at Visit 2 (Screening and Visit 2 Randomization can be combined into one visit). Subjects are randomized strictly sequentially, as subjects are eligible at the clinical sites.

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.

Based on the clinical judgement and requirements described in the protocol, the Investigator may provide a retreatment to the study subject. Only one retreatment is allowed per subject. The retreatment assignment must belong to the same treatment arm. In order to dispense the correct treatment, the following process is to be followed:

1. Study pharmacist will contact the Drug Depot, specifying subject's identifying information.

2. Drug Depot will specify which kit number shall be dispensed for retreatment.

The randomization scheme for treatment allocation will be used for statistical and reporting purposes. A sealed copy of the randomization assignment will be retained at each clinical site 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 in which the study subjects, the Investigator, the Study Coordinator, clinical staff, Sponsor (with the exception of the independent third party who generated the randomization code), and any personnel involved in the monitoring, evaluation, and analysis of study data will not be aware of treatment assignment for any subject until after the database for the study has been finalized. Members of the Data Monitoring Committee may, on occasion, use the treatment assignment codes provided by the unblinded statistician at the independent third party to determine the treatment assignment of a subject reviewed by the committee.

The packaging of the test and the reference products will be similar in appearance to make difference in treatment less obvious to the subjects. To maintain adequate blinding of Investigators and subject evaluators, it is recommended that the investigational product dispensation and accountability be performed by the study pharmacist, or designated study personnel who will not

be involved in any other activities of this study. Neither the Investigator nor the patient should be able to identify the received treatment. The dispensed investigational product will NOT be opened by the subject at the study center except in front of the study pharmacist, or designated study personnel. The randomization scheme will not be available to the physician, the study pharmacist or designated study personnel for investigational product dispensation and accountability and nursing staff or study coordinators involved in the collection, monitoring, revision, or evaluation of adverse events or to clinical staff who could have an impact on the outcome of the study.

A sealed copy of the randomization code will be supplied with each block of the investigational product and will be retained at each clinical site. Randomization codes must be available to the FDA or other regulatory agency investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

From Day 1 through the end of the study, the randomization code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Qualified Investigator for subject safety and medical care. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, Investigator will make every attempt to contact the Biorasi Project Manager by telephone, explaining the need for unblinding, before or no later than 24 hours of breaking the blinding. The Investigator must document the time, date, and reason for the unblinding and the names of the personnel involved on the CRF, in the site file, and in the medical notes. The Investigator must notify the Sponsor in writing as soon as possible following the unblinding event explaining the necessity of unblinding 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: The safety population is any randomized individual who: (a) was enrolled into the study, and (b) received at least one application of study treatment. Subjects will be analyzed according to the treatment received. This population will be used for safety assessment.

Modified Intent-to-Treat (mITT): A modified intent-to-treat subject is any randomized individual who: (a) was enrolled into the study, (b) met inclusion/exclusion criteria, (c) received at least one application of study treatment, and (d) had at least one post-baseline visit. Subjects will be analyzed according to the randomized treatment. This population will be used for secondary and primary efficacy analysis as supportive analysis.

Per Protocol (PP): A per-protocol subject is any randomized individual who: (a) enrolled into the study and met inclusion/exclusion criteria, (b)received the assigned study treatment, (c) had not taken any concomitant medications prohibited by the protocol or experienced any major deviations that interfered with or may have interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy, and (d) completed the primary endpoint evaluation within the designated visit window (±4 days).

Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of scabies 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, using Last Observation Carried Forward (LOCF).

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: Test and Reference. 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. Additionally, study therapy compliance will be summarized by treatment group.

Demographic data and baseline characteristics including age, ethnicity, race, gender, and severity of itching and burning sensations 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, and severity of itching and burning sensation) will be tabulated by treatment group and population (mITT and PP) for Baseline (Visit 2 or Visit 1 if applicable). 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 endpoint will be the proportion of patients that are identified as cured at the end of the treatment period on Study Day 28 (Visit 5). Cure is defined as the absence of new lesions and the healing of all old lesions. Residual, dry, non-inflammatory papules are not counted as active. 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). The results for the PP population will be considered definitive with those in the mITT population as supportive.

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, 1-sided tests will be conducted using a 5% level of significance.

In this case, the compound two, 1-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 = $\underline{(\widehat{p_T}(1-\widehat{p_T})/n_T + \widehat{p_R}(1-\widehat{p_R})/n_R)^{\frac{1}{2}}}$.

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

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

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

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 28. The 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;
```

5.2.3. Secondary Efficacy Endpoints

The secondary endpoint will be the proportion of patients that are identified as cured at the end of the treatment period on Study Day 14 (Visit 4). Descriptive statistics (number of subjects, number of subjects cured, and proportion of cured) for the secondary efficacy variable will be tabulated by treatment group and population (mITT and PP). The results for the PP population will be considered definitive with those in the mITT population as supportive.

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 procedure 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) 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 4 (Unbearable, Intense 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 (Marked, Intense).

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

Safety analyses will be presented for the Safety Population, defined as all subjects who receive at least one dose of study medication. Adverse events and vital signs measurements will be used as safety endpoints and summarized by treatment group. The previous and concomitant medications will also be summarized.

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

Concurrent medications and any medications taken in the 30 days prior to the start of the study will be recorded as prior/concomitant medications (using their generic and brand name, if known) with the corresponding indication. Concomitant medications will be coded using the WHO dictionary. These data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

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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3. The summary of self-assessment of itching and stinging. (mITT population).
4. The summary of self-assessment of itching and stinging. (PP population).
5. The summary of self-assessment of burning sensations at each visit. (mITT population).
6. The summary of self-assessment of burning sensations at each visit. (PP population).

APPENDIX A: ITCHING SENSATION SCALE

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

Score	Grade	Definition
0	None	No Itching.
1	Mild	Barely perceptible, slightly present itch
2	Moderate	Distinct presence of itch
3	Severe	Marked, intense, yet tolerable itch
4	Very Severe	Unbearable, intense itch

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