

Statistical Analysis Plan

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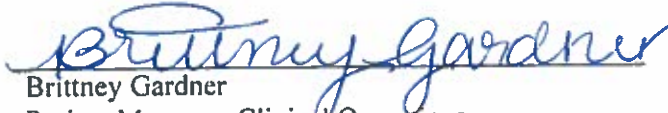
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LIST OF ABBREVIATIONS AND ACRONYMS

TERM	DEFINITION
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemistry
AUC	Area Under the Curve
CBC	Complete Blood Count
CI	Confidence Interval
C _{max}	Maximum drug concentration
CMH	Cochran-Mantel-Haenszel (general association test)
CV%	Percent coefficient of variation
ET	Early Termination
FDA	Food and Drug Administration
IP	Investigational Product
ITT	Intent-to-Treat
I-ITT	Index Intent-to-Treat
I-PP	Index Per Protocol
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
OC	Observed Cases
PI	Principal Investigator
PK	Pharmacokinetics
POC	Proof of Concept
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
T _{max}	Time of maximum (peak) drug concentration
WHO-DD	WHO-Drug Dictionary

1. PREFACE

This document presents a statistical analysis plan (SAP) for ParaPRO Protocol SPN-303-15 (*A Phase 3, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety, Efficacy and Pharmacokinetic of Natroba™ (spinosad) for the Treatment of Scabies*).

Reference materials for this statistical plan include the protocol SPN-303-15 (Amendment 5 Dated 20 September 2017).

The SAP described hereafter is an *a priori* plan. A version of the SAP will be prepared at the same time as the protocol is finalized. However, the primary and secondary efficacy endpoints and analyses on them will not be altered unless agreed upon with the Food and Drug Administration (FDA). SAP will be finalized before the database is unblinded.

Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes. In such an event, arbitrary treatment group assignments must be randomly linked to subjects, effectively rendering any inference based upon the output of programs meaningless.

For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan. Any deviations from the statistical analysis plan will be described in the clinical study report.

2. PROTOCOL OVERVIEW

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the safety and efficacy of topical Natroba™ (spinosad) versus Placebo for the complete cure of scabies after a single treatment.

2.1.2. Secondary Objective

The secondary objective is to assess pharmacokinetics (PK) of spinosad and benzyl alcohol following a single dose of Natroba™ in pediatric subjects 4-16 years of age.

2.2. Trial Design and Visit Structure

The primary study is a double blind, two-arm, 28-day, placebo-controlled study with approximately 120 infested “index” subjects enrolled and randomized 1:1 to Natroba™ or Placebo in order to achieve, with attrition, 96 subjects completed in the study.

All members of a household (no more than 6 individuals) with a suspected “index” subject must be screened at the first visit. In this study, “index” subjects are defined as the youngest infested household member (≥ 4 years). If the household has at least one member with active scabies infestation and meet all other criteria, they must all agree to participate in the study. Household members who do not present with scabies at the screening visit must also agree to apply the same blinded investigational product (IP) as household members who present with scabies (see Table 6-1 Schedule of Procedures in the protocol for status assessment). All household members must agree to participate in the study or none will be enrolled.

After screening on Day 1, all randomized subjects in the primary population will be dispensed IP (Natroba™ or Placebo) to apply at home later the same day. IP will be applied as a single treatment over the entire body from the neck down to the toes (including the soles of the feet) and to the scalp (if balding) or hairline, temples and forehead on the same day. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver. Subjects will rub the treatment into the skin followed by a 10-minute wait period before getting dressed. Showering or bathing must not occur earlier than 6 hours after treatment and no later than at least 1 hour prior to Day 2 visit.

A separate population of 24 pediatric “non-index” subjects that do not reside in the “index” subject’s household will be enrolled to assess the PK of spinosad and benzyl alcohol for 12 hours after open-label topical application on a single in-clinic visit (Day 1, or Day 2 if screening only on Day 1). There will be 12 male or female subjects 4 – 9 years of age (with a minimum of 6 male or female subjects 4 – 6 years of age) and 12 male or female subjects 10 – 16 years of age. With assistance from a caregiver, Natroba™ will be applied over entire body from the neck down and to the toes (including the soles of the feet) and to the hairline, temples and forehead. The open-label product will remain on the skin for at least 6 hours before bathing or showering. Bathing must occur after the 6 hour blood draw but prior to the 12 hour blood draw. The subjects will stay in the clinic until the 12-hour procedures are completed. Blood draws will be taken at 0 hours (just prior to treatment), and then at 0.5, 1.0, 3.0, 6.0 hours post-treatment and then at 12 hours post-treatment. Bathing must occur after the 6 hour blood draw but prior to the 12 hour blood draw. A ± 5 minute time window will be allowed for all post-treatment blood samples. Safety will be assessed using adverse events (AEs), general skin and eye irritation assessments, pre-dose and pre-discharge laboratory evaluations, and vital signs during the 12 hours in-clinic. Following the sample collections subjects will be released from the clinic with 5% permethrin for their household, and directed to their primary care physician for follow-up.

In the primary population (all household members), on Day 2 (Visit 2), general skin and eye assessments will be made for possible irritation, and to confirm that all IP was left on for a minimum of 6 hours before bathing or showering. If a subject reports an adverse event assessed as related by the principal investigator (PI) on Day 2 (Visit 2) then a follow-up visit with the investigator must be scheduled within 7 days of visit. Subjects will receive a well-being phone call on Day 14 to continue to emphasize instructions to prevent re-infestation, determine if any concomitant medications have been used, and check for

adverse events. If a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call, then a follow-up visit with the investigator must be scheduled within 7 days of phone call. On Day 28 (Visit 3), primary population subjects will return to the clinic for safety and efficacy assessments. The primary endpoint of complete cure will be assessed in the infested household members. If the infested subject is completely cured at Day 28, he or she will have completed the study and termination procedures will be conducted. If the subject is not completely cured at Day 28 (with Natroba™ or Placebo), the subject will receive 5% Permethrin and will be directed to their primary care physician for follow-up.

Safety assessments will be made for all household members and will include monitoring of adverse events (AEs) throughout the study, vital signs recording (Days 1 and 28), clinical laboratory analyses (Days 1 and 28), and general skin and eye irritation assessments (Days 1, 2, and 28).

The Day 28 procedures will also be completed for early termination (ET) except subjects will not receive rescue Permethrin but will be directed to follow-up with their primary care physician.

2.3. Study Treatment

2.3.1. Treatment Groups

Subjects will receive one of two treatments randomized 1:1 to the placebo or investigational product.

Treatments:

1	Investigational product: Natroba™ (spinosad) Topical Suspension (0.9%)
2	Placebo: Placebo Control

2.3.2. Sample Size Determination

Approximately 120 “index” subjects will be enrolled (includes anticipated 20% attrition) from 120 households and randomized 1:1 to Natroba™ (spinosad) and Placebo control. The index subject will be the youngest infested member of a household (≥ 4 years). Referencing to the Sponsor’s Proof of Concept (POC) study (SPN-401-12) and published literature, it is reasonable to assume a 60% complete cure rate for Natroba™ and 30% for placebo. A sample size of 48 study-completed “index” subjects per group will provide 80% power to declare the non-equivalency using a delta of 30% and Type I error rate of 0.05. Fisher exact test was used to calculate the sample size and the specified power in the following Table 1 (PASS 14; 2015, NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Table 1 Sample Size Needed to Declare Non-equivalency with Respect to the Proportion of Subjects Achieving Complete Cure with a Type I Error Rate=0.05 and Specified Power

Natroba™	Proportion in		Required Sample Size per Group	Power
	Placebo	Difference vs. Placebo		
55%	30%	25%	69	80.4%
60%	30%	30%	48	80.0%
65%	30%	35%	37	80.6%

Assuming a drop-out rate could be at most 20%, 120 subjects should guarantee at least 48 evaluable subjects for each treatment group at Day 28 assessment.

A sample size of an additional 24 subjects will be enrolled, which is based on the previous PK studies performed on children 6 months to 15 years of age with head lice infestations, in which Natroba™ was administered as a single open-label topical treatment and PK sampling was performed over a 12-hour period. In the current study, 24 male and female subjects (4-16 years of age) with scabies infestation will be enrolled: 12 male or female subjects 4 – 9 years of age (with a minimum of 6 male or female subjects 4 – 6 years of age) and 12 male or female subjects 10 – 16 years of age. No formal power calculations were performed for the PK sample size.

2.3.3. Method of Treatment Assignment and Randomization

As “index” subjects and other infested or non-infested household members become eligible for randomization at Visit 1 (Day 1), the site will locally assign a unique subject number to each of the qualified household members that combines a 3-digit site number (xxx), a 2-digit household number (yy), and a 2-digit household member number (zz). For example, the first subject of the first household at site 101 would be randomized to subject number 101-01-01, the second member to 101-01-02, the third member to 101-01-03, and so on. Since all household members receive the same treatment, each household is randomized to either Natroba™ (spinosad) or Placebo control. Non-infested household members will be assigned the same IP treatment as the infested members and will be assigned a subject number and randomization number. The assigned subject numbers to each household will correspond to unique bottle numbers on a scheme that unblinded site personnel will assign and distribute, to ensure approximately equal randomization of households to either treatment. Subject numbers must not be re-used once assigned, even if the subject does not take the IP. Randomization will be stratified by study site.

For the pediatric PK population, assignment of a unique subject number will occur as the subject becomes eligible for enrollment. Randomization numbers will not be assigned as IP is open-label.

2.3.4. Blinding Methods

Eligible subjects will be assigned to either treatment group, Natroba™ (spinosad) or Placebo control, by pre-specified un-blinded site personnel that may perform no other subject related study specific or subject treatment related study duties. The un-blinded site personnel will assign all members from the same household to the same treatment group. The assigned subject numbers in each household will correspond to unique bottle numbers on a scheme that unblinded site personnel will assign and distribute to ensure approximately equal randomization of households to either treatment. Subjects, blinded site personnel, and ParaPRO, LLC will remain blinded to the treatment until after database lock.

2.3.5. Procedures for Unblinding

In an emergency, the study blind may be broken only if:

- in the opinion of the investigator and/or the Medical Monitor, it is in the subject's best interest to do so;
- knowledge of the treatment will alter the clinical management of the subject;
- approval has been granted by the Medical Monitor and/or ParaPRO, LLC.

Whenever possible, the Medical Monitor should be notified prior to unblinding a treatment assignment. In the event that unblinding is necessary for the medical management of the subject, the prespecified un-blinded site personnel will access the randomization code by a treatment code list provided by Concentrics Research to each site. If a treatment assignment is unblinded, the date and reason for the unblinding must be recorded on the subject's source document, and the Medical Monitor notified within 24 hours.

2.4. Planned Analyses

The analysis of all study data will occur at the end of the trial. No interim analyses are planned. Study data will remain blinded to treatment assignment until all data have been collected and the clinical database has been locked for unblinding and analysis.

3. SAFETY PARAMETERS

3.1. Adverse Event

Adverse Events (AEs) will be collected on the Day 1 visit for PK population subjects, and Days 2, 14 (phone call, and a follow-up visit if AE is reported), and 28/ET for primary population subjects. See Section 6.4.1 for further details on which AEs will be assigned as treatment-emergent adverse events (TEAEs).

3.2. General Skin and Eye Assessments

On Day 1, the skin will be assessed to determine eligibility – no evidence of crusted scabies, normal skin in non-infested areas. On Days 1 and 2, the skin and eye assessments will include documentation of presence or absence of irritation, and verbal verification that

the treatment topical suspension remained on for at least 6 hours before being washed off. On Day 28/ET, skin and eye assessments will include evidence of irritation.

Eye irritation will be rated:

- 0 no irritation
- 1 mild scleral, lid, and/or conjunctiva injection
- 2 moderate scleral and or lid injection with conjunctival erythema
- 3 severe scleral and/or lid injection with conjunctival erythema and purulent drainage

3.3. Laboratory Assessments

For the primary population, safety laboratory assessments will be made on Days 1 (baseline counts) and 28/ET. The analyses will include complete blood count (CBC) with differential if abnormal, and serum chemistry. The Investigator will review the laboratory test results, evaluate, and document whether the results are non-clinically or clinically significant. Urine pregnancy testing will be performed by the sites on Days 1 and 28/ET.

For pediatric PK subjects, the pediatrics-specific laboratory will provide equipment for reduced blood volume to be collected at in-clinic Day 1: pre-dose and 12-hours post-dose (before discharge), as well as for PK sampling.

3.4. Vital Signs

Height (Day 1 only), weight, resting blood pressure and heart rate will be measured on Days 1 and 28/ET.

3.5. Prior and Concomitant Medications

For primary population subjects, prior medications will be collected on Day 1 and concomitant medications will be collected on Days 2, 14 (by phone), and 28/ET.

For PK population subjects, prior medications will be collected on Day 1 and concomitant medications will be collected from IP application until post dose/discharge.

4. EFFICACY PARAMETERS

4.1. Scabies Assessment

Skin will be examined on Days 1 and 28/ET to establish positive or negative evidence of active scabies infestation.

- Scabies diagnosis – active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic exam of skin scraping or dermatoscopy to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.

- Primary Efficacy Endpoint – complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows. This endpoint will not be assessed in the PK population.

Lesions should be indicated on a body diagram and/or marked with skin marker; count of existing and new lesions will be recorded.

5. ANALYSIS POPULATIONS

5.1. Safety Population

The safety population will comprise all study subjects (primary population and PK population) who received one dose of IP. Subjects will be analyzed as treated. The safety population includes the index subjects along with any household members enrolled in the study as well as all subjects in the pediatric PK analysis. Safety analyses will utilize the safety population. It is assumed that approximately 384 subjects will be enrolled and receive one administration of IP: 120 “index” subjects and 240 “non-index” subjects from the primary population, and 24 “non-index” subjects from the pediatric PK population.

5.2. Pharmacokinetic Population

The PK population comprises all pediatric PK subjects who are dosed with IP, who (or parent/guardian) give consent, are eligible and had blood drawn for PK assessment. No other populations will be used for the PK analyses.

5.3. Intent-to-Treat Population

The intent-to-treat (ITT) population will comprise all primary population subjects who were randomized. Subjects will be analyzed as randomized. This population includes the index subjects along with any household members enrolled in the study.

5.4. Index Intent-to-Treat Population

The “index” intent-to-treat (I-ITT) population will comprise of all index subjects who were randomized. Subjects will be analyzed as randomized. The index subject will be the youngest infested member of a household (≥ 4 years). Efficacy analyses will be based on this population.

5.5. Index Per Protocol Population

The “index” Per Protocol (I-PP) population is a subset of the I-ITT population. Index subjects will be excluded from the I-PP population for the following reasons:

1. Protocol deviations that would be in violation with the established Inclusion or Exclusion Criteria.
2. Protocol deviations that could confound the evaluation of efficacy outcomes:
 - Scabies assessment not performed (i.e. burrows, lesions, pruritis, skin scraping).
 - Subject received the wrong treatment.
 - Discontinuation prior to acquisition of Visit 3 (Day 28) efficacy measurements.
3. Protocol deviations that are a result of subject non-compliance:
 - Missed Day 2 appointment.
 - Use of another scabicide during the study.
 - Use of prescription or OTC medicated lotions during the study.

Prior to database lock, a memo will be generated identifying any subjects that were excluded from the I-PP population along with the reason why they were excluded.

The I-PP population will be established after a review of protocol deviations. This analysis population will be used for sensitivity analyses for the primary efficacy analysis.

6. STATISTICAL METHODOLOGY

6.1. Statistical and Analytical Issues

6.1.1. Statistical Methods

This statistical analysis plan (SAP) will describe statistical analyses for the study and be completed at the same time as the protocol. Any revisions (both alternative and additional methods) to the SAP, and reasons for such revisions, will be described in the final clinical study report.

Data collected in this study will be presented using summary tables, figures, and subject data listings. Summary tables will present data by treatment group and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the number of non-missing observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Figures may be used to support the presentation of certain data.

All tests of significance, unless otherwise stated, will be performed at a significance level of $\alpha=0.05$, two-sided.

Statistical programming and analyses will be performed using SAS® Software (SAS Institute Inc., Cary, NC) Version 9.2 or higher.

All subject study data, including data not appearing in tables or figures, will be presented in data listings.

6.1.2. Computed Variables

The following variables will be computed programmatically.

Age in years (truncated to an integer value) will be calculated using the formula:

$$\text{Age} = \text{integer part of } [(\text{Date of informed consent/assent date} - \text{date of birth} + 1)/365.25]$$

Total number of lesion can be categorized into improvement grades as defined below:

Mild = <50% reduction in total number of lesions

Moderate = \geq 50% in total number of lesions

Good = complete clearance of lesions

Baseline value will be the last measurement obtained prior to first dose.

The total number of lesions post-treatment is calculated using the following formula:

$$\begin{aligned} \text{Total post-treatment lesions} = \\ \text{total number of pre-existing lesions} + \text{total number of new lesions} \end{aligned}$$

The change from baseline is calculated using the formula:

$$\text{Change from baseline to post-treatment} = \text{Post-treatment Value} - \text{Baseline Value}$$

The percent reduction in lesions is calculated using the formula:

$$\begin{aligned} \text{Percent Reduction} = \\ [(\text{Baseline total number of lesions} - \text{Post-treatment total number of lesions}) / \\ (\text{Baseline total number of lesions})] * 100 \end{aligned}$$

6.1.3. Handling of Partial Dates

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications in determining whether the events occur during certain study period. Complete missing date will not be imputed.

Adverse events

A. Start Dates

- 1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- 2) If both the month and day is unknown, then:
 - i) If the year matches the first dose date year, then set the month and day to the same as the first dose date.

- ii) Otherwise, assign '1 January.'
- 3) If only the day is unknown, then:
 - i) If the month and year match the first dose date month and year, set the day to that of the first dose date.
 - ii) Otherwise, assign the first day of the month.

B. Stop Dates

- 1) If the year is unknown, then the date will not be imputed and will remain a missing date.
- 2) If the month is unknown, then assign 'December.'
- 3) If the day is unknown, then assign the last day of the month.

Prior/concomitant medications

Partial start dates of the concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of the completely missing stop date, medication will be assumed to be ongoing.

6.1.4. Handling of Laboratory Data

All continuous laboratory parameters will be summarized descriptively by absolute value at scheduled visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarized in the International System of Units (SI) standards. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Shift tables will be produced for each laboratory parameter to display low, normal, and high values. The shift tables will present baseline and post-baseline maximum/minimum value, as applicable. All post-baseline laboratory results, unscheduled or repeated, will be included. Shift tables will include only patients with both baseline and post-baseline data.

6.1.5. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study, the early termination visit data will be imputed. The imputation method depends on the reasons of missing, i.e. informative or non-informative missing. Please see more details about the reasons in Table 2 in Section 6.1.6.

For by visit summaries, the early termination visit data can be analyzed at the closest scheduled visit. If the closest visit has observed data, the early termination data will be assigned to the next available visit.

6.1.6. Data Imputation Specifications

For the safety analyses, no imputation of missing events or assessments are allowed.

For the primary efficacy endpoint (response variable of complete cure at Day 28), the algorithms listed below will be followed so as to include as complete as possible the I-ITT subjects that have information related to treatment effects.

If a subject has observed data at Day 28, the observed case (OC) will be used at Day 28.

If a subject discontinues the study before Day 28, use the table below to check the discontinuation reasons belonging to informative missing or not. Any informative missing will be counted in as non-responders (failures) in the estimation of the treatment complete cure rates. Any non-informative missing will be imputed using Last Observation Carried Forward (LOCF) in the estimation of the treatment complete cure rates.

Table 2 Informative or Non-Informative Missing

Dropouts Due to			
Lack of Efficacy	Drug Related Adverse Event	Lost to Follow-up	All Other
Informative	Informative	Non-informative	Non-informative

For sensitivity analyses regarding the primary endpoint, the Observed Cases (OC), LOCF and multiple imputation (MI) method will be used as appropriate approaches in addition to the imputation approach described for the primary efficacy analysis above. In addition, the Observed Case (OC) and LOCF methods will be used as sensitivity analyses for exploratory endpoints. Section 6.3 specifies in detail about imputation methods applicable to them.

The MI method assumes data are missing at random (MAR). The seed number is 626. The number of imputations is 5.

Step 1: Non-monotone missing data will be imputed using the fully conditional specification (FCS) method separately for each treatment arm since the response missingness could be due to treatment. A logistic regression will be used for binary data, and a discriminant function method will be used for ordinal data or classification variable with more than two levels if necessary. The following covariates will be included in the imputation model: treatment, clinical site (small sites pooled), baseline evidence of burrows and baseline score of lesions. In this step, MI procedure with FCS statement will be performed using SAS version 9.4.

Step 2: The combined imputed data sets will be analyzed using a Cochran-Mantel-Haenszel test and a logistic regression.

Step 3: The results from the analysis based on the multiply-imputed datasets will be combined by the MIANALYZE procedure in the SAS version 9.4. The p-value, estimate of odds ratio (NatrobaTM vs Placebo), and the 95% confidence interval of odds ratio estimate from each multiply-imputed data set will be combined (Wilson & Hilferty, 1931; Gorja, 1992; Rubin, 1987; Li et al., 1991).

6.1.7. Pooling of Study Sites

This is a study conducted at multiple study sites. Every effort will be made to have each site enroll at least 8 “index” subjects per arm. In case there are “small” sites each with fewer-than-8 “index” subjects per arm, these sites will be pooled together as a single, combined site for efficacy analyses if the combined site has at least 8 “index” subjects per arm. In the situation when the combined site still has less than 8 “index” subjects per arm, the smallest site with at least 8 “index” subjects per arm will be pooled to this combined site for efficacy analyses. Assessment of site-to-site variability will be conducted on the original sites prior to pooling.

6.2. Subject Characteristics

6.2.1. Subject Disposition and Deviations

The tabulation of number of subjects in each treatment group and overall will be displayed for all subjects who are screened, randomized, and in each analysis population.

The number and percent of subjects who completed or discontinued the study will be displayed for each treatment group and overall together with reasons for early termination, where the percent is with respect to the total number of randomized subjects in that treatment group.

Protocol deviations will be listed.

6.2.2. Treatment Compliance

The compliance data will be listed for each subject. Compliance data consist of two parts: 1. Subject questioning about the application and removal of Investigational Product, and 2. Evaluate by investigator as to whether or not the Investigational Product was applied as instructed.

6.2.3. Demographic and other Baseline Characteristics

Parameters collected at the screening and/or baseline visits will be summarized descriptively. In addition to the safety and efficacy scores listed in Sections 3 and 4, the following demographic and baseline characteristics will be presented:

- Demographic Characteristics

- Sex (male, female)
- Age (years)
- Ethnicity and Race (Hispanic or Latino, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White)
- Baseline assessments of scabies infestation
- Previous infestations

In addition, the above demographic and baseline characteristics will be presented by site before and after pooling the sites.

6.3. Efficacy Analysis

6.3.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of index subjects completely cured of scabies by Day 28. Complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows.

The primary analysis will be based on the data from the I-ITT population. The proportion of index subjects who exhibit complete cure (Yes or No) at Day 28 will be estimated by treatment group. Natroba™ will be compared versus placebo, and the difference with 2-sided 95% confidence interval (CI) will be provided. A Cochran-Mantel-Haenszel (CMH) general association test adjusted by study site (small sites pooled) stratification will be performed to test at an alpha level of 0.05 for equivalence in the complete cure rates between the two treatment groups.

Sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results using different methods of analysis and other populations.

The similar CMH test will be performed based on observed cases (OC) data, LOCF, and imputed data from MI method as sensitivity analyses.

A logistic regression analysis will be used assessing the treatment group difference in complete cure rate by Day 28. The model will include clinical site and treatment group as factors, and possibly additional baseline characteristics or a covariate, only if appropriate. The odds ratio, 95% CIs and p-value for the comparison will be provided. For logistic regression modelling, the data imputation approach specified in Section 6.1.6 for primary analysis will be applied for missing values at Day 28.

The similar logistic regression will also be performed based on observed cases (OC) data, LOCF, and imputed data from MI method as sensitivity analyses.

The complete cure rates at Day 28 will be summarized descriptively by treatment groups and by sites before and after pooling the sites.

Other additional sensitivity analyses include repeating the above two statistical analyses on I-PP population and ITT population.

6.3.2. Secondary Efficacy Analysis

Pharmacokinetic parameter estimates will be computed with non-compartmental methods for each subject. Individual elapsed sampling times (actual time) will be used in the pharmacokinetic analysis. The pharmacokinetic parameters to be computed for each subject include maximum drug concentration (C_{\max}), time of maximum peak drug concentration (T_{\max}), and area under the curve (AUC_{0-12h}).

Summary statistics of the plasma concentration levels for both spinosad and benzyl alcohol observed at each visit where plasma samples are collected will be provided. For continuous variables, Statistics will include number of non-missing observations, mean, standard deviation, coefficient of variation (CV%), median, minimum, and maximum, geometric mean and standard error of the geometric mean.

6.3.3. Exploratory Efficacy

All exploratory efficacy endpoints will be summarized by the treatment group at each scheduled visit. Descriptive statistics for continuous variables consists of mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, numbers and percentages will be summarized.

Additional analysis may be performed as appropriate for the following exploratory efficacy endpoints.

Clinical Cure

Clinical cure is defined as having all signs and symptoms completely resolved, including inflammatory/non-inflammatory lesions and pruritus.

The number and percent of subjects who exhibit clinical cure (Yes or No) at Day 28 will be presented by treatment group. A Cochran-Mantel-Haenszel test adjusted by study site stratification will be performed to compare the complete cure rates between the two treatment groups upon the same data imputation approach defined for primary endpoint.

CMH analysis can be performed on the I-ITT population on both OC and LOCF data as needed.

Microscopic Cure

Microscopic cure is defined as microscopic or dermatoscopic demonstration of the absence of mites, eggs, and/or scybala, and negative for burrows.

The number and percent of subjects who exhibit microscopic cure (Yes or No) at Day 28 will be presented by treatment group. A Cochran-Mantel-Haenszel general association test stratified by study site will be used to compare the two treatment groups upon the same data imputation approach defined for primary endpoint.

Additional analyses can be performed on the I-ITT population by applying a logistic regression model adjusted for baseline factors if there is necessity to further analyze this component of the complete cure.

CMH analysis can be performed on the I-ITT population on both OC and LOCF data as needed.

Number of New Lesions

The number of new lesions at Day 28 will be analyzed using a negative binomial regression model to compare the treatment difference. The model will include treatment group and study site (small sites pooled) as fixed factors, and baseline total lesion count as a covariate.

This analysis will be performed on the I-ITT population using LOCF approach.

Total Lesion Counts

Total lesion counts will be calculated as the sum of pre-existing lesions and new lesions. The baseline captures the total lesions on the day of first study drug administration.

The change from baseline to Day 28 will be analyzed using an analysis of covariance (ANCOVA) model with treatment and study site (small sites pooled) as factors and baseline total lesion counts as a covariate.

This analysis will be performed on the I-ITT population using LOCF approach. In addition, descriptive statistics will be provided by visit based on OC data.

Subset in ITT - subjects who were infested at baseline

A subset of subjects in ITT population who were infested at baseline will be summarized to display the proportion of the completely cured subjects.

The same analyses described for primary analysis will be performed for this subset of subjects using the similar data imputation approach described for primary analysis.

6.4. Safety Analyses

6.4.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group. All AEs will be captured throughout the study period from the enrollment to the final visit (Visit 3) or the ET visit. AEs that occur after the first dose of study treatment will be considered as treatment-emergent adverse events (TEAE). Within each SOC or PT, subjects will be counted only once if they had one or more than one event reported during the treatment period (the subject is counted for the event with the greatest severity).

Adverse events will be summarized by presenting:

- the number and percentage of subjects experiencing any TEAE
- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT
- the number and percentage of subjects experiencing any Serious Adverse Events (SAEs)
- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT and maximum severity
- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT and maximum relationship to IP
- the number and percentage of subjects experiencing any TEAE leading to study medication discontinuation.
- The number and percentages of subjects experiencing any unexpected life-threatening adverse reaction.

A listing will be produced for all subjects who reported SAEs or who discontinued study medication due to TEAEs.

All AEs (ie, pretreatment AEs and TEAEs) will be listed by subject. However, only TEAEs will be included in the summary tables.

6.4.2. General Skin and Eye Irritation Assessments

Skin and eye irritation will be captured as adverse events, as defined in Section 9.1 of the protocol. Eye irritation assessment ratings will be summarized descriptively for each treatment group by visit.

6.4.3. Laboratory Evaluations

Laboratory results will be summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value. In addition, laboratory shift tables will be provided for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained.

6.4.4. Vital Signs

Vital signs will be summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value.

6.4.5. Prior and Concomitant Medications

The number and percent of subjects who took prior medications will be summarized descriptively by the Anatomical Therapeutic Chemistry (ATC) class and Preferred Term as coded in the WHO-Drug dictionary (WHO-DD) for each treatment group. Prior medications include all medications that start prior to first dose of study medication. Concomitant medications will be summarized similarly.

Reference

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- Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. *Proceedings of the National Academy of Sciences, Washington*, 17, 684-688.