STATISTICAL ANALYSIS PLAN

A Phase 2, placebo-controlled, double-blind, randomized, dose ranging, efficacy and safety study of orally administered moxidectin in adults with scabies

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

List of Acronyms/ Abbreviations

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
BQL	Below the limit of quantification
CI	Confidence interval
cm	Centimeter
COVID-19	Coronavirus disease
CV	Coefficient of variation
ECG	12-lead electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FWER	Familywise error rate
IRT	Interactive response technology
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	Multiple imputation
MSAP	Modelling and Simulation Analysis Plan
N	Number
PK	Pharmacokinetic
PPAS	Per protocol analysis set
PT	Preferred term
SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Statistical analysis system
SfAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SI	International system of units
SOC	System organ class
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
TP	Tipping point
US	United States

1 INTRODUCTION

1.1 Background

Protocol MDGH-MOX-2002 is a Phase 2, multi-center, placebo-controlled, double-blind, randomized dose ranging study to evaluate the efficacy and safety of orally administered moxidectin in adults with scabies.

This Statistical Analysis Plan (SAP) specifies the planned analyses designed to address the study objectives outlined in clinical study protocol MDGH-MOX-2002 version 3 (including amendments 1 and 2), dated 28 Dec 2023. Where there are discrepancies, this SAP will supersede the statistical methods described in the protocol. This SAP will be finalized prior to unblinding study data for the Day 42 analysis. If the finalized SAP is amended prior to unblinding, amendments will be tracked, documented and a rationale provided for each new version. Deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report. Any analysis performed not prospectively defined in this document will be labeled as post hoc and exploratory.

For further information on study conduct, the reader of this SAP is advised to refer to the protocol and other related documents. The specifications for the Tables, Figures and Listings (TFLs) described in this SAP will be provided in a separate document.

1.2 Changes to Protocol Planned Analyses

The following changes have been made to the planned analyses described in the clinical study protocol MDGH-MOX-2002 Version 3 dated 28 Dec 2023:

- The description of the process for randomization, described under Section 10.1 of the current study protocol, was updated in this SAP Section 5.1. Instead of a unique screening number, a site specific sequential Subject Number was allocated to each subject who provided written informed consent. This Subject Number was used throughout the study to identify the subject. A unique Randomization Number was assigned to the subject upon randomization and this randomization number was only recorded on the Randomization electronic case report form (eCRF) page. Study drug was dispensed according to the Randomization Number, not according to the Subject Number.
- Two additional sensitivity analyses have been included to support the primary efficacy analysis:
    - A Completers Analysis excluding subjects with missing data for the primary endpoint with the exception of subjects exposed to scabicides.
    - An analysis that adjusts for Baseline lesion count as the sole covariate, other than randomized treatment group.
- The protocol states that sensitivity analyses will be conducted to assess the impact of missing data on the results. As such, a tipping point analysis has been included in the SAP.
- A repeat of the primary analysis within each Region will not be conducted due to anticipated small sample size within one of the Regions. However, descriptive analyses of the primary efficacy endpoint stratified by Region will be provided.

- Exploratory pairwise comparisons between each of the moxidectin dose groups have been added.
- For the non-informative missing data, the Complete Cure endpoint may be imputed via a fixed value using the methodology detailed in Appendix 1. Should the missing data due to non-informative reasons be 5% of the total sample size, (approximately 200 subjects), a multiple imputation (MI) approach will be implemented using the methodology detailed in Appendix 2.
- The following additional exploratory endpoints have been included in this SAP that are not otherwise listed in the current study protocol:
    - The Day 28 Complete Cure without regards to pruritus.
    - The proportion of index subjects achieving clearance for each individual component of the Complete Cure endpoint
- Pharmacokinetic (PK) data unblinding and analysis may be performed with the extended safety follow up analysis at Week 16.
- The Pharmacokinetic Analysis Plan described in the current protocol that may have been used to describe population-PK and PK/pharmacodynamic analyses will be replaced by Modelling and Simulation Analysis Plans (MSAP). There will be one MSAP to describe the incorporation of PK data into the moxidectin population-PK model, which will be finalized prior to the Day 42 blind break. Another MSAP will describe the PK/pharmacodynamic analyses and will be finalized after the Day 42 blind break.
- An All Randomized Set and Complete Analysis Set have been defined for the purposes of some descriptive tables or sensitivity analyses.

2 STUDY OVERVIEW

This Phase 2 study is a multinational, multi-center, randomized, double-blind, placebo-controlled efficacy and safety study. This study aims to assess the efficacy of a single oral administration of 8 milligrams (mg), 16 mg, or 32 mg moxidectin in achieving Complete Cure at Day 28. This study also aims to assess the safety of the three strengths of single moxidectin doses in patients aged 18 years and older with scabies.

Approximately 200 index subjects will be randomized in the study across sites in the United States and Latin American regions. Within each region, subjects will be randomized into one of 4 cohorts using an equal allocation ratio for a target of approximately 50 subjects per cohort. The cohorts are:

- Placebo
- Moxidectin 8 mg, single dose
- Moxidectin 16 mg, single dose
- Moxidectin 32 mg, single dose

This study will compare each of the three moxidectin doses to placebo in outpatients aged 18 years and older with scabies without significant comorbidities to assess the efficacy of moxidectin in achieving the primary endpoint of Complete Cure by Day 28. Only one subject will be enrolled per household; where more than one household member is screened for

participation in the study, the enrolled (index) subject will be the youngest eligible member of the household. Complete Cure is defined as a combination of clinical cure (all clinical features of the infestation have resolved) and microscopic or dermatoscopic cure (absence of mites and/or mite products and burrows)

Following randomization and treatment administration of eligible subjects on Day 0, all subjects undergo routine safety follow up on Day 7 and Day 14. Blood samples will be collected on Day 0 at 3 and 10 hours post study drug dose administration for the subjects randomly selected for inclusion in the PK subset. On Day 28, subjects will undergo a thorough full-body clinical and microscopic or dermatoscopic assessment to determine the primary efficacy endpoint, and blood samples will be collected for the subjects in the PK subset, a subset of randomly selected subjects for moxidectin plasma concentration analysis. A complete safety review will also be conducted. If at the Day 28 visit the subject has scabies mites confirmed by microscopy or dermoscopy, or their clinical presentation has significantly worsened from Day 0, the subject will receive standard of care treatment for scabies per local guidelines.

All subjects will return on Day 42 for routine safety follow-up including assessment for adverse events (AEs) and concomitant medications. The final blood sample will be collected from the PK subset on Day 42. Extended safety follow-up will occur for all subjects after Day 42, at a Week 12 and final Week 16 visit.

To meet the study objectives, the final analysis for efficacy, along with the analysis of safety data collected through Day 42, will take place after the last subject has completed the Day 42 visit, and when PK sampling is complete in the PK subset. For the Day 42 analyses, the blind will be broken once data through Day 42 have been cleaned, queries resolved, and the data through Day 42 has been "frozen/locked". This is further detailed in Section 5.2. The blind break will not be added to the clinical trial database but only applied to the Day 42 analysis files. Neither the individual blind break information (e.g., individual treatment assignments) nor the results will be provided to Investigators, study subjects, the clinical management team, or Medical Monitor involved in day-to-day study operations.

Following their Day 42 visit, all subjects will continue to be monitored for safety through the extended safety follow-up period to Week 16. Once the last subject has completed the extended safety follow-up period at Week 16, safety analyses completed for Day 42 safety data will be updated for data collected during the extended safety period. The operational individuals outlined above along with study subjects will remain blinded until subjects complete this extended safety follow up and the extended safety data has been cleaned and the clinical trial database locked

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of the study are:

- To compare the efficacy of a single oral administration of moxidectin for each of the three moxidectin doses to matching placebo with respect to the Day 28 Complete Cure rate.
- To compare the safety of a single oral administration of moxidectin for each of the three moxidectin doses with placebo.

3.2 Secondary Objective

There are no secondary objectives.

3.3 Exploratory Objectives

The exploratory objectives of the study are:

- For each of the three moxidectin doses, determine the Day 28 Complete Cure rate.

In each of the 4 groups determine:

- The Day 28 clinical cure rates,
- The Day 28 combined microscopic and dermatoscopic cure rates,
- The Day 28 Investigator-assessed Cure rates,
- The Day 28 Complete Cure without regards to pruritus,
- The proportion of index subjects achieving clearance for each individual component of the Complete Cure endpoint,
- The concordance between the Complete Cure rate and Investigator-assessed Cure rate,
- The change from Baseline in the total number of lesions at Day 28,

And assess:

- Secondary bacterial infection at Day 28,
- PK of moxidectin in a subset of subjects.

3.4 Estimand

The estimand for each of the primary efficacy hypotheses is the comparison of the Day 28 Complete Cure rate of moxidectin without use of rescue medication versus the Day 28 Complete Cure rate of placebo without use of rescue medication.

The summary of the estimand is shown in Table 1.

Table 1: Summary of Estimand for the Primary Endpoint

Primary Endpoint	Population	Intercurrent event(s)	Handling of Missing Data	Population-Level Summary
The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28.	The Full Analysis Set (FAS) will be the primary analysis set for the primary and, unless otherwise stated, all other efficacy analyses. The FAS is defined as all randomized index subjects receiving study drug. Subjects in the FAS will be analyzed according to the treatment group to which they were randomized.	Index subjects exposed to scabicides prior to Day 28 will be imputed as a non-responder	**Informative missing** will be imputed as non-responders. **Non-informative missing** will be imputed as a non-responder or a responder using either: 1. fixed imputation logistic regression model or 2. multiple imputation if the number of subjects with non-informative missing data is greater than 5% of the total sample size	Marginal Risk Difference for each of 3 moxidectin dose groups versus placebo adjusted for region (United States or Latin America).

4 SAMPLE SIZE DETERMINATION

Approximately 200 index subjects will be randomized into one of four cohorts using an equal allocation ratio. Only one subject will be enrolled per household; where more than one household member is screened for the study, the index subject is the youngest eligible member of the household.

The target sample sizes per randomized treatment group are shown in Table 2. The sample size was selected to address the study's primary efficacy objective.

Table 2: Sample Size by Randomized Treatment Group

Randomized Treatment Group	Target Sample Size
Placebo	N = 50
Moxidectin 8 mg, single dose	N = 50
Moxidectin 16 mg, single dose	N = 50
Moxidectin 32 mg, single dose	N = 50

A sample size of 50 subjects per randomized treatment group will yield an approximate power of 75% for the pairwise comparisons of each moxidectin dose group to placebo assuming a placebo Day 28 Complete Cure rate of 40% or less and a moxidectin Day 28 Complete Cure rate of 70% or more. Power calculations for each pairwise comparison were conducted via a Z test for two independent proportions with pooled variance at a two-tailed adjusted alpha of 0.019. The pairwise adjusted alpha of 0.019 is used to control the familywise error rate (FWER) at an overall two-tailed alpha of 0.05 using a large sample approximation to Dunnett's critical value for the 3 pairwise comparisons of each moxidectin dose group to placebo.

5 RANDOMIZATION AND BLINDING

5.1 Randomization

A unique subject number was allocated to each subject who provided written informed consent. The subject number was allocated sequentially by site. Subjects who failed screening and were approved to be rescreened retained their original subject number.

On Day 0, eligibility was reconfirmed prior to subject randomization using an Interactive Response Technology (IRT) system when each subject was assigned a unique randomization number.

Within the IRT system, the randomization of subjects to treatment is stratified by region (United States [US] and Latin America). Within each region, a permuted block randomization algorithm reflecting an equal allocation ratio among the 4 treatment cohorts of 1:1:1:1 was derived. The algorithm within each region was independent and may consist of randomly varying block sizes. Block sizes were not revealed to sites or Sponsor personnel involved in the conduct of the study. The algorithm was generated by an unblinded statistician who was otherwise independent of the study at the time the code was generated.

A subset of approximately 20 subjects will be randomly selected from each arm to provide sparse blood samples for PK analyses. To ensure the study drug allocation remains blinded, subjects from all arms of the study will be sampled.

5.2 Blinding

Clinic staff, subjects, operational Sponsor personnel and delegates were blinded as to which treatment each subject received until the last subject had completed their Week 16 visit. To maintain the blind, each subject received the same number of capsules, regardless of dose. Any break of the study blind, inadvertent or otherwise, was to be reported to the Sponsor without revealing the actual treatment assignment, as soon as possible. The site nominated an unblinded pharmacist to dispense the investigational medication per the randomization received from the IRT system.

Once all subjects have completed the Day 42 visit, the final analysis of efficacy and safety data collected through Day 42 will be conducted. For these analyses, the blind will be broken once data through Day 42 have been cleaned, queries resolved, and the data through Day 42 has been "frozen/locked". The blind break will not be added to the clinical trial database but only applied to the Day 42 analysis files. Neither the individual blind break information (e.g., individual treatment assignments) nor the results will be provided to Investigators, study subjects, the clinical management team, or Medical Monitor involved in day-to-day study operations. These individuals will remain blinded until subjects complete the extended safety follow up with the Week 16 visit and the extended safety data has been cleaned and the clinical trial database locked.

Members of the Moxidectin for Scabies Project Team may be unblinded at the Day 42 database lock point but will not be involved in oversight of post-Day 42 individual subject data. Details of study personnel who will be unblinded or remain blinded will be captured in a separate document to this SAP.

6 STUDY ENDPOINTS

6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both:

(1) Clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus).

and

(2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.

Complete Cure will be derived from the individual assessments captured on the Day 28 Scabies Assessment eCRF page where:

- Lesion count is 0, and,
- Pruritus is 'Absent', and,
- Mites are 'Absent', and,
- Eggs are 'Absent', and,
- Scybala are 'Absent', and,
- Burrows (by dermoscopy) are 'Absent'.

An index subject will be considered has having achieved Complete Cure at Day 28 if all of the 6 components are either 0 or "Absent" as specified above. If any of the 6 components are missing, whether because the individual component is missed or because the Day 28 visit was missed, the Complete Cure endpoint at Day 28 will be considered missing and the subject will be imputed as a non-responder (not cured). An exception will be made if the missed visit is non-informative. See Section 9.11.2 for further detail on handling missing data for the Day 28 Complete Cure endpoint.

The Day 28 Complete Cure endpoint for subjects exposed to scabicides prior to their Day 28 assessment will also be imputed as a non-responder (not cured). Scabicides are defined as any scabicide, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad used between Day 0 and Day 28. Scabicides do not include products used to manage the symptoms of scabies. Subjects exposed to scabicides as concomitant medications with unknown start dates will also be imputed as non-responders, unless the end date is known and after Day 28.

6.2 Secondary Efficacy Endpoints

There are no secondary efficacy endpoints.

6.3 Exploratory Endpoints

Exploratory endpoints will include but are not limited to, for each of the four treatment groups:

- **The proportion of index subjects demonstrating Clinical Cure without microscopic or dermatoscopic cure at Day 28**

  Clinical Cure is defined as the demonstration that all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus. Clinical cure will be derived from the individual assessments captured on the Day 28 Scabies Assessment eCRF page where:

  - Lesion count is 0, and,
  - Pruritus is 'Absent', and,
  - Burrows (by dermoscopy) are 'Absent'.

  There will be no imputation for this endpoint except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured). The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment.

- **The proportion of index subjects demonstrating Microscopic or Dermatoscopic cure without clinical cure at Day 28**

  Microscopic or Dermatoscopic Cure is defined as the demonstration of the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows. Microscopic or dermatoscopic cure will be derived from the individual assessments captured on the Day 28 Scabies Assessment eCRF page where:

  - Mites are 'Absent', and,
  - Eggs are 'Absent', and,
  - Scybala are 'Absent', and,

- Burrows (by dermoscopy) are 'Absent'.

There will be no imputation for this endpoint except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured). The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment.

- **The proportion of index subjects in each of the three categories of cure assessed by the Investigator at Day 28 (Investigator Assessed Cure)**

  The ***Investigator Assessed Cure*** corresponds to the Investigator selection of one of the three categories below that best describes the cure status of the subject at Day 28:

  1. The scabies infestation is clear with all signs resolved,
  2. The scabies infestation is clear with incomplete resolution of signs, and no additional treatment with standard of care is warranted,
  3. The scabies infestation is not clear and additional treatment with standard of care is warranted.

  There will be no imputation for this endpoint except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured). The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment.

- **The proportion of index subjects with concordant and discordant Day 28 cure rates, as assessed by the Investigator, and the Complete Cure rate**

  For this analysis, an index subject will be considered cured under the Investigator Assessed Cure if either the first or the second category of the assessment is selected. A subject will be considered as not achieving the Investigator Assessed Cure if the third category is selected.

  Concordance between Complete Cure and Investigator Assessed Cure will be defined as achieving cure status for both the primary efficacy Complete Cure endpoint and the Investigator Assessed Cure, or not achieving Cure status by both endpoints. Discordance will be defined as not achieving the same outcome by both endpoints.

  There will be no imputation for either the Complete Cure or Investigator Assessed Cure endpoints, or any of the components of the Complete Cure endpoint, except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured). The denominator for the proportion will be subjects in each treatment group with a non-missing data point for both of the Complete Cure and Investigator Assessed Cure.

- **The mean and median change from Baseline for index subjects in the total number of lesions to Day 28.**

  The change will be calculated as the total number of lesions at Day 28 minus the count at Baseline for each subject.

  There will be no imputation for this endpoint, and only subjects in each treatment group with a non-missing data point for both assessments (Day 0 and Day 28) will be included in the change from Baseline. The exception will be subjects exposed to scabicides prior

to their Day 28 assessment, who will have their Day 0 assessment carried forward to the Day 28 assessment for the purposes of calculating change from Baseline.

- **The proportion of index subjects with secondary bacterial skin infections at Day 28**

  This endpoint is derived from the secondary bacterial infection assessment captured on the Day 28 Scabies Assessment eCRF page where:

  - Secondary bacterial infection is "Present".

  There will be no imputation for this endpoint. The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment, with subjects exposed to scabicides prior to their Day 28 assessment excluded from the analysis.

- **Plasma concentrations of moxidectin in a subset of index subjects selected for sparse PK sampling**

  Approximately 20 subjects from each of the moxidectin cohorts (but not placebo) will be selected for sparse PK sampling. Moxidectin plasma concentrations will be determined at four time points, e.g., Day 0 (3- and 10-hours post-dose), Day 28, and Day 42. No pre-dose sample will be collected. Missing plasma concentrations will not be imputed.

- **The proportion of index subjects demonstrating all features of Complete Cure without regard to pruritus**

  This endpoint is similar in definition as the primary efficacy Complete Cure endpoint except the pruritus component is not included in the definition, e.g.,:

  (1) Clinical cure (all signs and symptoms have completely resolved, including burrows and inflammatory/noninflammatory lesions).

  and

  (2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.

  This will be derived from the individual assessments captured on the Day 28 Scabies Assessment eCRF page where:

  - Lesion count is 0, and,
  - Pruritus is 'Present' or 'Absent', and,
  - Mites are 'Absent', and,
  - Eggs are 'Absent', and,
  - Scybala are 'Absent', and,
  - Burrows (by dermoscopy) are 'Absent'.

  There will be no imputation for this endpoint except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured). The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment.

- **The proportion of index subjects achieving clearance for each individual component of the Complete Cure endpoint**

  This endpoint will examine each of the assessments captured on the Day 28 Scabies Assessment eCRF page individually. Subjects may be included in more than one component.

  - Lesion count is 0, or,
  - Pruritus is 'Absent', or,
  - Mites are 'Absent', or,
  - Eggs are 'Absent', or,
  - Scybala are 'Absent', or,
  - Burrows (by dermoscopy) are 'Absent'.

  There will be no imputation for this endpoint except for subjects exposed to scabicides prior to their Day 28 assessment, who will be imputed as a non-responder (not cured) for each individual component. The denominator for the proportion will be subjects in each treatment group with a non-missing data point for this assessment.

6.4 Safety Endpoints

- Incidence and severity of treatment emergent adverse events (TEAEs).
- Incidence of serious TEAEs.
- Incidence of TEAEs leading to study withdrawal and/or death.
- Incidence of TEAE attribution of relatedness to study drug.
- Changes from Baseline in 12-lead electrocardiograms (ECGs), laboratory assessments and vital signs.

Unless otherwise noted incidence refers to subject incidence.

7 DEFINITIONS

Terminology	Definitions
Age	Age will be calculated based on the month and year of birth entered in the Demography eCRF page, relative to the month and year of informed consent.
Baseline	The last non-missing assessment immediately prior to exposure to study drug
BMI	Body Mass Index, calculated as 'Weight (kg)/(Height (m))^2 (kg/m^2).
Clinical Cure	Demonstration that all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus.
Complete Cure	Demonstration of both: (1) Clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus). and

Terminology	Definitions
	(2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.
Complete Cure without regard to pruritus	Similar definition as Complete Cure except the pruritus component is not included in the definition, e.g., (1) Clinical cure (all signs and symptoms have completely resolved, including burrows and inflammatory/noninflammatory lesions). and (2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.
Concomitant Medication	Medication taken on the day of or after the first study drug exposure. Concomitant medication may start prior to study drug administration if continued on the day of/after study drug administration.
Dispensing Error	The subject was dispensed less than or more than 16 capsules of moxidectin and/or placebo, but received the assigned treatment
Dosing Error	The subject was dispensed 16 capsules of moxidectin and/or placebo, but did not receive the assigned treatment
Dosing and Dispensing Error	The subject was dispensed less than or more than 16 capsules of moxidectin and/or placebo, and also did not receive the assigned treatment
Investigator Assessed Cure	Investigator selection of one of the three categories below that best describes the cure status of the subject at Day 28: 1. The scabies infestation is clear with all signs resolved, 2. The scabies infestation is clear with incomplete resolution of signs, and no additional treatment with standard of care is warranted, 3. The scabies infestation is not clear and additional treatment with standard of care is warranted.
Microscopic or Dermatoscopic Cure	Demonstration of the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.
Randomized	A participant is considered randomized once the assignment of a Randomization Number for study MDGH-MOX-2002 is complete.
Scabicide	Scabicides are defined as any scabicide, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad used between Day 0 and Day 28. Scabicides do not include products used to manage the symptoms of scabies.
Screen Failure	Individuals who gave informed consent to screening but were not randomized.
Screened	Individuals who gave informed consent to screening.
Day 42 Completer	Subjects who completed the Day 42 visit in-clinic
Study Completer	Subject who completed the End of Study (Week 16) visit in-clinic.
Study Day	References to Study Day refer to the pre-specified visits defined in the protocol, where Day 0 is defined as the date subject was exposed to study drug. For randomized participants who do not receive study drug their Day 0 date will be their date of randomization. Study Day for events post Day 0 will be calculated as Event Date – Day 0 Date.

Terminology	Definitions
	Study Day for events prior to Day 0 will be calculated as Day 0 Date – Event Date.
Study drug-related TEAE	Any TEAE which the investigator considered definitely, probably, or possibly related to study drug.
Study drug-unrelated TEAE	Any TEAE which the investigator considered unlikely to be or unrelated to study drug.
TEAE	Adverse event with an onset date on or after the date of study drug administration or an adverse event present before the administration of study drug that increases in severity.

8 ANALYSIS POPULATIONS

The analysis populations to be used for the efficacy and safety analyses are described below.

8.1 All Randomized Set

The All Randomized Set is defined as all subjects who were randomized irrespective of whether they received the study drug. Unless otherwise noted, the All Randomized Set will be the analysis set for subject disposition and protocol deviations.

A listing will be provided for All Randomized subjects to identify which analysis populations subjects are excluded from and the reason why.

8.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized index subjects receiving study drug. Subjects in the FAS will be analyzed according to the treatment group to which they were randomized. The FAS will be the primary analysis set for the primary and, unless otherwise stated, all other efficacy analyses.

8.3 Safety Analysis Set

The Safety Analysis Set (SfAS) will include all index subjects exposed to study drug. Subjects will be analyzed according to the actual study drug received regardless of their randomized treatment group. Unless otherwise noted, the SfAS will be used for all safety analyses.

8.4 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will include all index subjects exposed to study drug without any major protocol deviations that could confound the assessment and/or interpretation of the efficacy results. These protocol deviations will be identified by the study team prior to breaking the study blind for the Day 42 analysis. Subjects in the PPAS will be analyzed according to the actual treatment received regardless of their randomized dose group. Unless otherwise stated, the PPAS will be used for sensitivity analyses for the primary efficacy analysis.

8.5 Complete Analysis Set

The Complete Analysis Set will include all FAS subjects, except those FAS subjects exposed to scabicides prior to Day 28 and any FAS subject with a missing Day 28 Complete Cure assessment (including if any of the individual components of the Complete Cure endpoint is missing).

8.6 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will include all index subjects who received at least one dose of moxidectin and provided at least one quantifiable post-dose plasma PK concentration.

9 STATISTICAL METHODS OF ANALYSIS

9.1 General Analytic and Reporting Principles

The results of the statistical analyses will be reported using summary tables and figures, with all data reported as listings. All analyses will be performed using SAS Version 9.4 or later.

Data will be summarized in tabular form by dose group in order of ascending dose (moxidectin 8 mg, moxidectin 16 mg, moxidectin 32 mg), placebo and overall subjects.

Summary statistics for continuous variables will consist of the number of non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum, unless specified otherwise. Summary statistics for categorical variables will include the number (count) and percentage of subjects. In general, the percents will be calculated using the denominators for each treatment group within the analysis population being considered. Percentages based on other denominators will be noted. If relevant, tabulations of categorical data will include all categories captured on the eCRF even if no observations in the database appear in those categories. In this situation a '0' will be inserted. For certain categorical variables the number of participants with missing data may also be provided; however, the number missing will not be included in the calculations of percentages.

For proportions, asymptotic Wald confidence intervals (CIs) will be calculated. When the normal approximation may not hold, exact CIs may also be calculated. Confidence intervals based on bootstrapped standard errors (SEs) will be flagged in tables if relevant.

No preliminary rounding will be performed. Any rounding will only occur after analysis for the purposes of data presentation.

For any analyses using a randomized component such as bootstrapped statistics or permutation tests, the randomization seeds used to produce the analysis will be saved and documented to enable the results to be reproducible.

9.1.1 Final Efficacy Analysis at Day 42

After the last subject has completed their Day 42 visit, the efficacy and safety data collected through Day 42 will be cleaned and a frozen/locked snapshot of the data will be made available for analysis. The Day 42 analysis will include the final analysis of the study's primary efficacy endpoint, the Complete Cure rate at Day 28, and other Day 28 exploratory efficacy endpoints. As no further efficacy data is collected beyond Day 28, these efficacy analyses will be considered final even though the study will continue to collect safety data through Week 16. In addition to the Day 28 efficacy data, the Day 42 analysis will also include the analysis of safety through Day 42. PK data, although collected up to and including Day 42, may be analyzed in the Week 16 analysis.

9.1.2 Extended Follow Up at Week 16

The additional safety data collected from Day 42 through Week 16, the extended safety follow up period, will be analyzed after the last subject has completed their Week 16 visit and the study has completed. The Week 16 analysis will be a rerun of selected outputs only where additional information was captured after the Day 42 visit. These additional data may include protocol

deviations, disposition (including completions and withdrawals), AEs, concomitant medications, physical examinations, vital signs, and pregnancy testing. For these data, the summary tables may include the Day 42 results from the Day 42 analysis summarized above, the extended follow up at Week 16 results for data collected after the Day 42 visit through Week 16, and a total summary that combines all data from randomization through Week 16. If the PK analysis is not run at Day 42, then the Week 16 outputs will include PK data summaries.

9.2 Multiplicity Adjustments

The three primary efficacy hypotheses to be tested are the comparison of the Day 28 Complete Cure rates (proportions) for each of three moxidectin dose groups to the placebo. As such, statistical significance will be based on a Dunnett adjusted two-tailed alpha level of 0.019 to account for the multiplicity of the three primary efficacy analyses and maintain a FWER of 0.05. For each comparison Wald type 95% CIs incorporating Dunnett's critical value. See Section 9.11.1 for the SE calculation to be used for the 95% CIs.

Other than those specified above, there will be no other multiplicity adjustments.

9.3 Interim Analysis

No interim analyses will be conducted for efficacy. The final analysis for efficacy will take place after the last subject has finished their Day 42 visit as described in Section 9.1.1.

9.4 Handling of Partial Dates

9.4.1 Investigational Product Administration

If the date of study drug administration is missing, the randomization date will be considered as the date of study drug administration. Line listings will flag any imputed study drug administration dates.

Partial dates or missing time of administration are not possible based on the mandatory fields configured in the eCRF.

9.4.2 Adverse Events and Prior and Concomitant Medications

Dates will not be imputed for Adverse Events or Medical History events. The sites were responsible for imputing start and end dates for TEAEs.

Prior and concomitant medications may have unknown start or end dates. The site makes the determination of whether the medication is a prior or concomitant medication when they enter the medication onto the Prior Medication or Concomitant Medication eCRF page. Partial or unknown dates are not imputed.

Medications entered into the Prior Medication eCRF page with a partial or unknown stop date will be analyzed as both prior and concomitant medications, unless the stop date is a month and/or year combination prior to the study drug administration date.

Subjects exposed to concomitant medications that are scabicides with unknown start dates will be imputed as non-responders, unless the end date of administration is known and is after Day 28.

9.5 Subject Disposition

The subject disposition summary will present the number (%) of subjects (as appropriate) who were:

- Screened (Number [N] only)
    - Screen Failures (n, % N Screened)
    - Reason for screen failure: not meeting eligibility criteria by eligibility criterion (n, % N Screen Failures)
- All Randomized (%, N Screened)
    - No exposure to study drug (n, % N All Randomized)
    - Exposed to study drug (n, % N All Randomized)
    - Full analysis set (n, % N All Randomized)
    - Per protocol analysis set (n, % N All Randomized)
    - Complete analysis set (n, % N All Randomized)
    - Safety analysis set (n, % N All Randomized)
    - PK Analysis Set (n, % N All Randomized)
    - Day 42 Completers (Day 42 summary only, n, % N All Randomized)
    - Subjects who prematurely discontinued the study prior to the Day 42 visit (Day 42 summary only, n, % N All Randomized)
    - Reasons for discontinuation prior to the Day 42 visit (Day 42 summary only, n, % N subjects who discontinued)
    - Week 16 Completers (Week 16 summary only, n, % N All Randomized)
    - Subjects who prematurely discontinued the study prior to the Week 16 visit (Week 16 summary only, n, % N All Randomized)
    - Reasons for discontinuation prior to the Week 16 visit (Week 16 summary only, n, % N subjects who discontinued)
    - Last scheduled assessment (Day 42 and Week 16 summaries, n, % N All Randomized)

Percent calculations with "N All Randomized" as the denominator will be calculated by randomized treatment group and overall. Subject disposition data will be presented in line listings. Subjects in the All Randomized set will be included in the disposition line listings.

9.6 Protocol Deviations

A blinded review of protocol deviations documented during the study will be completed prior to the database freeze/lock and blind break for the Day 42 analysis. Protocol deviations are categorized at the time of entry into the Protocol Deviation eCRF page, but categorization will be reviewed during blinded review of all protocol deviations, and they will also be classified as major/minor:

- Consent procedures
- Inclusion/exclusion criteria
- Randomization procedures

- Concomitant medication/therapy
- Study procedures
- Serious adverse event (SAE) reporting
- Dosing
- Unblinding
- Scabies Assessment outside the Day 28 Visit Window
- Other Visit schedule/ interval
- COVID-19 related
- Other

Major protocol deviations will be defined as deviations that could potentially have a meaningful impact on the efficacy or safety results. Subjects with major protocol deviations that might impact efficacy will be excluded from the PPAS.

Some categories of major protocol deviations that might be considered as having a meaningful impact on the efficacy results include but are not limited to:

- Subjects failing any eligibility criteria,
- Subjects with treatment administration errors,
- Subjects randomized but not exposed to study drug (exclusion from FAS, PPAS, SfAS), and PK,
- Significant non-compliance with specified study visits windows,
- Administration of scabicides prior to the Day 28 visit (note: the exposure to scabicides prior to Day 28 is considered a major protocol deviation and subjects will be considered non-responders for the primary analysis

Protocol deviations leading to missing data will also be reviewed to assess the reasons why the data are missing and whether they are considered informative or non-informative reasons for the purposes of handling of missing data described in Section 9.11.2. Where the reason(s) for missing data is unknown and/or not fully documented, the default will be to assume informative missing. Examples of non-informative missing data might be:

- Missed visit due to weather, travel, or childcare,
- Missed visit due to COVID-19 or COVID-19 exposure,
- Missed assessment due to equipment failure.

All determinations of informative and non-informative missing data will be fully documented and reported.

Prior to the Week 16 analysis, another blinded review will be conducted to assign deviations to the same categories listed above for deviations that occurred after Day 42 during the Extended Safety Follow Up period. Although unlikely, it is possible that a protocol deviation, or another issue, that might impact the final efficacy analysis conducted earlier at the Day 42 analysis, is discovered during the protocol deviation review of data collected during the extended safety

follow up. Should this be the case, the Sponsor will describe the error, the circumstances of the discovery, and an assessment of what impact, if any, it might have on the interpretation or conclusion of the final Day 28 efficacy analyses.

Summary tables describing the number and percent of subjects in each protocol deviation category for major deviations will be tabulated by randomized treatment group for all randomized subjects regardless of exposure to study drug. Subjects may be included in more than one category. If a major protocol deviation trend is identified in the 'Other' category and cannot be classified in an already identified category above, then an additional category will be defined at the time of analysis. All protocol deviations will be provided in line listings and include their category and major/minor classification.

9.7 Investigational Product Exposure and Treatment Compliance

Investigational product exposure and treatment compliance will be summarized by treatment group and overall for the All Randomized Set. The summary statistics will include:

- Subjects not dosed (n, % All Randomized)
- Subjects compliant with treatment (subjects swallowing all 16 capsules and the number of moxidectin capsules dispensed corresponds to the treatment assignment, n, % All Randomized)
- Subjects non-compliant with treatment:
    - Subjects with dosing errors (the number of moxidectin capsules does not correspond to the treatment assignment but the subject received 16 capsules overall, n, % All Randomized)
    - Subjects with dispensing errors (the number of capsules overall is not equal to 16, but the number of moxidectin capsules corresponds to the treatment assignment, n, % All Randomized)
    - Subjects with dosing and dispensing errors (the number of capsules overall is not equal to 16 and the number of moxidectin capsules does not match the treatment assignment, n, % All Randomized)
    - Subjects who did not swallow all 16 capsules (n, % All Randomized)

Study drug administration will be listed for the All Randomized Set.

9.8 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline data will be presented by randomized treatment group and overall for all participants included in the FAS. Should the number of participants randomized but not receiving study drug support aggregate tables by randomized treatment group, these tables may be repeated for this subgroup of participants.

9.8.1 Baseline Demographic Characteristics

Descriptive statistics of demographic data will be reported for FAS subjects by randomized treatment group and overall:

- Age (years) (note: age is derived from year of birth per the formula described in the SAP Definitions Table),
- Age groups

    - 18 to 64 (n, % FAS)
    - ≥ 65 (n, % FAS)
- Sex (n, % FAS),
- Race (n, % FAS),
- Ethnicity (n, % FAS)
- Region
    - United States (n, % FAS)
    - Latin America (n, % FAS)
- Height at Screening (cm)
- Weight at Screening (kg)
- BMI at Screening (kg/m2) (note: BMI is derived from height and weight per the formula described in the SAP Definitions Table)
- BMI categories
    - Underweight (BMI < 18.5 kg/m2) (n, % FAS)
    - Healthy weight (≥ 18.5 kg/m2, < 25 kg/m2) (n, % FAS)
    - Overweight (≥ 25 kg/m2, < 30 kg/m2) (n, % FAS)
    - Obese (≥ 30 kg/m2) (n, % FAS)

Descriptive statistics may be repeated if the difference between the All Randomized Set and FAS support aggregate tables by randomized treatment group for this subgroup of subjects.

Additionally, the above demographic characteristics will be repeated and stratified by region, summarized by randomized treatment group and overall.

Demography will be listed for all subjects in the FAS.

9.8.2 Baseline Scabies Disease Characteristics

Descriptive statistics will be reported for the following scabies assessment characteristics at baseline (Day 0) for FAS subjects by randomized treatment group and overall:

- Number of lesions
- Scabies Severity:
    - Mild (≤ 10 lesions) (n, % FAS)
    - Moderate (11 to 49 lesions) (n, % FAS)
    - Severe (≥ 50 lesions) (n, % FAS)
- Diagnosed method
    - By microscopy (n, % FAS)
    - By dermoscopy (n, % FAS)

- Evidence of burrows (n, % FAS)
- Evidence of pruritus (n, % FAS)
- Evidence of nodules (n, % FAS)
- Evidence of mites (n, % FAS)
- Evidence of eggs (n, % FAS)
- Evidence of scybala (n, % FAS)
- Day 0 Method of assessment for mites, eggs, and scybala
    - Microscopy of skin scrapings (n, % FAS)
    - Dermoscopy (n, % FAS)
- Evidence of secondary bacterial infection (n, % FAS with secondary bacterial infection present)
- Number of body regions affected

Should the number of subjects randomized but not receiving study drug support aggregate tables by randomized treatment group, these tables may be repeated for this subgroup of subjects.

Additionally, the above scabies assessment characteristics will be repeated and stratified by region, summarized by randomized treatment group and overall.

Disease characteristics at Baseline and Day 28 will be listed.

9.9 Medical History

Medical history events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version in place at the time of analysis. The version of MedDRA used will be indicated in the data summaries and listings.

The number and percentage of subjects with medical history events will be presented by system organ class (SOC), and preferred term (PT) in the All Randomized set, where SOC and PT will be presented in decreasing frequency of the total number of subjects with medical history events. The number and percentage of subjects with a history of any previous scabies infections will be included in the tabulation. The treatments used (permethrin cream, ivermectin or other) used by subjects with a prior history of scabies infection will be included in the tabulation. All events will be listed.

9.10 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) and will be classified according to the default anatomical therapeutic chemical (ATC) code classification and PT. The version of WHODD used will be indicated in the data summaries and listings.

Prior medications are defined as medications with a stop date prior to the start of study drug administration. Prior medications should be entered on the ‘Prior Medication’ form of the eCRF. Medications that are ongoing at the administration of study drug or started after the time of administration of study drug will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, the medication will be assumed to be concomitant.

Prior and concomitant medications will be summarized separately in the same tabulation, displaying n (%) of FAS subjects for each dose group by ATC class and PT. Prior medications that are continuing at the start of the study (flagged as 'ongoing' or with a stop date after randomization) will be analyzed and reported in both the prior medications and concomitant medications categories. See Section 9.4.2 for additional detail.

Subjects may have more than one medication per ATC class and PT. At each level of subject summarization, a subject will be counted only once if one or more medications are reported by the subject at the same level. ATC class and PT will be presented in decreasing frequency of the total number of subjects with medications.

All prior and concomitant medications will be provided in line listings.

The collection of concomitant medications continuing, ending or starting during the extended safety follow-up to Week 16 will also be described.

9.11 Efficacy Analysis

9.11.1 Primary Efficacy Analyses: Superiority of Moxidectin to Placebo – Day 28 Complete Cure Rate

The three primary efficacy hypotheses to be tested are the comparison of the Day 28 Complete Cure rates (proportions) for each of three moxidectin dose groups to the placebo group adjusted for region. Each analysis will be conducted as a test of superiority for the marginal risk difference adjusted for region using the standardized estimator as outlined by Steingrimsson et al (2017). The standardized estimator estimates the average treatment effect using logistic regression with treatment group and region as main effects and Day 28 Complete Cure as the outcome variable. Predicted probabilities for Day 28 Complete Cure for each treatment group are generated for all FAS subjects regardless of their actual randomized treatment group but using their actual region values. The predicted probability of Day 28 Complete Cure for each treatment group across all subjects are then averaged and the difference in these averages is the standardized estimator for the marginal risk difference adjusted for region. The randomization seeds used to produce the analysis will be saved and documented to enable the results to be reproducible

Statistical significance will be based on a Dunnett adjusted two-tailed alpha level of 0.019 to account for the multiplicity of the three primary efficacy analyses and maintain a FWER of 0.05. For each comparison Wald type 95% CIs incorporating Dunnett's critical value will also be calculated using the bootstrapped SE for the adjusted risk difference as suggested by Steingrimsson et al (2017). Should the bootstrap fail due to a small number of subjects in one of the two regions, the primary analysis will pool all subjects across regions (not adjust for region) and conduct the analysis using a Z-test for two independent proportions with pooled variance. Wald 95% CIs with unpooled variance incorporating Dunnett's critical value will also be provided. These analyses will be conducted using the FAS.

As supportive analyses, the Day 28 Complete Cure rates for each moxidectin group and placebo, as well as the risk difference and 95% CIs for each pairwise comparison, will be calculated within each region. For these region subgroup analyses the proportion of index subjects achieving a Day 28 Complete cure for each randomized treatment group within region will be the unadjusted proportions with Wald 95% CIs for a single proportion. The 95% CI for the risk difference will be the Wald CIs for the difference between two independent proportions using the unpooled variance. Any significance test of the risk difference conducted within region will

be viewed as supportive and exploratory due to the potential lack of power. The 95% CIs and any hypothesis tests for these supportive analyses will not be adjusted for multiplicity.

See Appendix 3 for specification of the logistic model and bootstrapping.

9.11.2 Handling of Missing Data for the Primary Analysis of Day 28 Complete Cure

For the Day 28 Complete Cure endpoint, subjects exposed to rescue medication (scabicides, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad) prior to the Day 28 assessment will be imputed as a non-responder. If a subject is exposed to a scabicide as a concomitant medication with an unknown start date, they will also be imputed as a non-responder unless the end date is known and is after Day 28. Additionally, subjects with missing Day 28 Complete Cure assessments due to missed visits or incomplete scabies assessments at Day 28 will also be imputed as non-responders. An exception would be if the missing Complete Cure endpoint was missing for reasons deemed as non-informative i.e. the Day 28 visit was missed because weather conditions prevented travel. For the non-informative missing data, the Complete Cure endpoint may be imputed via a fixed value using the methodology detailed in Appendix 1. Should the missing data due to non-informative reasons be greater than 5% of the total sample size (approximately 200 subjects), a multiple imputation approach will be implemented, see Appendix 2.

The determination of the use of rescue medication as well as informative vs non-informative missing data will be conducted prior to the blind break for the Day 42 analysis, see Section 9.6.

A subject line listing for subjects with imputed values for the primary efficacy endpoint will be provided. The line listing will include the randomized treatment group, the imputed value, observed value (if relevant), the reason for imputation (use of rescue medication, missed visit, incomplete scabies assessment etc.), and the type of imputation (non-responder, fixed value, multiple imputation). Note for any endpoint values imputed via multiple imputation the imputed value in the line listing will remain blank.

9.11.3 Sensitivity Analyses for Primary Analysis of Day 28 Complete Cure

9.11.3.1 PPAS and Complete Data Analyses

Sensitivity analyses for the above primary efficacy analysis will be conducted using the same methodology outlined above for the primary efficacy analysis. The first sensitivity analysis will repeat the primary efficacy analysis using the PPAS. The second sensitivity analysis will repeat the primary efficacy analysis for the Complete Analysis Set.

9.11.3.2 Tipping Point Analysis

A tipping point (TP) analysis will be conducted to determine the sensitivity of the primary efficacy result, if positive, to various patterns of outcomes in subjects with missing Day 28 Compute Cure endpoints. Initially, the first TP iteration will be to make a worst-case assumption that all subjects imputed as non-responders in the placebo group for the primary analysis are now imputed as responders for the first TP iteration. Conversely, all subjects in each of the moxidectin groups who were imputed as non-responders in the primary analysis remain non-responders in the first TP iteration. If the pairwise comparisons that were significant for the primary analysis continue to be statistically significant for this first “worst case” iteration, it may be assumed that an analysis using the true, but unknown, missing data would also be statistically significant.

If the “worst case” iteration fails to reject the null hypothesis for a pairwise comparison that was significant in the primary analysis, then the TP analysis will continue to determine how much the non-significant “worst case” iteration will need to be “relaxed” to achieve statistical significance. That is, one-by-one the imputed non-responders in the placebo group who were switched to a responder in the “worst case” iteration, will be switched back to their original non-responder status while the imputed non-responders in the moxidectin groups continue to be non-responders for all further TP iterations.

For example, if there were 8 imputed non-responders in the placebo group for the primary analysis, all 8 will simultaneously be considered responders for the worst-case iteration. If the worst-case iteration is non-significant, then the next TP iteration will switch one of the 8 participants back to a non-responder, re-run the primary analysis and calculate the adjusted p-value for each pairwise comparison of moxidectin to placebo. If this TP iteration is still non-significant a third TP iteration will be run where a second subject among the 8 is switched back to their original non-responder status – a total of 2 of 8 such subjects for the third TP iteration. At the 8th iteration, all the 8 subjects in the placebo group who were imputed non-responders will have been switched back to their original non-responder status. Since the imputed non-responders in the moxidectin groups remain non-responders regardless of iteration, in this hypothetical example, the 8th iteration would reflect an analysis where all imputed non-responders remain non-responders which is essentially the primary analysis.

The iteration prior to the first statistically significant result favoring moxidectin will be considered the TP for that particular pairwise comparison. It is recognized that this process does not examine all possible combinations of success/failure outcome iterations for all treatment groups; however, a TP analysis that sequentially iterates outcomes away from the worst case toward the outcomes imputed for the primary analysis should provide insight as to how robust the primary results are to missing data.

Since the primary analysis uses a method that produces a marginal risk difference in proportions adjusting for region, it is noted that region may differ among subjects in the original imputed non-responder subgroup. Hence, for each successive TP iteration following the worst-case analysis described above, the subject in the randomized placebo group, whose outcome will change from success to failure and be added to the cumulative number of subgroup subjects who already switched at previous TP iterations, will be randomly selected from the non-responder subgroup pool who have not yet been randomly selected from the placebo group at previous iterations.

For this TP sensitivity analysis, the analytic method used for the primary analysis will be repeated. If the primary analysis could not be adjusted for region due to small sample sizes in some stratified treatment groups, then the TP sensitivity analysis will not adjust for region either. Also, only those moxidectin dose groups that were statistically significant to placebo in the primary analysis will be included in the TP sensitivity analysis.

The imputed success/failure outcome used in the primary analysis will remain unchanged throughout the TP analyses for subjects whose outcome was missing due to non-informative reasons

9.11.4 Exploratory Analyses of the Primary Endpoint

9.11.4.1 Pairwise Comparisons Between the Three Moxidectin Dose Groups

An exploratory analysis comparing each of the 3 moxidectin dose groups to each other with respect to Complete Cure will also be conducted. These pairwise comparisons will be conducted using the same analysis used for the primary analysis as described in Appendix 3. For these pairwise comparisons, no p-values will be calculated, only the 95% CIs for the pairwise Risk Differences will be provided. Additionally, unlike the pairwise comparisons conducted for the primary analysis, the 95% CIs for these exploratory pairwise comparisons will not be adjusted for multiplicity.

9.11.4.2 Adjustment for Baseline Lesion Count

An additional exploratory sensitivity analysis will assess the risk difference between each moxidectin dose group versus placebo after adjusting for Baseline lesion count. The analysis will use the same methodology for the primary analysis with appropriate imputations, but the logistic model will include randomized treatment group and Baseline lesion count. Region will be excluded from the model to keep the number of covariates small relative to the FAS sample size. Baseline lesion count will be categorized into three groups. The three baseline lesion groups are:

- Subjects with ≤ 10 lesions
- Subjects with 11 to 49 lesions
- Subjects with ≥ 50 lesions

In the model, dummy variables will be created for the lesion count categories using the subjects with ≤ 10 lesions category as the reference group. Each of the individual group proportion of FAS subjects achieving Day 28 Complete Cure and the three pairwise risk differences of each moxidectin group compared to placebo will be presented adjusting for Baseline lesion count. The 95% CIs will be displayed for each of the adjusted point estimates. The p-values for the risk differences will also be provided. This analysis will not be adjusted for multiplicity.

An additional sensitivity analysis will include the continuous metric for Baseline lesion count as a covariate after taking the natural log for each subject's Baseline count. The logistic model will then only include randomized treatment group and the logged Baseline lesion counts. The point estimates, CIs, and p-values described above will be presented adjusting for the continuous log transformed Baseline lesion count. Additional *ad hoc* analyses may be conducted to further explore the relationship between Baseline lesion count and Complete Cure.

9.11.5 Analysis of Exploratory Endpoints

Exploratory endpoints will be analyzed and summarized using the FAS unless otherwise indicated. The exploratory endpoints will be assessed using descriptive summaries. However, if deemed of interest following review of the summaries, further analyses of these endpoints may be conducted and will considered post-hoc. None of the exploratory endpoint analyses will be adjusted for multiplicity.

9.11.5.1 Proportion of Subjects Reporting Day 28 Cure Rates

For FAS subjects, summary statistics for the exploratory endpoints listed below by randomized treatment group and overall will be provided. The definitions of each of the variations of cure endpoint are provided in Section 6.3. There will be no adjustment for region:

- Complete Cure, (n, % FAS)
- Clinical Cure, (n, % FAS)
- Microscopic or Dermatoscopic Cure, (n, % FAS)
- Complete Cure without regard to pruritus (n, % FAS)
- Investigator Assessed Cure:
    - The scabies infestation is clear with all signs resolved, (n, % FAS)
    - The scabies infestation is clear with incomplete resolution of signs, and no additional treatment with standard of care is warranted, (n, % FAS)
    - The scabies infestation is not clear and additional treatment with standard of care is warranted, (n, % FAS)

Along with the number and percent (proportion), the 95% CIs intervals for each treatment group and overall will also be provided. For each of the endpoints, the missing data and imputation methods are outlined under Section 6.3. In general, no imputation will be conducted except for subjects exposed to scabicides. The analysis will be conducted using the FAS.

Additionally, the table will be repeated with stratification by region, summarized by randomized treatment group and overall.

9.11.5.2 Concordance Between Complete Cure and Investigator Assessed Cure

The number and percent of subjects with concordant outcomes for the Complete Clinical Cure and Investigator Assessed Cure, as defined in Section 6.3, will be presented by randomized treatment group and overall. For each group and overall, there will be two concordant and two discordant outcome pairs, each pair corresponding to a cell in a 2x2 table. The results for each of the four outcome pairs will be provided. The Kappa statistic, a measure of agreement corrected for chance agreement, and its p-value, will also be calculated.

The analysis will be conducted using only FAS subjects with non-missing data.

9.11.5.3 Change From Baseline in Lesion Counts

Aggregate summary statistics for lesion counts will be provided by randomized treatment and overall using the FAS. For this analysis, descriptive statistics will be provided for the Baseline count, the Day 28 count, the change from Baseline difference and percent change from Baseline. Summary statistics will include the means, medians, SDs, minimums and maximum values and the number of non-missing FAS subjects in each calculation. The analysis will consist of observed data only with no imputation; however, subjects who used scabicides prior to their Day 28 visit will have their Day 0 value carried forward.

9.11.5.4 The Proportion of Subjects with Secondary Bacterial Skin Infections at Day 28

This analysis will present the number and percent (proportion) of index FAS subjects with secondary bacterial skin infections at Day 28. Only FAS subjects with observed data will be included in the analysis. There will be no imputation, and subjects receiving scabicides will be excluded from the analysis.

9.11.5.5 Plasma Concentrations of Moxidectin

Listings of individual moxidectin concentration versus time data by treatment group for each of the four collection timepoints will be provided for the Pharmacokinetic Analysis Set, showing any below the limit of quantification (BQL) and missing samples. Aggregate summary statistics for moxidectin concentration versus time data by dose for each of the four collection timepoints will be reported in tabular format. The number of observations, number of observations BQL, arithmetic mean (referred to as mean), median, SD, coefficient of variation (CV), minimum, maximum, geometric mean, geometric SD and geometric CV will be provided.

Individual moxidectin concentration data will also be used for population-PK and PK/pharmacodynamic analyses, which are outside the scope of this SAP. Further details pertaining to these analyses are outlined in separate MSAPs and the outcomes of the analyses will be reported separately.

9.11.6 Subgroup Analyses

Descriptive summaries for the primary efficacy endpoint (unadjusted for region) will also be provided for the following subgroups:

- Region
- Age (18 to 64 and ≥ 65)
- Gender
- Race
- Ethnicity
- Method of parasitological assessment at Baseline (microscopy or dermoscopy)
- Scabies Severity:
    - Mild (≤ 10 lesions)
    - Moderate (11 to 49 lesions)
    - Severe (≥ 50 lesions)
- Clinical Site (US sites that enroll less than 5 subjects will be pooled)

9.11.7 Extent and Pattern of Missing Data

The extent and pattern of missing data will focus on the primary efficacy endpoint, Complete Cure at Day 28. The number and percent of FAS subjects with imputed values for this endpoint will be provided by randomized treatment group and overall as well as by region. In addition to the endpoint, the number and percent of subjects missing each of the components from which the endpoint is derived will also be presented. A summary of the number and percent of subjects missing the Complete Cure primary endpoint due to a missed visit or one or more missing endpoint components will also be summarized.

9.12 Safety Analysis

The analysis of safety will include TEAEs, vital signs, physical exams, clinical laboratory assessments using the SfAS. The analysis of safety will be descriptive; however, statistical models and/or hypothesis testing may be conducted if determined to be helpful in the

interpretation of the results. All post hoc safety analyses will be identified as such. Summary data will be provided for each treatment cohort and overall. No safety data will be imputed.

It is anticipated that the overwhelming majority of participants will receive their planned dose of study drug; however, it is possible that dosing errors may result in some participants receiving the wrong study drug dose. Should this occur, a summary of the number and percent of participants with dosing errors resulting in the receipt of the incorrect study drug dose will be provided.

If multiple measurements within a time interval were taken, the last value taken within that time interval will be used. If the last value within the time interval cannot be determined, the worst value within the time interval will be used. All recorded values, including repeated measurements, will be included in listings. Values out of the normal range for the site will be flagged in the listings.

For participants in the SfAS, events occurring after signing of informed consent/assent but prior to the first exposure to study drug (i.e. non-TEAEs) will be provided in line listings only.

9.12.1 Adverse Events

9.12.1.1 General Principles

All AEs will be coded by primary SOC and PT according to the latest version of MedDRA.

The analysis of AEs will focus on TEAEs. TEAE summary tables will provide summaries of the number and percentage of subjects reporting an AE by SOC and PT. When multiple AEs are reported within an SOC/PT category by a subject, the AE will be included only once per subject per SOC/PT category (subject incidence). For severity, if a subject reports multiple events per SOC/PT over more than one severity category, the event with the highest severity will be reported. Similarly, for study drug relationship, if multiple events are recorded per category, the event with the highest attribution to study drug recorded per subject /category will be reported in the summary tables.

If the severity of AE is not reported, the event will be classified as a Grade 3 (severe) event and clearly footnoted. Imputed severities will also be noted in line listings with the observed and imputed values.

If the relationship to the study drug is not reported for an AE, the event will be assigned a relationship of ‘definite’ in tables of study-drug related AEs and clearly footnoted. Tables presenting related AEs will include all AEs with relationships of ‘possible’, ‘probable’, or ‘definite’ as assessed by the Investigator, or defined as ‘definite’ when no investigator assessment is made. Imputed relationships to study drug will also be noted in line listings with the observed and imputed values.

9.12.1.2 Missing or Partial Adverse Event Dates

Refer to Section 9.4.2.

9.12.1.3 All TEAEs

An overall summary table of TEAEs will be calculated including the number of TEAEs and subject incidence in each of the following categories:

- Any TEAE.
- Any SAE.

- Any TEAEs leading to death.
- Any TEAE leading to withdrawal from the study.
- TEAEs by severity grade (Grade 1 to Grade 4)
- TEAEs by relationship to study drug (unrelated, unlikely, possible, probable, definite) and pooled study drug related category (related [possible, probably and definite] or unrelated [unrelated, unlikely])
- The number and percent of participants with 0, 1, 2, 3, 4, 5, and > 5 TEAEs, and the mean, median, interquartile range, min and max number of TEAEs per participant.

By severity grade and relationship, if a subject reports more than one TEAE, then that subject will be counted once at the highest severity and/or relationship category.

At the Day 42 output, the summary table will only be issued for data collected up to Day 42 (start dates prior to the Day 42 visit), including TEAEs ongoing at the Day 42 visit. At the Week 16 output, the summary table will be issued for each of these three intervals:

- Day 0 to Day 42,
    - TEAEs with start dates on or after Day 0 but prior to the Day 42 visit, or
    - TEAEs with start dates before Day 0 that were on-going at Day 0, and worsened in severity on or after Day 0 but prior to the Day 42 visit.
- > Day 42 to Week 16,
    - TEAEs with start dates after the Day 42 visit, or
    - TEAEs with start dates prior to the Day 42 visit, were ongoing at the Day 42 visit, and worsened in severity on or after the Day 42 visit.
- Day 0 to Week 16.
    - All TEAEs starting prior to the Week 16 visit, or
    - All TEAEs with start dates before Day 0 that were on-going at Day 0, worsened in severity on or after Day 0 but prior to the Week 16 visit.

The following tables will also be presented for the SfAS:

- TEAEs by SOC and PT
- TEAEs by SOC and PT by severity
- TEAEs by SOC and PT by relationship to study drug
- SAEs by SOC and PT

At the Day 42 output, these tables will be issued for data collected up to Day 42 and for the Week 16 output, for all data collected up to Week 16.

AE data will be listed in full.

9.12.2 Vital Signs

Aggregate summary statistics for respiratory rate, heart rate, temperature (oral and aural) and blood pressure (systolic and diastolic) will be provided for Baseline and post-Baseline

assessments along with the changes from Baseline by SfAS treatment group and time point. Means, medians, SDs, minimums and maximum values will be provided.

All vital signs data, including height and weight, will be listed.

9.12.3 Clinical Laboratory Assessments

All laboratory values (hematology and serum chemistry) will be converted to the International System of Units (SI) for the purposes of summary and listing.

Hematology and serum chemistry data will be listed separately including change from Baseline and flagging all out-of-range values. Toxicity grades will be derived where possible for each hematology and biochemistry result as described in Appendix 1 of the current protocol (The 2007 FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials). Those grades will be included in the listings.

Aggregate summary data for hematology and serum chemistry test results will be provided for Baseline and post-Baseline assessments. These analyses will include changes from Baseline, to be presented only for subjects with non-missing assessments at both timepoints. Means, medians, SDs, minimum, and maximum values will be provided for both test results and for the individual change from Baseline.

A summary tabulation will show the number and proportion of subjects for the serum and hematology laboratory abnormalities graded using the scales shown in Appendix 1 of the current protocol.

9.12.4 12-Lead ECGs

An overall summary table will be provided for normal and abnormal 12-lead ECGs in the SfAS and in the PK Analysis set for the Hour 3 ECG. Abnormal 12-lead ECGs will be summarized by treatment group and overall and by whether they were normal/abnormal and if abnormal, clinically significant or not significant. ECG data are collected at Baseline and Week 16 only for subjects not selected for the PK Analysis set.

All 12-lead ECG data will be listed.

9.12.5 Pregnancy Test

Pregnancy test details and results will be listed.

9.12.6 Physical Examinations

Physical examination data will be listed for the full assessment carried out at Screening and the abbreviated assessments post-Screening.

9.12.7 Safety Follow-Up After Day 42

The analysis of TEAEs collected during the extended safety follow-up after Day 42 will be similar to those described in Section 9.12.1.3. Should the number of TEAEs reported during the extended follow-up not warrant aggregate summaries, then the data will be reported as line listings only. Interpretation of these extended safety data will be compared and contrasted to the safety data collected through Day 42 including continuing TEAEs that resolved or continued during the extended safety follow-up. Physical exams and pregnancy test results will be listed along with any laboratory. Vital signs and ECG summary tables will be reissued at the Week 16 analysis to include assessments completed at Week 16.

9.12.8 Subgroup Analyses

Safety summaries for All TEAEs and TEAEs by SOC and PT will also be provided for the following subgroups if the sample size within subgroups is sufficient:

- Age (18 to 64 and ≥ 65)
- Gender
- Race
- Ethnicity
- Region

10 REFERENCES

Carpenter, J.R. and Kenward, M.G. *Multiple Imputation and its Application.* John Wiley & Sons Ltd. N.Y., **2013**.

Steingrimsson, J. A., D. F. Hanley and M. Rosenblum. *Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions. Contemp Clin Trials* **2017**, 54, 18-24. Supplementary data to this article can be found online at: http://dx.doi.org/10.1016/j.cct.2016.12.026.

11 TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Assessment	Screening (Day -7 to Day -1)	Day 0 In-clinic				Day 7 By phone	Day 14 In-clinic	Day 28 In-clinic	Day 42 In-clinic	Week 12 By phone	Week 16 In-clinic
		Pre-dose	Hour 0	Hour 3	Hour 10						
Visit window	**N/A**	**N/A**	**N/A**	**± 30 minutes**	**± 2 hours**	**± 1 day**	**± 2 days**	**-2/+4 days**	**± 2 days**	**± 7 days**	**± 7 days**
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Scabies diagnosis[1]	X										
Medical history	X										
Physical examination[2]	X						X	X	X		X
Vital signs[3]	X	X					X	X	X		X
12-lead ECG		X[4]									X
Height	X										
Body weight	X										
Pregnancy testing[5]	X	(X)									X
Pharmacokinetic blood sample collection[6]				X	X			X	X		
Hematology and serum chemistry	X						X	X			X[7]
Scabies assessments		X						X			

[1] Scabies will be diagnosed upon clinical findings typical of active scabies infestation (burrows, typical inflammatory/noninflammatory lesions) and either microscopic or dermatoscopic confirmation of scabies mite, ova or mite feces.

[2] A full physical examination will be performed at Screening. At all subsequent time points, a symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and adverse events reported) will be performed.

[3] Vital signs (supine blood pressure, heart rate, respiratory rate, and body temperature) will be measured after the subject has rested for approximately 5 minutes.

[4] Standard 12-lead safety electrocardiograms will be performed after the subject has been supine for approximately 10 minutes at Baseline before randomization. An additional 12-lead ECG will be conducted 3 hours post dose in the subjects selected for pharmacokinetic blood sampling. ECGs will be performed before blood collection.

5 Serum pregnancy test at Screening and urine pregnancy tests during study. A pregnancy test on Day 0 will only be conducted if Screening was conducted more than 24 hours prior to Day 0.

6 PK sample collection will occur in a subset of approximately 20 subjects per arm selected at randomization. On Day 0, PK samples will be collected at 3 hours ± 30 minutes and 10 hours ± 2 hours.

7 If clinically relevant abnormalities were identified in safety hematology or serum chemistry at Day 28.

Assessment	Screening (Day -7 to Day -1)	Day 0 In-clinic				Day 7 By phone	Day 14 In-clinic	Day 28 In-clinic	Day 42 In-clinic	Week 12 By phone	Week 16 In-clinic
		Pre-dose	Hour 0	Hour 3	Hour 10						
Visit window	**N/A**	**N/A**	**N/A**	**± 30 minutes**	**± 2 hours**	**± 1 day**	**± 2 days**	**-2/+4 days**	**± 2 days**	**± 7 days**	**± 7 days**
Randomization[8]		X									
Investigational product administration[9]			X								
Adverse events[10]	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X

[8] Randomization will occur after subject eligibility has been confirmed on Day 0.

[9] Investigational product administration will occur after an overnight fast of at least 8 hours. Investigational product will be administered with at least 240 milliliters of water. No food will be allowed for 60 minutes after dosing; however, clear liquids can be taken ad libitum.

[10] Adverse events will be reported from informed consent onwards.

12 APPENDICES

Appendix 1: Fixed Imputation for Non-Informative Missing Day 28 Complete Cure Endpoints

For subjects missing a Day 28 Complete Cure endpoint because of non-informative reasons, their endpoint will be imputed as a non-responder or responder using a logistic regression. The process will follow the following steps:

1. Run a logistic regression model using FAS subjects with non-missing Day 28 responses. This will include those subjects whose Day 28 response was imputed because of informative missing data.
2. Using the coefficients from the logistic regression, calculate the probability of achieving a Day 28 Complete Cure for those subjects with missing outcomes due to non-informative missing.
3. If the predicted probability for the subjects with non-informative missing is > 0.50 then impute a responder/cured status for their Day 28 Complete Cure endpoint.
4. If the predicted probability for the subjects with non-informative missing is ≤ 0.50 then impute a non-responder/not cured status for their Day 28 Complete Cure endpoint.

The logistic model will include demographic and baseline covariates and is pre-specified to include randomized treatment group as listed below. Should the logistic regression fail to converge, or produce unreliable coefficients/SEs because of multicollinearity or other reasons, a backward stepwise selection of covariates for removal will be conducted until the logistic model converges. The backward stepwise model will begin by using a significance level for removal of 0.10. If the model still does not converge the significance level for removal will be set to 0.05. Randomized treatment group will be a "locked" covariate and not eligible for removal. If the logistic regression model still fails after attempts at backward elimination, the observed proportions of Complete Cure responders in each randomized treatment group will be calculated across all regions and including any "informative" imputations, but excluding the non-informative missing data subjects. For the non-informative missing data subjects, if the observed proportion for their randomized treatment group is > 0.50 they will be imputed as achieving Complete Cure at Day 28. If the observed proportion for their randomized treatment group is ≤ 0.50 they will be imputed as not achieving Complete Cure at Day 28.

Logistic Regression Model Covariates:

- Region
- Randomized Treatment Group
- Age
- Gender
- BMI
- Race (collapse or eliminate if too sparse)
- Previous history of scabies
- Number of lesions
- Evidence of burrows
- Evidence of pruritus

- Number of regions affected

The steps in the backwards stepwise model along with the final model covariates, coefficients, SEs and p-values will be provided.

Appendix 2: Non-Informative Missing - Multiple Imputation for Complete Cure

As described in Section 9.11.2, if the percent of FAS participants whose Day 28 Complete Cure (ComC) outcome is missing due to non-informative reasons exceeds 5%, the ComC outcome for these subjects will be imputed using multiple imputation (MI) for the primary efficacy analysis. The implementation of the MI will proceed according to the steps outlined below. The MI process described here also includes the individual treatment group point estimates of the ComC and the three exploratory pairwise comparisons comparing each moxidectin dose group to the other moxidectin dose groups.

All of the MI datasets, as well as the bootstrapped sampled datasets, will be available. Complete documentation of the seed(s) and program code for the imputation, bootstrap and final derivation of the MI estimators will be such that the imputed and bootstrapped datasets may be replicated. Should the imputation model fail to converge, produce unreliable SEs, or irrational imputations, the imputation for non-informative missing subjects will default to the methods outlined in Appendix 1.

Step 1: Derivation of the MI FAS Dataset

Define the MI FAS dataset as FAS subjects with an observed Day 28 ComC or a non-informative missing Day 28 ComC. Leave the missing Day 28 ComC for non-informative missing subjects as missing. For the MI FAS dataset, include subjects exposed to scabicides prior to Day 28 whether their Day 28 endpoint is observed or not and set their ComC to Not Cured. Exclude any subject missing a Day 28 ComC that is considered “informative” missing.

Step 2: Definition of the Imputation Model

Define the imputation model imputing the Day 28 ComC outcome, to be a logistic regression with the following covariates:

- Region
- Age
- Gender
- BMI
- Race (collapse or eliminate if too sparse)
- Previous history of scabies
- Number of lesions
- Evidence of burrows
- Evidence of pruritus
- Number of regions affected

If the model does not converge or fails, stepwise backward elimination will be implemented, similar to that outlined in Appendix 1.

Step 3: Generate M=50 Multiple Imputed Datasets

- Using the MI FAS data set in Step 1 and the imputation model in Step 2 above, generate 50 multiple imputed datasets stratified by randomized treatment group i.e. multiple imputed independently for each randomized treatment group (200 datasets total). Should

the imputation model fail to converge or produce unreliable SEs, or irrational imputations for any of the randomized treatment groups, the imputation for non-informative missing subjects will default to the methods outlined in Appendix 1 and no further attempts at MI will be made. If the imputation model is successful in generating the MI datasets continue with the remaining MI Steps.

- For each of the 50 imputation runs, append the 4 randomized group datasets together forming a single MI dataset that contains the data for all four treatment groups resulting in 50 datasets.
- Subjects with missing ComC due to "informative" reasons, and initially excluded from the MI FAS dataset, will now be added to each of the 50 MI datasets with their missing ComC outcome set to Not Cured for each of the 50 datasets.
- Refer to these M=50 datasets as the Final MI datasets.

Step 4: Derive the MI Estimator for the Average Predicted Probability for each Treatment Group and the Risk Difference for Each Pairwise Comparison (Substantive Model)

For each of the Final 50 MI datasets from Step 3 above, each of which now contains all FAS subjects, calculate the Average Predicted Probabilities for each randomized treatment group and the Risk Difference for all six pairwise comparisons using the methods outlined in Section 9.11.1. The six pairwise comparisons include the three primary analysis pairwise comparisons of each moxidectin dose group to placebo and the three pairwise comparisons of each moxidectin dose group to the other moxidectin dose groups.

Step 5: Derive the Bootstrapped SEs for the MI Estimator of the Group Average Predicted Probabilities and the Pairwise Risk Differences

For each of the Final 50 MI datasets using the methods outlined in step 3, generate B=1000 bootstrapped samples (with replacement) to calculate the SEs for the Average Predicted Probabilities and the Risk Differences calculated in Step 4.

Step 6: Use Rubin's Rule to Derive the MI Estimators and SEs

Using Rubin's Rule (Carpenter, J.R. and Kenward, M.G. 2013) generate the MI estimators and their variances/SEs for the Average Predicted Probabilities for each randomized treatment group and the Risk Difference for all six pairwise comparisons across the 50 MI datasets calculated in Step 5.

Step 7: Calculate p-values and 95% CI for the MI Estimators

- **Primary Efficacy Analysis: Pairwise Comparison of each Moxidectin Group to Placebo**

  Using the MI estimators of the Risk Difference and their variances/SEs, calculate Wald tests and 95% CIs for each the three pairwise moxidectin comparisons against placebo using the Z value corresponding to Dunnett's two-tailed adjusted alpha of 0.019.

- **Exploratory Efficacy Analysis: Pairwise Comparison of Each Moxidectin Group to Each Other**

  Using the MI estimators of the Risk Difference and their variances/SEs,, calculate Wald tests and 95% CIs for each of the three pairwise comparisons comparing each

moxidectin group to the other moxidectin groups using the Z value corresponding to a two-tailed unadjusted alpha of 0.05.

- **Average Predicted Probabilities for each Randomized Treatment Group**

  Using the MI estimators and the variances/SEs for the Average Predicted Probabilities for each randomized treatment groups, calculate the 95% CI for each treatment group using the Z value corresponding to a two-tailed unadjusted alpha of 0.05.

Appendix 3: Primary Efficacy Analysis – Marginal Risk Difference and Bootstrapped Standard Errors

For the primary efficacy analysis, the logistic regression model will include region and randomized treatment group as covariates and the Day 28 Complete Cure response as the binary outcome. All Complete Cure imputations as outlined in the SAP should be done prior to running the primary analysis.

The logistic regression model should be predicting a Complete Cure responder .

Logistic Regression Model: Dependent and Covariates

Binary Outcome: Cured/Responder = 1; Not Cured/Non-responder = 0

Placebo (reference group): Code as 0 for all subjects

Moxidectin 8 mg: Code as 1 if subject randomized to 8 mg moxidectin group; Code as 0 otherwise

Moxidectin 16 mg: Code as 1 if subject randomized to 16 mg moxidectin group; Code as 0 otherwise

Moxidectin 32 mg: Code as 1 if subject randomized to 32 mg moxidectin group; Code as 0 otherwise

Region: Code as 1 if subject belongs in LATAM stratum; Code as 0 if subject belongs in US stratum

Logistic Model: outcome = B0 + B1mox8 +B2mox16 +B3mox32 + B4region

Step 1: run logistic model as coded or otherwise if software automatically treats covariates as noted above

Step 2: obtain logistic regression coefficients (use logit metric – not exponentiated)

Step 3: For each FAS subject, calculate the "predicted logit values" as if they were all in each of the 4 treatment groups. Keep their actual region values as observed. Create 4 new variables for each subject:

1. Placebo_logit = B0 + B4region *Region
2. Moxi8mg_logit = B0 + B1mox8 + B4region *Region
3. Moxi16mg_logit = B0 + b2mox16 + B4region*Region
4. Moxi32mg_logit = B0 + B3mox32 + B4region*region

Step 4: From the logit values use an inverse logit function to get the predicted probabilities. Each subject will now have 4 probabilities for cure as if they were assigned to each of the 4 treatment groups.

1. Placebo_prob = invlogit(Placebo_logit)
2. Moxi8mg_prob = invlogit(Moxi8mg_logit)
3. Moxi16mg_prob = invlogit(Moxi16mg_logit)
4. Moxi32mg_prob = invlogit(Moxi32mg_logit)

Step 5: Calculate the Average (Mean) Predicted Probabilities for each Treatment Group

Across all subjects, regardless of treatment group, get the mean for each of the following variables:

1. Placebo_prob
2. Moxi8mg_prob
3. Moxi16mg_prob
4. Moxi32mg_prob

Step 6: Calculate the Standardized Risk Difference for each Pairwise Comparison Using the Average Predicted Probabilities calculated in Step 5.

5. Diff 8 vs Plb
6. Diff 16 vs Plb
7. Diff_32 vs Plb
8. Diff 16 vs 8
9. Diff 32 vs 16
10. Diff 32 vs 8

Step 7: Calculate the Bootstrapped SEs for the Average Predicted Probabilities in Step 5 and the Bootstrapped SEs for each pairwise Standardized Risk Difference calculated in Step 6.

- Bootstrap Step 1 through Step 6 1000 Times with Replacement.
- For 95% CIs for each the three pairwise comparisons against placebo use the relevant bootstrapped SE and the Z value corresponding to Dunnett's two-tailed adjusted alpha of 0.019
- For the 95% CI for each of the three pairwise comparisons comparing moxidectin groups use the relevant bootstrapped SE and the Z value corresponding to a two-tailed unadjusted alpha of 0.05

NOTE: The Process outlined in Steps 1 through 6 may be available in SAS using the "margins" statement in PROC GLIMMIX. See the following reference:

Wu, S. Computng Predictive Margins for Generalized Linear Models with PROC GLIMMIX, SAS Statistics Research and Applications, Paper #2022-03