A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies

Medicines Development for Global Health Study No: MDGH-MOX-2001
Veristat International Ltd Study No: MNT18001

Statistical Analysis Plan

Version: Final 1.0

Date: 16 February 2022

For Veristat International Ltd – Lead Statistician

[redacted]

For Medicines Development for Global Health

[redacted]

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Concentration time curve
BMI	Body Mass Index
C_{max}	Maximum Observed Plasma Concentration
CI	Confidence Interval
DMP	Data Management Plan
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
KM	Kaplan Meier
MDGH	Medicines Development for Global Health
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
PD	Pharmacodynamic
PK	Pharmacokinetic
PKAP	Pharmacometric Analysis Plan
PKAS	Pharmacokinetic Analysis Set
PKPDAS	Pharmacokinetic/Pharmacodynamic Analysis Set
PPAS	Per Protocol Analysis Set
PSC	Protocol Steering Committee
PT	Preferred Term
RCM	Reflectance confocal microscopy
SfAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO Drug	World Health Organization Drug Dictionary

1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Medicines Development for Global Health (MDGH) Protocol MDGH-MOX-2001: A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies.

The proposed analysis is based on the contents of Version 3 of the protocol (dated 19 June 2020). In the event of future amendments to the protocol, this Statistical Analysis Plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells are supplied in a separate document.

A separate Pharmacometric Analysis Plan (PKAP) will detail the derivation of pharmacokinetic (PK) parameters and associated analyses which are not covered by this SAP.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The primary objectives of the study are to:

- Identify an optimal dose of moxidectin for the treatment of scabies;
- Evaluate the safety of moxidectin in adults infected with scabies.

The secondary objective of the study is to characterize the plasma pharmacokinetics of moxidectin in adults infected with scabies.

The exploratory objectives of the study are to:

- Describe the impact of moxidectin on S. *scabiei*, including impact on morphology, motility and life cycle stages;
- Evaluate clinician and patient reported outcomes of treatment with moxidectin.

2.2 Study Endpoints

The primary endpoints of the study are as follows:

- Efficacy will be determined by death of the mites, defined as the degradation (loss of internal and/or external anatomic structures) of the adult mite observed by reflectance confocal microscopy (RCM). Mites will be assessed at Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28 in not less than two lesions nominated pre-treatment.
- Safety will be assessed by the incidence and severity of adverse events (AEs), physical examinations, and measurement of vital signs up to and including Week 12, and laboratory safety parameters up to and including Day 28.

The secondary endpoints are the key exposure metrics for moxidectin including area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}), which will be determined by non-compartmental analysis of moxidectin pharmacokinetic parameters or other methods as appropriate, assessed up to and including Day 28.

The exploratory endpoints are:

- At Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28, using assessment by RCM of burrows selected pre-treatment:
    - Changes in adult mite motility (peristalsis and/or movement) over at least 30 seconds of observation;
    - Presence, number, morphology and motility of juvenile scabies mites;
    - Presence of eggs and scybala in burrows.
- Presence and total number of mites and burrows assessed visually at Days 7, 14 and 28.
- Changes in assessment of clinician-reported scabies symptomology, including extent of symptoms on body regions assessed by the number of anatomically-defined regions affected, number of lesions and severity grading of excoriations and erythema.
- Changes in patient reported outcomes, measured by Numerical Rating Scale, 5-D Itch Scale and Dermatology Life Quality Index.
- Clinical cure rates at Days 7, 14 and 28. Clinical cure is defined as resolution of all scabies signs and symptoms present at Baseline, no new scabies signs and symptoms and no evidence of mites by dermoscopy.

2.3 Study Design

This is a randomized, double-blind, multicenter, parallel group, dose finding study of a single oral dose of moxidectin in adults with scabies. Initially, subjects will be randomized with a target allocation ratio of 1:1:1 to one of the following single dose treatment regimens:

- Treatment 1: Moxidectin 2 mg;
- Treatment 2: Moxidectin 8 mg;
- Treatment 3: Moxidectin 20 mg.

Once approximately three subjects have been recruited to these three dose groups and completed their Day 14 visit, a Protocol Steering Committee (PSC) will evaluate the unblinded safety and efficacy data and recommend:

- Continuation of the study with no dose modification to the target sample size of 6 subjects per dose group; or,
- Stopping recruitment of one of more of the current dose groups; and/or,
- The addition of a 36 mg single dose group.

Once the Committee has made their recommendation, randomization will continue into the same or revised dosing regimens with a final target sample size of 6 subjects per dose group. It is anticipated that a maximum of 36 subjects will be included in the study.

The on-study period per subject will be 13 weeks, consisting of up to one week for Screening and 12 weeks post-treatment.

The study is planned to be conducted in Australia and France in approximately four centers.

2.4 Visit Structure

The visit structure and scheduled assessments are detailed in Table 1, Table 2 and Section 9 of the protocol.

3 SAMPLE SIZE

The sample size chosen for this study, approximately 6 subjects per dose group, was selected to be practical and an adequate sample size for full characterization of PK profile across the dose ranges studied. Sample size was not based on formal power considerations with respect to statistical hypothesis testing.

4 RANDOMISATION

Potential subjects who provide written informed consent will be sequentially assigned a Screening Number prefixed by “S” (e.g. S001).

Initially for each site, a randomization scheme with equal allocation to each of the initial three moxidectin dose groups will be prepared. Treatment packs will be prepared according to the randomization scheme.

Randomization will take place before dosing on Day 0.

Following review of safety and efficacy data by the PSC, one or more dose group(s) may be discontinued and/or a new 36 mg dose group added. If required, the randomization plan will be revised to maintain the final target sample size of 6 subjects per dose group. The study will switch from a stratified randomization by site to a central randomization scheme for logistical reasons. However, random allocation of treatment assignment will be preserved in all cases.

5 INTERIM ANALYSIS

5.1 Protocol Steering Committee Review

No formal interim analysis is planned for this study.

The PSC will review relevant accumulated unblinded safety and efficacy data for all randomized subjects collected through to the review cutoff date. The review cutoff date will correspond to the date when approximately 3 subjects in each of the initial 3 treatment arms have completed their Day 14 evaluation. Based on a review of the available data, the Committee will recommend one or more of the actions described in Section 2.3.

The decision-making process of the Committee will be guided by:

- The mortality rate of adult scabies mites, or the time-to-death of adult scabies mites. Subject-level review may also be considered.
- Safety outcomes, such as the frequency, nature and severity of adverse events, and withdrawal rates.

- Pharmacokinetic data may be reviewed if available.

The Committee will not reveal the results of their data review or, barring any unanticipated safety issues, any decisions or recommendations to Investigators, study personnel, or Sponsor personnel involved in the management of day-to-day study activities.

Additional unblinded reviews and possible dose modification recommendations may also be undertaken by the Committee at any time at, or in lieu of the data review described above, at the request of the Sponsor. The analyses to be conducted during these interim reviews may entail review of individual subject line listings and/or aggregate data.

Since the study is exploratory and not powered to conduct hypothesis testing, no adjustments to the type I error rate for PSC data reviews will be implemented.

Further details can be found in the Protocol Steering Committee Charter.

5.2 Final Analysis

The study comprises two periods for the purposes of final statistical analysis as follows:

- Period 1: Commences at Screening and will finish on Day 28. The study blind will be maintained during this study period. After the last subject has completed the study through Period 1, the blind will be broken and the unblinded data from Period 1 will be analyzed. This analysis will be referred to as the Day 28 analysis throughout the SAP.
- Period 2: Runs from Day 29 to Week 12. Data from Period 2 will be analyzed after all subjects have completed the study through Week 12. Data for some subjects may be collected during Period 2 after the blind has been broken and the Period 1 study results known. The Period 2 data will be provided in an additional safety supplement. The safety supplement will be referred to as the Week 12 analysis throughout the SAP.

Although the blind will be broken after the last subject has completed their Day 28 visit or withdrawn (Period 1) for all other study personnel, the individual treatment assignment will not be communicated to the subject, Investigators, site personnel or the clinical operations team until the last subject has completed their Week 12 visit or withdrawn (Period 2).

The Day 28 analysis will consist of all efficacy and safety outputs as described in this SAP. Data for this analysis will be cut to exclude any assessment data entered after Day 28 for each subject (even if the subject has progressed beyond this point at the time of the analysis). PK analyses will also be completed at Day 28 and further details can be found in the PKAP.

The Week 12 analysis is a safety supplement and as such will include a rerun of selected outputs only where additional information was captured during Period 2 (i.e. including all data from study start up to the end of the study for these outputs). These additional data will include protocol deviations, disposition (including completions and withdrawals), adverse events, concomitant medications, physical examinations, vital signs (including weight) and pregnancy testing. Note that although additional data on post-baseline physical examination assessment times will be included in this rerun, these are not presented in the physical examinations listing and so the listing will not

be reproduced. In addition, it is possible that the additional concomitant medication data includes rescue medications taken after the Day 28 assessment. These will be included in the rerun of concomitant medication outputs. However, the analysis table summarizing rescue medications will not be rerun unless deemed useful post hoc.

The outputs to be repeated at Week 12 are detailed separately in the list 'MDGH-MOX-2001 (MNT18001) Week 12 Outputs'.

Efficacy and safety data obtained for subjects randomized to all doses, including doses that may have been discontinued or added based on the recommendation from the PSC, will be included in the final analysis and presented in the outputs.

6 ANALYSIS PLAN

6.1 General

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

For categorical variables the number and percentage of subjects in each category will be presented. Unless otherwise stated, this will be based on the number of non-missing observations apart from disposition of subjects, baseline and demographic characteristics, medical history, prior and concomitant medications and adverse events where the percentage will be based on the number of subjects in the analysis set.

It is acknowledged that the sample size was not based on formal power considerations with respect to statistical hypothesis testing, and as such, the focus of the statistical analysis will be descriptive and exploratory. Although p-values may be calculated they should be interpreted as exploratory rather than confirmatory given the small sample size, lack of multiplicity adjustment, and exploratory nature of the hypotheses they may be testing. Where statistical testing is performed, this will assume a two-tailed 5% overall significance level, unless otherwise stated. Any comparisons between the dose groups will be reported with 95% confidence intervals for the difference.

It is noted that particular attention may need to be given to the impact on key safety or efficacy assessments as a result of missing data associated with COVID-19. The amount of missing data will be monitored prior to database lock and, if deemed beneficial, a formal assessment of the impact on key assessments may be conducted. If this suggests that further investigation is beneficial, additional summaries and/or analyses of missing data may be added post hoc. This may also include additional sensitivity analyses using different approaches for handling of missing data if deemed worthwhile (see Sections 6.10.1.6 and 6.10.3.4 for more detail in relation to the primary endpoints and clinical cure rate exploratory endpoint).

6.2 General Derivations

This section provides details of general derivations. Derivations specific to a parameter of interest are detailed within the specific SAP sections.

- **Definition of study day**

  Throughout this SAP any references to 'Day XX' refer to the pre-specified visits defined in the protocol (where the study drug administration visit is Day 0).

  Data listings by visit will additionally present the duration from the administration of study drug in days, referred to as 'Study Day XX'. Study Day will be calculated relative to the date of administration of study drug in whole days. Thus, assessments completed on the day of study drug administration ('Day 0' visit) will be assigned a Study Day value of 1.

- **Definition of Baseline**

  Baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) prior to the subject receiving study drug.

- **Incomplete dates**

  For calculation purposes, incomplete dates will be completed using a worst case approach. For example, assuming the earliest or latest possible date given all available information to ensure a worst case applies for each respective case. Further details are provided in the relevant sections as required.

- **Non-numeric values**

  In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", then for analysis purposes a value of x will be taken. Where a range of values is quoted, the midpoint of the range will be taken.

- **Site pooling for statistical analyses**

  No analysis by center or country will be performed due to the small sample size of the study. Subjects from all centers will be pooled for summaries and analyses.

- **Methods for handling withdrawals and missing data**

  In general, data will not be imputed unless otherwise stated in relevant sections.

- **Definition of planned dose and actual dose received**

  Planned dose of study drug is defined as the dose group to which the subject was randomized and will be determined by the randomization list. Actual dose received is defined as the actual dose of study drug received regardless of randomized dose group. This will be determined once the blind has been broken using details provided by MDGH and/or captured on the electronic Case Report Form (eCRF) regarding actual doses received by subjects.

6.3 Analysis Sets

6.3.1 Definitions

The **Enrolled Set** includes all subjects who were randomized irrespective of whether they received the study drug.

The **Full Analysis Set** (FAS) will include all randomized subjects receiving at least one dose of study drug. Subjects in the FAS will be analyzed according to the dose group to which they were randomized. In general, the FAS will only be used for selective analyses such as sensitivity analyses.

The **Per-Protocol Analysis Set** (PPAS) will include all subjects exposed to study drug without any major protocol deviations that could confound the assessment and/or interpretation of the analytic results. Protocol deviations will be identified by the study team prior to breaking the study blind at the Day 28 analysis. Subjects in the PPAS will be analyzed according to the actual dose of study drug received regardless of their randomized dose group. In general, PPAS subjects with missing data for a specific analysis will be excluded from that analysis. However, imputation may be applied where considered appropriate. Details regarding any such imputation are given in the relevant sections of this SAP. As this is a proof-of-concept study, the PPAS will be the primary analysis set used to assess parasitological outcomes as well as clinical signs and symptom endpoints. Replacement subjects will be included in the PPAS if they meet the PPAS requirements.

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock for Day 28 analysis, and major deviations considered having a serious impact on the efficacy results will lead to the relevant subject being excluded from the PPAS. Some categories of major protocol deviations that might be considered as having a serious impact on the efficacy results include but are not limited to:

- Subjects failing any eligibility criteria.
- Any subjects with treatment administration errors.
- Significant non-compliance with specified study visit windows.

This is a non-exhaustive list and protocol deviations other than those specified above may be identified.

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

The **Pharmacokinetic Analysis Set** (PKAS) and the **Pharmacokinetic/Pharmacodynamic Analysis Set** (PKPDAS) will be defined in the PKAP together with the use of these populations for analysis of PK data and the relationship between efficacy endpoints and plasma concentrations of moxidectin.

6.3.2 Assignment

The Analysis Set Planning form indicates which analysis sets require individual subject assignments to be listed for Sponsor review and agreement prior to final analysis, as well as the timing of the reviews. Where the analysis set definitions are considered sufficient to determine the subjects included, it will not be considered necessary to complete listing and Sponsor review of the analysis set assignments and this will be indicated in the Analysis Set Planning form. Where analysis sets do require review of individual subject assignments, this will be completed and agreed prior to breaking the blind for the Day 28 analysis, once all relevant study data are available. Subject assignment to the PKAS and PKPDAS will be completed as part of the analysis detailed in the PKAP and will not be included in the activities covered by this SAP.

It is assumed that the analysis sets for the Week 12 analysis will remain as agreed for the Day 28 analysis. New protocol deviations occurring after Day 28 will be categorized as major/minor for the presentation of the deviations only. As protocol deviations occurring after Day 28 will have no impact on the efficacy analyses, they

will not be considered to impact the PPAS assignments or necessitate a review of these. Therefore, no update of the PPAS will occur after the Day 28 analysis.

6.4 Data Presentations

Data will be summarized in tabular form by dose group in order of ascending dose ('Moxidectin 2 mg', 'Moxidectin 8 mg', 'Moxidectin 20 mg', 'Moxidectin 36 mg' (if required)) and overall subjects.

Only scheduled post-Baseline assessments will be tabulated. Post-Baseline repeat/unscheduled assessments will not be tabulated, although they will be listed.

Data collected under the 'Period 1 Day 28 or Early Withdrawal' visit in the eCRF will be mapped to either 'Day 28' for subjects who complete the study up to and including the Day 28 assessment, or 'Early Withdrawal' for subjects who withdraw early and prior to completing the Day 28 assessment. The mapped visits will be used for all data presentations and analyses. Data presentations by visit will present 'Early Withdrawal' after all other visits.

Listings will be sorted by dose group, subject number and date/time of assessment. Dose groups will be presented in order of ascending dose.

Tables, figures and listings will be prepared using the following analysis sets:

Analysis Set	Tables	Figures	Listings
Enrolled	Analysis sets Study completion/withdrawal Medical history Demography		All non-safety
SfAS	Prior/concomitant medications Rescue medication analyses Safety		All safety
PPAS	Efficacy summaries[1] Efficacy analyses[1]	Efficacy[1]	

1. Where the difference between the PPAS and FAS is ≥1 subject, summaries and analyses of the primary efficacy endpoints may be repeated for the FAS post-hoc if deemed worthwhile to support the findings of the study. Selected exploratory efficacy endpoint summaries and analyses may also be repeated post-hoc, as indicated in the relevant sections of this SAP, but generally will be based on the PPAS only.

6.5 Disposition of Subjects

The number of subjects in the enrolled set, the number and percentage of subjects included in the FAS, PPAS and SfAS who were continuing the study (Day 28 summary) or completed the study (Week 12 summary), and who prematurely discontinued the study, will be summarized. The number and percentage of subjects will be summarized by their reasons for withdrawal from the study.

Study completion/withdrawal data will be listed. A separate listing will also present eligibility for each of the analysis sets along with reasons for exclusion and the protocol version participants were enrolled under.

6.6 Protocol Deviations

Prior to database lock and blind break for the Day 28 analysis, MDGH will review the individual deviations and classify them as major or minor. Subjects with deviations that are determined to impact the interpretation of the results will be excluded from the PPAS.

Additional deviations occurring during Period 2 (after the Day 28 database lock but prior to database lock at Week 12) will also be reviewed and classified by MDGH as major or minor. No reclassification of deviations occurring during Period 1 will take place at the review of Period 2 deviations.

Details of all protocol deviations (deviation start and end dates, deviation category, specific details and classification of major or minor) will be listed.

6.7 Baseline and Demographic Characteristics

6.7.1 Demography

Demographic characteristics (age, sex and race) and body measurements (height, weight and Body Mass Index (BMI)) collected at Screening will be summarized.

Age will be the collected age captured in the eCRF. Where age is missing on the eCRF it will derived from the year of birth as *Year of Screening Visit – Year of Birth*.

BMI will be derived from *(weight (kg)/height (m)²)*.

All subject demographic data including informed consent date will be listed.

6.7.2 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 and documented in the Data Management Plan (DMP). The version used will be indicated in the data summaries and listings. If updates to later versions are required during the study, this will be reflected in the DMP and the outputs. The number and percentage of subjects with medical history events will be presented by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of subjects with medical history events. All events will be listed.

6.8 Prior and Concomitant Medications

Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version in place at the time of analysis and documented in the DMP. The version used will be indicated in the data summaries and listings. If updates to later versions are required during the study, this will be reflected in the DMP and the outputs.

Prior medications are defined as those that started and ended prior to the administration of study drug. 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.

The number and percentage of subjects taking prior medications and the number and percentage of subjects taking concomitant medications will be summarized separately. The summaries will be presented by medication class and standardized medication name, where medication class and standardized medication name will be presented in decreasing frequency of the total number of subjects with medications. In summary tables, subjects taking multiple medications in the same medication class or having the same standardized medication recorded multiple times in the study will be counted only once for that specific medication class and standardized medication name.

Medication data will be listed and concomitant medications will be flagged.

6.8.1 Rescue Medication

Any concomitant medications deemed to be rescue medication will be indicated as such on the concomitant medications eCRF page.

All rescue medications will be flagged on the listing of prior and concomitant medications for the enrolled set. An analysis of rescue medication taken up to and including the Day 28 assessment for each subject will be conducted on the SfAS to assess any differences between dose groups in the requirement for rescue medication during this time period.

The number and percentage of subjects recording at least one concomitant medication identified as a rescue medication up to and including their Day 28 assessment will be presented by dose group for the SfAS.

Time to receipt of first concomitant rescue medication will also be derived in hours for each subject recording concomitant rescue medication up to and including Day 28 as:

(Start date and time of first concomitant rescue medication) – (Date and time of study drug administration).

Descriptive statistics will be presented for the time to receipt of concomitant rescue medication by dose group. The summary will be presented for the subset of subjects in the SfAS who record concomitant rescue medication in the time up and including to their Day 28 assessment.

Following review of the summaries described above, further post-hoc analyses of rescue medication may be conducted if considered worthwhile and there are sufficient subjects receiving rescue medication. Any post-hoc analyses to be performed will be fully defined in a SAP Addendum prior to conducting the analyses. This may include analysis of rescue medications taken up to Week 12 as appropriate.

6.9 Administration of Study Drug and Exposure

Details regarding date and time of study drug administration will be listed. The dose group the subject was randomized to and the dose group the subject received will also be included in this listing.

6.10 Efficacy Evaluation

6.10.1 Primary Endpoint

6.10.1.1 Primary Variable

The primary efficacy endpoint of the study will be determined by the death of adult scabies mites at each post-Baseline RCM assessment, with death defined as the degradation (homogenization of internal structures and/or external anatomic structures, and increased reflectance) of the adult mite observed by RCM.

A minimum of 2 and maximum of 4 live adult scabies mites, each within its own distinct lesion, will be identified at Baseline by RCM for each subject. Only those lesions confirmed by RCM to contain a live adult scabies mite at Baseline will be recorded on the eCRF. These identified lesions will then be further assessed by RCM at Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28 for changes in mite morphology, movement and peristalsis.

For the purposes of analysis of the primary variable, only the 2, 3 or 4 individual live adult mites identified at Baseline by RCM will be evaluated at post-Baseline time points. It is not expected that juvenile mites will mature into adults within a selected lesion being evaluated for the primary endpoint. If there is evidence to suggest that this has occurred, the data will be reviewed on a case by case basis to determine how this should be handled in the analysis.

6.10.1.2 Primary Endpoints

Four separate endpoints will be analyzed in order to assess death of adult scabies mites, all of which will be considered key primary efficacy endpoints. Analysis of the death of adult scabies mites will be performed using the individual scabies mite as the unit of analysis and also the subject as the unit of analysis.

The endpoints to be analyzed using the scabies mite as the unit of analysis will be:

- Mortality rate for adult scabies mites at each post-Baseline RCM time point. Mortality rate at each time point will be calculated as the proportion of the total number of dead adult scabies mites from among the total number of live adult scabies mites identified at Baseline.
- Time to death of adult scabies mites for those identified as live at Baseline. Time to death of each adult scabies mite will be calculated in hours as (Date and time of first RCM assessment where mite confirmed dead) – (Date and time of study drug administration), for mites with confirmed death during the study. For mites without confirmed death during the study, time to death will be calculated in hours as (Date and time of Day 28 RCM assessment) – (Date and time of study drug administration), i.e. worst case.

The endpoints to be analyzed using subject as the unit of analysis will be:

- Mean proportion of dead adult scabies mites per subject at each post-Baseline RCM time point. The proportion of dead adult scabies mites for each individual subject at each time point will be calculated as the number of dead adult scabies mites from among the live adult scabies mites identified at Baseline for that subject.

- Proportion of subjects with 100% dead adult scabies mites from among the live adult scabies mites identified at Baseline for that subject, at each post-Baseline RCM time point.

6.10.1.3 Mite Status Derivation, Imputation and Missing Data

The approach for identifying live versus dead mites for the above primary endpoints is described below.

At Baseline, live adult mites will be defined by the following responses to the RCM assessment and only those lesions satisfying both of these criteria will be recorded on the eCRF:

- The response to 'Describe the mite stages present in the lesion?' includes 'Adult mites';
- The response to 'Does the mite have intact morphology?' is 'Yes'.

As the identification of these lesions is a requirement for randomization into the study, no missing data is anticipated for the assessment of live mites at Baseline.

At post-Baseline RCM assessments, an adult mite will be considered to be dead if at least one of the following conditions are met, based on the responses from the RCM assessment of the respective selected lesion:

- The response to 'Does the mite have intact morphology' is 'No';
- The response to 'Describe the mite stages present in the lesion' does not include 'Adult mites';
- The response to 'Is the lesion still visible' is 'No'.

These conditions are hierarchical, such that if a lesion is no longer visible it will not be possible to identify the mite stages present or the morphology of any mites, therefore the mite will be considered dead. Similarly, if the response to 'Describe the mite stages present in the lesion' does not contain 'Adult mites' it will not be possible to confirm intact morphology, therefore the mite will be considered dead.

Due to the life cycle of the mite and the subjective nature of skin assessments, it is possible that responses from the post-Baseline RCM assessments suggest that a mite previously declared as dead could be declared as live at a future assessment. To allow for this, the following rules will be applied to the post-Baseline assessments. Regardless of these rules, the baseline assessments (i.e. of live mite) will not be changed.

1. Any response of 'Unsure' to 'Does the mite have intact morphology' will be considered as equivalent to a status of 'live'.
2. One assessment with a status of 'dead' is required in order to declare the mite dead for all subsequent visits, where the death of the mite will be assumed to have occurred at the first visit with a status of 'dead'.
    a. Where rescue medication has been taken (identified on the concomitant medications page of the eCRF), any mite death occurring after the start date of rescue medication will be ignored and the mite will continue to be considered alive. If the mite has already died prior to or on the start date of rescue medication, it will be considered dead for all subsequent visits as stated here.

3. Should the RCM responses indicate a status of 'live' at an assessment occurring after an assessment with a status of 'dead', this will be assumed to be a new infection and thus ignored, i.e. the mite identified at Baseline will still be assumed to have died. This will therefore not impact the analysis of the primary efficacy endpoints.
4. Where data are missing for any of the responses required to determine the status of a mite and therefore the mite status cannot be established, the status of the mite will be assumed not to have changed from the previous non-missing assessment (i.e. the last observation will be carried forward). This includes where a subject withdraws early, in which case the last observation will be carried forward for all remaining visits. Where the last observation is carried forward, this will still be subject to the above rules 1 to 3.

These imputation methods will be applied to all missing adult mite assessments, regardless of the number of lesions for which data are missing for a subject at a timepoint. If data are missing at the subject level (i.e. the RCM assessment is not completed for any lesion at a timepoint for a subject), all mites being evaluated will have their status imputed and therefore no subjects will be missing in the primary analysis summaries presented at each post-Baseline visit.

It should be noted that the above rules may not be exhaustive. If any ambiguity remains in the status of the mite after applying these rules, subject data will be reviewed on a case-by-case basis prior to breaking the blind.

All analyses of the dead/alive response described in the SAP for the primary endpoints will use the values obtained after applying the strategies for any imputation where there is ambiguity or missing data. Similarly references to 'first/last time point where dead/alive' refer to the first/last occurrence once these imputations have been applied. Following review of these analyses, post hoc sensitivity analyses may be considered to assess the impact of these imputations, as described in Section 6.10.1.6.

6.10.1.4 General Considerations

Due to the small sample size (n = 18) which was not based on formal power considerations with respect to statistical hypothesis testing, no formal hypothesis testing will be employed. Although p-values may be calculated they should be interpreted as exploratory rather than confirmatory given the small sample size, lack of multiplicity adjustment, and exploratory nature of the hypotheses they may be testing.

Instead, descriptive statistical techniques will be used to identify differences between the doses of moxidectin with the objective of describing an exposure-response association between the dose groups and parasitological outcomes, and/or observing a single dose that appears to have the 'best' parasitological effect while maintaining an acceptable safety profile.

All RCM assessment data will be listed, including the derived flag for mites considered dead at each time point and time to death of mite.

6.10.1.5 Summaries

Mortality rate for adult scabies mites

The summary of mortality rate data will include the number and percentage of dead adult scabies mites, presented by dose group for each post-Baseline RCM time point.

The total number of live adult scabies mites identified at Baseline (and used as the denominator for the percentages), will also be indicated in the summary. Clopper-Pearson 95% CIs will be presented for all percentages where independence among mites within subjects is assumed.

Time to death of adult scabies mites

Time-to-death of adult scabies mites (hours) for each mite identified as live at Baseline is defined as:

(Date and time of first RCM assessment where mite confirmed dead) – (Date and time of study drug administration).

The time-to-death of adult scabies mites will be interval censored. For those mites with confirmed death during the study, the beginning of the interval will be the administration of study drug and the end of the interval will be the first RCM assessment where the mite is confirmed dead. For mites without confirmed death during the study, or still alive prior to or on the start date of any rescue medication exposure, the time-to-death will be right censored where the beginning of the interval will be the administration of study drug and the end of the interval will be the Day 28 RCM assessment (i.e. worst case), calculated in hours as:

(Date and time of Day 28 RCM assessment) – (Date and time of study drug administration).

Descriptive statistics will be presented for the time-to-death of adult scabies mites by dose group. This will include a summary excluding mites without confirmed death during the study (or still alive prior to or on the start date of any rescue medication exposure), as well as a separate summary including mites without confirmed death during the study or still alive prior to or on the start date of any rescue medication exposure, with the time to death censored as described above. A separate summary will present for each dose group, the number of mites identified as alive at Baseline, and the number and percentage of dead mites at the end of the study along with the Clopper-Pearson 95% CI for the percentage where independence among mites within subjects is assumed. The number and percentage of mites that are censored will also be summarized, along with Kaplan Meier (KM) estimates for the 25th, 50th and 75th percentiles of time to mite death and corresponding 95% CIs. The time-to-death of adult scabies mites will also be presented graphically using a KM plot.

Proportion of dead adult scabies mites per subject

The proportion of dead adult scabies mites per subject (calculated from among the live adult scabies mites identified at Baseline for the subject) will be summarized via descriptive statistics including the mean proportion, presented by dose group for each post-Baseline RCM time point.

Proportion of subjects with 100% dead adult scabies mites

The number and percentage of subjects with 100% dead adult scabies mites from among the live adult scabies mites identified at Baseline for that subject will be presented, together with the Clopper-Pearson 95% CI for the percentage, by dose group for each post-Baseline RCM time point.

6.10.1.6 Sensitivity Analysis

Per Section 6.4, the primary analyses may be repeated on the FAS post hoc if deemed worthwhile to assess any impact to the conclusions made.

Further sensitivity analyses, for example using different missing data or imputation approaches, may be considered post-hoc. This may include a completers analysis, repeating selected primary endpoint analyses without imputation of mite status due to missing data. Sensitivity analyses may also be added to assess the impact of imputations due to rescue medication or apparent new infections.

6.10.1.7 Post-hoc Analysis

Where deemed appropriate following review of the summaries described above, post-hoc analyses for one or more of the primary endpoints may be considered in order to further evaluate any differences between dose groups.

Any post-hoc analyses to be performed will be fully defined in a SAP Addendum prior to conducting the analyses, including details on the models to be applied, the hypotheses to be tested and the presentation of the results.

6.10.2 Secondary Endpoints

PK and PD are described in further detail in Section 6.12 and Section 6.13 of this SAP.

6.10.3 Exploratory Endpoints

All exploratory endpoints will be analyzed and summarized using the PPAS as the primary analysis set. Per Section 6.4, selected exploratory endpoints may be repeated on the FAS post-hoc if deemed worthwhile to assess any impact to the conclusions made. Where this is the case, the following endpoints will be repeated:

- Presence and number of total mites and burrows assessed visually at Days 7, 14 and 28 (see Section 6.10.3.1).
- Changes in assessment of clinician-reported scabies symptomology (see Section 6.10.3.2).
- Clinical cure rate (see Section 6.10.3.4).

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 considered post-hoc.

With the exception of clinical cure rate, data are included in all exploratory endpoint summaries irrespective of any exposure to rescue medication. The impact of rescue medication on data used in the summaries for clinical cure rate are detailed further Section 6.10.3.4.

6.10.3.1 RCM Assessment

Changes in Adult Mite Motility

The presence and changes in adult mite motility (movement and peristalsis) over time will be assessed in an exploratory manner using descriptive summaries, and with the adult scabies mite as the unit of analysis.

The proportion of adult mites with and without movement respectively will be calculated at each RCM time point as the total number of adult scabies mites with and without movement from among the total number of live adult scabies mites recorded at Baseline.

The proportion of adult mites with and without peristalsis respectively will be calculated at each RCM time point as the total number of adult scabies mites with and without

peristalsis from among the total number of live adult scabies mites recorded at Baseline.

A summary will present for each dose group and RCM time point: the total number and percentage of lesions assessed across all subjects, the total number and percentage of adult scabies mites with each possible morphology response (intact/not intact/unsure), and the total number and percentage of adult scabies mites with/without movement and with/without peristalsis respectively. The denominator for all percentages will be the total number of live adult scabies mites recorded at Baseline across all subjects. The number of subjects with at least one missing or incomplete lesion assessment at each RCM time point will also be summarized, as well as the number of subjects who have been administered rescue medication prior to each respective RCM time point.

There will be no imputation of missing or inconsistent data prior to the summary of the morphology, movement and peristalsis responses. Missing responses (due to the subject missing the complete RCM assessment or missing the individual lesion assessment) will be included under a 'Missing' category for each respective summary. Where an adult mite is recorded as no longer present or where a lesion is recorded as no longer visible, responses will be assumed as follows: 'not intact' for morphology, 'without movement' and 'without peristalsis' for motility.

Presence, Number, Morphology and Motility of Juvenile Mites

The presence and characteristics of juvenile mites observed over time will be assessed in an exploratory manner using descriptive summaries.

The total number of juvenile mites across all subjects, the total number and percentage of lesions across all subjects that were assessed and the total number and percentage of lesions across all subjects where any juvenile mites were observed will be presented by dose group and RCM time point. The table will also present the total number and percentage of lesions across all subjects with each of the responses to whether any juvenile mite has intact morphology (intact/not intact/unsure), as well as the total number and percentage of lesions across all subjects where any juvenile mite does/does not exhibit movement or peristalsis respectively, by dose group and RCM time point. The denominator for all percentages will be the total number of lesions identified at Baseline across all subjects.

There will be no imputation of missing or inconsistent data prior to the summary of the juvenile mite responses. Missing responses (due to the subject missing the complete RCM assessment or missing the individual lesion assessment) will be included under a 'Missing' category for each respective summary. Where juvenile mites are recorded as no longer present or where a lesion is recorded as no longer visible, responses will be assumed as follows: 'not intact' for morphology, 'without movement' and 'without peristalsis' for motility.

Mite Stages Visible by RCM

The presence of adult mites, juvenile mites, eggs and scybala observed over time will be assessed in an exploratory manner using descriptive summaries.

A summary will present the number and percentage of subjects with at least one lesion identified as having presence of each of the following respectively, by dose group and RCM time point: adult mites, juvenile mites, eggs, scybala. The table will additionally present the number and percentage of subjects recording presence of any one of

these options in at least one lesion, by dose group and RCM time point. The denominator for all percentages will be the number of subjects in the population for the respective dose group.

There will be no imputation of missing or inconsistent data for individual lesions prior to summary of the responses for mite stages present. Presence of a mite stage will be determined from all non-missing lesion assessments at the respective time point for the subject, including lesions assessed as no longer visible (assumed to have no mite stages present). The summary may therefore include subjects with missing lesion assessments where at least one assessment is non-missing. Subjects with completely missing RCM assessment data for all lesions at a time point will be included under a 'Missing' category for the respective summary.

6.10.3.2 Clinician Reported Scabies Signs and Symptoms

Subjects will be assessed for the clinical signs and symptoms of scabies infestation at Baseline, Day 7, 14 and 28. The following exploratory endpoints will be assessed using this data:

- Presence and number of total mites and burrows assessed visually at Days 7, 14 and 28.
- Changes in assessment of clinician-reported scabies symptomology, including extent of symptoms on body regions assessed by the number of anatomically-defined regions affected, number of lesions and severity grading of excoriations and erythema.

The clinician reported scabies signs and symptoms endpoints will be assessed in an exploratory manner using descriptive summaries.

Summaries will be presented for the number of subjects exhibiting each of the parasitological and clinical features, as well as those with new signs and symptoms, across all regions assessed for the subject by dose group and visit. These summaries will include the number and percentage of subjects with any:

- Mites;
- Burrows;
- Any parasitological features (mites or burrows);
- Lesions;
- Nodules;
- Excoriations (overall and by grade of excoriation);
- Erythema (overall and by grade of erythema);
- Any clinical features (lesions, nodules, excoriations or erythema);
- Any parasitological or clinical features (mites, burrows, lesions, nodules, excoriations or erythema);
- New mites relative to previous visit;
- New burrows relative to previous visit;
- New lesions relative to previous visit (including 'Yes' or 'Unsure');

- Region status at post-Baseline visits ('New region', 'Region clear from previous assessment').

The denominator for all percentages will be the number of subjects in the dose group with a non-missing assessment for at least one region at the respective visit and this will also be presented in the summaries. If a region is assessed as clear from previous assessment, it will be assumed to have no parasitological or clinical features present. If a region is new compared to the previous assessment, all mites, burrows or lesions detected at that region will be assumed to be new.

In addition to the above, the number of anatomical regions affected per subject will be summarized using descriptive statistics. This summary will exclude any regions recorded as clear from previous assessment.

A further summary table will present the number and percentage of subjects recording each of the following lesion number categories by anatomical region, dose group and visit:

- 0 lesions;
- 1-10 lesions;
- 11-20 lesions;
- 21-30 lesions;
- 31-40 lesions;
- 41-50 lesions;
- >50 lesions;
- Total subjects with any lesions.

The denominator for all percentages will be the number of subjects with a non-missing assessment for the respective region, visit and dose group and this will also be presented in the summary. If a region is assessed as clear from previous assessment, it will be assumed to have zero lesions present. Only regions with at least 1 subject presenting with at least 1 lesion at any visit will be presented. Regions where no lesions are present for any subject at any visit will not be presented.

Further summaries will also be presented for the following:

- Number of mites per subject across all anatomical regions, by dose group and visit.
- Number of burrows per subject across all anatomical regions, by dose group and visit.

Descriptive statistics for these summaries will include all subjects with a non-missing assessment for at least one region for the dose group and visit. If a region is assessed as clear from previous assessment, it will be assumed to have zero mites or burrows present respectively.

All scabies signs and symptoms data will be listed.

6.10.3.3 Patient Reported Outcomes

Numerical Rating Scale (NRS)

The NRS is a commonly used unidimensional scale which will be used as a measure of itch intensity. Subjects will complete the NRS at Baseline and Days 7, 14 and 28. A recall period of 24 hours will be used during which subjects will be asked to rate their average itch intensity (overall score) over those 24 hours and the itch intensity during the worst moment (peak score) of those 24 hours. For both of these questions, the subject will select a whole number from 0 to 10 corresponding to their itch intensity, where 0 is no itch and 10 is the worst itch imaginable.

Scores will be categorized mild, moderate and severe where mild is a score between 1 and 3 inclusive, moderate is a score between 4 and 6 inclusive and severe is a score between 7 and 10 inclusive. A score of 0 will be assigned a category of 'none' for the summaries and listings.

Descriptive statistics will be presented for both the overall score and the peak score observed values by dose group and visit. In addition, the number and percentage of subjects recording overall and peak scores within each severity band (none/mild/moderate/severe) will be presented by dose group and visit. Finally, the number and percentage of subjects recording a decrease from Baseline of ≥4 points in the overall and peak scores respectively will be presented by dose group for each post-Baseline visit, together with the number and percentage of subjects recording this decrease at any time post-Baseline. The denominator for all percentages will be the number of subjects with a non-missing score for the respective dose group and visit. The denominator for the summary of subjects recording a decrease of ≥4 points at any time post-Baseline will be the number of subjects with at least one non-missing post-Baseline score for the respective dose group and visit. The values used as the denominator will be included in the summary.

All NRS data will be listed including the observed score for each of the overall score and the peak score at each visit.

5-D Itch Scale

The 5-D Itch Scale measures five dimensions (duration, degree, direction, disability and distribution) of the impact of itching on the subject. The questionnaire consists of five items relating directly to each of the five dimensions. Subjects will complete the 5-D Itch Scale at Baseline and Days 7, 14 and 28. A recall period of one week will be used.

Questions 1 to 3 will be answered using a five-point Likert scale. These questions are scored according to the value selected by the subject i.e. the lowest duration, degree or direction response is scored a 1 and the highest duration, degree or direction is scored a 5.

Question 4 is subdivided into four further subcategories of sleep, leisure/social, housework/errands and work/school also answered using a five-point Likert scale. The highest scoring response to these four sub-questions is taken as the score for question 4. The subcategories of leisure/social, housework/errands and work/school can be answered with an additional category of N/A, however as the highest score of the four subcategories is used for this question, and N/A is not an option for sleep, the overall score remains in the range of 1 to 5.

Question 5 requires the subject to indicate the areas in which they have experienced itching in the previous one week period. The number of body parts selected is then attributed the following scores: 0-2 body parts = 1, 3-5 body parts = 2, 6-10 body parts = 3, 11-13 body parts = 4 and 14-16 body parts = 5.

The overall score is calculated as the summation of the scores of Questions 1 to 3, the highest score of Question 4 and the collated score of Question 5. The overall score ranges from 5 to 25 where higher scores indicate an increased itch related impact.

Overall scores will be categorized mild, moderate and severe where mild is a score between 5 and 11 inclusive, moderate is a score between 12 and 17 inclusive and severe is a score between 18 and 25 inclusive.

Descriptive statistics will be presented for the overall 5-D Itch Scale score observed values over time, as well as summaries of subjects by severity band and subjects with a decrease from Baseline of ≥4 points as described for the NRS scores above.

All 5-D Itch Scale data will be listed including the observed score for each question and sub-question and the overall score at each visit.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire to assess health-related quality of life. Subjects will complete the DLQI at Baseline and Days 7, 14 and 28.

For questions 1 to 6 and 8 to 10, the following responses are required: “not at all,” “a little,” “a lot,” or “very much”. The scoring for each of these questions is as follows: Very much = 3, a lot/quite a lot = 2, a little = 1, not at all = 0, not relevant = 0, question unanswered = 0.

For question 7, if the answer is yes = 3, if no and no further information provided = 0, if no and the further question is asked then the responses are as follows: A lot = 2; a little = 1; Not at all, N/A or incomplete = 0.

The overall DLQI score is calculated as the total score over all items and ranges from 0 to 30 where higher scores indicate greater health-related quality of life impairment.

The overall DLQI score will also be categorized as mild, moderate and severe where mild is a score between 0 and 5 inclusive, moderate is a score between 6 and 10 inclusive and severe is a score between 11 and 30 inclusive.

Descriptive statistics will be presented for the overall DLQI score observed values over time, as well as summaries of subjects by severity band and subjects with a decrease from Baseline of ≥4 points as described for the NRS scores above.

All DLQI data will be listed including the observed score for each question as well as the overall score at each visit.

6.10.3.4 Clinical Cure Rate

Clinical cure rate is defined as resolution of all scabies signs and symptoms present at Baseline, no new scabies signs and symptoms and no evidence of mites by dermoscopy.

Clinical cure rate will be assessed at Days 7, 14 and 28. At each of these visits, a subject will be considered a responder, as determined by the clinician reported scabies signs and symptoms, if region status is ‘Region clear from previous assessment’, for each anatomical region assessed at that visit.

For each subject, imputation of missing assessments will be applied as follows. Where the scabies signs and symptoms assessment has been completed for a visit but this includes a missing assessment for a region previously assessed at an earlier time point, the region status will be imputed using the most recent previous assessment for the respective region (last observation carried forward). However, if the scabies signs and symptoms assessment has not been completed for a visit, or the assessments for all regions previously assessed are missing, no imputation will be applied and the subject will be excluded from the denominator for clinical cure rate at that visit.

Where rescue medication has been taken (identified on the concomitant medications page of the eCRF), any assessment indicating clinical cure response subsequent to the start date of rescue medication will be ignored and the subject will be considered a non-responder. Visit responses identified at any visit prior to or on the start date of rescue medication for the subject will be unaffected.

The number and percentage of responders, together with the Clopper-Pearson 95% CI for the percentage, will be presented for each dose group at each post-Baseline visit. The denominator for all percentages will be the number of subjects with a non-missing scabies signs and symptoms assessment for the respective dose group and visit and this will also be presented in the summary.

A flag will be added to the listing of scabies signs and symptoms data to indicate subjects identified as responders at each time point.

Following review of the above summaries, additional post hoc analyses may be considered, for example sensitivity analyses repeating the above clinical cure rate summary without imputation for missing assessments or the use of rescue medication. Any post-hoc analyses to be performed will be fully defined in a SAP Addendum prior to conducting the analyses.

6.11 Multiplicity

Given the exploratory nature of the study, no adjustment for multiple comparisons will be made.

6.12 Pharmacokinetics

Plasma for determining the pharmacokinetics of moxidectin will be collected at Baseline (pre-dose), Hours 2, 3, 4, 8, 24, 48 and 72, and at Days 7, 14 and 28.

A separate PKAP will describe the reporting of PK concentrations as well as the derivation and reporting of PK parameters.

6.13 Pharmacodynamics

Details will be included in the separate PKAP regarding analysis of the relationship between efficacy endpoints and plasma concentrations of moxidectin.

6.14 Safety Evaluation

The primary safety endpoint is the assessment of incidence and severity of AEs, physical examinations, and measurement of vital signs up to and including Week 12, and laboratory safety parameters up to and including Day 28.

Details regarding the evaluation of this data are given in the following respective sections.

6.14.1 Adverse Events

Adverse events (AEs) will be coded using the latest MedDRA dictionary version in place at the time of analysis and documented in the DMP. The version used will be indicated in the data summaries and listings. If updates to later versions are required during the study, this will be reflected in the DMP and the outputs.

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the administration study drug or worsened after study drug exposure. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

A study drug-related TEAE is defined as a TEAE that is possibly, probably or definitely related to the study drug. If the TEAE has a missing relationship it is assumed to be related to the study drug for analysis purposes.

Each AE will be graded for severity using the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials. Details regarding this grading are given in Appendix 18.1 of the protocol. For AEs not specifically identified in this grading table, Section 12.2.1 Table 10 of the protocol will be used to apply the severity grades.

A summary table will present the following:

- TEAEs (number of events and number of subjects);
- Serious TEAEs (number of events and number of subjects);
- Serious study drug-related TEAEs (number of events and number of subjects);
- TEAEs by severity grade (Grade 1 – 4) (number of events and number of subjects);
- TEAEs by relationship to study drug (Unrelated, Unlikely, Possible, Probably, Definite) and the pooled study drug related category (Related/Unrelated) (number of events and number of subjects);
- TEAEs leading to withdrawal from study (number of subjects only);
- TEAEs leading to death (number of subjects only).

In the above summaries, if a subject experienced more than one TEAE, the subject will be counted once using the most related event for the “by relationship to study drug” and “study drug-related” summaries and at the worst severity for the “by severity grade” summary.

The following tables will be presented:

- TEAEs by System Organ Class (SOC) and Preferred Term (PT);
- TEAEs by PT;
- TEAEs by SOC, PT and severity grade;

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs.

Further details of the above three tables are given below:

1. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT.

2. If a subject experienced more than one TEAE the subject will be counted once for each PT.
3. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT at the worst severity grade.

Adverse event data will be listed in full and this will also include a treatment emergent flag, the time of onset and cessation of event relative to dosing of study drug and duration of AE.

6.14.2 Clinical Laboratory Evaluation

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

Observed values and change from Baseline in hematology and biochemistry assessments will be summarized descriptively over time by dose group.

Hematology and biochemistry data will be listed separately including change from Baseline, flagging all out of range values. Toxicity grades will be derived, where possible, for each hematology and biochemistry result as described in Section 18.1 of the protocol and these derived grades will be included in the listings. Parameters will be presented in the same order as the eCRF.

6.14.3 Vital Signs

Vital sign observed values will be summarized over time by parameter (unit) and dose group.

Weight, collected at Baseline and Week 12, will be included in the vital signs summaries and listing.

Oral and aural body temperature measurements will be summarized and listed as separate parameters within the outputs.

All vital sign data will be listed.

6.14.4 Electrocardiography

Electrocardiography data will not be collected in the eCRF and will not be summarized or listed.

6.14.5 Physical Examination

Individual subject physical examination data will be listed for the full assessment carried out at screening. For subsequent assessments, any findings will be documented as AEs and the assessment timings will not be listed.

6.14.6 Pregnancy Test

Pregnancy test details and results will be listed.

6.15 Changes from the Protocol Planned Analysis

- The definition of the FAS has been amended to remove the statement regarding the requirement for ‘observed data for the particular analysis undertaken’. Instead, the inclusion/exclusion of subjects with missing data in analyses and summaries of the relevant endpoints on the FAS is addressed via the methods for handling missing data, as described in the respective sections of this SAP.

In addition, some imputation of missing data has been incorporated with respect to analysis and summary of the primary endpoint, rather than exclusion of any subjects with missing observations. These changes were considered more appropriate to ensure closer adherence to the intent to treat principle as well as to ensure clarity regarding the subjects included in the population and in each respective analysis.

- The exploratory endpoint ‘presence of eggs and scybala in burrows’ has been addressed via the summary of ‘mite stages visible by RCM’.