

CLINICAL STUDY PROTOCOL: MDGH-MOX-1008

**A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group
Study to Evaluate the Potential Effect of a Single Oral Dose of
Moxidectin on the Cardiac QT Interval of Healthy Volunteers**

Statistical Analysis Plan

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CONFIDENTIAL AND PROPRIETARY INFORMATION

Statistical Analysis Plan Signature Page

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Potential Effect of a Single Oral Dose of Moxidectin on the Cardiac QT Interval of Healthy Volunteers

Investigational Product: Moxidectin

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LIST OF ABBREVIATIONS

λ_z	terminal elimination rate constant
$Ae_{urine(0-24)}$	urinary recovery between 0 and 24 hours
$Ae_{urine(0-72)}$	urinary recovery between 0 and 72 hours
$Ae_{urine(24-48)}$	urinary recovery between 24 and 48 hours
$Ae_{urine(48-72)}$	urinary recovery between 48 and 72 hours
$Ae_{feces(0-24)}$	fecal recovery between 0 and 24 hours
$Ae_{feces(0-72)}$	fecal recovery between 0 and 72 hours
$Ae_{feces(24-48)}$	fecal recovery between 24 and 48 hours
$Ae_{feces(48-72)}$	fecal recovery between 48 and 72 hours
AE	adverse event
AIC	Akaike's information criterion
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-48}	area under the plasma concentration-time curve from time 0 to 48 hours
AUC_{0-72}	area under the plasma concentration-time curve from time 0 to 72 hours
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time 0 extrapolated to the last observed concentration
AUC_{24-48}	area under the plasma concentration-time curve from time 24 to 48 hours
AUC_{48-72}	area under the plasma concentration-time curve from time 48 to 72 hours
AUC_{ext}	percentage of AUC_{0-inf} obtained by extrapolation
BQL	below the quantitation limit
CI	confidence interval
CL/F	apparent clearance following extravascular administration
$CL_{r(0-24)}$	renal clearance from time 0 to 24 hours
$CL_{r(0-72)}$	renal clearance from time 0 to 72 hours
$CL_{r(24-48)}$	renal clearance from 24 to 48 hours
$CL_{r(48-72)}$	renal clearance from 48 to 72 hours
C_{max}	maximum observed plasma concentration
CRU	clinical research unit
C_{feces}	concentration of drug in feces
C_{urine}	concentration of drug in urine
CV%	percent coefficient of variation
ddQTcF	time-matched, placebo-corrected, baseline-adjusted QTcF

dQTcF	baseline-adjusted QTcF
ECG	electrocardiogram
eCRF	electronic case report form
E _{max}	maximum effect
HR	heart rate
LLOQ	lower limit of quantitation
MDGH	Medicines Development for Global Health
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
n	number
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
QTc	corrected QT interval
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
QTcI	QT interval with individual correction
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
t _{1/2}	terminal elimination half-life
TEAE	treatment-emergent adverse event
T _{max}	time to the maximum observed plasma concentration
U _{max}	time of maximal ddQTcF
V _d /F	apparent volume of distribution following extravascular administration
V _{urine}	urine volume
W _{feces}	fecal mass

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used for the analysis and summarization of pharmacokinetic (PK) and safety data from Protocol MDGH-MOX-1008 with Spaulding Clinical Research, LLC responsible for the analysis and presentation of the PK and safety data. In addition, the primary and exploratory endpoints detailing the pharmacodynamic (PD) analysis of electrocardiograms (ECGs) will be described in this analysis plan, with Mason Cardiac Safety Consultation responsible for the analysis and presentation of these data.

The analysis plan will be finalized prior to database lock. Any changes made after finalization of the analysis plan will be documented. Related documents are the study protocol and electronic case report forms (eCRFs).

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective is to analyze the effect of a single oral dose of moxidectin on the QT interval associated with plasma moxidectin concentrations.

2.2 Secondary Objective

The secondary objective is to assess the safety and PK of a single oral dose of moxidectin.

2.3 Exploratory Objectives

The exploratory objectives are:

- To gain preliminary information in humans on the metabolism and excretion of moxidectin;
- To evaluate the baseline-corrected changes in other ECG and cardiovascular parameters; and
- To evaluate the ECG morphologic changes related to cardiac repolarization (ST segment and T waves).

2.4 Endpoints

2.4.1 Pharmacokinetic Endpoints

The plasma PK parameters of moxidectin will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following plasma PK parameters will be estimated using noncompartmental parameters, unless otherwise specified:

1. AUC_{0-last} – area under the plasma concentration-time curve (AUC) from time 0 extrapolated to the last observed concentration;
2. AUC_{0-inf} – AUC from time 0 extrapolated to infinity;
3. AUC_{ext} – percentage of AUC_{0-inf} obtained by extrapolation (a diagnostic parameter calculated and listed in the data listing, but not included in the descriptive statistics);
4. AUC_{0-24} – AUC from time 0 to 24 hours;
5. AUC_{0-48} – AUC from time 0 to 48 hours;
6. AUC_{0-72} – AUC from time 0 to 72 hours;
7. AUC_{24-48} – AUC from time 24 to 48 hours;
8. AUC_{48-72} – AUC from time 48 to 72 hours;
9. C_{max} – maximum observed plasma concentration;
10. T_{max} – time to C_{max} ;
11. $t_{1/2}$ – terminal elimination half-life;
12. λ_z – terminal elimination rate constant;
13. CL/F – apparent clearance following extravascular administration;

14. V_d/F – apparent volume of distribution following extravascular administration.

In addition, exploratory endpoints include descriptions of metabolite concentrations over time for analytes in plasma, urine, and feces and metabolite to parent (molar equivalents) ratios over time for analytes in plasma and urine. The following parameters will be calculated for urine:

1. $Ae_{urine(0-72)}$ – urinary recovery between 0 and 72 hours;
2. $Ae_{urine(0-24)}$ – urinary recovery between 0 and 24 hours;
3. $Ae_{urine(24-48)}$ – urinary recovery between 24 and 48 hours;
4. $Ae_{urine(48-72)}$ – urinary recovery between 48 and 72 hours;
5. $CL_{r(0-72)}$ – renal clearance from time 0 to 72 hours;
6. $CL_{r(0-24)}$ – renal clearance from time 0 to 24 hours;
7. $CL_{r(24-48)}$ – renal clearance from 24 to 48 hours;
8. $CL_{r(48-72)}$ – renal clearance from 48 to 72 hours.

The following parameters will be calculated for feces:

1. $Ae_{feces(0-72)}$ – fecal recovery between 0 and 72 hours;
2. $Ae_{feces(0-24)}$ – fecal recovery between 0 and 24 hours;
3. $Ae_{feces(24-48)}$ – fecal recovery between 24 and 48 hours;
4. $Ae_{feces(48-72)}$ – fecal recovery between 48 and 72 hours.

The PK endpoints are considered secondary study endpoints. The main PK parameters of interest in this study are the cumulative and pre-specified time-window AUCs for moxidectin concentrations in plasma.

2.4.2 Pharmacodynamic Endpoints

The PD endpoints are calculated from the mean of the triplicate continuous 12-lead ECG data as:

1. $dQTcF$ – baseline-adjusted QT interval corrected by Fridericia's formula ($QTcF$);
2. $ddQTcF$ – time-matched, placebo-corrected, baseline-adjusted $QTcF$, which is calculated as the $dQTcF$ minus the time-matched mean $dQTcF$ of all placebo subjects at each postdose time point ($ddQTcF=[dQTcF(\text{active dose groups})-\text{mean } dQTcF(\text{placebo})]$);

The primary study endpoint is the $dQTcF$ matched to the plasma concentration of moxidectin collected at the same time point.

Analogous-derived exploratory endpoints are also calculated for heart rate (HR), and duration of PR, RR, and QRS interval parameters.

The ECG morphologic changes data are also considered an exploratory endpoint.

2.4.3 Safety and Tolerability Endpoints

The safety endpoints are:

1. Monitoring and reporting of adverse events (AEs);
2. Vital sign measurements;
3. Clinical laboratory test results (hematology, serum chemistry, urinalysis);
4. 12-lead safety ECG results;
5. Physical examination findings.

Secondary study endpoints include AEs, clinical laboratory test results, vital sign measurement, safety 12-lead ECG results, and physical examination findings.

3 STUDY DESIGN

3.1 Number of Subjects

There will be 60 generally healthy male subjects between 18 and 50 years old enrolled in the study.

3.2 Sample Size Considerations

The sample size of 60 subjects (10 subjects each in 6 treatment groups) is considered adequate to explore the effects of moxidectin on the corrected QT interval (QTc), as this design will yield 900 QTc-PK pairs in total. Additional subjects may be enrolled as alternates in this study should a subject choose to withdraw consent before study drug administration. Alternate subjects will remain in the clinical research unit (CRU) from Check-in until all subjects due to be dosed have completed dosing. Subjects who withdraw after dosing will not be replaced.

3.3 Study Design

This is a randomized, single-center, double-blind, placebo-controlled, parallel-group study in which healthy male subjects will be randomly assigned to one of the following treatments:

- Treatment 1: moxidectin 4 mg (n = 10)
- Treatment 2: moxidectin 8 mg (n = 10)
- Treatment 3: moxidectin 16 mg (n = 10)
- Treatment 4: moxidectin 24 mg (n = 10)
- Treatment 5: moxidectin 36 mg (n = 10)
- Treatment 6: matching placebo (n = 10)

Subjects will be screened for eligibility up to 28 days before randomization. Subjects who meet all of the inclusion and none of the exclusion criteria will be admitted to the CRU on Day -1 (not less than 12 hours before scheduled dosing). Subjects will remain in the CRU for at least 72 hours after dosing and will return to the CRU for further assessment on Days 8, 15, and 22, and Week 12. At Week 8, subjects will be contacted via telephone for recording of AEs and concomitant medication use.

Randomized subjects will be assigned unique subject numbers in sequential order based on their order of qualification. Randomization will take place before dosing on Day 1, with equal random assignment to each treatment. Subjects are considered as enrolled once randomized.

The duration of participation in the study for each subject will be up to approximately 112 days, including Screening.

For purposes of statistical analysis, this study is divided into 2 study periods:

- Period 1: Commences at Screening and will finish on Day 22. 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 data from Period 1 will be analyzed.
- Period 2: Runs from Day 23 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.

The overall schedule of events is provided in Table 1 and the Period 1, Day -1 to Day 4 schedule of events is provided in Table 2.

Table 1. Overall Schedule of Events

Assessment	Screening D-28 to D-2	Period 1									Period 2										
		D-1	Baseline D1 (Predose)	D1	D2	D3	D4	D8	D15	D22	W8	W12 ^f									
Outpatient visit	X	Refer to Table 2: Schedule of Events for Period 1 (Day -1 to Day 4)									X	X	X		X						
Informed consent	X																				
Telephone call																				X	
Inclusion/exclusion criteria review	X																				
Demographic information	X																				
Medical and medication history	X																				
Physical examination ^a	X															X	X	X			X
Vital signs ^b	X																	X			X
Height	X																				
Body weight	X																				
Calculation of body mass index	X																				
Hematology, serum chemistry, and urinalysis ^c	X																	X			X
Urine drug screen	X																				
Serology	X																				
Safety 12-lead electrocardiogram ^d	X																	X			X
Continuous 12-lead electrocardiogram																					
PK blood sample collection ^e																X	X	X			
PK feces sample collection																					
PK urine sample collection																					
Randomization																					
Study drug administration																					
Adverse events	X																				
Concomitant medications	X																				

Abbreviations: D, day; PK, pharmacokinetic; W, week.

- a. 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.
- b. Vital signs (supine blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured after the subject has rested for approximately 5 minutes.
- c. Blood samples for hematology and serum chemistry and a urine sample for urinalysis will be collected at Screening, on Days -1, 2, 3, 4, 22, and Week 12. Subjects must fast for at least 8 hours before clinical laboratory testing.
- d. Standard 12-lead safety electrocardiograms will be performed after the subject has been supine for approximately 10 minutes. At each relevant time point, safety 12-lead electrocardiograms will be performed before blood collection.
- e. Blood samples will be collected for PK assessments at Baseline (0 hour; within 15 minutes before dosing) and at 0.5, 1, 2, 3, 4*, 5, 6, 8, 12*, 24*, 36*, 48, 60*, and 72 hours after dosing, and on Days 8, 15, and 22. (* Planned time points for analysis of moxidectin metabolite concentrations, 8-mg cohort only)
- f. If a subject discontinues from the study or is withdrawn, the investigator will notify the sponsor and, when possible, will perform the following procedures: vital sign measurements; safety 12-lead electrocardiogram; symptom-based physical examination; collection of adverse events; and clinical laboratory evaluation (including hematology, serum chemistry, and urinalysis).

Table 2. Schedule of Events for Period 1 (Day –1 to Day 4)

Assessment	Period 1																
	Day –1	Day 1 (Predose)	Day 1										Day 2		Day 3		Day 4
Hour relative to dosing	≤-24		0	0.5	1	2	3	4	5	6	8	12	24	36	48	60	72
Admission to unit	X																
Discharge from unit																	X
Confirmation of eligibility	X																
Physical examination ^a	X							X				X	X		X		X
Body weight	X																
Hematology, serum chemistry, and urinalysis	X												X		X		X
Urine drug screen	X																
Randomization		X															
Commence fasting ^b	X																
Study drug administration ^b			X														
Consumption of a standardized meal								X									
Safety 12-lead electrocardiogram ^c				X	X	X	X	X	X	X	X	X	X		X		X
Continuous 12-lead electrocardiogram ^d			←-----X-----→														
Vital signs ^e		X															X
PK blood sample collection ^f		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK feces sample collection ^g		X	←-----X-----→										←--X--→		←-----X-----→		
PK urine sample collection ^h		X	←-----X-----→										←--X--→		←-----X-----→		
Adverse events	X	X	←-----X-----→														
Concomitant medications	X	X	←-----X-----→														

Abbreviation: PK, pharmacokinetic.

- a. 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.
- b. On Day –1, subjects will begin fasting as instructed and water can be taken ad libitum. On Day 1, study drug administration (moxidectin or placebo) will occur after an overnight fast of at least 10 hours. Study drug will be administered with at least 240 milliliters of water. No food will be allowed for 4 hours after dosing; however, water can be taken ad libitum.
- c. Standard 12-lead safety electrocardiograms (ECGs) will be performed after the subject has been supine for approximately 10 minutes. At each relevant time point, safety 12-lead ECGs will be performed before blood collection.
- d. Continuous 12-lead ECG data will be obtained using a Mortara continuous 12-lead digital ECG recorder, with triplicate 10-second ECG recordings (approximately 1 minute apart) extracted at the following time points: Baseline (before dosing on Day 1) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing.
- e. Vital signs (supine blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured after the subject has rested for approximately 5 minutes.
- f. Blood samples will be collected for PK assessments at Baseline (0 hour; within 15 minutes before dosing) and at 0.5, 1, 2, 3, 4*, 5, 6, 8, 12*, 24*, 36*, 48, 60*, and 72 hours after dosing, and on Days 8, 15, and 22. (* Planned time points for analysis of moxidectin metabolite concentrations, 8-mg cohort only)

- g. Feces samples will be collected for PK assessments before dosing (single predose collection*) and each bowel motion during confinement in the clinical research unit. Samples will be pooled at the central laboratory for intervals of 0 to 24, 24 to 48, and 48 to 72 hours after dosing (up to 4 samples). (* Feces specimens [the whole bowel movement] may be collected by subjects [at home] within 2 days of submitting them to study staff on Day -1. Collection instructions will be provided at Screening.)
- h. Urine samples will be collected for PK assessments before dosing (single predose collection; first void sample in the morning is acceptable and volume recording is not required) and for pooled intervals of 0 to 24, 24 to 48, and 48 to 72 hours after dosing (4 samples).

3.4 Unblinding Procedures

The study will be double-blind and the blind will be maintained through the use of blinding envelopes held by the dispensing pharmacist. All randomization information will be secured and housed in a locked storage area, accessible only by the randomization personnel, the assigned pharmacist, and his or her verifier(s). Neither the subjects nor CRU staff administering the study drug will know the study drug being administered. To maintain the blind, each subject will receive 18 matching tablets. The placebo tablets will be matched in appearance to the active study drug, and will contain the same excipients as moxidectin tablets but will not contain moxidectin.

The study drug blind will not be broken by the investigator or designee unless information concerning the study drug is necessary for the medical treatment of the subject. The blinding envelopes containing randomization information for each subject will be sent to the CRU. The sponsor or medical monitor must be notified immediately if the study drug blind is broken. The date, time, and reason that the blind was broken will be recorded in the source documents.

For Period 1, which commences at Screening, the study blind will be maintained for all personnel through Day 22. Once all subjects complete Period 1, the database will be locked for all data to Day 22. The database will not yet include study data from Week 8 or 12. To allow primary analysis after completion of Day 22, the study blind will be broken for data management, the study statistician, primary and validation programmers, the Cardiac Safety Expert (Mason Cardiac Safety Consultation), the PK vendor (Nuventra Pharma Sciences, Inc), medical writers, and the sponsor for purposes of data analysis and review. All other personnel, including those conducting subject procedures and assessments, will remain blinded.

The study will then be unblinded for all other personnel including the clinic and other biometrics roles after all subjects complete the Week 12 assessments and the data collected in Period 2 is locked.

3.5 Interim Analyses

The primary analysis will be performed once all subjects have completed Day 22. An additional safety supplement will be provided once all subjects complete Week 12. In addition, concentrations of moxidectin in urine and feces and moxidectin metabolites in plasma and urine and associated PK parameters will not be included in the primary analyses after Day 22; however, those data will be analyzed after Period 2 and included in the safety supplement. No interim analysis and early termination is planned. However, the overall safety pattern will be monitored closely and the study may be discontinued for valid scientific or administrative reasons.

Only 1 set of datasets, tables, listings, and graphs are outlined in this SAP. The intent is to summarize all available data after Period 1, and then, rather than producing 2 sets of datasets and tables (1 for each period), the datasets and tables will be reproduced with the

additional data added from Period 2 to replace the existing datasets and TLFs from Period 1.

4 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined prior to breaking the blind. All other analyses, if any, designed subsequent to breaking the blind will be considered post hoc analyses and will be applied as exploratory methodology. All post hoc analyses will be identified as such in the clinical study report.

All statistical tests will be tested at $\alpha=0.05$, 2-sided significance level, unless otherwise stated. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. Confidence intervals (CIs) will be presented where appropriate. Descriptive statistics for categorical variables will consist of frequency and percentage.

All analyses will be conducted with SAS[®] Version 9.4 or later using procedures appropriate for the particular analysis.

5 ANALYSIS POPULATIONS

5.1 Safety Population

The safety population will include all subjects who receive at least 1 dose of study drug. Subjects in this population will be used for demographic and safety summaries. Subjects in this population will be analyzed according to the drug received (actual drug concentration).

5.2 Pharmacokinetic Population

The PK population will include all subjects who receive at least 1 dose of moxidectin and provide an adequate number of blood samples for the determination of plasma PK parameters. Subjects in this population will be used for all PK summaries. Subjects in this population will be analyzed according to the drug received (actual drug concentration).

5.3 Electrocardiogram Population

The ECG population will include all subjects who receive at least 1 dose of study drug and have at least 1 pair of predose and postdose QTc data for at least 1 time point. Subjects in this population will be used for all digital ECG summaries and analyses. Subjects in this population will be analyzed as randomized.

5.4 Pharmacokinetic/Pharmacodynamic Population

The PK/PD population will include all subjects in the ECG population who have time-matched plasma concentrations for the active moxidectin treatments. Subjects in this population will be analyzed according to the drug received (actual drug concentration).

5.5 Handling of Missing Data

Missing data will not be imputed, except in the case of missing dates or times, for which values will be imputed if needed for analysis (ie, use of nominal time point value if elapsed time is missing). Data that are excluded from the descriptive or inferential analyses will be included in the data listings. This will include those measurements from excluded subjects, or measurements from unscheduled collections or extra measurements that may arise from 2 or more analyses of the plasma sample from the same time point.

In calculation of the concentration summaries and display in graphs, if values are below the quantitation limit (BQL) they will be set to zero; however, they will be presented as BQL in data listings. If all concentrations at a given time point are BQL, the mean will be presented as zero and the SD and percent coefficient of variation (CV%) will be reported as not applicable. If a mean concentration is BQL, it will be flagged in the summary table. For the calculation of PK parameters, BQL values that occur before dose administration will be set to zero. The BQL values that occur after dose administration, but before the first measurable concentration will be set to zero. If a BQL value occurs at the end of the collection interval (after the last quantifiable concentration) it will be treated as missing data. If 2 BQL values occur in succession after C_{max} , the profile will be deemed to have terminated at the first BQL value and any subsequent concentrations will

be omitted from the PK calculations.

5.6 Key Definitions

Baseline value is defined as the last available off-treatment value collected prior to the time of the first dose.

Relative study day is defined as number of days from the first dose date and will be presented on all listings where a complete date is presented.

6 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

6.1 Subject Discontinuation

The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study and the primary reason for withdrawal or discontinuation will be summarized.

A data listing of subject disposition including study completion status and reason for study discontinuation will be provided. In addition, subject populations and reasons for exclusion from the population will be provided in a data listing.

6.2 Protocol Deviations

Protocol deviations will be captured as a log from clinical monitoring and presented in a data listing.

6.3 Demographics and Baseline Characteristics

Descriptive statistics (ie, mean, SD, median, minimum, and maximum) will be calculated for continuous demographic and baseline characteristics variables (age, weight at Screening, height, and body mass index at Screening) and frequency counts and percentages will be tabulated for categorical demographic variables (sex, race, and ethnicity) for each treatment and overall.

A data listing will be provided for all demographic data. In addition, the baseline characteristics of weight, height, and body mass index will be included in the vital sign data listing.

6.4 Medical History

Medical history data will be mapped using the current version of Medical Dictionary for Regulatory Activities (MedDRA) to system organ class (SOC) and preferred term (PT) and will be listed by subject identification number, medical condition reported term, onset date, and ongoing status/resolution date.

6.5 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria not met will be provided in a data listing.

7 PHARMACOKINETIC ANALYSES

7.1 Moxidectin and Metabolite Concentrations

Moxidectin concentrations in plasma will be collected and analyzed for all subjects. Moxidectin concentrations in urine and feces and metabolite concentrations in plasma and urine will be analyzed for the subset of subjects who receive the 8-mg dose (See Table 3).

Table 3. Analyses for Each Matrix

Matrix	Analysis for moxidectin	Analysis for moxidectin metabolites
Plasma	✓ ^a	✓ ^b
Urine	✓ ^b	✓ ^b
Feces	✓ ^b	not analyzed

^a All subjects ^b 8-mg cohort

For plasma, the time course of concentrations of moxidectin will be presented and summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by time point and treatment. For urine and feces, the amount of moxidectin excreted by collection interval will be presented and summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by time point and treatment.

For plasma and urine, amount of metabolite by collection interval and metabolite to parent (molar equivalents) ratios will be presented and summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by collection interval and treatment.

Concentrations that are BQL will be treated as outlined in Section 5.5. Mean plasma concentration-time profiles will be plotted by treatment on linear and semilogarithmic scales using nominal times. Individual concentration-time plots and spaghetti plots with subject concentration-time profiles overlaid by respective treatments will be included in the appendices using linear and semilogarithmic scales.

7.2 Pharmacokinetic Parameters

All PK analyses will be performed according to applicable standard operating procedures and protocol specifications. Pharmacokinetic parameters will be calculated for the PK population using Phoenix[®] WinNonlin[®] version 6.3 or later (Certara, Princeton, New Jersey) using actual sampling times. If actual times are missing, nominal times may be used and will be noted in the appropriate data listing.

The PK parameters for plasma moxidectin will be estimated as follows (data permitting):

AUC _{0-last} :	AUC from time 0 extrapolated to the last observed concentration, calculated by a combination of linear and logarithmic trapezoidal methods (linear up/log down method).
AUC _{0-inf} :	AUC from time 0 extrapolated to infinity, calculated as AUC _{0-last} + C _{last} /λ _z where, C _{last} is the last measurable concentration.
AUC _{ext} :	Percentage of AUC _{0-inf} obtained by extrapolation, calculated as [(AUC _{0-inf} – AUC _{0-last})/AUC _{0-inf}] * 100 (a diagnostic parameter calculated and listed in the data listing, but not included in the descriptive statistics).
AUC ₀₋₂₄ :	AUC from time 0 to 24 hours.
AUC ₀₋₄₈ :	AUC from time 0 to 48 hours.
AUC ₀₋₇₂ :	AUC from time 0 to 72 hours.
AUC ₂₄₋₄₈ :	AUC from time 24 to 48 hours.
AUC ₄₈₋₇₂ :	AUC from time 48 to 72 hours.
C _{max} :	Maximum observed plasma concentration, observed by inspection of individual study participant plasma concentration-time plots.
T _{max} :	Time to C _{max} , obtained directly from the observed concentration-time data.
t _{1/2} :	Terminal elimination half-life, calculated using the equation (ln[2]/λ _z).
λ _z :	Terminal elimination rate constant, estimated by linear regression of logarithmically transformed concentration-time data. Calculation of λ _z requires a minimum of 3 data points after (and not including) C _{max} . The coefficient of determination (R ²), for the linear regression must be at least 0.95.
CL/F:	Apparent clearance following extravascular administration, calculated as Dose/AUC _{0-inf} .
V _d /F	Apparent volume of distribution following extravascular administration, calculated as Dose/(λ _z * AUC _{0-inf}).

All subjects in the PK population will be included in the descriptive statistics for the PK parameters. No value for λ_z, AUC_{0-inf}, AUC_{ext}, CL/F, V_d/F, or t_{1/2} will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile. No PK parameters will be calculated for subjects with fewer than 4 quantifiable concentrations following BQL imputation. Additional PK parameters may be calculated, as necessary, to fully characterize the PK profile of moxidectin.

The PK parameters for urine moxidectin will be estimated as follows (data permitting):

$Ae_{urine(0-72)}$:	Urinary recovery between 0 and 72 hours, where $Ae_{(0-t)} = \sum_{n=1}^t (C_{urine,i} * V_{urine,i})$, where $C_{urine,i}$ represents the concentration of drug in urine during collection interval i, and $V_{urine,i}$ represents the cumulative urine volume during collection interval i.
$Ae_{urine(0-24)}$:	Urinary recovery between 0 and 24 hours, where $Ae_{(0-24)} = C_{urine(0-24)} * V_{urine(0-24)}$.
$Ae_{urine(24-48)}$:	Urinary recovery between 24 and 48 hours, where $Ae_{(24-48)} = C_{urine(24-48)} * V_{urine(24-48)}$.
$Ae_{urine(48-72)}$:	Urinary recovery between 48 and 72 hours, where $Ae_{(48-72)} = C_{urine(48-72)} * V_{urine(48-72)}$.
$CL_{r(0-72)}$:	Renal clearance from 0 to 72 hours, where $Ae_{(0-72)}/AUC_{(0-72)}$.
$CL_{r(0-24)}$:	Renal clearance from 0 to 24 hours, where $Ae_{(0-24)}/AUC_{(0-24)}$.
$CL_{r(24-48)}$:	Renal clearance from 24 to 48 hours, where $Ae_{(24-48)}/AUC_{(24-48)}$.
$CL_{r(48-72)}$:	Renal clearance from 48 to 72 hours, where $Ae_{(48-72)}/AUC_{(48-72)}$.

The PK parameters for feces moxidectin will be estimated as follows (data permitting):

$Ae_{feces(0-72)}$:	Fecal recovery between 0 and 72 hours, where $Ae_{(0-t)} = \sum_{n=1}^t (C_{feces,i} * W_{feces,i})$, where $C_{feces,i}$ represents the concentration of drug in feces (ng/g) during collection interval i, and $W_{feces,i}$ represents the total fecal mass during collection interval i.
$Ae_{feces(0-24)}$:	Fecal recovery between 0 and 24 hours, where $Ae_{(0-24)} = C_{feces(0-24)} * W_{feces(0-24)}$.
$Ae_{feces(24-48)}$:	Fecal recovery between 24 and 48 hours, where $Ae_{(24-48)} = C_{feces(24-48)} * W_{feces(24-48)}$.
$Ae_{feces(48-72)}$:	Fecal recovery between 48 and 72 hours, where $Ae_{(48-72)} = C_{feces(48-72)} * W_{feces(48-72)}$.

Descriptive statistics of PK parameters for moxidectin will be provided for the PK population by treatment and will include n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV% (where applicable).

8 PHARMACODYNAMIC ANALYSES

The PD analyses for the continuous 12-lead ECG data is outlined in this section, but will be the responsibility of Mason Cardiac Safety Consultation.

8.1 Continuous 12-Lead Electrocardiogram Assessments

Pharmacodynamics will be assessed via ECGs obtained using a Mortara continuous 12-lead digital ECG recorder, which will be reviewed and analyzed by the central ECG laboratory. The device will remain connected to the subject during the confinement period. The ECG data will be transmitted wirelessly to the Surveyor system, which will extract triplicate 10-second ECG recordings (approximately 1 minute apart) at baseline (before dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing. A window of ± 5 minutes around each time point will be utilized to capture ECGs of adequate quality, although every effort should be made to capture them as close to the scheduled time points as possible. The ECG extractions will be time-matched to the PK samples but obtained before the actual sampling time to avoid changes in autonomic tone associated with the psychological aspects of blood collection as well as the reduction in blood volume subsequent to blood collection.

The continuous ECG data will be sent to the central ECG laboratory for a high-resolution measurement of the cardiac intervals and morphological assessment. The ECG core laboratory staff will be blinded to treatment, time, and study day identifiers.

The 12-lead continuous digital ECG signal for each subject will be recorded continuously during subject confinement.

Digital ECGs will be transmitted to the central ECG laboratory's validated data management system. If targeted ECG time points are artifactual and of poor quality, the central ECG laboratory will extract analyzable 10-second ECGs as close as possible to the targeted time points. The cardiologists responsible for interpreting the ECGs will be blinded to all study drug identifiers and collection times.

Lead II is the lead of choice for the over-reads and the baseline and on-treatment ECGs will be based on the same lead. All ECGs from a particular subject will be read by a single reader.

If lead II is not analyzable, ECG analysis will be conducted in lead V₅. If lead V₅ is not analyzable, the most appropriate lead will be used (eg, lead V₂).

8.2 General Summaries

All continuous 12-lead ECG data collected will be presented in data listings. Data from subjects excluded from the analysis populations will be presented in the data listings, but not included in the calculation of summary statistics. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, SD, 2-sided confidence bounds [90% for the QTcF interval or 95% for other parameters], median, 25th percentile, 75th percentile, minimum, and maximum). The mean of the triplicate 0-hour time point on Day 1 will be used as the

baseline. The continuous 12-lead ECG parameters (QTcF, HR, PR, RR, and QRS) and the corresponding changes from Baseline (denoted as dQTcF, dHR, dPR, dRR, and dQRS) and placebo-adjusted endpoints (denoted as ddQTcF, ddHR, ddPR, ddRR, and ddQRS) will be summarized by treatment and time point.

The means and 90% CIs for the dQTcF and placebo-adjusted (algebraic) ddQTcF will be calculated across all subjects for each time point and each active treatment and displayed graphically. Secondary endpoints will also be displayed using 95% CI, if applicable.

8.3 Statistical Analyses

Primary Analysis

The relationship between time-matched, baseline-adjusted QTcF (dQTcF) and moxidectin concentrations will be investigated by linear mixed-effects modeling. The ddQTcF value will be calculated as the placebo-corrected dQTcF estimated from the model.

Before modeling, the concentration-ddQTcF relationship will be explored graphically to determine the presence of hysteresis. Hysteresis will be assumed if, on average (or median), there are at least 3 time points with ddQTcF >5 msec and the time to maximum observed plasma concentration (T_{max}) and the time of maximal ddQTcF (U_{max}) differ by 30 minutes or more and the 1-sided, 1-sample Wilcoxon test for the difference between ddQTcF at T_{max} and at U_{max} is significant at the 1% level. If hysteresis is present, the possibility of fitting a population PK model with an effect compartment will be explored.

The primary analysis will be provided for the ECG population using a mixed-effects model with dQTcF as the dependent variable and treatment (active and placebo), time point, and treatment by time point interaction as the independent variables with baseline QTcF as a covariate and time-matched concentrations of moxidectin (observed if hysteresis is not present; predicted from the effect compartment if hysteresis is present) as a covariate with random effects of intercept and slope. Concentrations of zero will be used for the placebo treatment. A spatial power law covariance structure (a time-dependent first-order autoregressive covariance designed for unequally-spaced time points) will be used. If the model does not converge then unstructured (UN) or compound symmetry (CS) structures will be assessed, in that order. The model will be used for predicting population average and 90% 2-sided bootstrapped CI of the baseline-adjusted difference (ie, ddQTcF) between active and placebo at each time point bound at clinically relevant concentrations. The bootstrap method will be based on percentile CI using the 5th and 95th percentiles in the resampling distribution using 1000 iterations.

The criterion for negative QT assessment will be the upper bound of the 2-sided 90% bootstrapped CI for ddQTcF being below 10 msec at the largest geometric mean C_{max} value. In addition, the significance and magnitude of parameter estimates of the treatment covariate (active vs. placebo) will be considered.

At the request of the United States Food and Drug Administration, the primary endpoint in the study has been updated to dQTcF and this is the dependent variable in the primary analysis, which includes plasma concentrations as covariates with random slope and intercept as well as treatment and time point as categorical independent variables. However, in addition to obtaining the plasma concentration intercept and slope estimates, the estimated dQTcF values from the primary analysis will be compared by calculating the differences overall and at each time point between the active treatment and placebo, resulting in estimates of ddQTcF, which will be presented. In addition, a secondary analysis with ddQTcF as the dependent variable will be performed, as is typical and well understood, to assess correlation and overall profile of ddQTcF and plasma concentrations. We believe it is important to do these analyses in addition to the primary analysis, because the dQTcF analysis could yield a spuriously positive or negative regression slope based on the relationship between the well-known spontaneous circadian change in dQTcF and the concentration-time profile of the investigational drug. For example, if the early to midday circadian increase in dQTcF concurred with a rise in plasma concentration of moxidectin, this could create the appearance of a positive relationship that might exceed the upper confidence boundary of 10 msec within the drug's clinically-expected concentration range. Converse timing between circadian change and plasma concentration change could produce the opposite effect. In the ddQTcF analysis, the placebo group's circadian change largely eliminates this type of spurious observation. Thus, in addition to examining the dQTcF model, if the primary analysis produces a significantly positive or negative regression slope, we will also examine the relationship between the investigational drug's plasma concentration-time course in relationship to the circadian change of dQTcF in the placebo group, to determine if a positive or negative correlation could have affected the dQTcF-plasma concentration relationship.

The relevant SAS code statements are:

```
PROC MIXED DATA = DATA;  
  CLASS SUBJID TRT ATPTN;  
  MODEL dQTcF = BASE TRT ATPTN TRT*ATPTN CONC /SOLUTION  
RESIDUAL OUTP=PRED;  
  RANDOM INTERCEPT CONC / SUBJECT = SUBJID;  
  REPEATED ATPTN / type=SP(POW) (ATPTN) SUBJECT=SUBJID;  
  LSMEANS TRT TRT*ATPTN /DIFF ALPHA=0.1 CL at CONC=xx.x;  
  LSMEANS TRT TRT*ATPTN /DIFF ALPHA=0.1 CL;  
RUN;
```

In the above statements:

- TRT represents the treatment (active or placebo);
- ATPTN represents the postdose nominal time point;
- BASE represents the baseline value for QTcF;
- CONC represents measured plasma concentrations of moxidectin;

- SP(POW) is a spatial power law covariance structure (a time-dependent first-order autoregressive covariance designed for unequally-spaced time points), if the model does not converge then unstructured or compound symmetry structures will be assessed, in that order;
- LSMEAN differences between the treatments at the Geometric C_{\max} value and at the average concentration value, where xx.x represents the largest geometric mean C_{\max} value among the doses, most likely for the 36-mg dose, will be provided.

Model assumptions will be reviewed with plots of standardized residuals versus fitted values and normal Q-Q plots of the standardized residuals. If nonlinearity is present, a log linear and/or maximum effect (E_{\max}) or other model will be considered.

Similar analyses will be repeated for HR, PR, and QRS, however, bootstrap percentiles will be based on the 2.5th and 97.5th percentiles, corresponding to a 2-sided 95% CI rather than the 2-sided 90% CI.

Secondary Analysis: Pharmacokinetic/Pharmacodynamic Analyses

To evaluate the relationship between placebo-corrected mean change from Baseline in QTcF (ie, ddQTcF) versus plasma concentrations of moxidectin for all subjects in the PK/PD population, both graphical and mixed-effects analyses of plasma concentration of ddQTcF versus plasma concentration of moxidectin will be performed. The mixed-effects model will be used to account for the clustering effects within each subject at different time points. The mixed-effects model will contain ddQTcF as the dependent variable and include the corresponding time-matched plasma moxidectin concentrations as the independent variable. The mixed-effects model will be used to estimate, for all subjects, the predicted population mean ddQTcF and its corresponding upper 95% 1-sided (equivalent to the upper 90% 2-sided) CI over a range of observed plasma concentrations. A negative result (ie, the model indicates no plasma concentration effect) is a slope of approximately zero.

The adequacy of the linear assumption between ddQTcF and plasma concentrations will be determined by adding a quadratic term to the mixed-effects model. If the quadratic term is different than zero, having $P < 0.05$, and Akaike's information criterion (AIC) is smaller in comparison with the linear model's AIC, then a quadratic term may be added. In addition, a transformation of the concentrations (eg, $\log[C/LLOQ]$, where LLOQ is the lower limit of quantitation of the assay and all values below the LLOQ are replaced with the LLOQ) may also be assessed. The best model fit will be determined by the lowest AIC.

The predicted mean expected ddQTcF and the 90% 2-sided CI will be calculated using the estimates of the slopes from the mixed-effect models, for all subjects, at relevant concentration levels (ie, the mean maximum plasma concentration under each dose level).

The relevant SAS code statements are:

```
PROC MIXED DATA = DATA;  
  CLASS SUBJID;  
  MODEL ddQTcF = CONC /SOLUTION OUTPM=PRED ALPHA=0.05;  
  RANDOM INTERCEPT CONC / TYPE=UN SUBJECT = SUBJID;  
RUN;
```

In the above statements:

- CONC represents the measured plasma concentrations of moxidectin;
- Type=UN means an unstructured covariance matrix, which is used for the correlated random effects (INTERCEPT and CONC). If the model does not converge other covariance structures will be investigated.

A plot will be provided to show CI of each treatment using the following model, adding in the treatment variable as follows:

```
PROC MIXED DATA = DATA;  
  CLASS SUBJID TRT;  
  MODEL ddQTcF = CONC TRT/SOLUTION OUTP=PRED;  
  RANDOM INTERCEPT CONC /TYPE=UN SUBJECT = SUBJID;  
RUN;
```

Where TRT represents the individual treatments (moxidectin 4 mg, moxidectin 8 mg, moxidectin 16 mg, moxidectin 24 mg, and moxidectin 36 mg).

A plot of the observed median-decile drug concentrations and associated mean ddQTcF (90% CI) together with the mean model-predicted ddQTcF will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship.

Categorical QTc Findings

Categorical summaries using the largest postdose QTcF and largest change from Baseline (dQTcF) will be performed to determine the number and percentage of subjects, by treatment, who meet each of the following criteria:

- Result ≤ 450 msec;
- Result > 450 and ≤ 480 msec;
- Result > 480 and ≤ 500 msec;
- Result > 500 msec;
- dQTcF ≤ 30 msec;
- dQTcF > 30 and ≤ 60 msec;
- dQTcF > 60 msec.

Categorical Analysis of Other ECG Intervals

Categorical summaries of outliers will be provided for other ECG variables (PR, QRS, and HR) as follows:

- PR outliers postdose (PR >200 msec and a 25% or greater increase from Baseline);
- QRS outliers postdose (QRS >100 msec and a 25% or greater increase from Baseline);
- HR outliers postdose (HR <50 beats/minute and a 25% or greater decrease from Baseline);
- HR outliers postdose (HR >100 beats/minute and a 25% or greater increase from Baseline).

Any instance in 1, 2, or 3 of the triplicate ECGs of any subject overall and at each time point will be counted as 1 outlier event.

ECG Diagnostic Statement Analysis

Abnormal diagnostic statements will be tallied and tabulated for each treatment and time point. The variety of diagnostic statements with the same meaning will be aggregated into defined categories. For example, T wave inversion and lead V₂ and T wave flattening in lead II will both be categorized as nonspecific T wave abnormality. The incidence rate of diagnostic statements will be tabulated for both predose and postdose assessments, and also tabulated with diagnostic statements categorized as treatment-emergent diagnostic statements (ie, diagnostic statements not present on any baseline assessment). All abnormal ECG diagnostic findings will be listed.

Adequacy of HR Correction

The adequacy of the correction formula will be assessed by determining the linear relationship of QTcF to RR. Adequacy is defined as a population QTcF:RR slope of <|0.045|, and a slope of <|0.045| in at least 50% of individual subjects.

The QT interval with individual correction (QTcI) is mentioned in the International Council for Harmonisation E14 Guidance as an ancillary correction method.

The QTcI, if needed, will be calculated for each subject, using all available QT/RR predose pairs by first determining the slope of each subject's QT:RR relationship using all available predose data. Then QTcI will be calculated from each subject's individual ECG time point QT and RR interval values with the formula: $QTcI = QT + \text{slope} (1000 - RR)$.

9 SAFETY ANALYSIS

9.1 Adverse Events

Adverse events will be coded using the current version of MedDRA. Each verbatim term will be mapped to SOC and PT.

A treatment-emergent AE (TEAE) is defined as any AE that began or worsened following the start of study drug.

An overall summary of TEAEs will be provided summarizing subjects with at least 1 of the following: TEAE, related TEAE, Grade 3 or 4 TEAE, serious TEAE, related serious TEAE, TEAE leading to study discontinuation, and related TEAE leading to study discontinuation as well as the number of events with each of the previously mentioned categories by treatment and overall.

In addition, summaries of unique TEAEs will be presented by SOC, PT, and by treatment and overall and will include number and percentage of subjects who experienced the unique event for:

1. All TEAEs,
2. All TEAEs by relationship,
3. All TEAEs by severity grade,
4. All TEAEs leading to study discontinuation.

Related TEAEs include all those classified by the investigator as possibly, probably, or definitely related. Unrelated TEAEs are those events classified as not related.

For summaries by relationship, the most related event will be selected. For summaries by severity grade, the most severe grade will be selected.

Multiple events will be counted once only per subject and treatment in each of the previously mentioned summaries by treatment and overall. In the presentation, SOC and PT will be sorted in alphabetical order.

All AEs captured in the database will be listed in by-subject data listings; however, only TEAEs will be summarized.

MedDRA version will be footnoted in both tables and data listings.

9.2 Clinical Laboratory Evaluations (Serum Chemistry, Hematology, Urinalysis)

Clinical laboratory evaluations of serum chemistry, hematology, and urinalysis will be performed. Results and change from Baseline will be summarized by treatment and scheduled visit/time point using descriptive statistics for numeric parameters and using counts and percentages for categorical parameters. Baseline is defined as stated in Section 5.6. Values reported with a “<” or “>” sign will be converted to numeric values and summarized.

Shifts from Baseline to values outside of the normal range will be presented using the worst-case result by parameter and treatment that occurred postdose and summarized using the number and percentage of subjects with laboratory test results below, within, and above normal ranges for numeric parameters and normal, abnormal for categorical parameters. The denominators for calculating the percentages will be based on the number of subjects with nonmissing assessments for each parameter.

Clinically significant laboratory values (as determined by the investigator) will be provided in a data listing including all values for a given parameter for subjects who had at least 1 postbaseline clinically significant value.

All clinical laboratory data will also be presented in data listings in chronological order by date if unscheduled or repeated values.

9.3 Vital Signs

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for vital sign measurements collected at Baseline and each scheduled postbaseline time point will be summarized by treatment. In addition, change from Baseline will be calculated, where baseline is defined as stated in Section 5.6.

Vital sign measurements will be presented in a data listing.

9.4 Safety 12-Lead Electrocardiogram

Results and changes from Baseline will be presented for each safety ECG parameter and summarized by treatment at Baseline and scheduled postdose time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Baseline is defined as stated in Section 5.6. The results will be interpreted as normal, abnormal not clinically significant, or abnormal clinically significant, and the interpretation will be summarized for each treatment and scheduled time point using counts and percentages. The denominators for calculating the percentages will be based on the number of subjects with nonmissing assessments at each time point.

A categorical summary of QTcF interval and QT interval corrected by Bazett’s formula (QTcB) will be provided using counts and percentages at Baseline and maximum postbaseline by treatment for the following categories:

- Result ≤ 450 msec;

- Result >450 and ≤ 480 msec;
- Result >480 and ≤ 500 msec;
- Result >500 msec;
- Change from Baseline ≤ 30 msec;
- Change from Baseline >30 and ≤ 60 msec;
- Change from Baseline >60 msec.

Safety 12-lead ECG data will be provided in a data listing.

9.5 Concomitant Medications

Prior and concomitant medications will be classified according to the World Health Organization Drug dictionary and presented in a data listing by anatomical therapeutic chemical class level 3 and preferred drug name.

Medications with a start and end date occurring before the first dose date/time date will be identified as prior medications. Medications with an end date occurring on or after the first dose date/time or that have unknown or ongoing end dates will be identified as concomitant medications. In the event of a partial date, it will be compared to the first dose date/time and if year and or month is clearly prior to the first dose date, and the medication's end date is partial, but clearly prior to the first dose date/time then the medication will be classified as prior medication. However, if the partial date overlaps with the first dose/date as having the same year and/or month then the medication will be classified as concomitant medication.

9.6 Extent of Exposure

Study drug administration dates and times will be presented in a data listing.

9.7 Other Safety Assessments

The physical examination findings and other safety assessments will be presented in data listings.

10 REFERENCES

Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (US). Guidance for Industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. October 2005.

E14 Implementation Working Group ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions & Answers (R3). 10 December 2015 Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf

APPENDIX A: LIST OF TABLES, LISTINGS, AND FIGURES

Shells of the tables, listings, and graphs will be provided as a separate document. Titles may change slightly from what is presented here in this appendix, where this appendix is designed to give the reader an understanding of what is intended to be presented, in creating the shells, the tables may need to be presented differently to adhere to the actual data collected.

14 TABLES, LISTINGS AND GRAPHS REFERRED TO BUT NOT PRESENTED IN THE TEXT

14.1 Disposition and Demographic Data Summary Tables

Table 14.1.1	Subject Disposition (All Randomized Subjects)
Table 14.1.2	Demographic and Baseline Characteristics (Safety Population)
Table 14.1.3	Demographic and Baseline Characteristics (PK Population)
Table 14.1.4	Demographic and Baseline Characteristics (ECG Population)
Table 14.1.5	Demographic and Baseline Characteristics (PK/PD Population)

14.2 Pharmacokinetic and Pharmacodynamic Summary Tables

14.2.1 Concentration and Pharmacokinetic Summaries, Analyses, and Figures

Table 14.2.1.1	Summary of Plasma Concentrations Over Time (PK Population)
Table 14.2.1.2	Summary of Plasma Pharmacokinetic Parameters (PK Population)
Table 14.2.1.3	Summary of Urine Pharmacokinetic Parameters (PK Population)
Table 14.2.1.4	Summary of Feces Pharmacokinetic Parameters (PK Population)
Figure 14.2.1.1	Mean \pm SD Plasma Moxidectin Concentration (ng/mL)-Time Profile, Linear Scale (PK Population)
Figure 14.2.1.2	Mean Plasma Moxidectin Concentration (ng/mL)-Time Profile, Semilogarithmic Scale (PK Population)
Figure 14.2.1.3	Mean \pm SD Plasma Moxidectin Metabolite Concentration (ng/mL)-Time Profile, Linear Scale (PK Population)
Figure 14.2.1.4	Mean Plasma Moxidectin Metabolite Concentration (ng/mL)-Time Profile, Semilogarithmic Scale (PK Population)
Figure 14.2.1.5	Mean \pm SD Plasma Moxidectin Metabolite to Parent (molar equivalents) Ratios Over Time (PK Population)
Figure 14.2.1.6	Mean \pm SD Urine Moxidectin Amount Excreted Over Time (PK Population)
Figure 14.2.1.7	Mean \pm SD Urine Moxidectin Metabolite Amount Excreted Over Time (PK Population)
Figure 14.2.1.8	Mean \pm SD Urine Moxidectin Metabolite to Parent Amount Excreted (molar equivalents) Ratios Over Time (PK Population)
Figure 14.2.1.9	Mean \pm SD Feces Moxidectin Amount Excreted Over Time (PK Population)

14.2.2 Pharmacodynamic Summaries, Analyses, and Figures

Table 14.2.2.1	Summary of Continuous ECG Parameter Results and Change From Baseline (ECG Population)
Table 14.2.2.2	Summary of Simple/Unadjusted Continuous ECG Parameters (ECG Population)
Table 14.2.2.3	Summary of Primary Analysis Mixed-Effects Model Parameters (ECG Population)

Table 14.2.2.4	Summary of Primary Analysis Mixed-Effects Model Predicted ddECG and Predicted Interval at Geometric Mean Maximum Plasma Concentration (ECG Population)
Table 14.2.2.5	Summary of Secondary Analyses Mixed-Effects Model Predicted Regression Slope Estimates and Predictions (PK/PD Population)
Table 14.2.2.6	Summary of Continuous QTcF Interval Categories (ECG Population)
Table 14.2.2.7	Summary of Continuous PR, QRS, and HR Outliers (ECG Population)
Table 14.2.2.8	Summary of Continuous ECG Diagnostic Statements (ECG Population)
Table 14.2.2.9	Summary of Treatment-Emergent Continuous ECG Diagnostic Statements (ECG Population)
Figure 14.2.2.1	dQTcF Interval vs. Time Showing Mean and 2-sided 90% Confidence Bounds (ECG Population)
Figure 14.2.2.2	dHR vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.3	dPR Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.4	dQRS Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.5	dRR Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.6	ddQTcF Interval vs. Time Showing Mean and 2-sided 90% Confidence Bounds (ECG Population)
Figure 14.2.2.7	ddHR vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.8	ddPR Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.9	ddQRS Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.10	ddRR Interval vs. Time Showing Mean and 2-sided 95% Confidence Bounds (ECG Population)
Figure 14.2.2.11	Residual Plots From Primary Analyses by Parameter (ECG Population)
Figure 14.2.2.12	ddQTcF Interval vs. Plasma Moxidectin Concentrations (PK/PD Population)
Figure 14.2.2.13	ddQTcF Interval vs. Plasma Moxidectin Concentration by Treatment (PK/PD Population)
Figure 14.2.2.14	Observed Median-decile Plasma Moxidectin Concentrations and Associated Mean ddQTcF Interval (90% CI) Together With the Mean (90% CI) Predicted ddQTcF Interval (PK/PD Population)
Figure 14.2.2.15	Residual Plots From Secondary Analysis (PK/PD Population)
Figure 14.2.2.16	Scatter Plot and Linear Regression for QTcF Interval vs. RR Interval (ECG Population)

14.3 Safety Data Summary Tables

14.3.1 Adverse Events

Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug (Safety Population)
Table 14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity Grade (Safety Population)
Table 14.3.1.5	Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class, Preferred Term, and Relationship (Safety Population)

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Listing 14.3.2.1	Serious Adverse Events and Deaths (Safety Population)
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14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Provided by Clinical, if applicable.

14.3.4 Abnormal Laboratory Value Listings

Listing 14.3.4.1	Clinically Significant Laboratory Results (Safety Population)
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14.3.5 Other Observations Related to Safety

Table 14.3.5.1	Vital Sign Results and Change From Baseline (Safety Population)
Table 14.3.5.2	Hematology Parameter Results and Change From Baseline (Safety Population)
Table 14.3.5.3	Hematology Parameter Shifts From Baseline (Safety Population)
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