CLINICAL STUDY PROTOCOL

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

PROTOCOL NO. MDGH-MOX-1008

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Protocol Version:	2.0
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Amendment 1 Date:	01 March 2017

Signature Page

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Mark Sullivan Managing Director Medicines Development for Global Health	Date
Jolanta Airey Consultant Clinical Development Physician SJA Consultancy Services	Date
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Investigator Signature Page

I agree to conduct the study as outlined in the protocol entitled "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" in accordance with the International Council for Harmonisation guidelines and all applicable government regulations including United States Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Carlos Sanabria, MD Principal Investigator	Date

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1. Protocol Synopsis

Protocol number:	MDGH-MOX-1008
Protocol 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
Study phase:	1
Study site:	Spaulding Clinical Research, LLC 525 South Silverbrook Drive West Bend, Wisconsin 53095 United States
Objectives:	Primary objective: To analyze the effect of a single oral dose of moxidectin on the QT interval associated with moxidectin plasma concentrations. Secondary objective: To assess the safety and pharmacokinetics (PK) of a single oral dose of moxidectin. Exploratory objectives: • To gain preliminary information in humans on the metabolism and excretion of moxidectin; • To evaluate the baseline-corrected changes in other electrocardiogram (ECG) and cardiovascular parameters; and • To evaluate the ECG morphologic changes related to cardiac repolarization (ST segment and T waves).
Subject population:	The study will enroll at least 60 healthy male subjects who meet all of the inclusion criteria and none of the exclusion criteria.
Inclusion criteria:	A subject must meet all of the following inclusion criteria to participate in this study: 1. Healthy male between 18 and 50 years of age (inclusive); 2. Body mass index of 18 to 30 kilograms/meters^2 (inclusive) and a minimum weight of 50 kilograms (110 pounds); 3. Biologically or surgically sterile or must commit to using 2 reliable (in the opinion of the investigator) methods of contraception, simultaneously, from Screening through the duration of the study period (to Week 12); 4. Willing and able to give written informed consent.
Exclusion criteria:	A subject will be excluded from participation in this study if he meets any of the following criteria: 1. Unwilling to abstain from alcohol, caffeine, xanthine-containing products, Seville oranges, grapefruit juices, and fish liver oils within 72 hours before Check-in (Day –1) and throughout the inpatient period of the study; 2. Less than 1 bowel movement every 24 hours in the absence of any laxative, suppository, or enema use during the month before Screening; 3. Abnormal fecal consistency within 24 hours of Check-in (Day –1);

	4. Clinically relevant abnormal findings on medical history, clinical laboratory test results, vital sign measurements, safety 12-lead ECG results, or physical examination at Screening or Baseline which, in the opinion of the investigator, would interfere with dosing, jeopardize the safety of the subject, or impact the validity of the study results; 5. History of clinically significant dermatologic, gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the investigator, would interfere with dosing, jeopardize the safety of the subject, or impact the validity of the study results; 6. History of hypersensitivity or allergic reactions to ivermectin, moxidectin, or any of the ingredients in the study drug as described in the Investigator's Brochure; 7. Any condition that may affect oral drug absorption (e.g., previous surgery on the gastrointestinal tract including removal of parts of the stomach, bowel, liver, gall bladder, or pancreas); 8. History of risk factors for torsades de pointes, including unexplained syncope, known long QT syndrome, heart failure, myocardial infarction, angina, or clinically significant abnormal laboratory assessments including hypokalemia, hypercalcemia, or hypomagnesemia. Subjects are also excluded if there is a family history of long QT syndrome or Brugada syndrome; 9. A sustained supine systolic blood pressure >150 millimeters of mercury (mm Hg) or <90 mm Hg or a sustained supine diastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in (Day –1). Blood pressure may be retested twice in the supine position. The blood pressure abnormality is considered sustained if either the systolic or the diastolic blood pressure values are outside of the stated limits for 3 assessments, and the subject will not to be randomized; 10. A resting heart rate of <40 beats per minute or >100 beats per minute at Screening or Check-in (Day –1); 11. An uninterpretable or abnormal screening ECG indicating a second- or third-degree atrioventricular block, or 1 or more of the following: QRS interval >110 milliseconds (msec); QT interval corrected by Fridericia's formula (QTcF) >450 msec; PR interval >200 msec; or any rhythm other than sinus rhythm that is interpreted by the investigator to be clinically significant; 12. Concomitant use of prescription medications, including medications known to prolong the corrected QT interval (QTc) or herbal preparations, within 14 days or 5 half-lives (whichever is longer) before study drug dosing, or use of an over-the-counter medication or vitamins within 7 days before study drug dosing; 13. Received an investigational drug during the 30 days, or 5 half-lives of the study drug (whichever is longer), before Check-in (Day –1), or is planning to receive another investigational drug at any time during the study;

	14. History or presence of alcohol abuse (defined as consumption of more than 210 milliliters of alcohol per week, or the equivalent of fourteen 4-ounce glasses of wine or fourteen 12-ounce cans/bottles of beer or wine coolers per week) within 6 months before Screening or a positive alcohol test at Screening or Check-in (Day –1); 15. History or presence of substance abuse within the past 2 years or a positive drug screen test at Screening or Check in (Day –1); 16. Current use or has used tobacco- or nicotine-containing products (e.g., cigarettes, e-cigarettes, cigars, chewing tobacco, snuff) within 14 days before study drug dosing; 17. Blood donation or significant blood loss within 30 days before Check-in (Day –1) or plasma donation within 7 days before Check-in (Day –1); 18. Presence of hepatitis B surface antigen or antibodies to human immunodeficiency virus or hepatitis C virus at Screening; 19. Poor venous access in both arms; 20. Clinical signs of active infection and/or a temperature of >38.0 degrees Celsius at Screening; 21. Unable to understand verbal or written English or any other language for which a certified translation of the informed consent form is available; 22. For any reason, is deemed by the investigator or medically qualified designee to be inappropriate for this study, including a subject who is unable to communicate or cooperate with the investigator, and/or is unwilling to comply with protocol-defined procedures and complete the study.
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 milligrams (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 provide written informed consent before undergoing any study-related procedures. 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 clinical research unit (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 assessment of adverse events (AEs) and concomitant medication use. The duration of participation in the study for each subject will be up to approximately 112 days, including Screening.

Study drug, dosage, and route of administration:	Moxidectin, 2-mg tablets, administered orally as a single dose of 4, 8, 16, 24, or 36 mg
Reference drug, dosage, and route of administration:	Placebo matched to moxidectin tablets, administered orally as a single dose
Pharmacodynamic 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 the following time points: Baseline (before dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing. 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.
Pharmacokinetic assessments:	Blood samples will be collected to determine the PK of moxidectin and metabolites in plasma. 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 Urine and feces samples for PK assessments will be collected from each subject as follows: • Urine: Before dosing (single pre-dose 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) • Feces: Before dosing (single pre-dose collection*) and each bowel motion during confinement in the CRU. 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. Specific PK parameters for moxidectin in plasma will include: • $AUC_{0\text{-last}}$: area under the plasma concentration-time curve (AUC) from time 0 extrapolated to the last observed concentration • $AUC_{0\text{-inf}}$: AUC from time 0 extrapolated to infinity • $cumAUC_{0\text{-t}}$: cumulative AUC from time 0 extrapolated to time t (where t = 24, 48, and 72 hours) • $AUC_{0\text{-}24}$: AUC from time 0 to 24 hours after dosing • $AUC_{24\text{-}48}$: AUC from 24 to 48 hours after dosing • $AUC_{48\text{-}72}$: AUC from 48 to 72 hours after dosing

	• C_{max}: maximum observed plasma concentration • T_{max}: time to maximum observed plasma concentration • $t_{1/2}$: terminal elimination half-life Blood sampling time points will coincide with the ECG time points. The blood samples will be collected as close to the scheduled time point as possible, within 5 minutes and no later than 10 minutes after the ECG, unless otherwise noted. Additional PK parameters, including apparent clearance, volume of distribution, and others may be determined as appropriate. The PK parameters will be expressed in units adjusted for molecular weight where appropriate.
Safety assessments:	Safety and tolerability will be evaluated in terms of AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and physical examination findings.
Sample size:	The sample size of 60 subjects (10 subjects each in 6 treatment groups) is considered adequate to explore the effects of moxidectin on the QTc interval, 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 CRU from Check-in until all subjects due to be dosed have completed dosing. Subjects who withdraw after dosing will not be replaced.
Statistical methods:	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: 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. **Pharmacodynamics:** The primary endpoint is the baseline-adjusted QTcF (dQTcF) matched to the plasma concentration of moxidectin collected at the same time point. The relationship between time-matched 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 confidence interval (CI) of the baseline-adjusted difference (i.e., 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 versus placebo) will be considered. 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. **Pharmacokinetics:** Non-compartmental analysis will be implemented for the calculation of PK parameters. The main PK parameters of interest are the cumulative and pre-specified time-window AUCs for moxidectin concentrations in plasma. Computed PK parameters for moxidectin in plasma will be summarized and listed for moxidectin, including mean, geometric mean, SD, median, and range, as appropriate. Moxidectin concentrations in urine and feces as well as plasma:urine and plasma:feces concentration ratios will be summarized. Summary statistics describing the time course of concentrations of moxidectin metabolites and parent to metabolite ratios in plasma will be presented. Metabolite concentrations in urine as well as metabolite plasma:urine concentration ratios will be summarized as appropriate. **Pharmacokinetic/Pharmacodynamic:** To evaluate the relationship between placebo-corrected mean change from Baseline in QTcF (i.e., ddQTcF) versus plasma concentrations of moxidectin for all subjects, both graphical and mixed-effects analyses of plasma concentration of ddQTcF versus plasma concentration of moxidectin will be performed. The mixed-effects model will contain ddQTcF as the dependent variable and include the corresponding moxidectin plasma 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 CI over a range of observed plasma concentrations. A negative result (i.e., the model indicates no plasma concentration effect) is a slope of approximately zero. **Safety:** All safety assessments, including AEs, clinical laboratory test results, vital sign measurements, and safety 12-lead ECG results will be summarized using descriptive statistics and presented in data listings. Physical examination findings and concomitant medications will be presented in data listings. All safety summary tables and figures will be generated using SAS®. No inferential statistics will be performed on the safety data.
Date of protocol:	23 September 2016
Date of amendment 1:	01 March 2017

Table 1-1 Overall Schedule of Events

Assessment	Period 1										Period 2	
	Screening D-28 to D-2	**D-1**	**Baseline D1 (Pre-dose)**	**D1**	**D2**	**D3**	**D4**	**D8**	**D15**	**D22**	**W8**	**W12[f]**
Outpatient visit	X	Refer to Table 1-2: 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							←----------X----------→				
Concomitant medications	X							←----------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 ECGs 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 1-2 Schedule of Events for Period 1 (Day –1 to Day 4)

	Period 1																
Assessment	**Day –1**	**Day 1 (Pre-dose)**	**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 pre-dose 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 pre-dose 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).

2. List of Abbreviations

Abbreviation	Definition
°C	degrees Celsius
°F	degrees Fahrenheit
µg	microgram(s)
µM	micromolar
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIC	Akaike's information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours after dosing
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 24 to 48 hours after dosing
AUC_{48-72}	area under the plasma concentration-time curve from 48 to 72 hours after dosing
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeter(s)
C_{max}	maximum observed plasma concentration
CNS	central nervous system
Conc	linear term for plasma concentration
Conc2	quadratic term for plasma concentration
cQT	concentration QT
CRU	clinical research unit
CS	compound symmetry
CSRC	Cardiac Safety Research Consortium

$cumAUC_{0-t}$	cumulative AUC from time 0 extrapolated to time t (where t = 24, 48, and 72 hours)
CYP	cytochrome P450
D	day
DAIDS	Division of Acquired Immune Deficiency Syndrome
ddQTc	time-matched, placebo-corrected, baseline-adjusted QTc
ddQTcF	time-matched, placebo-corrected, baseline-adjusted QTcF
dQTcF	baseline-adjusted QTcF
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum effect
ER	exposure response
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
gm	gram(s)
hERG	human ether-à-go-go
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IQ	Innovation and Quality in Pharmaceutical Development
IRB	institutional review board
IV	intravenous
kg	kilogram(s)
lb	pound(s)
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation of the assay
m	meter(s)
MDGH	Medicines Development for Global Health
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
mm Hg	millimeters of mercury
msec	millisecond(s)
n	number
ng	nanogram(s)
NOAEL	no observed adverse effect level
OTC	over the counter

oz	ounce
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
ppm	parts per million
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
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration
TQT	thorough QT
U_{max}	time of maximal ddQTcF
UN	unstructured
US	United States
Vd	volume of distribution
W	week
WHO	World Health Organization

3. Introduction

3.1. Background

Onchocerciasis (river blindness) is a serious, debilitating, and stigmatizing parasitic disease caused by the helminth *Onchocerca volvulus* (*O. volvulus*). It is recognized as an important public health issue by health authorities worldwide and is listed by the World Health Organization (WHO) and United States (US) Food and Drug Administration (FDA) as one of the neglected tropical diseases for which new treatments are sought.[1]

Onchocerciasis primarily affects individuals living in remote and impoverished areas of low-income countries. More than 99% of the 37 million people with onchocerciasis globally live in 31 sub-Saharan African countries. It is estimated that 89 million people are at risk of infection. The disease also exists in some foci in Latin America and Yemen.

O. volvulus larvae are transmitted to humans by the bite of black flies (genus *Simulium*), which breed in fast-flowing rivers and streams. The larvae develop into mature adult worms (macrofilariae) and become encapsulated in skin nodules, from which they release millions of microfilariae that migrate through the skin and eyes, a critical step in the cycle of reinfection and disease perpetuation. Macrofilariae persist in the human body and have an estimated life span of approximately 10 to 14 years.[2]

The *O. volvulus* microfilariae cause the ocular and clinical manifestations of onchocerciasis. Symptoms include pruritus, dermatitis, depigmentation and atrophy of the skin, lymphadenitis, and visual impairment leading to blindness. Onchocerciasis is the second leading infectious cause of blindness in the world.[3] In addition to substantial ocular and cutaneous morbidity, excess mortality of visually impaired and non-impaired individuals with heavy onchocercal infection accounted for 5% of deaths in the Onchocerciasis Control Program (a WHO/United Nations collaboration that ran from 1974 to 2002) area in West Africa.[4-6]

The public health and socioeconomic importance of this disease in severely affected communities is also profound; the disease reduces income-generating capacity, incurs substantial health expenditures, and exerts a devastating socioeconomic effect on already challenged communities.

3.2. Current Treatment and Unmet Need

Ivermectin is a broad-spectrum endectocide that was approved by the FDA for the treatment of onchocerciasis in 1996 and is the current standard of care. The recommended regimen for the treatment of onchocerciasis is a single oral dose of

150 micrograms (µg)/kilogram (kg). In international treatment programs, the most commonly used dose interval is 12 months. The aim of these international, community-directed ivermectin treatment programs is to achieve control in affected communities and, ultimately, work towards elimination of onchocerciasis in areas currently assessed as meso- or hyper-endemic for *O. volvulus* infection.[7]

Despite the positive impact of 25 years of ivermectin treatment, onchocerciasis is still a cause of significant morbidity. It remains both a leading infectious cause of blindness and the fourth leading cause of preventable blindness after cataracts, glaucoma, and trachoma.[8] Suboptimal responses to ivermectin have been observed in onchocerciasis populations in Africa over several years, which manifest as either incomplete reduction in skin microfilarial counts or a short-lived decline followed by rapid repopulation of skin microfilarial levels. This phenomenon has been reported in the literature in both ivermectin-naïve and ivermectin-experienced patients[8-16] and was also seen among the ivermectin treatment-naïve recipients enrolled in the Phase 2 and Phase 3 studies in the moxidectin development program.[16]

3.3. Moxidectin

Moxidectin is a macrocyclic lactone that is derived from the actinomycete *Streptomyces cyanogriseus*. Moxidectin is licensed and marketed worldwide by a number of companies as a veterinary anthelmintic agent for use in cattle, sheep, swine, horses, and dogs.

Moxidectin is a milbemycin and a potent broad-spectrum endectocide being developed for the treatment of onchocerciasis. During the development of moxidectin, extensive safety and metabolism studies were conducted in animals. Summaries of those studies considered relevant to the proposed clinical development are included in the Investigator's Brochure.

3.3.1 Non-Clinical

3.3.1.1 Pharmacodynamics

The mechanism of action of moxidectin is multifaceted; studies indicate that moxidectin binds to gated chloride channels in the neurons and muscle cells of parasites, including glutamate and gamma-aminobutyric acid (GABA)-gated channels. Binding to the ion channel results in hyperpolarization of the nerve and muscle fibers, leading to paralysis and death of the parasitic organism. Specificity of moxidectin for the parasite versus the mammalian host is a result of this compound having low affinity for mammalian chloride channels. For more information, please refer to the Investigator's Brochure.

Moxidectin has been found to be 2 to 10 times more potent in nematodes than ivermectin on a dose-per-kg basis and to reduce the motility and viability of adult worms *in vitro* and *in vivo*. Moxidectin is minimally metabolized with a higher lipophilicity leading to deposition in adipose tissue, particularly skin subcutaneous fat. This is reflected in its terminal elimination half-life ($t_{1/2}$) of 20 to 43 days as opposed to 18 hours for ivermectin.[17] The physicochemical differences of moxidectin compared with ivermectin result in a different pharmacodynamic (PD) profile for the parasite, and make moxidectin an important new potential treatment for onchocerciasis. In *O. volvulus* infection, moxidectin is both microfilaricidal and affects the fecundity of adult worms.

3.3.1.2 Metabolism and Excretion

The non-clinical pharmacokinetic (PK) profile of moxidectin, as profiled in rats and dogs, is characterized by low oral absorption (rats), low plasma clearance, and a high volume of distribution, leading to a long $t_{1/2}$. In radiolabeled absorption, distribution, metabolism, and excretion (ADME) oral dosing studies in rats, moxidectin radioactivity was primarily eliminated in the feces. Most of the radioactivity was comprised of moxidectin, although oxidative metabolites were also detected. Urinary excretion was low (<2%) in rats. These data indicate that moxidectin is likely cleared by a combination of biliary excretion of unchanged drug and oxidative metabolism.

Moxidectin is not a potent P-glycoprotein (P-gp) substrate or inhibitor and it is unlikely that clinical drug-drug interactions involving cytochrome P450 (CYP) enzyme inhibition or P-gp will occur. Results of studies in human hepatocytes and using a CYP3A4-luciferase reporter gene assay suggest that moxidectin is an inducer of CYP3A4 at concentrations higher than 0.05 micromolar (μM); therefore, a clinical drug-drug interaction study was conducted. Moxidectin did not have an effect on the PK of midazolam, a sensitive CYP3A4 probe substrate. Therefore, although moxidectin can induce CYP3A4 *in vitro*, it is not an inducer *in vivo* at the therapeutic dose. For further information, please refer to the Investigator's Brochure.

3.3.1.3 Safety

In a pivotal single-dose oral (capsule) study in adult and juvenile dogs designed to assess the planned clinical dosing regimen (once yearly administration), central nervous system (CNS)-related clinical signs were evident in both the adult and juvenile dogs after a single dose at the highest dose evaluated (3 milligrams (mg)/kg). In adult dogs (juvenile dogs discussed later), these observations included tremors, ataxia, abnormal posture, decreased motor activity, salivation, emesis, increased vocalization, mydriasis, and retropulsion. These clinical signs were not considered adverse because they were

transient, occurring only within 2 days after dosing, and the animals did not require medical treatment. There were no moxidectin-related clinical signs at lower doses, and no other parameters were affected by moxidectin. Therefore, the no observed adverse effect level (NOAEL) in adult dogs was 3 mg/kg.

In repeat-dose oral (diet) studies in mice, rats, and dogs, moxidectin was well tolerated at the NOAELs in each of these studies. The NOAEL was 6.9 mg/kg/day in the 4-week mouse study, 12.2 mg/kg/day in the 4-week rat study, 3.9 mg/kg/day in the 13-week rat study, and 0.8 mg/kg/day in the 4-week dog study. Findings at the next highest dose included mortality in the 4-week studies in mice and rats, decreased body weight and food consumption in the rat and dog studies, increased organ weights of the adrenal gland and kidney in the 13-week rat study and CNS-related clinical observations in all studies. Additional findings in dogs at the next highest dose of 2.4 mg/kg/day included decreased colloid in the thyroid and decreased testes weight and spermatogenic activity, which may have been related to the degree of maturation of the 5- to 6-month old dogs as they were not observed in the 1-year dog study. In the 13-week and 1-year studies in dogs, there were no adverse effects; therefore, the NOAELs were the highest doses tested, 1.6 and 1.1 mg/kg/day, respectively. The CNS-related clinical observations observed in the repeat-dose diet studies included tremors observed in all 3 species, ataxia observed in rats and dogs, hypersensitivity to touch observed in mice and rats, and mydriasis observed in dogs.

Moxidectin was not genotoxic in a battery of genotoxicity assays, *in vitro* or *in vivo*, and was not carcinogenic in mice or rats. The reproductive NOAELs were 5 mg/kg/day in both the rat and rabbit developmental studies and at 5 parts per million (ppm) (0.4 mg/kg/day) in the rat 3-generation study. In female dogs administered a single subcutaneous 1.5-mg/kg injection of moxidectin canine sustained-release injectable formulation 1 month before mating, 1 day after mating, 28 days after mating, or 5 days after whelping, there were no adverse effects on the female animals, breeding behavior, reproductive capacity, pup survival, or pup body weight. The adverse fetal effects observed in the rat and rabbit toxicity studies occurred only in the presence of maternal toxicity. For further information, please refer to the Investigator's Brochure.

The results of the non-clinical safety program supported the subsequent implementation of 5 healthy volunteer Phase 1 studies using singles doses of moxidectin up to 36 mg. Phase 2 and 3 studies have since been conducted in adult and adolescent patients with onchocerciasis (see Section 3.3.2).

3.3.2 Clinical

The moxidectin clinical program encompasses 7 completed single oral dose clinical studies spanning Phases 1 to 3. The PK and safety data from these studies are summarized below. For further information, please refer to the Investigator's Brochure.

3.3.2.1 Pharmacokinetics

Moxidectin is a biopharmaceutics classification system Class 2 drug with low solubility and high permeability. Moxidectin PK data are available from 193 healthy subjects from five Phase 1 studies and 98 patients with *O. volvulus* infection from the Phase 2 study. In all studies, subjects received a single moxidectin dose ranging from 2 to 36 mg.

Following a single dose of moxidectin in humans, plasma concentrations increased until approximately 3 to 4 hours and then decayed in a multiphasic manner, with rapid distribution resulting in concentrations declining 10-fold during the first 24 to 48 hours following drug administration. Thereafter, plasma concentrations declined slowly, in accordance with a long terminal half-life, likely due to sequestration in adipose and skin tissue. Administration of moxidectin with food resulted in an increase in maximum observed plasma concentration (C_{max}) and area under the plasma-concentration time curve (AUC) of 34% and 39%, respectively.

High performance liquid chromatography (HPLC) methods with fluorescence detection were validated for the quantitation of moxidectin in human plasma and breast milk. Based on a 0.5-milliliter (mL) sample volume, the assays were linear from 0.08 to 120 nanograms (ng)/mL. For further information, please refer to the Investigator's Brochure.

3.3.2.2 Clinical Studies of Moxidectin

Moxidectin has been administered to 194 healthy volunteers in five Phase 1 studies, and in 1105 patients with onchocerciasis in one Phase 2 and one Phase 3 study. For further information, please refer to the Investigator's Brochure.

Phase 1 studies of moxidectin evaluated single oral doses of 3 to 36 mg of moxidectin under fasted and fed conditions in healthy men and women. Moxidectin was well tolerated across the dose range. All of the adverse events (AEs) reported across all 5 studies were mild to moderate in intensity, with the exception of one Grade 3 event (enteritis) in a subject who received 36 mg (which was deemed unrelated to test article). There were no Grade 4 events and no clinically relevant abnormalities observed in vital sign measurements, electrocardiograms (ECGs), or safety laboratory tests. None of the subjects died or experienced a serious adverse event (SAE) in any study, and there were

no discontinuations from the study because of AEs. There was no relationship between either the incidence or type of AEs and the dose of moxidectin administered.

The most commonly reported AEs in all subjects who took moxidectin were headache, infection/upper respiratory tract infection/viral infection, nausea, pharyngitis, cough increased, rhinitis leukopenia, dizziness, pain, aspartate aminotransferase increased, alanine aminotransferase increased, somnolence, rhinitis, flatulence, gastroenteritis, myalgia, and asthenia.

The Phase 2 study was a randomized, single-ascending dose, double-blind, parallel-design, active (ivermectin)-controlled, inpatient/outpatient study conducted at a single center, the Onchocerciasis Chemotherapy Research Center in Ghana, an onchocerciasis endemic region of Africa. Of the 172 subjects in the safety population, 170 subjects (98.8%) experienced at least one AE. In assessing the safety of chemotherapeutics in the treatment of onchocerciasis, a generally universal observation among treated patients is the Mazzotti reaction, which is a constellation of symptoms caused by an immunologically mediated reaction to the dying microfilariae. Common systemic clinical manifestations of the Mazzotti reaction include pruritus, rash, lymphadenitis, headache, myalgia, arthralgia, hypotension (including severe symptomatic postural hypotension), fever, and swelling of the face and limbs. Ocular events include epiphora (excessive lacrimation), photophobia, conjunctival injection, limbitis, anterior uveitis, chorioretinitis, and optic neuritis.

At least 1 AE consistent with the effects of the dying microfilariae was reported for 38 subjects (86.4%) treated with 2-mg moxidectin, 45 subjects (100%) treated with 4-mg moxidectin, 37 subjects (97.4%) treated with 8-mg moxidectin, and 43 subjects (95.6%) treated with ivermectin, occurring more commonly in moxidectin recipients. The events were not life threatening in either moxidectin or ivermectin recipients. No clinically relevant treatment-related non-Mazzotti AEs were observed in any of the treatment groups. No subject was withdrawn from the study due to an AE. Eight subjects experienced SAEs in the study: 5, 1, and 2 subjects in the moxidectin 2-, 4-, and 8-mg treatment groups, respectively. None of the SAEs were considered related to test article by the investigator. One subject (moxidectin 2 mg) died on Day 310 from a snakebite.

All moxidectin doses (except 2 mg at the 18-month time point) resulted in statistically significantly lower skin microfilaria levels at all time points after treatment when compared with ivermectin.

A large (n = 1472) multicenter (multinational), double-blind, randomized (moxidectin 2:ivermectin 1), stratified (gender, baseline microfilarial load, site),

ivermectin-controlled Phase 3 study was conducted in subjects infected with *O. volvulus*: 1472 subjects were enrolled across 4 sites and treated with either a single 8-mg dose of moxidectin (n = 978) or a single 150-µg/kg dose of ivermectin (n = 494). Subjects participated in a 30-day screening period, a minimum 6-day inpatient evaluation period following administration of study drug, and follow-up visits at Day 14 and at Months 1, 3, 6, 12, and (for a subset of subjects) 18 months. Study follow-up of at least 12 months was completed for greater than 95% of study subjects. The study met the pre-defined primary endpoint of superiority of moxidectin over ivermectin at Month 12 ($P < 0.0001$). Furthermore, treatment differences were observed early and persisted to 18 months. Similar efficacy was seen across the different level of infection subsets.

All 978 subjects (100%) in the moxidectin treatment group and 491 subjects (99.4%) in the ivermectin treatment group experienced treatment-emergent AEs (TEAEs) during the active phase of the study (defined as the date of study drug administration and up to 180 days after this date).

A total of 966/978 subjects (98.8%) in the moxidectin treatment group and 480/494 subjects (95.6%) in the ivermectin treatment group experienced at least 1 AE consistent with the effects of the dying microfilariae. Reactions occurring more frequently in the moxidectin treated subjects included lymph node pain, lymphadenitis, tachycardia, pruritus (skin or eye), edema, rash, urticaria, and orthostatic hypotension; this is consistent with a more extensive decrease in skin microfilariae and faster reduction in skin microfilariae generally observed with moxidectin treatment as compared with ivermectin treatment. A total of 205/978 subjects (21.0%) in the moxidectin treatment group and 79/494 subjects (16.0%) in the ivermectin treatment group experienced ocular TEAEs, the most common of which were eye pain, eye pruritis, and eyelid edema.

Only 25 subjects (2.6%) in the moxidectin treatment group and 13 subjects (2.6%) in the ivermectin group experienced adverse drug reactions, assessed by the investigator as drug related but not associated with efficacy reactions.

No AEs during the active phase of the study led to withdrawal.

In total, 57 subjects (3.8%) experienced 77 SAEs during the active phase of the study. In the moxidectin treatment group, 39/978 subjects (4.0%) experienced 52 events, and in the ivermectin treatment group, 18/494 subjects (3.6%) experienced 25 events. None of the SAEs were considered related to test article by the investigator. One subject (moxidectin 2 mg) died on Day 310 from a snakebite. Four subjects died during the active phase of the study, 2 subjects (0.2%) in each group. In the moxidectin group, 1 subject died due to peritonitis and cardiac arrest following complications after surgical intervention for a

vesico-vaginal fistular surgical repair and a second subject died following an acute asthma attack. In the ivermectin group, 1 subject died due to sepsis following falciparum malaria infection and a second subject died after experiencing diabetic acidotic coma secondary to malaria and meningeal syndrome.

The full and final analysis of the Phase 3 study data is ongoing and will be concluded in the fourth quarter of 2016.

3.3.2.3 Cardiovascular Safety

Non-clinical data supportive of the cardiovascular safety of moxidectin consists of the following:

- A lack of binding to ion channels, including calcium Type L and Type N, ATP-sensitive potassium, Ca-activated V1 potassium, IKr (human ether-à-go-go [hERG]) potassium and Site 2 sodium channels in a NovaScreen assay;
- Minimal effect on hERG current in HEK293 cells *in vitro* at concentrations approximately 100-fold higher than C_{max} in adult patients in a Phase 2 study; and
- Lack of effect on corrected QT interval (QTc) monitored over 72 hours in a dog cardiovascular-telemetered study at an oral dose of 1 mg/kg, approximately 16.5-fold in excess of the proposed human dose on C_{max} and 24.7-fold higher on AUC.

In all clinical studies, participants received a single moxidectin dose, with doses ranging from 2 to 36 mg. The review of currently available clinical cardiac safety data, including ECGs from the 6 analyzed studies, indicates no identifiable proarrhythmic risk to date. Specifically, in the five Phase 1 studies, there were no deaths, SAEs, or premature discontinuations due to AEs and there were no clinically meaningful changes in ECGs. In the Phase 2 study, which investigated 3 dose levels of moxidectin versus standard-of-care ivermectin, there were no SAEs in the system organ class (SOC) of cardiac disorders. There was 1 SAE of grand mal convulsion (moxidectin 2 mg), 2 non-serious AEs of syncope (moxidectin 2 mg and 4 mg), and 1 non-serious AE of ventricular extrasystole (moxidectin 2 mg). There was no evidence of QTc prolongation in these patients.

Two patients receiving moxidectin (4 mg and 8 mg) who had a post-baseline QT interval corrected by Bazett's formula (QTcB) of >450 milliseconds (msec) with a >10% increase from Baseline did not have any AEs in the SOC of cardiac disorders or AEs suggestive of delayed repolarization (Medical Dictionary for Regulatory Activities [MedDRA] query "Torsade de pointes/QT prolongation"). One subject in the moxidectin 8-mg treatment group on Day 1 had a QTc interval >480 msec. This subject, a 59-year-old female with history of chloroquine allergy and palpitation and a baseline QTc of 468.55 msec, had a

QTc of 495.49 msec on Day 1 after study treatment. There were no associated cardiac AEs. Her QTc interval on Day 8 was 475.39 msec. No subject in any of the treatment groups had a QTc interval greater than 500 msec. There was no statistically significant difference (P >0.05) between moxidectin and ivermectin treatment groups for any QTc interval change greater than 30 msec or 60 msec, or with values greater than 450 msec, 480 msec, or 500 msec during the study. For further information, please refer to the current Investigator's Brochure.

3.4. Study Rationale

Even though the available non-clinical and clinical data is not suggestive of a QT liability, the aim of the current study is to definitively assess the QT prolongation potential of moxidectin through a dedicated dose-ranging design with intensive and time-matched PK and ECG collections using a concentration QT (cQT) analysis approach.

The study will enroll healthy male volunteers. The rationale for including only males is that moxidectin plasma concentration predictions have been derived from PK data from the Phase 1 study (3110A1-1005-EU) in which only males 18 to 50 years were enrolled. Protocol 3110A1-1005-EU had the largest number of subjects with PK data, and utilized the batch of moxidectin tablets that was subsequently administered in the pivotal Phase 3 clinical trial of male and female patients with onchocerciasis. Therefore, protocol MDGH-MOX-1008 seeks to enroll subjects that are concordant in baseline characteristics of those enrolled in Protocol 3110A1-1005-EU, enabling informal comparisons of PK data from 3110A1-1005-EU and MDGH-MOX-1008. Further, the effects of moxidectin during pregnancy are unknown and the inclusion of women of childbearing potential would require a particularly long-term commitment to a double-barrier method of protection given the relatively long half-life of moxidectin. The equivalent of approximately 5 half-lives of moxidectin is 6 months, and this represents an onerous obligation in this healthy subject population.

3.4.1 Rationale for Study Design

A definitive human QT prolongation risk-assessment study has not been performed with moxidectin. The results of this study will provide an understanding of the cardiac safety profile of moxidectin that is appropriate for the proposed use, a single oral 8-mg dose.

Given the PK characteristics of moxidectin (i.e., long half-life), a standard 4-way crossover thorough QT (TQT) study cannot be conducted as described in International Council for Harmonisation (ICH) E14. ICH E14 suggests conduct of a 4-arm

parallel-group study for drugs with a long half-life where a crossover design is not feasible.[18]

The December 2014 joint meeting between the FDA, the Clinical Pharmacology Leadership Group of the Consortium for Innovation and Quality in Pharmaceutical Development (IQ), and the Cardiac Safety Research Consortium (CSRC) has provided the impetus for using a cQT approach for replacing the TQT study;[19,20] most typically by adding intensive ECGs into the first-in-human dose-ranging study and utilizing exposure-response (ER) analyses to detect QT effects. The experience with ER analyses of ECG data has increased over the last decade and ER analyses have become an integral part of FDA Interdisciplinary Review Team review of data from QT assessment studies.[21] The ER analyses allow for a wide range of plasma concentrations to be analyzed, which improves the power to detect and exclude small QT effects[22,23] compared with the by-time-point analyses conducted for TQT studies. Experience with QT-prolonging drugs demonstrates that the effect on the QT interval is related to plasma levels of the drug or main metabolites, which further supports analyses in relation to plasma concentration. In contrast, by-time-point analyses as conducted in a standard ICH E14 parallel-group study design do not incorporate the concept of ER.[21] The results of the prospective IQ-CSRC study further support the cQT approach as a sensitive means to detect positive QT signals[20] and is the reason a cQT study is proposed to assess the QT prolongation potential for moxidectin.

Although the first-in-human dose-ranging study for moxidectin has been completed, conducting a QT study similar to a first-in-human dose-ranging study using an ER approach, if properly designed, will be at least as sensitive in detecting a QT signal as the by-time-point ICH E14-recommended parallel-group study. Furthermore, such an approach will require fewer subjects for enrollment. This cQT study is similar in design to a first-in-human dose-ranging study; however, there will be no need to stagger enrollment into cohorts for safety (which has already been established).

Subjects will be randomized into 6 treatment groups (5:1 moxidectin:placebo) with 10 subjects per group. The dose range will provide for a 12-fold dose margin (4.7-fold exposure margin at C_{max}), exceeding the 4.5-fold range that is typically suggested if there is no positive control to diminish the risk of a false negative.[21] Triplicate ECGs will be assessed at Baseline and at pre-specified time points matched with PK sampling for 3 days in all subjects (see Section 5.6.1). With 15 sampling time points, this design will yield 900 QTc-PK pairs in total. After placebo and baseline subtraction, there will be 700 time-matched, placebo-corrected, baseline-adjusted QTc (ddQTc)-PK pairs. In

contrast, the Ferber design[20,24] used in the IQ-CSRC study yielded 315 QTc-PK pairs and 189 ddQTc-PK pairs per drug.

3.4.2 Doses Selected

The proposed human dose for the treatment of onchocerciasis is 8 mg. This study will assess moxidectin as a single oral dose at doses up to 36 mg in tablet form and in the fasted state. In addition to the non-clinical safety pharmacology and toxicology studies, which provided adequate safety margin multiples in reference to the 36-mg dose, moxidectin has previously been administered at doses up to 36 mg in healthy human subjects and was well tolerated. Specifically, in Study 3110A1-100-EU, there was no evidence of clinically relevant safety findings after administration of moxidectin (oral liquid). No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory test results during the study. A slightly higher incidence of CNS AEs (somnolence and mild dizziness) was observed in the 36-mg fed and fasted treatment groups (moxidectin or placebo). As this was prior to study unblinding and the dose was well above the predicted therapeutic dose, the decision was made to end the study prior to enrollment of a planned 54-mg cohort. There was found to be no major difference in the pattern and severity of AEs and the AEs reported during the study were mild to moderate in intensity with the exception of one Grade 3 event (enteritis) in the 36-mg group, which was deemed unrelated to test article. There were no SAEs and no subjects discontinued the study due to an AE.

Increased exposure to moxidectin has been observed in liquid presentations compared with tablets and when moxidectin is given with food. Of the 10 subjects who received moxidectin as an oral solution at 36 mg in Study 3110A1-100-EU, the fasted mean (±SE) AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) was 451 (±48.2) ng*days/mL compared with fed $AUC_{0\text{-}inf}$ of 624 (±41.6) ng*days/mL. Therefore, moxidectin administered in tablet form and in the fasted state should ensure that exposure is less than or equal to existing clinical experience.

Further information on the safety findings and PK of moxidectin are included in the Investigator's Brochure.

4. Study Objectives

4.1. Primary Objective

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

4.2. Secondary Objective

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

4.3. Exploratory Objectives

The exploratory objectives of the study 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).

5. Investigational Plan

5.1. 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)

5.2. Study Duration

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 clinical research unit (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.

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

5.3. Selection of Study Population

Eligibility will be determined at Screening and reconfirmed at Check-in on Day –1. The investigator or medically qualified designee will be responsible for confirming subject eligibility by documenting in the electronic case report form (eCRF) that each subject meets all of the inclusion criteria in Section 5.3.1 and does not meet any of the exclusion criteria in Section 5.3.2.

5.3.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria to participate in this study:

1. Healthy male between 18 and 50 years of age (inclusive);

2. Body mass index (BMI) of 18 to 30 kg/meters $(m)^2$ (inclusive) and a minimum weight of 50 kg (110 pounds [lb]);
3. Biologically or surgically sterile or must commit to using 2 reliable (in the opinion of the investigator) methods of contraception, simultaneously, from Screening through the duration of the study period (to Week 12);
4. Willing and able to give written informed consent.

5.3.2 Exclusion Criteria

A subject will be excluded from participation in this study if he meets any of the following criteria:

1. Unwilling to abstain from alcohol, caffeine, xanthine-containing products, Seville oranges, grapefruit juices, and fish liver oils within 72 hours before Check-in (Day –1) and throughout the inpatient period of the study;
2. Less than 1 bowel movement every 24 hours in the absence of any laxative, suppository, or enema use during the month before Screening;
3. Abnormal fecal consistency within 24 hours of Check-in (Day –1);
4. Clinically relevant abnormal findings on medical history, clinical laboratory test results, vital sign measurements, safety 12-lead ECG results, or physical examination at Screening or Baseline which, in the opinion of the investigator, would interfere with dosing, jeopardize the safety of the subject, or impact the validity of the study results;
5. History of clinically significant dermatologic, gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the investigator, would interfere with dosing, jeopardize the safety of the subject, or impact the validity of the study results;
6. History of hypersensitivity or allergic reactions to ivermectin, moxidectin, or any of the ingredients in the study drug as described in the Investigator's Brochure;
7. Any condition that may affect oral drug absorption (e.g., previous surgery on the gastrointestinal tract including removal of parts of the stomach, bowel, liver, gall bladder, or pancreas);
8. History of risk factors for torsades de pointes, including unexplained syncope, known long QT syndrome, heart failure, myocardial infarction, angina, or clinically significant abnormal laboratory assessments including hypokalemia, hypercalcemia,

or hypomagnesemia. Subjects are also excluded if there is a family history of long QT syndrome or Brugada syndrome;

9. A sustained supine systolic blood pressure >150 millimeters of mercury (mm Hg) or <90 mm Hg or a sustained supine diastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in (Day –1). Blood pressure may be retested twice in the supine position. The blood pressure abnormality is considered sustained if either the systolic or the diastolic blood pressure values are outside of the stated limits for 3 assessments, and the subject will not to be randomized;
10. A resting heart rate (HR) of <40 beats per minute (bpm) or >100 bpm at Screening or Check-in (Day –1);
11. An uninterpretable or abnormal screening ECG indicating a second- or third-degree atrioventricular block, or 1 or more of the following: QRS interval >110 msec; QT interval corrected by Fridericia's formula (QTcF) >450 msec; PR interval >200 msec; or any rhythm other than sinus rhythm that is interpreted by the investigator to be clinically significant;
12. Concomitant use of prescription medications, including medications known to prolong the QTc or herbal preparations, within 14 days or 5 half-lives (whichever is longer) before study drug dosing, or use of an over-the-counter (OTC) medication or vitamins within 7 days before study drug dosing;
13. Received an investigational drug during the 30 days, or 5 half-lives of the study drug (whichever is longer), before Check-in (Day –1), or is planning to receive another investigational drug at any time during the study;
14. History or presence of alcohol abuse (defined as consumption of more than 210 mL of alcohol per week, or the equivalent of fourteen 4-ounce [oz] glasses of wine or fourteen 12-oz cans/bottles of beer or wine coolers per week) within 6 months before Screening or a positive alcohol test at Screening or Check-in (Day –1);
15. History or presence of substance abuse within the past 2 years or a positive drug screen test at Screening or Check-in (Day –1);
16. Current use or has used tobacco- or nicotine-containing products (e.g., cigarettes, e-cigarettes, cigars, chewing tobacco, snuff) within 14 days before study drug dosing;
17. Blood donation or significant blood loss within 30 days before Check-in (Day –1) or plasma donation within 7 days before Check-in (Day –1);

18. Presence of hepatitis B surface antigen or antibodies to human immunodeficiency virus (HIV) or hepatitis C virus at Screening;
19. Poor venous access in both arms;
20. Clinical signs of active infection and/or a temperature of >38.0 degrees Celsius (°C) at Screening;
21. Unable to understand verbal or written English or any other language for which a certified translation of the informed consent form is available;
22. For any reason, is deemed by the investigator or medically qualified designee to be inappropriate for this study, including a subject who is unable to communicate or cooperate with the investigator, and/or is unwilling to comply with protocol-defined procedures and complete the study.

5.4. Withdrawal of Subjects from the Study

A subject may withdraw from the study for any reason and at any time.

The investigator must make every reasonable effort to keep each subject in the study except where termination or withdrawal is for reasons of safety. The investigator also has the right to withdraw subjects from study in the event of concurrent illness, AE, protocol violation, administrative reason, or other reason.

It is understood by all concerned that an excessive rate of withdrawal from the study can render the study difficult to interpret.

5.4.1 Reasons for Withdrawal

The primary reason for treatment discontinuation will be noted using the following categories:

1. AE: The subject experiences an AE that, in the opinion of the investigator, requires early termination. If a subject is discontinued from the study due to an AE, the investigator or medically qualified designee will be required to follow-up with the subject until the event resolves or becomes stable. If a subject death occurs during the study, the cause of death will be reported as an SAE, with an outcome of death noted in the eCRF.

   A subject will be withdrawn from the study if he has an ECG with a manually measured QTcF of >500 msec at any time point after dosing that is confirmed by the investigator. It will be recorded as an AE and reported immediately to the medical monitor.

2. Protocol deviation: The subject fails to meet protocol entry criteria or does not adhere to protocol requirements, and continued participation will pose an unnecessary risk to the subject's health.
3. Voluntary withdrawal of consent: The subject wishes to withdraw from the study in the absence of a medical need.
4. Study termination: The sponsor, institutional review board (IRB), FDA, or other regulatory agency terminates the study.
5. Other.

   Note: This category includes withdrawals caused by an accidental or a medical emergency, unblinding, or other rare cases. The specific reasons will be recorded in the eCRF.

5.4.2 Handling of Withdrawals

The investigator may terminate a subject's study participation at any time during the study if the subject meets the withdrawal criteria described in Section 5.4.1. In addition, a subject may discontinue his participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded.

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 ECG; symptom-based physical examination; collection of AEs; and clinical laboratory evaluation (including hematology, serum chemistry, and urinalysis).

5.4.3 Replacement Subjects

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 CRU from Check-in until all subjects due to be dosed have completed dosing. Subjects who withdraw after dosing will not be replaced.

5.5. Study Procedures

5.5.1 Schedule of Events

The schedules of events are presented in Table 1-1 and Table 1-2.

5.5.2 Study Procedures and Assessment Periods

The study procedures to be performed for each subject enrolled in the study are listed in the following sections. Additional details of the study procedures are provided in Section 5.6. Any deviation from procedures planned in the protocol must be recorded in the source documents and the sponsor must be notified.

All laboratory tests on blood samples will be performed at the selected laboratory. Information on collection and shipment of all required study samples will be described in the Study Reference Manual.

Additional visits and/or assessments may be conducted as clinically indicated. For these additional assessments, visit-specific data will not be collected in the eCRF, although all AEs and concurrent medications must be recorded throughout the study period.

5.5.3 Period 1

5.5.3.1 Screening

Subjects will be screened up to 28 days before randomization (range: Day –28 to Day –2) to determine eligibility for participation in the study. Screening assessments may be conducted on different days if required. At Screening, the following procedures will be performed and documented:

- Written informed consent obtained before any study-related procedures (see Section 6.3)
- Review of inclusion/exclusion criteria (see Section 5.3)
- Recording of demographic information including date of birth, gender, ethnicity, and race (see Section 5.6.4)
- Medical and medication history (see Section 5.6.4)
- Full physical examination (see Section 5.6.3.6)
- Vital signs (supine blood pressure, HR, respiratory rate, oral body temperature) (see Section 5.6.3.4)
- Height and body weight measurement and calculation of BMI (see Section 5.6.3.6)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis (see Section 5.6.3.3)
- Urine drug screen (see Section 5.6.3.3)

- Serology (hepatitis B surface antigen, antibodies to HIV and hepatitis C virus) (see Section 5.6.3.3)
- Safety 12-lead ECG (see Section 5.6.3.5)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

Results of all screening tests must be available and reviewed before the subject's Check-in Visit. Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the CRU for Check-in on Day –1.

5.5.3.2 Day –1

Subjects will be admitted to the CRU on Day –1 (not less than 12 hours before scheduled dosing) and continued eligibility will be confirmed through the review of the inclusion and exclusion criteria. Subjects will begin fasting as instructed and water can be taken *ad libitum*. On Day –1, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) (see Section 5.6.3.6)
- Body weight measurement (see Section 5.6.3.6)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis (see Section 5.6.3.3)
- Urine drug screen (see Section 5.6.3.3)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.3 Day 1

5.5.3.3.1 Pre-Dose

On Day 1, the following procedures will be performed and documented before dosing:

- Randomization (see Section 5.7.1). Subjects will have a final assessment of eligibility before randomization; those subjects meeting all of the inclusion and none of the exclusion criteria will be randomized and will continue fasting until dosing.
- Vital signs (supine blood pressure, HR, respiratory rate, oral body temperature) within 15 minutes before dosing (see Section 5.6.3.4)

- Begin continuous 12-lead ECG (see Section 5.6.1.1)
- Blood sample for PK assessment (collected within 15 minutes before dosing) (see Section 5.6.2.1)
- Pre-dose feces sample collection for PK assessment (see Section 5.6.2.2)
- Pre-dose urine sample collection for PK assessment (see Section 5.6.2.2)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.3.2 Dosing

At Hour 0 on Day 1, the following procedures will be performed and documented:

- Study drug administration (see Section 5.7.2)

5.5.3.3.3 Post-Dose

After dosing on Day 1, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) at 4 and 12 hours after dosing (see Section 5.6.3.6)
- Safety 12-lead ECG at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing (see Section 5.6.3.5)
- Continuous 12-lead ECG with extractions at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing (see Section 5.6.1.1)
- Blood samples for PK assessment (collected at 0.5, 1, 2, 3, 4*, 5, 6, 8, and 12* hours after dosing on Day 1. (* Planned time points for analysis of moxidectin metabolite concentrations) (see Section 5.6.2.1)
- Standardized meal (lunch) served approximately 4 hours after dosing (see Section 5.7.8)
- Feces sample for PK assessment (collected from 0-24 hours after dosing on Day 1) (see Section 5.6.2.2)
- Urine sample for PK assessment (collected from 0-24 hours after dosing on Day 1) (see Section 5.6.2.2)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.4 Day 2

On Day 2, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) at 24 hours after dosing (see Section 5.6.3.6)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis at 24 hours after dosing (see Section 5.6.3.3)
- Safety 12-lead ECG at 24 hours after dosing (see Section 5.6.3.5)
- Continuous 12-lead ECG with extractions at 24 and 36 hours after dosing (see Section 5.6.1.1)
- Blood samples for PK assessment (collected at 24* and 36* hours after dosing on Day 1. (* Planned time points for analysis of moxidectin metabolite concentrations) (see Section 5.6.2.1)
- Feces sample for PK assessment (collected from 24-48 hours after dosing on Day 1) (see Section 5.6.2.2)
- Urine sample for PK assessment (collected from 24-48 hours after dosing on Day 1) (see Section 5.6.2.2)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.5 Day 3

On Day 3, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) at 48 hours after dosing (see Section 5.6.3.6)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis at 48 hours after dosing (see Section 5.6.3.3)
- Safety 12-lead ECG at 48 hours after dosing (see Section 5.6.3.5)
- Continuous 12-lead ECG with extractions at 48 and 60 hours after dosing (see Section 5.6.1.1)
- Blood samples for PK assessment (collected at 48 and 60* hours after dosing on Day 1. (* Planned time points for analysis of moxidectin metabolite concentrations) (see Section 5.6.2.1)

- Feces sample for PK assessment (collected from 24-48 hours after dosing on Day 1) (see Section 5.6.2.2)
- Urine sample for PK assessment (collected from 24-48 hours after dosing on Day 1) (see Section 5.6.2.2)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.6 Day 4

On Day 4, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) at 72 hours after dosing (see Section 5.6.3.6)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis at 72 hours after dosing (see Section 5.6.3.3)
- Safety 12-lead ECG at 72 hours after dosing (see Section 5.6.3.5)
- Continuous 12-lead ECG with extraction at 72 hours after dosing (see Section 5.6.1.1)
- Vital signs (supine blood pressure, HR, respiratory rate, oral body temperature) at 72 hours after dosing (see Section 5.6.3.4)
- Blood sample for PK assessment (collected at 72 hours after dosing) (see Section 5.6.2.1)
- Feces sample for PK assessment (collected from 48-72 hours after dosing) (see Section 5.6.2.2)
- Urine sample for PK assessment (collected from 48-72 hours after dosing) (see Section 5.6.2.2)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)
- Discharge from the CRU (after all study procedures are completed at 72 hours after moxidectin administration)

5.5.3.7 Day 8

On Day 8, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) (see Section 5.6.3.6)
- Blood sample for PK assessment (see Section 5.6.2.1)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.8 Day 15

On Day 15, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) (see Section 5.6.3.6)
- Blood sample for PK assessment (see Section 5.6.2.1)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.3.9 Day 22

On Day 22, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) (see Section 5.6.3.6)
- Vital signs (supine blood pressure, HR, respiratory rate, oral body temperature) (see Section 5.6.3.4)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis (see Section 5.6.3.3)
- Safety 12-lead ECG (see Section 5.6.3.5)
- Blood sample for PK assessment (see Section 5.6.2.1)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.5.4 Period 2

5.5.4.1 Week 8

At Week 8, subjects will be contacted via telephone for recording of AEs and concomitant medications. These data will be documented.

5.5.4.2 Week 12

At Week 12, the following procedures will be performed and documented:

- Symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) (see Section 5.6.3.6)
- Vital signs (supine blood pressure, HR, respiratory rate, oral body temperature) (see Section 5.6.3.4)
- Blood samples for hematology and serum chemistry and urine sample for urinalysis (see Section 5.6.3.3)
- Safety 12-lead ECG (see Section 5.6.3.5)
- Recording of AEs (see Section 5.6.3.1)
- Recording of concomitant medications (see Section 5.6.5)

5.6. Details of Study Procedures

5.6.1 Pharmacodynamic Assessments

5.6.1.1 Continuous 12-Lead Electrocardiogram Acquisition

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. Subjects may be allowed to shower at times that do not conflict with scheduled study procedures (i.e., showers will not be permitted on Day 1 due to the frequency of scheduled study procedures on that particular day). The ECG data will be transmitted wirelessly to the Surveyor system, which will extract triplicate 10-second ECG recordings (approximately 1 minute apart) at the following time points:

- 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.

Subjects will refrain from talking and will be required to be in a supine position in a quiet room with no external stimuli (e.g., music or television) for approximately 10 minutes before and 5 minutes after the defined ECG collection time points.

5.6.1.2 Continuous 12-Lead Electrocardiogram Analysis Methods

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 (e.g., lead V2) will be used.

5.6.2 Pharmacokinetic Assessments

5.6.2.1 Blood Samples

Blood samples will be collected to determine the PK of moxidectin and metabolites in plasma. Plasma aliquots will be stored frozen at the CRU before being shipped to a specialized laboratory for analysis. 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

Blood sampling time points will coincide with the ECG time points. The blood samples will be collected as close to the scheduled time point as possible, within 5 minutes and no later than 10 minutes after the ECG, unless otherwise noted.

Sample collection, processing, and storage will be described in the Study Reference Manual.

5.6.2.2 Urine and Feces Samples

Urine and feces for PK assessments will be collected from each subject at the following time points:

- Urine: Before dosing (single pre-dose 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)
- Feces: Before dosing (single pre-dose collection*) and each bowel motion during confinement in the CRU. 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.

At Screening, subjects will be provided with materials to collect feces so that when the subject has a bowel movement on or before Day –1 (-2 days), this can be collected if it occurs before admission to the CRU (or up to and including 0.5 hours before dosing as necessary to obtain a collection before dosing). A sample may be collected at the CRU on Day –1. Subjects will be instructed to refrigerate any feces specimen collected before admission to the CRU.

The weight of each feces specimen will be measured (grams) and recorded to the whole number. Urine volumes will be pooled over each interval and the total volume obtained; a single sample from the total volume will be obtained for PK assessments.

Urine and feces samples will be stored frozen at the CRU before being shipped to a specialized laboratory for analysis. Sample collection, processing, and storage will be described in the Study Reference Manual.

5.6.3 Safety Assessments

5.6.3.1 Adverse Events

An AE is defined (per ICH E2A) as any untoward medical occurrence in a patient or clinical investigation subject that is administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a medicinal (investigational) product, whether or not the incident is considered related to the medicinal (investigational) product.

Adverse event monitoring will begin after the subject signs the informed consent form (ICF) and will continue until Week 12. Before dosing of the study drug, AEs will be assessed for their relationship to study procedure(s) by the investigator.

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question such as, “How have you been feeling since your last visit?” will be asked. Subjects may report AEs that occur at any other time during the study.

Each AE will be graded for severity using the following guidance:

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life Threatening
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 gm/24 hours	4-5 stools or 400-800 gm/ 24 hours	6 or more watery stools or >800 gm/ 24 hours or requires outpatient IV hydration	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever <24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Abbreviations: gm, gram(s); IV, intravenous.
Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (2014) and the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

All laboratory values must be reviewed in real time by the investigator. Given that all laboratory data are collected and statistically analyzed according to their respective toxicity grades, laboratory abnormalities that occur without related clinical symptoms and signs should generally not be recorded as an AE unless they represent a clinically significant event. Where possible, the overall diagnosis rather than the laboratory abnormality should be recorded in the AE eCRF. This will avoid duplication of laboratory abnormalities in both the AE and laboratory reports. Abnormal laboratory results that are of clinical significance will be reviewed by the medical monitor.

Any laboratory test result that meets the criteria for an SAE (refer to Section 5.6.3.1.1) should be recorded as an AE, the AE page of the eCRF completed, and an SAE form also completed in order for the sponsor to collect additional information about that abnormality, including information regarding relationship to study product or other causes, any action taken, and resolution.

Each AE will be assessed for causality using the following criteria:

- Definitely related: The experience follows a reasonable temporal sequence from administration of the study drug or in which the drug level has been established in body fluids or tissues; the experience follows a known response pattern to the suspected drug and this is confirmed by improvement upon stopping the drug (dechallenge) and reappearance of the reaction upon repeated exposure (rechallenge).
- Probably related: The experience follows a reasonable temporal sequence from administration of the study drug; the experience follows a known response pattern to the suspected drug and this is confirmed by dechallenge; the experience could not be reasonably explained by the known characteristics of the subject's clinical state.
- Possibly related: The experience follows a reasonable temporal sequence from administration of the study drug; the experience follows a known response pattern to the suspected drug; the experience could be produced by the subject's clinical state or other modes of therapy administered to the subject.
- Not related: The experience occurs before administration of the study drug; the experience follows a reasonable temporal sequence from administration of the study drug but does not follow a known response pattern to the suspected drug and could be reasonably explained by the known characteristics of the subject's clinical state; the experience is proven to be caused by the subject's disease or condition or another drug through rechallenge; the experience does not recur following rechallenge.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed.

All AEs are documented in the eCRF, whether or not the investigator concludes the event to be related to the study drug. The event term, start and stop date, and severity are documented, along with the investigator's opinion of the causal relationship between the event and study drug administration (not related, possible, probable, or definite).

All AEs will be followed until resolution or until the investigator determines that further follow-up is not necessary. The type of follow-up (telephone call or CRU visit) will be based on medical judgment and the severity of the event.

5.6.3.1.1 Serious Adverse Events

An SAE is an AE that results in any of the following:

- Death
- Is life threatening (i.e., the subject was at risk of death from the event. "Life threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: Emergency department visits are not considered hospitalizations
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect

An AE may be considered serious (i.e., an important medical event) if based on medical and scientific judgment, the event may not be immediately life threatening or result in death, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

If an SAE occurs, appropriate therapy will be administered based on the investigator's judgment. Subjects will then be monitored closely as appropriate.

5.6.3.2 Additional Points to Consider for Adverse Events

Diagnoses versus signs and symptoms:

- Each AE will be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms will NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) will be recorded as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation).

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only will be reported as an AE.

Pre-existing conditions:

- Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and will NOT be recorded as AEs. However, if the subject experiences a worsening (severity or frequency) or complication of such a concurrent condition, the worsening or complication will be recorded as an AE. The investigator will ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Pre-planned surgeries or procedures:

- Procedures (surgeries or therapies) that were planned before the start of AE collection are not considered AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition will be captured as an AE.

Elective surgeries or procedures:

- Elective procedures planned or performed where there is no change in the subject's medical condition will not be recorded as AEs, but will be documented in the subject's source documents.

Overdose:

- Cases of study drug overdose without manifested side effects are NOT considered AEs.

5.6.3.2.1 Reporting of Serious Adverse Events

Reports of SAEs require immediate reporting to the sponsor and the medical monitor, within 24 hours of the investigator's knowledge of the event, whether or not the investigator believes that the experience is related to study drug.

An SAE form must be completed, signed by the investigator, and include at a minimum: the event term(s), a short description of the AE, the reason why the AE is categorized as serious, the investigator's current opinion of the relationship between the event and the study drug (causality assessment), as well as the subject's identification number, gender, age, and relevant medical history.

Additional information, as appropriate, will be sent to the sponsor and medical monitor when it becomes available (e.g., copies of relevant subject records, autopsy reports, and other documents).

Reporting of a suspected SAE will not be delayed in order to obtain additional information.

Any additional information, if collected, can be reported as a follow-up to the initial report.

For each SAE, a corresponding AE eCRF must also be completed.

The investigator is responsible for notifying the IRB in writing of any SAE. All SAEs are to be documented in the eCRF with the date of onset and resolution, frequency, determination of seriousness, severity, action taken, outcome, and relationship to study drug.

Any SAE, including death, occurring while the subject is receiving study drug, irrespective of the investigator's opinion regarding study drug relationship, will be reported by telephone immediately to one of the following individuals:

Name: Nicole Kruger or Sally Kinrade

Telephone: +61 425 846 036 or +61 419 301 193

Email: SAE@medicinesdevelopment.com

Any SAEs that occur within 30 days after the last dose of study drug that come to the attention of the investigator, and are thought to be related to study drug, will be reported to the sponsor and the medical monitor.

5.6.3.2.2 Follow-Up of Serious Adverse Events

All SAEs will be followed until the outcome is known or the subject's condition has stabilized.

All follow-up information on SAEs is to be reported within 1 working day of receipt by the investigator in the manner described previously.

The FDA requires that all SAEs that are unexpected and potentially related to the study drug must be reported to the FDA in writing within 15 calendar days of notification of Medicines Development for Global Health (MDGH). Serious AEs that meet the criterion for death or are immediately life threatening require MDGH to notify the FDA by telephone, fax, or in writing as soon as possible but no later than 7 calendar days after the

first knowledge that the case qualifies, followed up by a complete report within 8 additional calendar days.

MDGH or delegate will prepare an expedited report for the FDA based on information provided by Spaulding, and copies will be distributed to the investigator.

Expedited reports, as addenda to the Investigator's Brochure, will be filed with the Investigator's Brochure by the investigator upon receipt. The investigator also will forward a copy of all expedited reports to the IRB as required.

5.6.3.2.3 Subject Deaths

All deaths of subjects, regardless of cause, occurring within 30 days after subject termination, and which are known to the investigator, will be reported on the appropriate page of the eCRF.

Documentation of the subject's cause of death and a copy of the autopsy report, if any, will also be provided. MDGH must be notified immediately by telephone of all subject deaths; written follow-up must be received within 3 working days of initial notification.

Death will not be reported as an SAE, but as a clinical outcome. The cause of death on a source document, such as the medical record, death certificate or autopsy report, will be used as the event term for the SAE.

For subjects in which concurrent AEs or SAEs are present at the time of death, such AEs or SAEs will be marked as resolved with the date of resolution entered as the date of death.

Only the SAE that caused the subject's death will be marked with an outcome of "Fatal."

5.6.3.2.4 Reporting of Pregnancy

This study will only enroll male subjects. If their female partner is of childbearing potential, male subjects must commit to using 2 reliable (in the opinion of the investigator) methods of contraception, simultaneously, from Screening through the duration of the study period (to Week 12).

5.6.3.3 Clinical Laboratory Tests

Clinical laboratory samples and the diagnostic screening samples will be collected as specified in the schedule of events (Table 1-1 and Table 1-2). All samples will be collected in accordance with acceptable laboratory procedures. The tests that will be performed are presented in Table 5-1. Subjects must fast for at least 8 hours before clinical laboratory testing.

Results will be reviewed by the investigator or medically qualified designee. Any values outside of the reference range will be evaluated for clinical significance. The investigator or medically qualified designee may repeat the laboratory safety tests if deemed appropriate.

Table 5-1 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Complete Blood Count (CBC) Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Direct bilirubin Glucose Lactic dehydrogenase (LDH) Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein Uric acid	Appearance Bilirubin Blood Color Glucose Ketones Leukocyte esterase Microscopic examination: red blood cells; white blood cells; epithelial cells; bacteria, crystals, casts, etc. (if present) Nitrite pH Protein Specific gravity Urobilinogen
Diagnostic Screening Tests:		
Serology	**Urine Drug Screen**	
Hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and human immunodeficiency virus antibody (Screening only)	Urine drug screen will include: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates, phencyclidine, propoxyphene, cotinine, and methadone (Screening and Check-in [Day –1])	

Laboratory testing for hematology, serum chemistry, urinalysis, and diagnostic screening tests will be performed at a Clinical Laboratory Improvement Amendments (CLIA)-credentialed and regulated laboratory. The results of laboratory tests will be returned to the investigator or medically qualified designee, who will review the results together with the data in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges used by the laboratory.

5.6.3.4 Vital Sign Measurements

Vital sign measurements will be performed as specified in the schedule of events (Table 1-1 and Table 1-2). Vital signs (supine blood pressure, HR, respiratory rate, and oral body temperature [°C]) will be measured after the subject has rested for approximately 5 minutes.

When multiple procedures occur at the same time point, the vital sign measurements will be obtained first, followed by the 12-lead ECG conducted at the scheduled time point, followed by blood collection (as close to the scheduled time point as possible, within 5 minutes and no later than 10 minutes after the ECG, unless otherwise noted), followed by the physical examination, followed by the meal (if scheduled). A window of ±5 minutes around each time point will be utilized for vital sign measurements.

5.6.3.5 Safety 12-Lead Electrocardiograms and Electrocardiogram Discontinuation Criteria

Standard 12-lead digital safety ECGs will be performed as specified in the schedule of events (Table 1-1 and Table 1-2) 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.

A subject will be withdrawn from the study if he has an ECG with a manually measured QTcF of >500 msec at any time point after dosing that is confirmed by the investigator.

5.6.3.6 Physical Examinations

Physical examinations will be performed at the time points specified in the schedule of events (Table 1-1 and Table 1-2). A full physical examination will be performed at Screening. At all subsequent time points, a symptom-based physical examination (informed by concurrent conditions, signs and symptoms, and AEs reported) will be performed. The screening physical examination will consist of the following body systems: eyes, ears, nose, and throat; cardiovascular system; respiratory system; gastrointestinal system; dermatological system; extremities; musculoskeletal system; nervous system; and lymph nodes.

The subject's weight (kg) and height (centimeters [cm]) will be measured using a calibrated scale while the subject is wearing light street clothing and no shoes. The subject's BMI will be calculated using metric units and rounded to the nearest whole number according to the following formula: BMI = weight (kg)/height $(m)^2$.

5.6.4 Demographics, Medical History, and Other Baseline Assessments

A complete medical history will include a review of all major body systems. Medical history will include conditions and diseases that have a stop date before or on the screening date. Conditions and diseases that are ongoing at Screening or start between Screening and the start of study drug will be recorded on the Concurrent Conditions page of the eCRF. The history of smoking (tobacco and/or nicotine use), alcohol and caffeine use, and all medications taken for 28 days before Check-in will also be recorded in the

source documents only. Demographics will include the date of birth, gender, ethnicity, and race as described by the subject.

5.6.5 Documentation of Concomitant Medications

Beginning at Screening, all medication use, including vitamins, oral herbal preparations, and weight-loss preparations will be documented. Relevant information (i.e., name of medication, dose, units, frequency of administration, dates, and reasons for use) will be recorded in the source documents and in the eCRF. All changes in medication will be noted. If the reason for use meets the definition of an AE, the AE will be recorded on the appropriate page of the eCRF and in the source documents for that subject. All medications taken before the signing of the ICF will be recorded as prior medications.

5.6.6 Total Blood Volume

The approximate total blood volume to be collected per subject, including all safety clinical laboratory and PK evaluations for the entire study, will be specified in the ICF. Additional blood samples may be collected at the investigator's discretion if required for appropriate medical management or follow-up.

5.7. Study Treatments

5.7.1 Method of Assigning Subjects to Treatment

A statistician unblinded to treatment allocation and otherwise independent of study conduct will generate the randomization schedule. 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).

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 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)

5.7.2 Treatments Administered

Study drug administration (moxidectin or placebo) will occur after an overnight fast of at least 10 hours. On the morning of Day 1, subjects will receive either moxidectin (Treatments 1 through 5) or placebo matched to moxidectin (Treatment 6) according to the randomization schedule. Study drug will be administered orally in a double-blind manner (Section 5.7.5). To maintain the blind, each subject will receive 18 matching tablets. Study drug will be administered with at least 240 mL of water. No food will be allowed for 4 hours after dosing; however, water can be taken *ad libitum*. Thereafter, meals (lunch, dinner, and evening snack) will be served as regularly scheduled. Meal timing and components, activity levels, and general conditions in the CRU will be as similar as possible for all treatment groups.

5.7.3 Identity of Study Drug

Moxidectin has a white or pale yellow powder appearance. For the current study, moxidectin will be provided as tablets containing 2-mg moxidectin with microcrystalline cellulose, anhydrous lactose, sodium lauryl sulfate, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

The placebo tablets will be matched in appearance to the active study drug, and will contain the same excipients but will not contain moxidectin.

5.7.4 Management of Clinical Supplies

5.7.4.1 Study Drug Packaging and Storage

Study drug will be kept in a secure cabinet or room with access restricted to necessary study site personnel. Moxidectin and placebo tablets will be stored at 15°C to 25°C (59 degrees Fahrenheit [°F] to 77°F), protected from light and moisture, and must not be frozen. Temperature excursions are permitted up to 30°C (86°F).

5.7.4.2 Study Drug Accountability

In accordance with federal regulations (21 Code of Federal Regulations [CFR] 312.62), the investigator is required to keep accurate records showing final disposition of all investigational drugs.

THE INVESTIGATOR MUST NOT USE MATERIAL PROVIDED FOR THIS PARTICULAR STUDY IN ANOTHER STUDY WITHOUT PRIOR WRITTEN APPROVAL FROM MDGH.

The Investigator or his/her designee will record:

- Person Responsible: If the same individual signs the forms from day to day, his/her title need not be recorded after the first time.
- Lot Number: The lot number may be indicated on the label applied to each container of the product.
- Manufacture/Expiration Date: The manufacture and expiration date may be listed on the label of the product and should be recorded in the accountability logs.
- Date Used: Date administered or dispensed to the subject.
- Disposition of Material: Indicate if administered, destroyed, damaged in transit and destroyed, or other final disposition of material. Material cannot be transferred for pre-clinical or other use without prior written approval from MDGH.
- Date Returned to MDGH or Destroyed: At the termination of the study, unused and opened and partially used containers may be returned to MDGH or designee. However, the investigator or medically qualified designee will not destroy the supplies without immediate prior consultation with MDGH. Indicate date when unused containers are returned (day/mo/yr-Ret.) or destroyed (day/mo/yr-Des.).

Ultimate accountability for receiving, dispensing, and inventory of the test material lies with the investigator or medically qualified designee. Federal regulation requires that storage of the substance be in a secure enclosure, access to which is limited, to prevent theft or diversion, and in accordance with the labeling and storage guidelines.

Material remaining at the completion of the study will be returned to MDGH or will be handled otherwise according to written instructions from MDGH.

5.7.5 Blinding

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.

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 Cardiatric 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.

5.7.5.1 Breaking the Blind

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.

5.7.6 Treatment Compliance

Study drug will be administered in the CRU under direct observation of study personnel and recorded in the eCRF. The CRU personnel will confirm that the subject has ingested the entire dose of study drug.

5.7.7 Prior and Concomitant Medications

Subjects may not have received an investigational drug during the 30 days, or 5 half-lives of the study drug (whichever is longer), before Check-in (Day –1) and cannot be planning to receive another investigational drug at any time during the study period.

Prescription medications, including medications known to prolong the QTc interval or herbal preparations, will be prohibited within 14 days or 5 half-lives (whichever is longer) before study drug dosing. In addition, tobacco- or nicotine containing products (e.g., cigarettes, e-cigarettes, cigars, chewing tobacco, snuff) are also prohibited within 14 days before study drug dosing and throughout the course of the study.

Any OTC medication or vitamins are prohibited within 7 days before study drug dosing and throughout the course of the study (except medication approved by the sponsor on a case-by-case basis).

The following are prohibited for 72 hours before Check-in (Day –1) and during participation in the inpatient period of the study:

- Alcohol, caffeine, and xanthine-containing products (e.g., tea, coffee, chocolate, cola)
- Seville oranges and grapefruit juices
- Fish liver oils

Medications and supplements taken before study enrollment and throughout the study will be recorded in the eCRF.

5.7.8 Diet, Fluid, Activity Control, and Subject Housing

Subjects will be confined in the CRU from the day of Check-in (Day –1) until all study procedures are completed at 72 hours after moxidectin administration (Day 4). Subjects will return to the CRU for outpatient visits on Days 8, 15, and 22, and Week 12.

In this study, subjects will receive a menu for the dosing period to include 3 meals and an evening snack. Breakfast will be served on nonfasting days (Days 2, 3, and 4). On Day 1, lunch will be served approximately 4 hours after dosing, dinner will be served approximately 9 to 10 hours after dosing, and if needed a light snack will be served beginning approximately 13 hours after dosing.

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 mL of water. No food will be allowed for 4 hours after dosing; however, water can be taken *ad libitum*. Thereafter, meals (lunch, dinner, and evening snack) will be served as regularly scheduled. Meal timing and components, activity levels, and general conditions in the CRU will be as similar as possible for all treatment groups.

When multiple procedures occur at the same time point, the vital sign measurements will be obtained first, followed by the 12-lead ECG conducted at the scheduled time point, followed by blood collection (as close to the scheduled time point as possible, within 5 minutes and no later than 10 minutes after the ECG, unless otherwise noted), followed by the physical examination, followed by the meal (if scheduled).

Subjects will not be allowed to engage in strenuous exercise (defined at the investigator's discretion) throughout the course of the study. Subjects will not be allowed to sleep during ECG conduction or recording since the QT-RR relationship is different during sleep. The subject's body position will be controlled to maintain supine positioning before and during the ECG extraction time points.

5.8. Statistical Analysis Plan

Details of all planned statistical analyses will be described in a separate statistical analysis plan.

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: 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.

All data collected will be presented in data listings. Missing data will not be imputed. Measurements that are excluded from the descriptive and inferential analyses will be included in the subject 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.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, arithmetic mean, SD, median, minimum, and maximum).

Demographic and background characteristics will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who discontinue and reasons for discontinuation will be presented.

5.8.1 Pharmacodynamic Endpoints

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

1. dQTcF –baseline-adjusted 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 post-dose time point (ddQTcF = [dQTcF (active dose groups) – mean dQTcF (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 HR and duration of PR, RR, and QRS interval parameters.

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

5.8.2 Safety and Tolerability Endpoints

The safety endpoints are:

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

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

5.8.3 Sample Size Calculation

The sample size of 60 subjects (10 subjects each in 6 treatment groups) is considered adequate to explore the effects of moxidectin on the QTc interval, 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 CRU from Check-in until all subjects due to be dosed have completed dosing. Subjects who withdraw after dosing will not be replaced.

5.8.4 Analysis Populations

For this study, 4 study populations will be defined:

- The ECG population will include all subjects who receive at least 1 dose of study drug and have at least 1 pair of pre-dose and post-dose 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.
- 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).

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

5.9. Statistical Analyses

5.9.1 Pharmacodynamic Analyses

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% confidence intervals (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.

5.9.1.1 Primary Analysis of the Primary Pharmacodynamic Endpoint

The relationship between time-matched 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 (i.e., 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 versus placebo) will be considered.

At the request of the FDA, 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. The sponsor believes 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, the relationship between the investigational drug's plasma concentration-time course in relationship to the circadian change of dQTcF in the placebo group will also be examined, to determine if a positive or negative correlation could have affected the dQTcF-plasma concentration relationship.

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.

5.9.1.2 Secondary Analysis: Pharmacokinetic/Pharmacodynamic Analyses

To evaluate the relationship between placebo-corrected mean change from Baseline in QTcF (i.e., 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 (i.e., 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 (e.g., 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 (i.e., the mean maximum plasma concentration under each dose level).

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.

5.9.1.3 Categorical QTc Findings

Categorical summaries using the largest postdose QTcF and largest 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.

5.9.1.4 Categorical Analysis of Other Electrocardiogram 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.

5.9.1.5 Electrocardiogram 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 pre-dose and post-dose assessments, and also tabulated with diagnostic statements categorized as treatment-emergent diagnostic statements (i.e., diagnostic statements not present on any baseline assessment). All abnormal ECG diagnostic findings will be listed.

5.9.1.6 Adequacy of Heart Rate 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 ICH E14 Guidance as an ancillary correction method.

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

5.9.2 Pharmacokinetic Analyses

5.9.2.1 Moxidectin Concentrations

Moxidectin concentrations in urine and feces as well as plasma:urine and plasma:feces concentration ratios will be summarized.

Summary statistics describing the time course of concentrations of moxidectin metabolites and parent to metabolite ratios in plasma will be presented. Metabolite concentrations in urine as well as metabolite plasma:urine concentration ratios will be summarized as appropriate.

5.9.2.2 Pharmacokinetic Parameters

Non-compartmental analysis, using Phoenix WinNonlin version 6.4, will be implemented for the calculation of PK parameters. The C_{max} will be excluded from all estimations of elimination rate constants for non-compartmental analysis. The elimination rate constant will be estimated if a given subject has more than 2 concentration values in the terminal portion of the curve and R-square greater than 0.95. Computed PK parameters for moxidectin in plasma will be summarized and listed for moxidectin, including mean, geometric mean, SD, median, and range, as appropriate.

Specific PK parameters for moxidectin in plasma will include:

- $AUC_{0\text{-last}}$: AUC from time 0 extrapolated to the last observed concentration
- $AUC_{0\text{-inf}}$: AUC from time 0 extrapolated to infinity
- $cumAUC_{0\text{-t}}$: cumulative AUC from time 0 extrapolated to time t (where t = 24, 48, and 72 hours)
- $AUC_{0\text{-}24}$: AUC from time 0 to 24 hours after dosing
- $AUC_{24\text{-}48}$: AUC from 24 to 48 hours after dosing
- $AUC_{48\text{-}72}$: AUC from 48 to 72 hours after dosing
- C_{max}: maximum observed plasma concentration
- T_{max}: time to maximum observed plasma concentration
- $t_{1/2}$: terminal elimination half-life

Additional PK parameters, including apparent clearance (CL), volume of distribution (Vd), and others may be determined as appropriate. The PK parameters will be expressed in units adjusted for molecular weight where appropriate.

5.9.3 Safety Analyses

All safety assessments, including AEs, clinical laboratory test results, vital sign measurements, and safety 12-lead ECG results will be summarized using descriptive statistics and presented in data listings. Physical examination findings and concomitant medications will be presented in data listings. All safety summary tables and figures will be generated using SAS®. No inferential statistics will be performed on the safety data.

5.9.3.1 Adverse Events

Summary tables for TEAEs will include numbers and percentages of subjects experiencing TEAEs by SOC and preferred term (PT). If a subject has more than 1 TEAE

that codes to the same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than 1 TEAE within a SOC category, the subject will be counted only once in that SOC category. The following summary tables will be included in the clinical study report for each treatment and overall: summary of TEAEs, relationship of TEAEs to study drug, severity of TEAEs, TEAEs leading to study discontinuation, and SAEs.

Data listings will be provided for all AEs, AEs leading to study discontinuation, and SAEs.

5.9.3.2 Clinical Laboratory Tests

Individual results of clinical laboratory tests (hematology, serum chemistry, and urinalysis) that are outside of the reference range will be flagged in the data listings. Clinical laboratory data will be presented in data listings and summarized by treatment and by toxicity grade.

5.9.3.3 Vital Sign Measurements

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) of each vital sign measurement and change from Baseline will be summarized for each treatment. All vital sign data will be presented in data listings.

5.9.3.4 Safety 12-Lead Electrocardiograms

Individual results of safety 12-lead ECGs, which meet pre-defined very high or very low criteria, will be flagged and displayed in a summary table. Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) of each vital sign measurement will be summarized for each treatment. All ECG data will be listed in the data listings.

5.9.3.5 Other Safety Data

The physical examination findings will be presented in the data listings. Clinically significant changes from Baseline in physical examination findings will be recorded as AEs.

5.9.3.6 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.

5.10. Data Quality Assurance

The sponsor or designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the principal investigator generating the data. Before subjects are enrolled, the sponsor or designee will explain the protocol, Investigator's Brochure, and eCRFs to the investigator. In addition, the clinical monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

At its discretion, the sponsor may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP), the protocol, standard operating procedures (SOPs), and all applicable regulatory requirements. Audits will be independent of, and separate from, the routine monitoring and quality control functions. The CRU may also be compelled to undergo an inspection by a regulatory authority.

6. Investigator's Obligations

The following administrative items are meant to guide the principal investigator or sub-investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not necessarily result in protocol amendments.

The investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s) with direct access to all of the required source documents and associated records. Source documents and records must be preserved for at least 15 years after the completion, discontinuation of, or withdrawal from the study or 2 years after the last approval of a marketing application by the sponsor in an ICH region, whichever is the longest.

6.1. Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification (ID) number. As permitted by all applicable laws and regulations, limited subject attributes such as sex, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires that the investigator permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the sponsor's designated auditors, and the appropriate IRB to review the subject's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 6.3).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected in the subject's eCRF).

All information concerning the study treatment, MDGH, and its operations, such as patent applications, formulae, manufacturing processes, basic scientific data, and material not previously published are considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing the

current study and will not use it for any other purposes without written consent from the sponsor.

6.2. Institutional Review

The IRB must be constituted according to the applicable state and federal requirements of the participating region. The sponsor or designee will require documentation noting the constitution of the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Any IRB unwilling to provide names and titles of all members due to privacy and conflict of interest concerns will instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to the IRB for approval. Written approval by the IRB of the protocol and ICF must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the study drug). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date.

The site must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to the IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or designee.

6.3. Subject Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and in accordance with all applicable laws and regulations. The ICF will describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF will explain the nature of the study, its objectives, and potential risks and benefits, and documents the date that informed consent is given. The ICF will detail the requirements of the participant and the fact that he is free

to withdraw at any time without giving a reason and without prejudice to his further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by both the IRB and the sponsor before use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF to the subject. Information will be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event that the subject is not capable of rendering adequate written informed consent, the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: 1) inquire about details of the study, and 2) decide whether or not to participate in the study. If the subject, or subject's legally acceptable representative, determines that he will participate in the study, then the ICF must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject will be instructed to sign using his legal name, using blue or black ballpoint ink. The investigator must also sign and date the ICF at the time of consent and before the subject enters into the study.

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date that the subject signs the ICF in the subject's medical or unit record. A copy of the signed ICF will be given to the subject.

All revised ICFs must be reviewed and signed in the same manner as the original ICF. The date that the revised consent was obtained will be recorded in the subject's medical or unit record and the subject will receive a copy of the revised ICF.

6.4. Study Reporting Requirements

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to the investigator or to regulatory agencies, except as required by law or regulation. In addition, the principal investigator or sub-investigator agrees to submit annual reports to his IRB as appropriate.

6.5. Financial Disclosure and Obligations

The principal investigator or sub-investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or

disclosure statements required under 21 CFR 54. In addition, the principal investigator or sub-investigators must provide to the sponsor a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor Spaulding is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor Spaulding is financially responsible for further treatment of the subject's disease.

6.6. Investigator Documentation

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act and in a form satisfactory to the sponsor.

6.7. Study Conduct

The principal investigator agrees that the study will be conducted according to the principles of the ICH E6(R1). The principal investigator will conduct all aspects of this study in accordance with US FDA regulations, the ICH E6(R1) GCP, and applicable local, state, and federal laws.

6.8. Data Collection

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse events, medical history, and concurrent conditions will be coded using the current version of MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary.

6.8.1 Case Report Forms and Source Documents

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry is accomplished through the ClinSpark® (Foundry Health) remote data capture application, which allows for on-site data entry and data management. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely

manner. Each person involved with the study will have an individual ID code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records. Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and associated files are the sole property of the sponsor and will not be made available in any form to third parties, except for authorized business representatives or appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded in the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or designee and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

6.9. Adherence to the Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with the ICH E6(R1) and all applicable guidelines and regulations.

6.10. Reporting Adverse Events

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol.

6.11. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, will inform the institution; the investigator or institution will provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any required reports.

6.12. Records Retention

The investigator agrees to keep the records stipulated in Section 6.8.1 and those documents that include (but are not limited to) the study-specific documents, ID log of all participating subjects, medical records, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the sponsor, or designees. Furthermore, ICH 4.9.5 requires the investigator to retain essential documents specified in ICH E6 until at least 2 years after the approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records will be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator will contact and receive written approval from the sponsor before disposing of any such documents.

6.13. Publications

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail. The publication of the study in its entirety will be the first data to be published; any subset of the study data may be published only after the primary study publication has been made.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days before such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the

investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further, upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

7. Study Management

7.1. Monitoring

7.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary contact through telephone, email, and letter. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. All aspects of the study will be carefully monitored by the sponsor or designee for compliance with applicable government regulation with respect to GCP and current SOPs.

7.1.2 Inspection of Records

The investigator involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s). In the event of an audit or inspection, the investigator agrees to allow the sponsor, representatives of the sponsor, the competent authority, or other regulatory agency access to all study records. The investigator will promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

7.2. Management of Protocol Amendments and Deviations

7.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the principal investigator's or sub-investigator's IRB for approval before subjects can be enrolled into an amended protocol.

7.2.2 Protocol Deviations

The investigator will not implement any deviations from or change to the protocol without agreement by the sponsor except where necessary to eliminate an immediate hazard to study subjects. Protocol deviations fall into 2 categories: those with approval before the event (protocol exemptions) and those occurring during the course of the study without prior approval (protocol violations). If an exemption from the protocol design (e.g., a missed study visit) is desired for an individual subject, other than those to

eliminate immediate hazard, the investigator must request an exemption from the sponsor or designee. If an exemption is granted, the investigator must notify the IRB, if required. The exemption and rationale will be documented at the site and in the sponsor files. Exemptions will not be granted for eligibility criteria.

For any protocol violation, the site will document the protocol violation in the subject's source documents. In the event of a significant violation, the site will notify the sponsor or designee. Significant violations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments.

7.3. Study Termination

The study will be completed as planned unless the following criteria are satisfied that require early termination of the study.

- New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the investigational medicinal product, such that the risk/benefit is no longer acceptable for subjects participating in the study;
- Significant violation of GCP that compromises the ability to achieve the primary study objective or compromises subject safety.

7.3.1 Criteria for Termination of the Study

The study site may be terminated if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, or is unable to ensure adequate performance of the study.

7.3.2 Criteria for Termination of Investigational Site

In the event that the sponsor elects to terminate the study or the investigational site, a study-specific procedure for early termination will be provided by the sponsor; the procedure will be followed by the investigational site during the course of termination.

7.4. Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure preparation of the clinical study reports and provision of them to the regulatory agency(ies) as required by the applicable regulatory requirement(s). They or their designee will also ensure that the clinical study reports in marketing applications meet the standards of the ICH guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

8. Appendices

8.1. Appendix A: Responsibilities of the Investigator

Sponsored clinical research studies are subject to the regulations of the FDA. The responsibilities imposed on an investigator by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in this protocol.
3. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
4. Secure prior approval of the study and any changes by an appropriate IRB that conform to FDA requirements.
5. Ensure that the IRB will be responsible for initial, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB and issue a final report within 3 months of study completion.
6. Ensure that requirements for informed consent as outlined in 21 CFR Part 50 are met.
7. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Each ICF will contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
8. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain this data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the FDA has approved the New Drug Application. Before disposing of any records, the sponsor must be contacted.

9. Allow possible inspection and copying by the FDA of eCRFs and records of drug distribution.
10. Maintain current records of the receipt, administration, and disposition of study drug, and return all unused study drug to the sponsor.
11. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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