Clinical Study Protocol

Study Title:	A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies			
Sponsor:	Medicines Development for Global Health Limited			
Investigational New Drug (IND) No (If applicable):	Not applicable			
Protocol Number:	MDGH-MOX-2001			
EudraCT Number	2019-001775-37			
Medical Monitor:	Jolanta Airey [redacted]			
Protocol Version/Date:	**Current**	3 (incorporating Amendments 1 and 2)	**Date**	19 Jun 2020
	Prior version	2 (incorporating Amendment 1)	**Date**	26 Aug 2019

CONFIDENTIALITY STATEMENT

This study is being performed in compliance with the guidelines of Good Clinical Practice (GCP) and all essential documents are being archived.

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MEDICINES DEVELOPMENT FOR GLOBAL HEALTH

LEVEL 1, 18 KAVANAGH STREET

SOUTHBANK, VIC 3006, AUSTRALIA

STUDY ACKNOWLEDGEMENT

MDGH-MOX-2001

A PHASE II, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP DOSE FINDING STUDY OF SINGLE ORAL DOSES OF MOXIDECTIN IN ADULTS WITH SCABIES

VERSION 3 (INCORPORATING AMENDMENTS 1 AND 2), 19 JUNE 2020

This protocol has been approved by the Sponsor. The following signature documents this approval.

[redacted] Mark Sullivan Managing Director		20 June 2020 Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Sponsor. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator's Name (Printed)		Signature
Site number		Date (dd mmm yyyy)

1 PROTOCOL SYNOPSIS

Protocol Number:	MDGH-MOX-2001
Study Title:	A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies
Investigational Product:	Moxidectin
Indication:	Treatment of scabies due to *Sarcoptes scabiei*
Development Phase:	Phase II
Background:	Scabies is an ectoparasitic infection caused by the mite *Sarcoptes scabiei* variant *hominis*. Scabies was recently included on the World Health Organisation's list of neglected tropical diseases. It most affects people living in tropical regions and in overcrowded conditions, which are optimal for person-to-person transmission of infection. It is estimated that more than 200 million people worldwide are affected at any time. Oral ivermectin is currently the only oral treatment available for scabies. The recommended regimen for oral ivermectin is one or two 200 micrograms/kilogram (µg/kg) doses separated by 7 to 14 days to ensure elimination of mites hatching after the initial treatment. Moxidectin, a macrocyclic lactone of the milbemycin class, has broad activity against filarial and ectoparasitic diseases. Moxidectin has been shown in clinical trials to be well tolerated when administered as a single dose of between 2 and 36 milligrams (mg). A Phase III clinical trial completed in adults and adolescents (aged 12 years and over) with onchocerciasis demonstrated that moxidectin provided superior skin microfilariae suppression compared to ivermectin (Mectizan®; Merck & Co., Inc.), the current standard of care for onchocerciasis. Moxidectin 8 mg as a single oral dose is approved by the United States Food and Drug Administration for the treatment of onchocerciasis in patients aged 12 years and over. Moxidectin is well-established in veterinary practice for the treatment of sarcoptic mange in companion animals and livestock, and was shown to be effective against scabies in a porcine model of the disease. In that model, a single oral dose of 300 µg/kg moxidectin was shown to be more efficacious than two oral doses of ivermectin 200 µg/kg 10 days apart at eliminating scabies. Moxidectin's long terminal half-life (20 to 43 days) may enable a single oral dosing regimen that would provide advantages over ivermectin. The effective dose of moxidectin to treat human scabies is not known. This study aims to provide proof of concept that a single dose of moxidectin is effective in eliminating the scabies parasite in humans and to enable the determination of an optimal dose of moxidectin for treatment of scabies for further clinical studies.
Design:	Parallel, double blind, multicenter, randomized, pharmacokinetic/pharmacodynamic study.
Number of Subjects:	A maximum of approximately 36 subjects will be enrolled
Number of Centers:	Approximately four

Design Details and Dose Regimens:	Initially, three cohorts of approximately six subjects per cohort are planned. Subjects will be randomized 1:1:1 to receive 2, 8 or 20 mg moxidectin as a single oral dose. Once approximately three subjects have been recruited to these three dose cohorts, a Protocol Steering Committee will evaluate the unblinded safety and efficacy data and recommend: • Continuation of the study with no dose modification to the target sample size of 6 subjects per cohort; or, • Stopping recruitment of one of more of the current dose cohorts; and/or, • The addition of a 36 mg single dose cohort. Once the Committee has made their recommendation, randomization will continue into the same or revised dosing regimens with a final target sample size of 6 subjects per arm. Subjects may receive a maximum of 18 tablets comprised of moxidectin 2 mg tablets and matched placebo to maintain the blind.
Protocol Steering Committee	A Protocol Steering Committee will maintain oversight on emerging efficacy and safety data to ensure that the study meets its objective to identify a well-tolerated and optimally effective dose of moxidectin for scabies.
Primary objectives:	• Identify an optimal dose of moxidectin for the treatment of scabies. • Evaluate the safety of moxidectin in adults infected with scabies.
Secondary objectives:	• Characterize the plasma pharmacokinetics of moxidectin in adults infected with scabies.
Exploratory objectives:	• Describe the impact of moxidectin on *S. scabiei*, including impact on morphology, motility and life cycle stages. • Evaluate clinician and patient reported outcomes of treatment with moxidectin.
Primary endpoints:	• Efficacy will be determined by death of the mites, defined as the degradation (loss of internal and/or external anatomic structures) of the adult mite observed by reflectance confocal microscopy (RCM). Mites will be assessed at Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28 in not less than two lesions nominated pre-treatment. • Safety will be assessed by the incidence and severity of adverse event (AEs), physical examinations, and measurement of vital signs up to and including Week 12, and laboratory safety parameters up to and including Day 28.
Secondary endpoints:	• Key exposure metrics for moxidectin including area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}), will be determined by non-compartmental analysis of moxidectin pharmacokinetic parameters or other methods as appropriate, assessed up to and including Day 28.

Exploratory endpoints:	• At Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28, using assessment by RCM of burrows selected pre-treatment:
	  ○ changes in adult mite motility (peristalsis and/or movement) over at least 30 seconds of observation;
	  ○ presence, number, morphology and motility of juvenile scabies mites; and,
	  ○ presence of eggs and scybala in burrows.
	• Presence and total number of mites and burrows assessed visually at Days 7, 14 and 28.
	• Changes in assessment of clinician-reported scabies symptomology, including extent of symptoms on body regions assessed by the number of anatomically-defined regions affected, number of lesions and severity grading of excoriations and erythema.
	• Changes in patient reported outcomes, measured by Numerical Rating Scale, 5-D Itch Scale and Dermatology Life Quality Index.

Inclusion criteria:	1. Aged ≥ 18 years. 2. Provision of written informed consent. 3. Parasitologically confirmed active *Sarcoptes scabiei* infestation, defined as the presence of at least two lesions (which may include burrows), each containing at least one live (internal and/or external structures discernable) adult *Sarcoptes scabiei* mite observed by RCM. 4. Agree to the use of reliable contraceptive measures if female or male partner of a female of child-bearing potential from Screening until 6 months after treatment with study drug.

Exclusion criteria:	1. History of chronic or recurring dermatologic disease (other than scabies) that could interfere with the diagnosis and/or subsequent clinical assessment of scabies.
	2. Diagnosis of crusted/Norwegian scabies or scabies that, in the opinion of the Investigator, would require treatment with more than one standard of care (e.g. scabies requiring concurrent topical and oral treatment).
	3. Received any treatment for scabies within 7 days of Screening, including but not limited to permethrin, ivermectin, benzyl benzoate, lindane, crotamiton, malathion, and/or tea tree oil.
	4. Presence of any other clinically relevant condition, including infection, immunological disorder, malignant disease, and/or other underlying condition or circumstance at Screening or Baseline that would put the subject at increased risk from participating in the study or confound study evaluations.
	5. Poor venous access.
	6. Received an investigational agent within 28 days of Screening (or 5 half-lives of the investigational agent, whichever is longer).
	7. Body Mass Index over 35 kg/m^2.
	8. Clinically relevant abnormal findings in vital signs, 12-lead electrocardiogram (ECG), or physical examination at Screening and/or Baseline in the opinion of the Investigator.
	9. Clinically relevant laboratory abnormalities at Screening, including:
	  a. alanine aminotransferase or aspartate aminotransferase > 2.5 x upper limit of reference range;
	  b. creatinine > 2.0 milligrams per deciliter (mg/dL);
	  c. hemoglobin < 9.5 g/dL (female) or <10.5 g/dL (male);
	  d. amylase > 2.0 x upper limit of reference range.

	10. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin. 11. Use of systemic steroids within 14 days of Screening, or history of prolonged use of systemic and/or high-dose inhaled corticosteroids, or use of topical steroids for 7 out of the 14 days prior to Screening. 12. Subjects with known or suspected *Loa loa* coinfection. 13. Difficulty swallowing tablets. 14. Pregnant or breastfeeding, or planning to become pregnant. 15. Known or suspected alcohol or illicit substance abuse. 16. Unwilling, unlikely or unable to comply with all protocol specified assessments. 17. Previous enrolment and treatment with moxidectin in this study.
Study product:	Moxidectin tablets 2 mg (plain-faced)
Reference product:	Placebo to match moxidectin tablets, as required for blinding
Comparator:	None
Duration of treatment per participant:	Up to 91 days, including: • Screening: up to 7 days prior to Baseline (Day 0) • Day patient (Day 0) • Outpatient (Hour 24 to Day 28) • Safety follow up (Week 12)
Clinical procedures / assessments:	Subjects identified based on presumptive scabies diagnosis by a physician or healthcare worker will have the diagnosis confirmed by the study center. After obtaining written informed consent, the presence of mites and not less than two scabies lesions, each containing at least one live adult mite will be visually confirmed (defined as the presence of peristalsis and/or movement and morphology consistent with *S. scabiei* by RCM). If the subject has confirmed scabies infection, other Screening assessments will be performed (up to Day -1). Subjects will present to the clinic on the morning of Day 0 for Baseline assessment, randomization, treatment and post-treatment assessment throughout the day. They will return to the clinic for assessment at Hours 24, 48 and 72, Days, 7, 14 and 28 and at Week 12 for safety review. For further details of clinical study procedures, please refer to Table 1 and Table 2.
Specialized analyses:	**Pharmacodynamics** RCM will be used to evaluate the presence, number and morphology of *S. scabiei* mites by stage (adults, juvenile stages) and the presence of eggs and scybala within a minimum of 2 scabies lesions. Z-stack photos of mites, eggs and scybala in each of the lesions will be obtained at the following time points: • Baseline (up to 60 minutes prior to dosing); • Hours 4, 8, 24, 48 and 72; and, • Days 7, 14 and 28 after dosing. Clinician reported outcomes, including assessment of scabies signs and symptoms, will be performed by the Investigator at the following time points: • Baseline (within 60 minutes prior to dosing)

	• Days 7, 14 and 28 after dosing. Patient reported outcomes will be captured through the relevant questionnaires administered to the subject at the following time points: • Baseline (within 60 minutes prior to dosing) • Days 7, 14 and 28 after dosing. **Pharmacokinetics** Blood will be drawn for analysis of plasma moxidectin concentrations at the following time points: • Baseline (within 15 minutes prior to dosing) • Hours 2, 3, 4, 8, 24, 48 and 72 and Days 7, 14 and 28. **NOTE**: pharmacokinetic sampling and pharmacodynamic assessment should be conducted within a 15 minute window of each other.
Sample size determination:	No formal sample size calculations were performed for this study. Dose cohorts of approximately n = 6 are considered to be practical and adequate to provide information for the full characterization of pharmacokinetics across the dose range.
Statistical analyses:	All statistical analyses will be prospectively described in full in a statistical analysis plan which will be finalized prior to breaking the blind for the final analysis. **Analysis of key efficacy endpoints** The focus of the statistical analysis will be descriptive and exploratory. Statistical models for estimation and/or hypothesis testing to assess various parasitological assessments with respect to dose may be conducted **Analysis of pharmacokinetics** Non-compartmental analysis (NCA) or *post-hoc* model-based exposure estimates will be implemented for the calculation of pharmacokinetic parameters as appropriate. Pharmacokinetic parameters include: • area under the concentration time curve (AUC); and, • observed maximum plasma concentration (C_{max}). Other pharmacokinetic parameters may be determined as appropriate. **Analysis of pharmacokinetics/pharmacodynamics** Key exposure metrics, including C_{max} and AUC, and pharmacodynamic data will be pooled across the study. The relationship between efficacy endpoints and plasma concentrations of moxidectin will be assessed graphically using scatterplots or box plots, as appropriate to the pharmacodynamic endpoint. Pharmacokinetic/pharmacodynamic analysis techniques will be applied as appropriate, such as logistic regression or time-to-event modelling approaches where a binary pharmacodynamic outcome is desired, or nonlinear or quantile regression response (E_{max}) in the analysis of continuous pharmacodynamic data. If deemed appropriate at the conclusion of the study, an existing moxidectin population-pharmacokinetic model will be updated with the pharmacokinetic data from this study to enable formal comparison of the moxidectin pharmacokinetic characteristics observed within the scabies patient population to other populations administered moxidectin. Where appropriate, this refreshed population-pharmacokinetic model will then be linked to critical

	pharmacodynamic responses observed during the study to enable selection of dose regimens for future clinical studies by clinical trial simulations. **Analysis of safety** All safety assessments, including adverse clinical laboratory test results and vital sign measurements will be summarized using descriptive statistics and presented in data listings. No inferential statistics will be performed on the safety data.
Special protocol requirement / issues:	The close personal contacts (including household and sexual contacts) of all enrolled subjects will be offered the current standard of care for treatment of scabies and instructed in its use.

Table 1 Overall Schedule of Assessments

		Period 1							Period 2
Assessment	**Screening (D-7 to D-1)**	**D0**	**D1**	**D2**	**D3**	**D7**	**D14**	**D28**	**Week 12**
Allowable assessment window period						**± 2 days**	**± 2 days**	**± 3 days**	**± 7 days**
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history	X								
Physical examination[a]	X					X	X	X	X
Confirmation of scabies infection with dermoscopy/RCM[b]	X								
Vital signs[c]	X					X	X	X	X
12-lead ECG[d]	X								
Height	X								
Body weight	X	See Table 2 for further information on schedule of assessments for Day 0 to Day 3 of Period 1							X
Pregnancy testing	X								X
Hematology and serum chemistry	X					X		X	
Pharmacokinetic blood sample collection						X	X	X	
Plasma banking						X	X	X	
Mite assessment and photography with RCM and dermoscopy						X	X	X	
Patient reported outcomes (NRS, 5-D itch scale and DLQI)						X	X	X	
Clinician reported outcomes						X	X	X	
Adverse events		<----------X---------->							
Concomitant medications	X	<----------X---------->							

Abbreviations: D, Day; M, Month; ECG, electrocardiogram; RCM, reflectance confocal microscopy; NRS, Numerical Rating Scale; DLQI, Dermatology Life Quality Index.

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. Two live adult mites must be demonstrated by RCM in at least two representative lesions for study eligibility.
c. Vital signs (supine blood pressure, heart rate, respiratory rate, and body temperature) will be measured after the subject has rested for approximately 5 minutes.
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.

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-directed physical examination; collection of AEs; and clinical laboratory evaluation (hematology and serum chemistry (up to Day 28) and pregnancy).

Table 2 Period 1 (Baseline to Day 3) Schedule of Assessments

	D0						D1	D2	D3
	Baseline (pre-dose)								
Hour relative to dosing	**Up to -1**	**0**	**2**	**3**	**4**	**8**	**24**	**48**	**72**
Allowable assessment window period			**± 15 mins**	**± 15 mins**	**± 30 mins**	**± 1 hr**	**± 4 hrs**	**± 4 hrs**	**± 4 hrs**
Assessment									
Physical examination[a]	X						X		X
Scabies infection review and lesion selection[b]	X								
Hematology and serum chemistry sample collection									
Vital signs[c]	X					X	X		X
Randomization, followed by Study drug administration[d]		X							
Pharmacokinetic blood sample collection[e]	X		X	X	X	X	X	X	X
Plasma banking	X		X	X	X	X	X	X	X
Mite assessment and photography with RCM[e]	X				X	X	X	X	X
Mite assessment and photography with dermoscopy	X								X
Patient reported outcomes (NRS, 5-D itch scale and DLQI)	X								
Clinician reported outcomes	X								
Adverse events	<----------X---------->								
Concomitant medications	<----------X---------->								

Abbreviations: D, day; ECG, electrocardiogram; hr, hour; mins, minutes; RCM, Reflectance Confocal Microscopy; NRS, Numerical Rating Scale; DLQI, Dermatology Life Quality Index.

a. A full physical examination will be performed at Screening. At all subsequent time points, a symptom-directed physical examination (informed by concurrent conditions, signs and symptoms, and adverse events reported) will be performed.
b. Live mites in at least two representative lesions must be demonstrated for study eligibility. Up to four lesions will be selected and assessed throughout the study.

c. 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.
d. On Day 0, study drug administration (moxidectin) will occur after an overnight fast of at least 8 hours. Study drug will be administered with at least 240 milliliters of water. No food will be allowed for 2 hours after dosing; however, clear liquids can be taken ad libitum.
e. Windows apply to pharmacokinetic sampling followed immediately by mite assessment by RCM (as required). At Baseline pharmacokinetic sample will be collected within 15 minutes of study drug administration.

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0\text{-last}}$	AUC from time 0 extrapolated to the last observed concentration
$AUC_{0\text{-inf}}$	AUC from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	AUC from time 0 extrapolated to time t
BCRP1/ABCG2	breast cancer resistance protein
bpm	beats per minute
CL/F	apparent plasma clearance
C_{max}	maximum observed plasma concentration
cm	centimeter
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
CYP	cytochrome
°C	degrees Celsius
DALY	disability-adjusted life year
dL	deciliter
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
FAS	full analysis set
FDA	United States Food and Drug Administration
g	gram
GCP	good clinical practice
GEE	generalized estimating equation
GLMMs	generalized linear mixed models
hERG	human éther-a-go-go
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IMP	investigational medicinal product
IRB	Institutional review board
kg	kilogram
L	liters
MDGH	Medicines Development for Global Health
MED	minimum effective dose
mg	milligram
mL/h	milliliters per hour
mmHg	millimeters of mercury
NCA	non-compartmental analysis
NTD	neglected tropical disease
OED	optimal effective dose
PK	pharmacokinetics
PD	pharmacodynamics
PKAS	pharmacokinetic analysis set
PKPDAS	Pharmacokinetic/Pharmacodynamic Analysis Set
PPAS	per protocol analysis set
RCM	Vivascope 3000® Reflectance Confocal Microscope
SAE	serious adverse event
SfAS	safety analysis set
SAP	statistical analysis plan
SD	standard deviation

SOP	standard operating procedure
SRM	study reference manual
S. scabiei	*Sarcoptes scabiei*
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed plasma concentration
µg	microgram
Vd	apparent volume of distribution
WHO	World Health Organization

4 STUDY CONTACTS

Please refer to the Study Reference Manual (SRM) for full study contacts.

5 INTRODUCTION

5.1 Scabies

Scabies is a skin disease caused by infestation with the human ectoparasite *Sarcoptes scabiei* variant *hominis*. Scabies is a common dermatological condition, estimated to affect between 100 and 300 million people per year and around 200 million people worldwide at any time (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). Globally, scabies was responsible for 0.21% of all disability-adjusted life years (DALYs) from all conditions studied in the most recent Global Burden of Diseases study (Karimkhani, et al. 2017). The highest incidence of the disease occurs in tropical climates in socioeconomically disadvantaged populations, the main risk factors for infestation being poverty and overcrowding (Romani, et al. 2015b). The World Health Organization (WHO) Scientific and Technical Advisory Group, at its meeting in March 2017, included scabies on its list of neglected tropical diseases (NTD) (Strategic and Technical Advisory Group for Neglected Tropical Diseases 2017). Scabies was considered to meet all the criteria for classification as an NTD as it i) disproportionately affects populations living in poverty and causes important morbidity and mortality; ii) primarily affects populations living in tropical and sub-tropical areas; iii) is immediately amenable to broad control, elimination or eradication, and iv) is relatively neglected by research.

Scabies infestation is contagious, usually spread by direct skin-to-skin contact and occasionally via exposure to bed-linen or clothing of an infected person, which occurs more commonly in cases of hyperinfestation. Transmission between close contacts and in institutional settings such as nursing homes or prisons is common.

The adult female mite burrows into the top layer of the skin (stratum corneum) where it lays eggs that hatch and develop into adults within approximately 2 weeks. The burrow is a pathognomonic sign of scabies but may not always be visible. Scabies is characterized by the development of an intensely itchy rash caused by an allergic reaction to the presence of mite antigens and feces in the skin. In a first infestation symptoms may take 4 to 6 weeks to manifest, but may appear after only a few days in second or subsequent infestations. The itch is often reported to be worse at night. The rash is papular in nature and typically, although not exclusively, occurs in locations that correspond to sites of predilection for infestation such as on the finger webs, wrists, flexures and genitalia. The mite burden in typical scabies infestations is thought to be 10 to 15, though hyperinfestation with hundreds of mites has been reported (Chosidow 2006, Currie and McCarthy 2014). Crusted scabies, the most severe form of the disease, occurs when the susceptible host is infected with millions of mites and hyperkeratotic skin crusts form, potentially due to an inability to immunologically control the infestation (Davis, et al. 2013).

A presumptive diagnosis of scabies is be made based on itch characteristics, clinical presentation of scabies lesions (including burrows and rash) in sites of predilection and suggestive history such as presence of a close contact with scabies or similar itch (Engelman, et al. 2018). A definitive diagnosis can be made using non-invasive microscopy (most commonly low-magnification dermoscopy) of suspected infestation sites or microscopic examination of skin scrapings to identify mites, eggs and/or fecal pellets (Engelman, et al. 2018). Reflectance confocal microscopy (RCM), a newer imaging technique using laser scanning to examine the top 300 to 500 µm of skin, can also be used to diagnose scabies (Cinotti, et al. 2015, Cinotti, et al. 2016, Micali, et al. 2016).

5.2 Current Treatment and Unmet Need

Treatment either with a topical acaricide or oral treatment with ivermectin is the current standard of care for scabies (Rosumeck, et al. 2018). Topical treatments, such as permethrin 5% cream and

benzyl benzoate 10 to 25% lotion, are the mainstay of treatment and must be applied to all areas of the skin from head to toe and left on overnight before washing off. A second application may be necessary within 7 days of the first application if there are signs that the infestation persists, such as lesions that persist or new lesions. Although effective when applied in compliance with the prescribing information, these treatments have limited patient acceptability and compliance is often poor. Oral treatment with ivermectin tablets 200 μg/kg is approved in only a few countries and limited to second line treatment in the case of Australia. As ivermectin is not ovicidal, administration of a second dose within 7 to 14 days to ensure that mites from hatching eggs are also eliminated is recommended. Although current topical and oral treatments are effective when used as prescribed, acceptability of topical treatment and the need to treat more than once are barriers to optimal disease control. The necessity to treat the close contacts of scabies patients represents another barrier to disease control as failure to treat may otherwise contribute to re-infestation of the patient.

The inability to effectively treat scabies contributes to considerable economic burden and health disparities in endemic regions (Worth, et al. 2012a, Worth, et al. 2012b). The direct effects of the itch that is characteristic of the disease include loss of sleep, school and work absences and psychological distress. Scabies infestation has also been associated with numerous serious complications, including secondary bacterial skin infestations (impetigo) due to *Staphylococcus aureus* and *Streptococcus pyogenes*. These skin infestations may result in potentially life-threatening *Staphylococcus aureus* bacteremia or subsequent post-streptococcal sequelae such as glomerulonephritis, rheumatic fever or rheumatic heart disease. Recent studies have shown that mass drug administration with ivermectin or permethrin, without additional antibacterial therapy, led to parallel reductions in both scabies and impetigo prevalence in endemic populations (Marks, et al. 2018, Romani, et al. 2015c).

5.3 Moxidectin

This section presents a brief summary of the known preclinical and clinical profile of moxidectin. A detailed description of the chemistry, pharmacology, efficacy and safety of moxidectin is provided in the Investigator's Brochure. Moxidectin has not been fully characterized in scabies patients and is unapproved for scabies in any jurisdiction. Moxidectin 8 mg per oral (single dose) has been approved for use in the treatment of onchocerciasis by the United States Food and Drug Administration (FDA).

The current approved prescribing information for use of moxidectin tablets for onchocerciasis is available at Drugs@FDA (www.fda.gov/drugsatfda). Additional information is available in the Investigator's Brochure.

5.3.1 Nonclinical

5.3.1.1 Pharmacology

Glutamate-gated chloride channels present in arthropods and nematodes are the primary biological target of moxidectin. Moxidectin also acts on gamma-aminobutyric acid-gated channels.

The activity of moxidectin against *S. scabiei* has been evaluated *in vitro*, in a porcine model of human scabies and several other natural *S. scabiei* infestations in animals such as dogs, cattle, sheep and goats. The precise mechanism of action in *S. scabiei* is not known, though a ligand-gated chloride channel capable of activation by ivermectin has been described in *S. scabiei*, suggesting the macrocyclic lactones may exert their efficacy in arachnids in a similar manner to other invertebrates.

5.3.1.2 Safety Pharmacology

The safety pharmacology of moxidectin has been assessed *in vitro* using the human ether-a-go-go (hERG) channel assay and a range of human biological receptors (NovaScreen). *In vivo* studies were conducted in rodent and non-rodent species using the rat for neurofunctional and pulmonary assessment and the dog for cardiovascular safety. These studies have shown minor effects on neurofunctional and respiratory parameters, and a mild reduction in heart rate in dogs relative to controls. For more information, please refer to the Investigator's Brochure.

5.3.1.3 Toxicology

The toxicology profile of moxidectin is characterized by low acute toxicity, consisting mostly of transient central nervous system-related clinical signs. Decreased body weight and/or body weight gain were also common findings, which were attributed to reduced consumption of food. In single and repeat dose toxicity studies with moxidectin, transient central nervous system signs were reported in mice, rats and dogs. There was no target organ toxicity in any of the studies based on evaluation by gross necropsy, clinical and anatomic pathology. Moxidectin was not genotoxic and showed no carcinogenic potential in lifetime mouse and rat bioassays. Moxidectin resulted in increased incidence of malformations in rats at maternally toxic doses, but not in rabbits, and decreased pup survival during the lactation period in one and three generation pre- and post-natal rat studies.

There are adequate nonclinical safety margins determined in oral acute (single-dose) safety pharmacology and chronic (repeat-dose) toxicology studies in relation to the use of moxidectin doses in humans up to a maximum of 36 mg. These margins were determined to be greater than one for the majority of studies, regardless of whether margins were calculated with dose or exposure parameters. Consistent with these safety margins, existing safety data from the clinical trials conducted to date do not suggest any dose-limiting toxicities following administration of single oral moxidectin doses up to and including 36 mg (Section 5.3.2.2).

For more information, please refer to the Investigator's Brochure.

5.3.1.4 Absorption, Distribution, Metabolism and Excretion

The pharmacokinetics of moxidectin in rats and dogs were characterized by oral absorption, low plasma clearance, and a high volume of distribution, leading to a long terminal elimination half-life ($t_{½}$). The distribution of moxidectin is governed primarily by its high degree of lipophilicity; in rats, moxidectin was shown to be distributed to and reside predominantly in fat, including the subcutaneous layer which acts as a reservoir for moxidectin. Moxidectin is minimally metabolized *in vivo*. Moxidectin has also been shown to be a weak substrate of breast cancer resistance protein (BCRP1/ABCG2). Moxidectin produced weak or no inhibition of seven major human cytochrome (CYP) P450 enzymes *in vitro* but did induce CYP3A4 mRNA and activity *in vitro*. However, a subsequent clinical study showed that moxidectin was not a CYP3A4 inducer *in vivo* (Section 5.3.2.1).

In rat studies, moxidectin is likely cleared by a combination of biliary excretion of unchanged drug and oxidative metabolism. For more information, please refer to the Investigator's Brochure.

5.3.2 Clinical

The moxidectin clinical program encompasses eight completed single oral dose trials spanning Phases I to III and involving a total of 1904 subjects.

In six completed Phase I studies, 244 healthy volunteers received moxidectin at doses of 3 to 36 mg and 16 healthy volunteers received placebo. The studies were:

- A single-ascending dose, placebo-controlled, double-masked, safety, tolerability, and pharmacokinetic study of orally administered moxidectin in normal volunteers (3110A1-100-EU).
- A study of the relative bioavailability of a tablet and a liquid formulation of moxidectin in healthy subjects (3110A1-101-EU).
- An open-label, single-dose study to evaluate the excretion of moxidectin into the breast milk of lactating, non-breastfeeding women (3110A1-1002-EU).
- An open-label, single-dose, 4-period, sequential study to determine the effect of moxidectin on CYP3A4 activity in healthy subjects using midazolam as a probe substrate (3110A1-1004-EU).
- An open-label, randomized, single-dose, parallel-group study to determine the effect of a high-fat meal on the relative bioavailability and pharmacokinetics of a single dose of moxidectin administered orally to healthy subjects (3110A1-1005-EU).
- 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 (MDGH-MOX-1008).

In one Phase II and one Phase III study enrolling subjects with onchocerciasis, 1105 subjects received moxidectin at doses of 2 mg to 8 mg while 539 received ivermectin at the standard-of-care dose of 150 μg/kg. The studies were:

- A randomized, single-ascending-dose, ivermectin-controlled, double-blind, safety, tolerability, pharmacokinetic, and efficacy study of orally administered moxidectin in subjects with *Onchocerca volvulus* infection (3110A1-200-GH; Phase II)
- A single dose, ivermectin-controlled, double blind, efficacy, safety, and tolerability study of orally administered moxidectin in subjects infected with *Onchocerca volvulus* (ONCBL60801; Phase III)

The safety and efficacy of moxidectin has not been evaluated in patients with *S. scabiei* infestation.

5.3.2.1 Clinical Pharmacology

Moxidectin displays linear, dose-proportional pharmacokinetics. Following a single oral moxidectin dose (ranging from 3 mg to 36 mg, tablet or solution) administered to fasting healthy volunteers, the non-compartmentally-derived apparent moxidectin plasma clearance (CL/F) ranged from 1785 to 3506 mL/h and the mean $t_{½}$ ranged from 485 to 1139 hours (approximately 20 to 47 days). Moxidectin was rapidly absorbed; the median time of maximum observed plasma concentration (t_{max}) in a fasted state was 3 to 4 hours post-dose. Moxidectin has a large apparent volume of distribution, and rapid decline of moxidectin concentrations occurred within 48 hours of dose administration in all studies, and, thereafter, plasma concentrations declined slowly in accordance with the long $t_{½}$. Population pharmacokinetic analyses showed that the long $t_{½}$ was governed by tissue distribution rate-limited elimination.

There was no clinically relevant effects of age, gender, race, weight, renal function or hepatic function on the pharmacokinetics of moxidectin from a population-pharmacokinetic model. Moxidectin absorption is resilient to the effects of food. Administration of moxidectin in a fed state modestly slows absorption and increases bioavailability, although not to a clinically relevant extent. Moxidectin does not induce or inhibit clinically relevant drug-drug interactions and it is unlikely to be a victim of drug-drug interactions via concomitant medications.

Moxidectin is minimally metabolized and primarily excreted unchanged in the feces. Renal clearance of moxidectin and its metabolites is low. Moxidectin was observed in the breast milk of lactating women after single dose administration at a relative infant dose of less than 10% of the maternal dose.

5.3.2.2 Clinical Safety and Efficacy

5.3.2.2.1 Overview of Safety in Healthy Volunteers

Safety data are available from 6 studies in healthy adult volunteers. Moxidectin was well tolerated when given as a single dose of between 3 and 36 mg to healthy volunteers (Table 3). There was no treatment or dose related relationship in the incidence, nature and severity of adverse events (AEs) identified. There were no clinically relevant or treatment-related changes in laboratory parameters, physical examination findings, vital signs or electrocardiograms (ECGs)/cardiac function. In placebo-controlled studies, moxidectin had a safety profile similar to placebo. No subject withdrew due to an AE and there were no serious adverse events (SAEs) or deaths.

Table 3 Number of Subjects per Dose Regimen in Healthy Volunteer Studies

Regimen	Fed/Fasted	Formulation	Study						Total
			100	101	1002	1004[a]	1005	1008	
Placebo	Not applicable	Not applicable	6					10	**16**
3 mg	Fasted	Liquid	5						**5**
4 mg	Fasted	Tablet						10	**10**
8 mg	Fasted	Tablet					27	10	**37**
8 mg	Fed	Tablet			12	38	27		**77**
9 mg	Fasted	Liquid	5						**5**
9 mg	Fed	Liquid	6						**6**
10 mg	Fasted	Liquid		29					**29**
10 mg	Fasted	Tablet		29					**29**
16 mg	Fasted	Tablet						10	**10**
18 mg	Fasted	Liquid	5						**5**
24 mg	Fasted	Tablet						10	**10**
36 mg	Fasted	Liquid	5						**5**
36 mg	Fasted	Tablet						10	**10**
36 mg	Fed	Liquid	5						**5**
		Total	**37**	**58**	**12**	**38**	**54**	**60**	**259**

Abbreviations: 100: Study 3110A1-100-EU, 101: Study 3110A1-101-EU, 1002: Study 3110A1-1002-EU, 1004: Study 3110A1-1004-EU, 1005: Study 3110A1-1005-EU, 1008: Study MDGH-MOX-1008

[a] One subject was enrolled and dosed with midazolam alone prior to withdrawal from the study and is not included.

One hundred and fourteen (114) healthy volunteers have been administered single moxidectin doses in excess of the dose approved for the treatment of onchocerciasis (an 8 mg single dose). Of these, 20 subjects have received a single dose of 36 mg moxidectin in two clinical studies, Study 3110A1-100-EU and Study MDGH-MOX-1008. In both studies, which were placebo-controlled, moxidectin had a similar safety profile to placebo. There was no dose-response

relationship identified between the dose of moxidectin administered and frequency and nature of AEs, no dose-limiting toxicities and no SAEs or deaths in either study.

MDGH-MOX-1008 was a randomized, placebo-controlled, double-blind, parallel-group study designed to evaluate the potential impact of moxidectin on the QT interval in healthy adult volunteers. Moxidectin was administered at doses between 4 and 36 mg as tablets under fasted conditions. The primary safety evaluation period was Day 1 to Day 22 but subjects received follow-up evaluations at Weeks 8 and 12 due to the long half-life of moxidectin. Safety laboratory analyses were undertaken and AEs were reported throughout. An overview of treatment-emergent AEs reported during the primary safety period to Day 22 is provided in Table 4.

Table 4 Number of Treatment-Emergent Adverse Events Reported to Day 22 in Study 1008

Regimen (Number enrolled)	Treatment Emergent Adverse Events (Number of Subjects)				
	All AE	Related AE	Severe AE	Withdrawn due to AE	SAE
Placebo (n=10)	2 (1)	2	0	0	0
4 mg (n=10)	3 (3)	1	0	0	0
8 mg (n=10)	3 (3)	2	0	0	0
16 mg (n=10)	1 (1)	0	0	0	0
24 mg (n=10)	0	0	0	0	0
36 mg (n=10)	3 (2)	0	0	0	0
Total (n=60)	**12 (10)**	**5**	**0**	**0**	**0**

A further two treatment-emergent AEs were reported to Week 12. Neither AE was considered by the Investigator to be related to treatment. Table 5 summarizes AEs reported by all subjects to Week 12. Each AE was reported by no more than one subject at any dose level. There was no dose-response relationship identified across the dose groups and moxidectin had a similar safety profile to placebo.

Table 5 Number of Subjects (%) with Treatment-Emergent Adverse Events in Study 1008 to Week 12

Preferred Term	Treatment						Total
	MOX (4 mg) n=10	MOX (8 mg) n=10	MOX (16 mg) n=10	MOX (24 mg) n=10	MOX (36 mg) n=10	Placebo n=10	n=60
Eye irritation	0	1 (10.0)	0	0	0	0	1 (1.7)
Abdominal discomfort	0	0	0	0	0	1 (10.0)	1 (1.7)
Diarrhea	1 (10.0)	0	0	0	0	0	1 (1.7)
Medical device site reaction	1 (10.0)	0	0	0	0	0	1 (1.7)
Aspartate aminotransferase increased	0	0	1 (10.0)	0	0	0	1 (1.7)
Elevated total bilirubin	0	0	0	0	1 (10.0)	0	1 (1.7)
Blood cholesterol increased	1 (10.0)	0	0	0	0	0	1 (1.7)
Neck pain	0	0	0	0	1 (10.0)	0	1 (1.7)
Arthralgia (hip pain)	1 (10.0)	0	0	0	0	0	1 (1.7)
Pain in extremity	0	0	0	0	1 (10.0)	0	1 (1.7)
Dizziness	0	0	0	0	0	1 (10.0)	1 (1.7)
Headache	0	1 (10.0)	0	0	0	0	1 (1.7)

Preferred Term	Treatment						Total
	MOX (4 mg) n=10	MOX (8 mg) n=10	MOX (16 mg) n=10	MOX (24 mg) n=10	MOX (36 mg) n=10	Placebo n=10	n=60
Nasal congestion	0	1 (10.0)	0	0	0	0	1 (1.7)
Oropharyngeal pain	0	0	0	0	1 (10.0)	0	1 (1.7)
TOTAL	**4 (40.0)**	**3 (30.0)**	**1 (10.0)**	**0**	**4 (40.0)**	**2 (20.0)**	**14 (26.7)**

All AEs were considered Grade 1 (mild) in severity except for arthralgia (Grade 2, moderate) which occurred in Subject 1037 (moxidectin 4 mg) in the period between Day 22 and Week 12. All AEs were transient. The Investigator considered the following AEs to be at least possibly related to study drug: abdominal discomfort (Subject 1038, placebo), diarrhea (Subject 1037, moxidectin 4 mg), dizziness (Subject 1038, placebo), headache (Subject 1053, moxidectin 8 mg), and nasal congestion (Subject 1031, moxidectin 8 mg).

There were no patterns of clinically relevant changes in any clinical laboratory values, vital signs, or physical examination findings in any group. Single events of raised AST and total bilirubin were reported in Subject 1041 (moxidectin 16 mg) at Day 22 and Subject 1047 (moxidectin 36 mg) at Week 12, respectively. Neither event was considered to be related to study drug by the Investigator.

Moxidectin had no statistically or clinically significant effect on QT interval at any dose level, including the maximum 36 mg dose. There were also no clinically significant effects of moxidectin at any dose on HR, PR and QRS intervals or abnormal diagnostic statements.

3110A1-100-EU was a single-ascending dose, placebo controlled, double blind, safety, tolerability, and pharmacokinetic study of single oral doses between 3 and 36 mg. Moxidectin was administered as an oral solution under fed and fasted conditions.

Like MDGH-MOX-1008, there was no trend for an increase in the incidence or type of AEs, or clinically relevant laboratory abnormalities with increasing dose of moxidectin. There were no Grade 4 AEs or laboratory abnormalities and only one Grade 3 AE (enteritis, verbatim “food poisoning”) experienced by Subject 501 in the 36 mg moxidectin fasted group. The event occurred 57 days after administration of test article and resolved the following day. It was considered by the Investigator to be unrelated to treatment.

Modestly increased exposure to moxidectin has been observed in liquid presentations compared with tablets and when moxidectin is given with food. Moxidectin administered in the tablet form under a fasted state, as proposed in MDGH-MOX-2001, should ensure that exposure is less than or equal to existing clinical experience, which includes administration of 36 mg following a high-fat meal as a liquid solution.

Adverse event and laboratory findings reported for each of the completed Phase I studies are further summarized in the Investigator’s Brochure.

5.3.2.2.2 Overview of Safety in Patients with Onchocerciasis

The safety of moxidectin has been evaluated in patients with onchocerciasis. Signs and symptoms associated with microfilarial death, sometimes referred to as the “Mazzotti reaction” were commonly observed. These reactions are caused by an immunologically-mediated reaction to the death of microfilariae and manifest as pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia. Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision,

photophobia, changes in visual acuity, hyperemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment.

In the two studies conducted in onchocerciasis patients (3110A1-200-GH and ONCBL60801), the profile of AEs reported for moxidectin was similar to the profile in ivermectin recipients. In these studies, the most commonly occurring events were pruritus, edema, headache, hypotension and compensatory tachycardia, rash and urticaria, myalgia, arthralgia, pyrexia and chills, lymphadenopathy, paresthesia and asthenia (Table 6). These events were transient and self-limiting, generally occurring and resolving within the first week of treatment. In general, there was a transient (first 48 hours) increase in the number of moxidectin subjects reporting efficacy-associated AEs compared to ivermectin. There was not an increased need for medical or therapeutic intervention for management of efficacy-related events with moxidectin when compared to ivermectin. Given that the spectrum of symptoms and severity were similar, the guidance to patients and physicians are otherwise unchanged compared to ivermectin for onchocerciasis patients.

Table 6 Adverse Reactions Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III)

Adverse Reaction	Moxidectin N = 978 n (%)	Ivermectin N = 494 n (%)
Eosinophilia	721 (74)	390 (79)
Pruritus	640 (65)	268 (54)
Musculoskeletal pain [a]	623 (64)	257 (52)
Headache	566 (58)	267 (54)
Lymphocytopenia*	470 (48)	215 (44)
Tachycardia [b]	382 (39)	148(30)
Orthostatic tachycardia [c]	333 (34)	130 (26)
Non-orthostatic tachycardia [d]	179 (18)	57 (12)
Rash [e]	358 (37)	103 (21)
Abdominal pain [f]	305 (31)	173 (35)
Hypotension [g]	289 (30)	125 (25)
Orthostatic hypotension [h]	212 (22)	81 (16)
Pyrexia/Chills	268 (27)	88 (18)
Leukocytosis	240 (25)	125 (25)
Influenza like illness	226 (23)	102 (21)
Neutropenia**	197 (20)	112 (23)
Cough	168 (17)	88 (18)
Lymph node pain	129 (13)	28 (6)
Dizziness	121 (12)	44 (9)
Diarrhea/Gastroenteritis/Enteritis	144 (15)	84 (17)
Hyponatremia	112 (12)	65 (13)
Peripheral swelling	107 (11)	30 (6)

[a] Includes “myalgia”, “arthralgia”, “musculoskeletal pain”, “pain” and “back pain”
[b] Includes “orthostatic heart rate increased”, “postural orthostatic tachycardia syndrome”, “heart rate increased” and “sinus tachycardia”
[c] Includes “orthostatic heart rate increased” and “postural orthostatic tachycardia syndrome”
[d] Includes “heart rate increased”, “tachycardia”, and “sinus tachycardia”
[e] Includes “rash,” “papular rash” and “urticaria”
[f] Includes “abdominal pain”, “abdominal pain upper” and “abdominal pain lower”
[g] Includes “orthostatic hypotension”, “blood pressure orthostatic decreased”, “blood pressure decreased”, “mean arterial pressure decreased”, “hypotension”
[h] Includes “orthostatic hypotension”, and “blood pressure orthostatic decreased”
*Lymphocytopenia is defined as absolute lymphocyte count less than 1 x 10^9/L
**Neutropenia is defined as absolute neutrophil count less than 1 x 10^9/L

There was no pattern indicating a temporal association with treatment or with body system of SAEs occurring in either the 3110A1-200-GH or the ONCBL60801 studies. In both studies, there were no SAEs regarded by the investigator (or Sponsor) as being treatment-related. Treatment-emergent SAEs (occurring during the first 180 days post-dose) are shown in Table 7.

Table 7 Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events (ONCBL60801)

Preferred Term	Moxidectin n=978 n (%)	Ivermectin n=494 n (%)
No. subjects with ≥ 1 treatment emergent serious adverse event	39 (4.0)	18 (3.6)*
No. of treatment emergent serious adverse events	52	25
Malaria	15 (1.5)	9 (1.8)
Gastroenteritis	2 (0.2)	0

Preferred Term	Moxidectin n=978 n (%)	Ivermectin n=494 n (%)
Respiratory tract infection	0	2 (0.4)
Diarrhea	1 (0.1)	3 (0.6)
Loss of consciousness	2 (0.2)	0
Enteritis	2 (0.2)	0
Gastritis	2 (0.2)	1 (0.2)
Abdominal abscess	0	1 (0.2)
Abscess limb	1 (0.1)	0
Cellulitis	1 (0.1)	0
Fungal skin infection	1 (0.1)	0
Peritonitis	1 (0.1)	0
Pneumonia	1 (0.1)	1 (0.2)
Sepsis	0	1 (0.2)
Shigella infection	1 (0.1)	0
Abdominal pain	1 (0.1)	0
Abdominal pain lower	1 (0.1)	0
Abdominal pain upper	0	1 (0.2)
Hematemesis	1 (0.1)	0
Alcohol poisoning	1 (0.1)	0
Clavicle fracture	1 (0.1)	0
Contusion	0	1 (0.2)
Head injury	1 (0.1)	0
Limb injury	1 (0.1)	0
Snake bite	1 (0.1)	0
Splenic rupture	1 (0.1)	0
Diabetic ketoacidotic hyperglycemic coma	0	1 (0.2)
Hemiplegia	1 (0.1)	0
Meningism	0	1 (0.2)
Cardiac arrest	1 (0.1)	0
Cardiac failure congestive	1 (0.1)	0
Chills	0	1 (0.2)
Influenza like illness	0	1 (0.2)
Asthma	1 (0.1)	0
Cough	0	1 (0.2)
Macular hole	1 (0.1)	0
Hepatitis chronic active	1 (0.1)	0
Dehydration	1 (0.1)	0
Rheumatic disorder	1 (0.1)	0
Dysmenorrhea	1 (0.1)	0
Skin ulcer	1 (0.1)	0

* This includes a pre-treatment hospitalization for respiratory tract infection included as a result of missing date information

5.3.2.2.3 Safety and Efficacy in Scabies

This is the first study of moxidectin in patients with *S. scabiei* infestation.

5.4 Rationale

This study aims to provide proof of concept that a single dose of moxidectin is effective in treating the scabies parasite in humans and to enable the determination of an optimal dose of moxidectin for treatment of scabies for further investigation. This study also aims to assess the safety of orally administered single moxidectin doses in adults with scabies.

5.4.1 Moxidectin

Poor adherence to topical and oral regimens prescribed for the treatment of scabies are a significant barrier to optimal treatment outcomes. Topical treatments, applied head to toe by the infected person and to all their close contacts, are generally effective. However, successful treatment is limited by poor compliance and low patient acceptability due to limited ease of use and side effects (e.g. irritation, eczematisation). Ivermectin (200 µg/kg per oral) is the only oral treatment currently available with two doses (separated by one to two weeks) the accepted regimen. Two doses are required to avoid recurrence of infestation as ivermectin not ovicidal and its relatively short plasma half-life of approximately 18 hours is insufficient to clear any mites that hatch subsequent to treatment.

Moxidectin is well-established in veterinary practice for the treatment of *S. scabiei* infestation in companion animals such as dogs, and livestock such as cattle, sheep and goats (Fourie, et al. 2006, Fthenakis, et al. 2000, Giadinis, et al. 2011, Losson and Lonneux 1993). Moxidectin also has the potential advantage of longer exposures that may abrogate the need for a second dose and enable a once only, oral dosing paradigm in humans. Comparison of moxidectin and ivermectin pharmacokinetics in the porcine scabies model indicates that moxidectin has enhanced persistence in blood and skin compared to ivermectin, providing exposures that may cover the entire mite life-cycle (Bernigaud, et al. 2016).

5.4.2 Dose Selection

The minimal and optimal effective doses (MED and OED) of moxidectin to treat human scabies are not known. Previous clinical studies have examined the safety of single moxidectin doses up to 36 mg, which were well-tolerated in healthy volunteers (Section 5.3.2.2.1). Taking the available clinical data into account as well as existing moxidectin exposure margins, model-based estimations of human moxidectin pharmacokinetic and pharmacokinetic data from the porcine scabies model, the range of doses to potentially be evaluated in the current trial will include single oral doses of moxidectin up to a maximum of 36 mg. A single oral dose was selected as the long terminal half-life ($t_{1/2}$) of moxidectin is expected to provide adequate exposure coverage for the entire life cycle of the scabies mite and eliminate hatching mites.

The lowest dose (2 mg per oral) was chosen as this dose was shown to be effective at eliminating microfilariae in onchocerciasis patients. The efficacy of the 2 mg moxidectin dose in onchocerciasis provides evidence of its activity in the skin, a target organ of both onchocerciasis microfilariae and scabies mites. Twenty mg per oral was initially selected as the upper dose for this study as it is similar on a weight for weight basis to the dose shown to be effective against *S. scabiei* in the porcine model of scabies. In this model, scabies-infected pigs were administered 300 µg/kg moxidectin per oral, equivalent to a 21 mg dose in a 70 kg human. Although the 20 mg dose may be effective in humans, to robustly determine the OED, additional doses up to a maximum of 36 mg may need to be evaluated. As described in Section 5.3.2.2.1, 36 mg was well tolerated in previous clinical studies and is within the established clinical and nonclinical safety margins for moxidectin.

5.4.3 Study Design

This study is a multicenter, randomized, double-blind, parallel group, pharmacokinetic/pharmacodynamic dose finding study of single oral doses of moxidectin in adults with scabies.

In previous clinical studies, there was no evidence of clinically relevant safety findings after administration of moxidectin at single oral dosages of up to 36 mg to healthy adult subjects. The safety of moxidectin in adults with scabies has not previously been evaluated. However, as the adverse reactions seen in onchocerciasis patients are due to host immune responses to dying *O. volvulus* microfilariae it is anticipated that the safety profile of moxidectin in scabies patient will be similar to that seen in healthy volunteer studies. Therefore, a parallel design has been selected as the doses proposed for evaluation in this study will not exceed the doses previously studied. No subject will receive more than a single oral dose of moxidectin. Only adult subjects will participate in this study as there are limited data on the pediatric use of moxidectin, which has only been administered to adolescents 12 years and older.

In this protocol, scabies infestation is defined as a minimum of two lesions, each lesion containing at least one live adult *S. scabiei* mite distinguishable by a trained operator using a Vivascope® 3000 RCM. RCM is a non-invasive imaging technique that enables visualization of the upper 300 µm of the skin (from upper epidermis to superficial dermis) using a laser light source. Although RCM is in widespread use for the diagnosis of skin malignancies such as melanoma, its clinical applications also extend to infectious diseases of the skin such as scabies (Cinotti, et al. 2015). RCM has been selected over more conventional techniques such as skin scraping or dermoscopy as it permits repeated and detailed visualization of the scabies mite. Unlike dermoscopy, adult and juvenile mites, eggs and scybala can be distinguished by RCM (Cinotti, et al. 2016). RCM can be used to assess the impact of treatment as it permits differentiation of live and dead mites on the basis of parasite morphology and movement. Treatment of scabies patients using permethrin 5% cream resulted in loss of anatomical structures, peristalsis function and movement of the mite within the burrow (D. Tilakaratne, unpublished). Further, unlike skin scraping, which results in the physical removal of mites from the affected individual, RCM permits repeat *in vivo* visualization of the impact of treatment on the scabies mite.

Time-matched, repeat RCM assessments examining mite viability and measurement of moxidectin plasma concentrations will be used to describe the moxidectin exposure-response in scabies-infected patients. The pharmacokinetic and RCM sampling schedule has been designed to minimize the in-stay period for each patient by taking into account existing moxidectin pharmacokinetic data and population-pharmacokinetic model, which will enable robust estimations of individual exposure estimations. Increased moxidectin exposure has been observed when moxidectin is given with food, so subjects will be administered moxidectin fasting to minimize variability of moxidectin pharmacokinetics. Dose cohorts of approximately 3 to 6 subjects will receive moxidectin doses of 2, 8, or 20 mg. A dose of 36 mg may be added, depending on the pharmacodynamic response observed in the study. The target sample size of the additional dose cohort will be approximately 6 subjects. As pharmacokinetic and pharmacodynamic data will be pooled across the dose cohorts, this design will result in a broad range of individual subject pharmacokinetic exposure profiles. This is considered an adequate range to allow examination of pharmacokinetic/pharmacodynamic relationships and determine the therapeutic exposure required to effectively treat scabies infestation.

Dose cohorts of approximately 6 subjects were also considered to be practical for recruitment of the study. Multiple centers are planned as the prevalence of scabies in countries such as Australia and France is generally considered to be low (approximately 1%) with higher prevalence observed in

socio-economically disadvantaged or vulnerable populations such as Australian Aboriginal and Torres Strait Islander people (La Vincente, et al. 2009) or refugees and the homeless in Europe (Arnaud, et al. 2016, Beeres, et al. 2018). Scabies is also a disease that occurs less frequently in adults than in children (Kearns, et al. 2013, Romani, et al. 2015a). The additional assessments required in this protocol (including RCM) are also likely to preclude recruitment of sufficient subjects in a single reference hospital.

Moxidectin efficacy will be determined through a series of RCM assessments conducted over 28 days with a further safety assessment at 12 weeks due to moxidectin's long $t_{1/2}$. This first 28-day period will also allow for exploratory assessment of clinical signs and symptoms following resolution of infestation. Scabies symptoms result from a sensitization of the host to mite antigens and are known to persist for several days or weeks after treatment. Twenty-eight days is considered a minimum period for the resolution of all symptoms after the infestation has been cleared, and is consistent with other studies in scabies and FDA guidance for the development of permethrin 5% formulations for the treatment of scabies (United States Food and Drug Administration 2017). Comprehensive clinical assessments will be conducted as variation in diagnostic criteria, examination techniques and clinical experience has limited the development of consensus criteria for the assessment of treatment response in scabies to date.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives

6.1.1 Primary Objectives

The primary objectives of the study are to:

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

6.1.2 Secondary Objective

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

6.1.3 Exploratory Objectives

The exploratory objectives of the study are to:

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

6.2 Endpoints

6.2.1 Primary Endpoints

The primary endpoints of the study are:

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

6.2.2 Secondary Endpoints

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

6.2.3 Exploratory Endpoints

The exploratory endpoints of the study are:

- At Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28, using assessment by RCM of burrows selected pre-treatment:
    - Changes in adult mite motility (peristalsis and/or movement) over at least 30 seconds of observation.
    - Presence, number, morphology and motility of juvenile scabies mites.
    - Presence of eggs and scybala in burrows
- Presence and total number of mites and burrows assessed visually at Days 7, 14 and 28.

- Changes in assessment of clinician-reported scabies symptomology, including extent of symptoms on body regions assessed by the number of anatomically-defined regions affected, number of lesions and severity grading of excoriations and erythema.
- Changes in patient reported outcomes, measured by Numerical Rating Scale, 5-D Itch Scale and Dermatology Life Quality Index.

7 STUDY DESIGN

7.1 Study Design

This is a randomized, double-blind, multicenter, parallel group, dose finding study of a single oral dose of moxidectin in adults with scabies.

7.2 Dosing Regimens

Initially, subjects will be randomized with a target allocation ratio of 1:1:1 to one of the following single dose treatment regimens:

- Moxidectin 2 mg
- Moxidectin 8 mg
- Moxidectin 20 mg

Once approximately three subjects have been recruited to these three dose cohorts and completed their Day 14 visit, a Protocol Steering Committee (see Section 13) will evaluate the unblinded safety and efficacy data and recommend:

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

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

7.3 Study Sites

This is a multicenter study.

7.4 Estimated Duration of the Study

The study is expected to take approximately 18 months to complete. The on-study period per subject is 13 weeks, consisting of one week for Screening and 12 weeks post-treatment.

8 SUBJECT POPULATION

8.1 Selection of Subjects

The nature of the study and the potential risks will be explained to all candidates. Written informed consent will be obtained from each subject prior to performing Screening procedures.

Subjects who meet all of the inclusion and none of the exclusion criteria described in Sections 8.2 and 8.3 will be eligible for randomization. Once randomized, subjects will be considered enrolled and will receive treatment with moxidectin. Once randomized, subjects will not be permitted to be re-randomized or given a second course of treatment.

Inclusion and exclusion criteria are to be assessed at the Screening assessment, unless otherwise indicated.

8.2 Inclusion Criteria

A subject must meet all of the following inclusion criteria:

1. Aged ≥ 18 years.
2. Provision of written informed consent.
3. Parasitologically confirmed active *Sarcoptes scabiei* infestation, defined as the presence of at least two lesions (which may include burrows), each containing at least one live (internal and/or external structures discernable) adult *Sarcoptes scabiei* mite observed by RCM.
4. Agree to the use of reliable contraceptive measures if female or male partner of a female of child-bearing potential from Screening until 6 months after treatment with study drug (Section 8.4.2).

8.3 Exclusion Criteria

A subject will be excluded from the study if they meet any of the following criteria:

1. History of chronic or recurring dermatologic disease (other than scabies) that could interfere with the diagnosis and/or subsequent clinical assessment of scabies.
2. Diagnosis of crusted/Norwegian scabies or scabies that, in the opinion of the Investigator, would require treatment with more than one standard of care (e.g. scabies requiring concurrent topical and oral treatment).
3. Received any treatment for scabies within 7 days of Screening, including but not limited to permethrin, ivermectin, benzyl benzoate, lindane, crotamiton, malathion, and/or tea tree oil.
4. Presence of any other clinically relevant condition, including infection, immunological disorder, malignant disease, and/or other underlying condition or circumstance at Screening or Baseline that would put the subject at increased risk from participating in the study or confound study evaluations.
5. Poor venous access.
6. Received an investigational agent within 28 days of Screening (or 5 half-lives of the investigational agent, whichever is longer).
7. Body Mass Index over 35 kg/m^2.
8. Clinically relevant abnormal findings in vital signs, 12-lead ECG, or physical examination at Screening and/or Baseline in the opinion of the Investigator.
9. Clinically relevant laboratory abnormalities at Screening, including:
    a. alanine aminotransferase or aspartate aminotransferase > 2.5 x upper limit of reference range;
    b. creatinine > 2.0 milligrams per deciliter (mg/dL);
    c. hemoglobin < 9.5 g/dL (female) or <10.5 g/dL (male);

d. amylase > 2.0 x upper limit of reference range.

10. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin.
11. Use of systemic steroids within 14 days of Screening, history of prolonged use of systemic and/or high-dose inhaled corticosteroids, or use of topical steroids for 7 out of the 14 days prior to Screening.
12. Subjects with known or suspected *Loa loa* coinfection.
13. Difficulty swallowing tablets.
14. Pregnant or breastfeeding, or planning to become pregnant.
15. Known or suspected alcohol or illicit substance abuse.
16. Unwilling, unlikely or unable to comply with all protocol specified assessments.
17. Previous enrolment and treatment with moxidectin in this study.

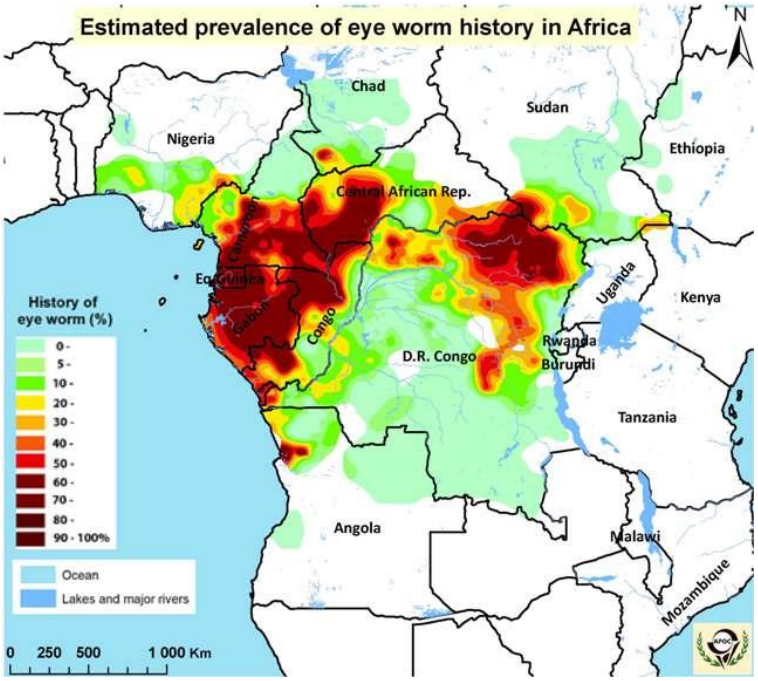
8.4 Other Study Eligibility Criteria Considerations

In order to assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study product(s) being used in this study. Such documents may include the Investigator's Brochure (IB) and the Prescribing Information.

8.4.1 *Loa loa* Co-Endemicity

Patients with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with macrocyclic lactones, including moxidectin. Moxidectin has not been studied in patients infected with *Loa loa*. It is recommended that individuals who have had exposure to *Loa loa*-endemic areas undergo diagnostic screening for loaisis prior to treatment with moxidectin. *Loa loa* parasites are found in West and Central Africa, including Cameroon, Democratic Republic of the Congo, Gabon, and Nigeria (Figure 1).

Figure 1 Map of Estimated Prevalence of Eye Worm History in Africa



Source: World Health Organization/African Programme for Onchocerciasis Control. Online at: http://www.who.int/apoc/raploa/en/ accessed 07 Sep 2018.

8.4.2 Contraception

All women of child-bearing potential (defined as sexually mature women who have had menses within the preceding 24 months and have not undergone hysterectomy, bilateral oophorectomy or tubal ligation) must have a negative pregnancy test at Screening. Pregnancy testing may be performed by analysis of serum or urine and should be confirmed at Baseline prior to study drug administration. Pregnancy testing will be repeated at Week 12.

Women of child-bearing potential must agree not to attempt to become pregnant. If participating in sexual activity that could lead to pregnancy, women of child-bearing potential and male partners of women of child-bearing potential must agree to use a reliable method of contraception during the study and for the 6 months following study drug administration.

Women who are not of reproductive potential (who have been postmenopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral oophorectomy or tubal ligation) are not required to use contraception.

8.4.3 Rescreening

Subjects who are determined to be ineligible for the study on the basis of laboratory abnormalities may be re-screened for eligibility once. All other subjects may only be rescreened once discussed and agreed with the Sponsor.

8.5 Special Protocol Issues

8.5.1 Treatment of Contacts

As untreated contacts may be a source of scabies re-infestation, all close personal contacts of enrolled subjects, including household, family and sexual contacts, will be offered the approved current standard of care scabies treatment.

The participant must be counselled to avoid contact with any treatments taken by their close personal contacts.

9 SCHEDULE OF ASSESSMENTS AND PROCEDURES

9.1 Study Schedule of Evaluations

The schedule of assessments is presented in Table 1 and Table 2.

9.2 Visit Windows

Screening must be conducted after informed consent has been given, in the window of Day -7 to Day -1.

All visit days are calculated from Day 0, which is the date of the Baseline (pre-dose) assessments and study drug administration. Hours are calculated based on the time of administration of moxidectin.

Windows for each study assessment are:

- ± 15 minutes for Hours 2 and 3,
- ± 30 minutes for Hour 4,
- ± 1 hour for Hour 8,
- ± 4 hours for Hours 24, 48 and 72,
- ± 2 days for Days 7 and 14,
- ± 3 days for Day 28,
- ± 7 days for Week 12.

9.3 Study Procedures

The study procedures to be conducted are listed below. Further detail on the study procedures is provided in Section 9.4. Any deviation from protocol procedures must be noted in the source documents and the Sponsor is to be notified.

All laboratory tests on blood and urine samples will be performed at the selected laboratory. Refer to the SRM and/or central laboratory instruction manuals for information on sample collection and shipment of all required study samples

Additional visits and/or assessments may be conducted as clinically indicated.

9.3.1 Screening Visit (Day -7 to Day -1)

Subjects will be screened up to 7 days prior to randomization to determine eligibility for participation in the study. Screening assessments may be conducted on different days if required. The following procedures will be performed and documented during Screening:

- Obtain written informed consent prior to any study related procedures (see Section 16.1.2).
- Parasitological assessment including confirmation of the presence of at least 2 lesions with live adult *S. scabiei* mites for assessment throughout the study by RCM (see Section 9.4.7).
- Medical history (see Section 9.4.2).
- A complete physical examination (see Section 9.4.3) including:
    - assessment of all appropriate body systems to determine study eligibility;
    - measurement of height and weight.
- Vital signs while in the supine position (see Section 9.4.4)
- A 12-lead ECG (see Section 9.4.5)
- Concurrent medication assessment (see Section 11)
- Blood samples drawn for hematology and clinical chemistry (see Section 9.4.6.1)
- Pregnancy test for women of childbearing potential (see Section 9.4.6.2)

Results of all Screening tests must be available and reviewed prior to the subject's Baseline visit. Subjects meeting all the inclusion criteria and none of the exclusion criteria will return to the clinic within 7 days of commencement of Screening for randomization into the study.

Subjects will be required to fast overnight (from midnight) prior to the Baseline visit (Day 0). Water may be consumed *ad libitum.*

9.3.2 Baseline (Day 0)

9.3.2.1 Pre-Treatment

Subjects will return to the clinic for final eligibility confirmation through the following assessments:

- Targeted physical examination (see Section 9.4.3).
- Parasitological assessment (see Section 9.4.7), which includes:
  - selection of at least 2 (but not more than 4) lesions with live adult *S. scabiei* mites for assessment throughout the study by RCM; and
  - photographs of the selected live adult *S. scabiei* mites using a dermatoscope and RCM.
- Concurrent medication assessment (see Section 11).
- For women of childbearing potential, confirmation of a negative pregnancy test (see Section 9.4.6.2).

Subjects meeting all of the inclusion and none of the exclusion criteria will be randomized to a treatment group and then have the following performed:

- Vital signs (see Section 9.4.4)
- Cannulation for collection of blood samples (see Section 9.4.6.3) for:
  - pharmacokinetic assessments;
  - plasma storage;
  - if Screening was conducted more than 72 hours before Baseline, blood samples should also be collected for hematology and clinical chemistry (see Section 9.4.6.1)
- Assessment of clinical signs of scabies infestation, which includes:
  - mapping, counting and grading of scabies inflammatory and non-inflammatory lesions (see Section 9.4.8.1); and
  - administration of patient reported outcome questionnaires including the Numerical Rating Scale itch score, 5-D itch score and Dermatology Life Quality Index (see Section 9.4.8.2)
- Adverse event assessment (see Section 12)

9.3.2.2 Dosing

Study drug will be administered observed by site staff with water as described in Section 10.4.4. The time of dosing (Hour 0) will be recorded in the Case Report Form (CRF).

9.3.2.3 Post-dose (Hours 2, 3, 4 and 8)

Subject will remain in the clinic for 8 hours following treatment. In addition to monitoring the subject throughout, the following will be performed on Hours 2 (± 15 minutes), 3 (± 15 minutes), 4 (± 30 minutes), and 8 (± 1 hour) and recorded in the CRF:

- Continuous adverse event assessment (see Section 12).
- Continuous recording of concurrent medications (see Section 11).
- A modified physical examination as clinically indicated (see Section 9.4.3).

- Blood samples for pharmacokinetic assessment at Hours 2, 3, 4 and 8 post-dosing (see Section 9.4.6.3).
- Parasitological assessment (see Section 9.4.7): assessment of the viability and photographs of the selected scabies mites will be taken with the RCM at Hours 4 (± 15 minutes of pharmacokinetic blood sampling) and 8 (± 15 minutes of pharmacokinetic blood sampling)
- Vital signs assessment at Hour 8 (see Section 9.4.4).

Food may be offered from two hours post-dosing. Clear liquids may be provided *ad libitum*.

Upon completion of the assessments and if the investigator is satisfied that the subject is well, the subject should be discharged from the clinic at Hour 8.

9.3.3 On-study Clinic Visits (Hours 24, 48 and 72, and Days 7, 14 and 28)

Subjects will return to the clinic for assessments on Hours 24 (± 4 hours), 48 (± 4 hours) and 72 (± 4 hours), and Days 7 (± 2 days), 14 (± 2 days) and 28 (± 3 days). The following assessments will be performed and documented as indicated on the CRF:

- Adverse event assessment at each visit (see Section 12).
- Recording of concurrent medications at each visit (see Section 11).
- A modified physical examination at Hour 24 and 72, and Days 7, 14 and 28, and as clinically indicated at other times (see Section 9.4.3).
- Vital signs assessment at Hour 24 and 72, and Days 7, 14 and 28 (see Section 9.4.4).
- Blood samples for:
    - pharmacokinetic assessment and plasma banking at each visit (see Section 9.4.6.3);
    - hematology and clinical chemistry to be performed at Day 7 and Day 28 (see Section 9.4.6.1).
- Parasitology (see Section 9.4.7) assessments which include:
    - assessment of the viability and photographs of the selected scabies mites will be taken with RCM within 15 minutes of pharmacokinetic blood sampling at Hours 24, 48 and 72, and Day 7, 14 and 28;
    - photographs by dermatoscope at Hour 72 and Day 7, 14 and 28;
    - subjects with viable mites from Day 14 may be offered standard of care (see Section 11.2.3).
- Assessment of clinical signs of scabies infestation at Day 7, 14 and 28, which includes:
    - mapping, counting and grading of scabies inflammatory and non-inflammatory lesions (see Section 9.4.8.1);
    - administration of patient reported outcome questionnaires including the Numerical Rating Scale itch score, 5-D itch score and Dermatology Life Quality Index (see Section 9.4.8.2).

9.3.4 Study Conclusion (Week 12)

At Week 12, the subject will return to the clinic for the following assessments:

- Adverse event assessment (see Section 12).
- Recording of concurrent medications (see Section 11).
- A modified physical examination including body weight (see Section 9.4.3).
- Vital signs assessment (see Section 9.4.4).
- For women of childbearing potential, confirmation of a negative pregnancy test (see Section 9.4.6.2).

9.3.5 Unscheduled Visits

If the subject returns to the clinic outside of the standard visit schedule, in addition to providing the required clinical care, for their presenting condition, the following should be performed:

- Adverse event assessment (see Section 12).
- Recording of concurrent medications (see Section 11).
- A modified physical examination (see Section 9.4.3).
- Vital signs assessment (see Section 9.4.4).

9.3.6 Early Withdrawal

Subjects should be encouraged to stay in the study for until the end of study visit at Week 12. Should a subject decide to withdraw from the study (see Section 14), all efforts will be made to complete the following study procedures as thoroughly as possible:

- Adverse event assessment (see Section 12).
- Recording of concurrent medications (see Section 11).
- A modified physical examination (see Section 9.4.3).
- Vital signs assessment (see Section 9.4.4).
- For women of childbearing potential, confirmation of a negative pregnancy test (see Section 9.4.6.2).
- Blood samples for:
    - hematology and clinical chemistry (see Section 9.4.6.1)
    - plasma for banking (see Section 9.4.6.3)

If withdrawal occurs prior to the Day 28 visit, all efforts will be made to complete the following additional study procedures:

- Blood samples for pharmacokinetic assessment (see Section 9.4.6.3)
- Parasitology (see Section 9.4.7) assessments, which include:
    - photographs of the live adult scabies mites will be taken with RCM within 15 minutes of pharmacokinetic blood sampling;
    - photographs by dermatoscope.
- Assessment of clinical signs of scabies infestation at Day 7, 14 and 28, which includes:
    - mapping, counting and grading of scabies inflammatory and non-inflammatory lesions (see Section 9.4.8.1);
    - administration of patient reported outcome questionnaires including the Numerical Rating Scale itch score, 5-D itch score and Dermatology Life Quality Index (see Section 9.4.8.2).

9.3.7 Modification of Scheduled Procedures due to COVID-19

The safety and wellbeing of research subjects and the study team is paramount. Adherence to official public health guidance, government or site governance directives issued in response to the COVID-19 pandemic should take precedence over the procedures in this protocol.

Subjects should be informed of the importance of notifying the study team in advance if they are experiencing one or more symptoms suggestive of SARS-CoV-2 infection or other infectious disease that includes respiratory symptoms, or have been in close contact with someone who is known to have contracted SARS-CoV-2. The Principal Investigator or delegate may advise the subject to present to the relevant health service for further investigation.

Subjects who are unwilling or unable to attend clinic visits or complete other trial activities due to the pandemic may be asked to comply with study procedures. However, subjects are entitled to withdraw from the study at any time or for any reason and their decision is to be respected.

The majority of assessments in this protocol require physical attendance at the clinic. Exceptions may be made at the Investigator's discretion for assessments that are able to be conducted remotely (such as Week 12). If subjects become unable to undertake protocol required assessments due to self-isolation or have been advised to stay away from the clinic, resulting protocol deviations should be documented to enable appropriate evaluation for the study.

If biospecimens are collected from subjects known to be actively infected with COVID-19, this information should be noted in the documentation that accompanies any sample transfer activities.

In addition to the provisions outlined in Section 14, subjects with missing key efficacy assessments due to COVID-19 may be replaced.

9.4 Details of Scheduled Assessments

9.4.1 Demographic Data

Demographic data will be recorded in the clinic notes and CRF at Screening and include sex, ethnicity and date of birth.

9.4.2 Medical History

The medical history will be recorded in the clinic notes and CRF at Screening and include any diagnosed medical conditions and/or recurrent medical conditions, or significant medical or surgical history. It will include a review of all major body systems including the skin.

Any worsening of Baseline conditions detected during medical history review must be recorded on source documents as well as in the AE section of the CRF.

9.4.3 Physical Examination

A complete physical examination (including head, ears, nose, throat, lungs, lymph nodes, heart, abdomen and skin) will be conducted at Screening to determine study eligibility and recorded in the clinic notes and CRF.

A symptom-based physical examination will be conducted at visits conducted after Screening, according to prior findings and informed by concurrent conditions, signs and symptoms, and AEs reported. A full physical examination is recommended if, in the opinion of the Investigator, any clinical changes are suggested by the subject's interim clinical history. These data should be recorded in the clinic notes. Any new abnormalities or worsening of Baseline conditions detected during physical examinations must be recorded on source documents as well as in the AE section of the CRF.

Body weight (kilograms [kg], without shoes) and height (centimeters [cm], without shoes) will be measured at Screening and recorded in the clinic notes and CRF.

9.4.4 Vital Signs

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.

Vital signs will be measured after the subject has been semi-supine for 5 minutes:

- Oral/aural body temperature (degrees Celsius [°C])
- Respiratory rate (breaths per minute)
- Pulse rate (beats per minute [bpm])
- Blood pressure (millimeters of mercury [mmHg])

Vital signs should also be measured at other times if deemed clinically appropriate. These data will be recorded in the clinic notes and CRF.

9.4.5 Electrocardiograms

12-lead ECG will be performed in triplicate over approximately 10 minutes after the subject has been supine for approximately 10 minutes at Screening. ECGs will be performed before blood collection. Repeat measurements will be performed if there are any clinical abnormalities observed or artifacts are present. All ECG recordings will be reviewed by the Investigator or nominee and retained in the clinic notes.

9.4.6 Biological Samples

Safety laboratory parameters, pharmacokinetic samples and plasma banking samples are required throughout the study.

The first 8 hours after dosing requires sequential blood samples to be collected in order to appropriately characterize moxidectin pharmacokinetics. An intravascular catheter should be used to facilitate venous access and use of an effective topical anesthetic for application to the skin for sample collection.

9.4.6.1 Safety Laboratory Tests

All safety laboratory tests will be conducted at the nominated laboratory. Refer to the SRM for detailed instructions on sample collection, handling and processing.

Blood samples for hematology and serum chemistry will be collected at Screening, Baseline (before dosing, if Screening samples were collected more than 72 hours before Baseline), Day 7 and Day 28. It is expected that a copy of these data will be directly transferred to the Sponsor rather than require transcription into the CRF.

Samples will be collected for the safety laboratory tests shown in Table 8.

Table 8 Hematology and Serum Chemistry Tests

Hematology	Hemoglobin Hematocrit Red blood cell (RBC) and RBC morphology (if abnormal) White blood cell and differential white blood cell count Platelet count Mean corpuscular volume Mean corpuscular hemoglobin concentration
Serum clinical chemistry	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Bilirubin, total and direct Blood urea nitrogen or urea Calcium Chloride Creatinine, estimated creatinine clearance Creatine phosphokinase Gamma glutamyltransferase Glucose Lactate dehydrogenase Phosphorus Potassium Serum amylase Sodium Total protein Uric acid

9.4.6.2 Pregnancy Testing

A pregnancy test will be performed for all women of childbearing potential at Screening, Baseline and Week 12 using a blood or urine sample. A negative pregnancy test result is required prior to IMP administration.

9.4.6.3 Pharmacokinetic Samples and Samples for Plasma Banking

Plasma for determining the pharmacokinetics of moxidectin will be collected at Baseline (pre-dose), Hours 2, 3, 4, 8, 24, 48 and 72 Hours, and at Days 7, 14 and 28. All samples (except those taken at Hours 2 and 3) will coincide with an RCM assessment (see Section 9.4.7) and will be collected as close to the scheduled time point as possible. Collection of pharmacokinetic samples and RCM assessments should be performed within a 15-minute window.

A portion of blood samples collected for pharmacokinetic analysis will be banked for the development of tests to characterize biomarkers of scabies infestation. As a neglected disease, there have been no assays developed for the diagnosis of scabies infection and/or monitoring of efficacy outcomes of treatment. Such an assay would greatly improve the diagnosis and management of this disease. For this purpose, plasma will be prepared from blood samples and divided into two aliquots stored at -20°C or -80°C conditions. Details of the collection, processing, storage and shipping of pharmacokinetic samples and samples for banking are further detailed in the SRM.

9.4.6.4 Handling and Processing of Biological Specimens

Blood and urine specimens collected during the trial may contain harmful pathogens. All personnel involved in collecting and handling biological specimens should follow appropriate precautionary procedures for handling biohazardous materials as currently recommended by the national

regulatory authority. The processing of all biological specimens will be in accordance with relevant institutional Standard Operating Procedures (SOPs).

Further details of the handling of blood samples can be found in the SRM.

9.4.7 Parasitology Assessments of the Scabies Mite

In vivo assessments will be conducted on a minimum of 2 and a maximum of 4 live adult scabies mites, each within a distinct lesion. These assessments will be conducted using the Vivascope 3000® RCM. Some RCM assessments will be paired with high magnification dermatoscope assessments:

- RCM and dermoscopy: Baseline, and Hour 72, and Days 7, 14 and 28.
- RCM alone: Screening, and Hours 4, 8, 24 and 48.

By RCM, live adult scabies mites are defined by an inhomogenous (i.e. with internal structures discernable) ovoid refractive body. Short legs may be visible and vital functions such as peristalsis or movement within the burrow may be observable. Dermoscopy may be used to identify the location of mites before assessment by RCM. The lesions selected for assessment should be delineated to facilitate follow up, for example directly on the skin or using appropriate methods to map their location.

Once the assessable mites have been identified, optical sections will be captured using the RCM. Videos may also be captured as appropriate. Photographs at a minimum 10x magnification should be captured at the specified time points with a dermatoscope. Following image acquisition, the RCM and/or dermatoscope should be appropriately decontaminated.

These data will be recorded in the CRF. The full procedure for RCM and dermatoscope handling and image acquisition is detailed in the SRM.

9.4.8 Clinical Assessments

9.4.8.1 Clinician Reported Outcomes

Subjects will be assessed for the clinical signs and symptoms of scabies infestation at Baseline, Day 7, 14 and 28. Signs and symptoms include visible mites, burrows, inflammatory lesions such as papules, vesicles and/or nodules, and non-inflammatory lesions such as excoriations and erythema.

The procedure for reporting signs and symptoms is outlined below:

- Signs and symptoms of scabies infestation will be mapped according to pre-specified anatomical body regions.
- Regions showing signs and symptoms of scabies infestation should be photographed where possible. All efforts should be made to maintain photography conditions (e.g. lighting, distance and position) at each visit.
- If present, mites and burrows, observed using dermoscopy, and inflammatory lesions will be counted by affected region.
- Excoriations will be noted if present
- If present, the severity of erythema will be graded.

These data will be recorded in the clinic notes and CRF. Signs and symptoms of scabies that worsen or emerge after commencement of treatment should also be reported as AEs in the CRF.

Complete details of these study procedures are available in the SRM.

9.4.8.2 Patient Reported Outcomes

The subject will be asked to complete the following questionnaires:

- Numerical Rating Scale for itch;
- 5-D itch scale;
- Dermatology Life Quality Index.

These questionnaires will be administered at Baseline pre-dose and on Day 7, 14 and 28. Responses will be transcribed to the CRF. Details of these questionnaires are available in the SRM.

10 INVESTIGATIONAL MEDICINAL PRODUCT

10.1 Randomization Process

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

For each site, a randomization scheme with equal allocation to each of the initial three moxidectin treatment groups will be prepared in advance by an unblinded statistician otherwise independent of study conduct using a computer-generated system according to relevant SOPs. Treatment packs will be prepared according to the randomization scheme.

Randomization will take place before dosing on Day 0, with equal random assignment to one of the following treatments:

- Treatment 1: moxidectin 2 mg
- Treatment 2: moxidectin 8 mg
- Treatment 3: moxidectin 20 mg

Randomization to treatment will be accomplished by sequential assignment of treatment numbers, corresponding to the pre-packaged individual drug supplies provided.

Following review of safety and efficacy data by the Protocol Steering Committee (see Section 13 for more information), one or more dose cohort(s) may be discontinued and/or a new 36 mg dose cohort added. If required, the randomization plan will be revised to maintain the final target sample size of 6 subjects per cohort.

The study may switch from a stratified randomization by site to a central randomization scheme for logistical reasons. This approach would allow greater control over the number of subjects randomized to each dose cohort across all sites. However, random allocation of treatment assignment will be preserved in all cases.

Further details on the randomization procedure, and treatment dispensing and accountability is provided in the SRM.

10.2 Blinding

Neither the subjects, staff administering the study drug nor Sponsor staff directly involved in the conduct of the study will know the dose of study drug being administered. To maintain the blind, each subject will receive the same number of tablets, regardless of dose, in pre-packed bottles. Each bottle will contain moxidectin 2 mg tablets and placebo tablets as required to maintain the blind. 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.

A maximum of 18 tablets may be required to blind the doses. Investigational product will be packaged to permit this in line with Section 10.4.

The Protocol Steering Committee will be unblinded. No member of the Committee will be directly involved in the day-to-day conduct of the study.

10.3 Method of Unblinding

10.3.1 Medical Emergency

No open key to the random code will be available to the study centers and Sponsor. Sealed code break envelopes will be held by the clinical site, medical monitor and/or Sponsor. In an emergency, the Investigator or other study team member may need to break the treatment code immediately, or

as quickly as possible if this is in the best interest of the trial subject. The breaking of the blind should only occur where knowledge of the study medication treatment will affect the subject's clinical management. The Medical Monitor should be consulted prior to the breaking of the blind.

If the code is broken the envelope must be signed and dated by the individual who broke the code, and information entered into the subject's source documents, explaining the reason and date that it was opened, identity of the person who authorized the code break, and documenting the identity of the study product allocated to the subject. This must be countersigned by the Investigator.

10.3.2 End of Study

The randomization code will be broken by the blinded Study Statistician once data entry has been completed, the database locked, and the per-protocol population for analysis established. Sponsor will provide written permission to the Study Statistician prior to the breaking of the randomization code.

10.4 Investigational Products

10.4.1 Supply

Moxidectin will be supplied by the Sponsor as 100 mg uncoated, oval-shaped tablets containing the components listed in Table 9. Moxidectin tablets contain 2 mg moxidectin.

Table 9 Moxidectin Tablet Components

Component	Quality Reference	Function
Micronized moxidectin	United States Pharmacopeia	Active ingredient
Microcrystalline cellulose	National Formulary	Diluent
Lactose, anhydrous	National Formulary	Diluent
Sodium lauryl sulfate	National Formulary	Surfactant
Colloidal silicon dioxide	National Formulary	Glidant
Croscarmellose sodium	National Formulary	Disintegrant
Magnesium stearate	National Formulary	Lubricant
Nitrogen	National Formulary	Processing aid

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

10.4.2 Packaging and Labelling

Moxidectin will be supplied to the site packaged in high density polyethylene bottles. Moxidectin will be shipped to site after receipt of required documentation of study approval and in accordance with applicable regulatory requirements.

Product labelling will be in accordance with local regulations and requirements and will include at a minimum:

- Sponsor name
- Protocol number
- Product name or drug code
- Dose or product strength
- Route of administration
- Lot number
- Directions for use
- Expiry date or retest date (on outer packaging)
- 'For Clinical Trial Use Only'

- Subject Number

Any specific cautionary statements will be included according to local law.

10.4.3 Storage and Handling

Moxidectin tablets and placebo to match must be stored at controlled room temperature (25°C) and protected from light and moisture. Tablets must not be frozen. Temperature excursions are permitted up to 30°C for up to 12 months.

Only participants enrolled in the study may receive investigational products. Prior to dispensing, moxidectin supplies will be stored securely under the appropriate conditions at the clinical trial site in a secure area with access limited to authorized staff, and according to relevant regulations.

The Investigator or authorized designee will ensure that the IMP is safely and securely stored in compliance with Good Laboratory Practice storage requirements. The Investigator is responsible for ensuring that the IMP is dispensed in accordance with the protocol and only to participants enrolled in the study. Authorized study personnel will dispense moxidectin.

10.4.4 Dosage and Administration of Test Drugs

Subjects may receive a maximum of 18 tablets for oral administration comprised of moxidectin 2 mg tablets and matched placebo to maintain the blind and accommodate the 36 mg dose. Administration will be observed by clinic staff to ensure compliance.

This pill burden is considered reasonable for this phase of study. Each moxidectin 2 mg and placebo to match tablet is 100 mg total weight and < 1 cm in length. Eighteen (18) tablets were administered without issue in MDGH-MOX-1008, where 60 healthy volunteers received 18 moxidectin 2 mg and/or matched placebo tablets per oral of the current formulation. No acceptability or compliance issues were reported in this study and all subjects were able to (and observed to) swallow the 18 tablets.

The dose of moxidectin will be administered on Day 0 after fasting from at least midnight and preferably overnight. Subjects will be required to swallow moxidectin with water. Subjects must continue to fast for 2 hours post-dose. Clear liquids may be consumed *ad libitum*.

10.4.5 Dispensing and Accountability

All IMP supplied is only for use in this clinical study and should not be used for any other purpose.

The Investigator or designee is responsible for maintaining accurate records for all study medications dispensed and returned. The inventory and dispensing logs must be available for inspection by the study monitor. Study product supplies, including partially used or empty bottles must be accounted for by the Investigator or designee and verified by the study monitor and returned to the drug repository for destruction at the end of the study.

When requested in writing by the Sponsor, unused study medication supplies may be destroyed by the Investigator provided such disposition can be performed safely. Records shall be maintained by the Investigator or any such alternate disposition of the study medication. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the test substance. Such records shall be submitted to the Sponsor.

11 CONCURRENT MEDICATIONS AND TREATMENTS

At each study visit or contact, the Investigator should question the subject about any medication taken. Concomitant therapies should be brought to the attention of the Investigator. Any such medications will be recorded on the CRF. Any changes in doses or introduction of new medications during the course of the study will also be recorded.

If the medication is related to the occurrence of an AE, ensure that details are recorded in the CRF.

11.1 Special Dietary Requirements

There are no special dietary requirements.

11.2 Concurrent Medications and Treatments

11.2.1 Prior to Study Entry

Refer to Exclusion Criteria in Section 8.3.

11.2.2 During the Study Dosing Period

Every effort should be made to keep concurrent medications for chronic or ongoing medical issues stable throughout the study period.

All concurrent medications, including vitamin supplements and herbal remedies, must be recorded in the appropriate section of the CRF. All changes in medication will be noted. If the reason for use meets the definition of an AE, the AE will be recorded in the source documents for that subject and on the appropriate page of the CRF.

Except as specified in Section 11.2.3, subjects may not receive treatment with any scabicide, including ivermectin, permethrin, benzyl benzoate, lindane, crotamiton, malathion or tea tree oil at any time up to and including Week 12.

Scabies symptoms including pruritus may persist for several weeks after successful treatment of the infestation. Subjects should not receive supportive therapies to manage their scabies symptoms or treatment with other anti-parasitic treatments (in addition to those listed above) up to and including Day 28. Should the subject report scabies symptoms that are intolerable, oral antihistamines may be used at the discretion of the Investigator.

Topical steroids and topical preparations containing zinc, calamine, tar or salicylic acid (including medicated emollients) are prohibited after Screening up to and including Day 28.

Unmedicated emollient creams are permitted at any time.

11.2.3 Rescue Therapy

If subjects are shown to be either newly or persistently infected with confirmed scabies mites by RCM on or at any time from Day 14, standard of care may be offered. Rescue therapy may not be offered in the absence of scabies mites or based on symptomology only.

12 ADVERSE EVENTS AND TOXICITY MANAGEMENT

12.1 Safety Parameters

Safety assessments will include physical examination, AEs, vital signs and clinical laboratory tests.

12.2 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an Investigational Product (whether it is the experimental product or control) and which does not necessarily have a causal relationship with the Investigational Product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing events that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials will also be considered as an AE. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g. invasive procedures such as biopsies).

Any AE (i.e. a new event or an exacerbation of a pre-existing condition) with an onset date after informed consent up to the last day on study (including the follow-up, off study medication period of the study), should be recorded as an AE on the appropriate CRF page(s).

An AE **does not** include:

- medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE;
- pre-existing diseases or conditions present or detected prior to start of study product administration, that do not worsen;
- situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study product or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.

12.2.1 Assessment of Adverse Events

All AEs will be assessed by the Investigator and recorded on the appropriate CRF page, including the date of onset and resolution, severity, relationship to study product, outcome and action taken with study medication. Each AE will be graded for severity using the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials in Appendix 18.1. For the purpose of monitoring toxicities, the Baseline value is defined as the last value prior to the administration of IMP.

For AEs not specifically identified in the grading table, the grades presented in Table 10 should be applied

Table 10 Grading of Adverse Events

Grade	Severity	Comments
1	Mild	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
2	Moderate	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
3	Severe	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated

Grade	Severity	Comments
4	Life-threatening	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

The relationship to IMP therapy should be assessed using the definitions presented in Table 11.

Table 11 Assessment of Relationship of Adverse Events to Investigational Medicinal Product

Causality	Comment
Unrelated	AE is clearly due to extraneous causes (e.g. underlying disease, environment, known effect of another drug)
Unlikely	The temporal association between the AE and study drug is such that study drug is not likely to have any reasonable association with the AE
Possible	The AE could have been produced by the subject's clinical state or study drug
Probable	The AE follows a reasonable temporal sequence from the time of study drug administration, abates upon discontinuation of the study drug and cannot be reasonably explained by the known characteristics of the subject's clinical state
Definite	The AE follows a reasonable temporal sequence from the time of study drug administration, abates upon discontinuation of the study drug and/or reappears when study drug is re-introduced

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study product, then an alternative explanation should be provided.

12.2.2 Adverse Event Reporting Period

All AEs, regardless of severity, causality or seriousness must be reported from the date of informed consent until the end of the study or 28 days after the last dose of study medication, whichever is later. However, any AE that the Investigator believes is at least possibly related to study medication should be reported regardless of time elapsed from the final dose.

12.3 Serious Adverse Events

12.3.1 Serious Adverse Event Definition

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death;
- life-threatening situation (subject is at immediate risk of death);
- inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events);
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect in the offspring of a subject who received study product;

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- blood dyscrasias or convulsions that do not result in hospitalization;
- development of drug dependency or drug abuse.

12.3.2 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study product(s).
- All deaths, regardless of cause, must be reported to the Sponsor for subjects on study and for deaths occurring within 30 days of last study product dose or within 30 days of last study evaluation, whichever is longer.
- "Occurring at any dose" does not imply that the subject is receiving study product at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is a SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

12.3.3 Serious Adverse Event Reporting Requirements

12.3.3.1 All Serious Adverse Events

The Sponsor has requirements for expedited reporting of SAEs meeting specific requirements to worldwide regulatory authorities; therefore, all appropriate parties must be notified immediately regarding the occurrence of any SAE that occurs during the study. The procedures for reporting all SAEs, regardless of whether the Investigator believes that the experience is related to study drug, are as follows:

1) Complete the "Serious Adverse Event Report Form"
2) Send the completed "Serious Adverse Event Report Form" to the Sponsor Safety Desk [redacted] within 24 hours of the Investigator's knowledge of the event.
3) For fatal or life-threatening events, also submit copies of hospital case reports, autopsy reports, and other documents when requested and applicable

Additional detail on reporting SAEs is included in the SRM.

The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concurrent medication section of the subject's CRF.

12.3.3.2 Investigator Reporting Requirements for Serious Adverse Events

An SAE may qualify for reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the study product and is unexpected (Suspected Unexpected Serious

Adverse Reaction [SUSAR]) based upon the current Investigator's Brochure. In this case for multi-center studies, all Investigators will receive a formal notification describing the SAE.

Where this is required by local regulatory authorities, and in accordance with the local institutional policy, the Investigator should notify (in writing) the local Independent Ethics Committee (IEC) of SAEs as soon as is practical.

12.4 Follow up of Serious and Non-Serious Adverse Events

Follow-up of serious and non-serious AEs will continue through the last day on study (including the follow-up, off study medication period of the study), until the Investigator determines that the subject's condition is stable, or up to 30 days after the last dose of Study Product, whichever is longer. The Sponsor may request that certain AEs be followed until resolution.

12.5 Additional Considerations for Reporting Adverse Events

12.5.1 Diagnosis 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).

12.5.2 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…").

12.5.3 Elective or 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 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.

12.5.4 Overdose Reporting

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

12.5.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

All laboratory values must be reviewed by the Investigator or medically qualified designee as soon as practical after the data are available.

Any laboratory values outside the reference range will be evaluated for clinical significance. Laboratory abnormalities that occur without related clinical symptoms and signs should generally not be recorded as AE unless they represent a clinically significant event. Where possible, the overall diagnosis rather than the laboratory abnormality should be recorded on the AE CRF. This will avoid duplication of laboratory abnormalities in both the AE and laboratory reports. Abnormal laboratory results that are of clinical significance should be reviewed by the Medical Monitor.

Any laboratory test result that meets the criteria for a SAE (refer to Section 12.3) should be recorded as an AE, the AE page of the CRF completed and a 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.

12.6 Guidance for Dose Modification or Discontinuation of Treatment

Dose modification or discontinuation of treatment are not applicable in this single dose study.

12.7 Warnings and Precautions

For information regarding precautions and AEs with the investigational drug, the Investigator is referred to the Investigator's Brochure and Prescribing Information for moxidectin.

12.8 Risks for Women of Childbearing Potential or During Pregnancy

The risks of treatment with moxidectin during pregnancy have not been evaluated. Women of child-bearing potential must agree not to attempt to become pregnant. If participating in sexual activity that could lead to pregnancy, women of child-bearing potential and male partners of women of child-bearing potential must agree to use a reliable method of contraception during the study and for the 6 months following study drug administration.

12.9 Procedures to be Followed in the Event of Pregnancy

The subject must be instructed to inform the Investigator **immediately** if she becomes pregnant during the study period or if his partner becomes pregnant. The Investigator should report all pregnancies to the Sponsor or designee within 24 hours of becoming aware of the pregnancy. Pregnancies should be reported using Clinical Pregnancy Notification Form provided by the Sponsor for reporting the occurrence and outcome of pregnancies in subject enrolled in the study.

The subject should be monitored until the end of the pregnancy and the outcome of the pregnancy should be reported to the Sponsor.

13 PROTOCOL STEERING COMMITTEE

The Protocol Steering Committee will ensure the study meets its objectives to identify a well-tolerated and optimally effective dose of moxidectin for scabies. The Committee will be comprised of up to two external experts, up to two Sponsor representatives not directly involved in management of the study, and a statistician.

The Committee will review relevant accumulated unblinded safety and efficacy data for all randomized subjects collected through to the review cutoff date. The data review cutoff date will correspond to the date when the first 3 subjects in each of the 3 initial treatment arms have completed their Day 14 study evaluation. Study recruitment may be paused during the review period.

Based on a review of the available data, the Committee will recommend one or more of the following actions:

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

Should design modifications be recommended, the study will maintain the randomized allocation of subjects to the remaining/additional treatment cohorts, to a target sample size of 6 subjects.

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

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

The Committee will not reveal the results of their data review or, barring any unanticipated safety issues, any decisions or recommendations to Investigators, study personnel, or Sponsor personnel involved in the management of day-to-day study activities (Section 10.2).

Minutes of the Protocol Steering Committee meetings as well as the interim data reviewed will be documented but remain confidential until the study's conclusion. Additional unblinded reviews and possible dose modification recommendations may also be undertaken by the Committee at any time at, or in lieu of the data review described above, at the request of the Sponsor.

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

14 SUBJECT COMPLETION/WITHDRAWAL

14.1 Subject Completion

A subject will be deemed to have completed the study once all trial procedures have been conducted. Any AEs or SAEs still ongoing at the time of the Exit Evaluation will be followed in accordance with Section 12.

14.2 Criteria for Premature Withdrawal from Treatment or the Study

Subjects have the right to withdraw from the study at any time for any reason. 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 patients from treatment or the study in the event of concurrent illness, AEs, pregnancy, treatment failure after a prescribed procedure, protocol violations, administrative reasons or other reasons. The reasons for withdrawal of the subject must be recorded on the CRF.

It is understood by all concerned that an excessive rate of withdrawals from the study can render the study difficult to interpret. Unnecessary withdrawal of subjects from the study should be avoided.

14.3 Withdrawal of Subjects from Study Product

Treatment withdrawal is not relevant in this single dose study.

If a subject is unable to swallow all required tablets and take the full dose of IMP, they should remain on-study and be followed up according to the protocol.

14.4 Withdrawal of Subjects from the Study

Should a subject decide to withdraw from the study, all efforts will be made to complete the study procedures as thoroughly as possible.

If possible, the reason for withdrawal should be determined. The reason for withdrawal should be established by the Investigator through phone contact, a personal visit or by contacting a responsible relative. The reason for withdrawal should be included in a complete final evaluation which should be conducted at the time of the subject withdrawal. If applicable, where possible, subjects should be followed until ongoing AEs have been resolved or abnormal laboratory tests have returned to normal.

14.5 Replacement of Withdrawn Subjects

Any subjects who discontinues in a clinical study of their own volition or by the Investigator are defined as “withdrawals”. Replacement subjects may be enrolled into the study at the request of the Sponsor. They will receive the same treatment allocation as the withdrawn subject by use of a matching replacement subject number pre-assigned for each subject. This is to ensure that blinding is maintained. Further details are provided in the Study Reference Manual.

14.6 Premature Termination of the Study

The study will be completed as planned unless the following criteria are met:

- New information regarding the safety or efficacy of the study drug that indicates a change in the risk/benefit profile of the IMP, such that the risks and benefits of the study are no longer acceptable to study subjects.
- Significant violation of good clinical practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.

Conduct of the study at an investigational site may be terminated if the Investigator or site staff are found in significant violation of GCP, the protocol or other contractual agreements, or are unable to ensure adequate performance of the study.

In the event that the Sponsor elects to terminate the study or an investigational site, an early termination procedure will be provided by the Sponsor, which will be followed by the investigational site(s) during the course of termination.

15 STATISTICAL ANALYSIS

15.1 Statistical Methods

The study is a randomized, double-blind, proof-of-concept trial designed to describe the association between single moxidectin doses and various parasitological outcomes observed over a 28-day follow-up period. Subjects will continue to be followed for safety to Week 12. Following Screening, eligible consenting subjects will be randomized to one of the 3 initial moxidectin dose groups, 2, 8, or 20 mg. The randomization will be stratified by site and within each site subjects will be randomized using a 1:1:1 allocation ratio. After review of the accumulating data by the Protocol Steering Committee, the randomization scheme may be modified to accommodate the addition or deletion of doses such that the final target sample size of 6 subjects per dose retained/added after the unblinded data review is accommodated. The primary objective of this proof-of-concept study is to identify an optimal dose of moxidectin for further study.

The target sample size, n = 6 per completed dose group, was selected to be practical and an adequate sample size for full characterization of pharmacokinetic profile across the dose ranges studied. Sample size was not based on formal power considerations with respect to statistical hypothesis testing, and as such, the focus of the statistical analysis will be descriptive and exploratory. Nonetheless, statistical models for estimation and hypothesis testing to assess various parasitological assessments with respect to dose may be conducted. It is recognized that the sample size may not adequately support more complex models. When this is the case it will be noted. Given the exploratory nature of the study, no adjustment for multiple comparisons or Protocol Steering Committee data reviews will be made. Given the small sample size per dose group, descriptive analyses per site may be difficult to interpret.

For most analyses, the unit of analysis will be the subject; however, some analyses may be conducted where the unit of analysis may be the individual scabies mite. When this is the case, the unit of analysis will be clearly identified. Analyses using the individual scabies mite as the unit of analysis will address the potential lack of independence between mites belonging to the same subject.

General statistical methods of analysis are described below with more detailed descriptions to be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to breaking the blind for the final analysis. Any changes to the statistical analysis plan made after the blind break will be identified in the clinical study report (CSR).

15.2 Hypothesis

Study data will be analyzed in a descriptive manner with the objective of describing an exposure-response association between the moxidectin dose groups and parasitological outcomes and/or observing a single exposure or dose that appears to have the “best” parasitological effect while maintaining an acceptable safety profile.

15.3 Sample Size Determination

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

15.4 Analysis Sets

15.4.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects receiving at least one dose of study drug with observed data for the particular analysis undertaken. Subjects in the FAS analysis set will be analyzed according to the dose group to which they were randomized. In general, the FAS will be used for selective analyses such as sensitivity analyses.

15.4.2 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will include all subjects exposed to study drug without any major protocol deviations that could confound the assessment and/or interpretation of the analytic results. The identification of these protocol deviations will be identified by the study team prior to breaking the study blind. Subjects in the PPAS will be analyzed according to the actual treatment received regardless of their randomized dose group. In general, PPAS subjects with missing data for a specific analysis will be excluded from that analysis. It is not anticipated that missing data will be imputed. As this is a proof-of-concept study, the PPAS will be the primary analysis set used to assess parasitological outcomes as well as clinical signs and symptoms endpoints. Replacement subjects will be included in the PPAS if they meet the PPAS requirements.

15.4.3 Safety Analysis Set

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

15.4.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) will include all subjects who received at least one dose of moxidectin and provide an adequate number of blood samples for the determination of plasma pharmacokinetic parameters using the methods described in Section 15.7.4.

15.4.5 Pharmacokinetic/Pharmacodynamic Analysis Set

The Pharmacokinetic/Pharmacodynamic Analysis Set (PKPDAS) will include all subjects who received at least one dose of moxidectin and provide blood samples for the determination of plasma pharmacokinetic parameters matched with RCM assessments of parasitological outcomes.

15.5 Analysis Periods and Interim Analysis

15.5.1 Protocol Steering Committee Data Review

No formal interim analysis is planned. The Protocol Steering Committee will review unblinded safety and efficacy data as described in Section 13 and with the ability to make dose modification recommendations. The analyses to be conducted during these interim reviews may entail review of individual subject line listings and/or aggregate data. Since the study is exploratory and not powered to conduct hypothesis testing, no adjustments to the type I error rate will be implemented. Further details will be provided in the SAP and Protocol Steering Committee Charter.

15.5.2 Final Analysis

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

- Period 1: Commences at Screening and will finish on Day 28. The study blind will be maintained during this study period. After the last subject has completed the study through Period 1, the blind will be broken and the data from Period 1 will be analyzed.

- Period 2: Runs from Day 29 to Week 12. Data from Period 2 will be analyzed after all subjects have completed the study through Week 12. Data for some subjects may be collected during Period 2 after the blind has been broken and the Period 1 study results known. The Period 2 data will be provided in an additional safety supplement. Although the blind will be broken after the last subject completes Period 1, the individual treatment assignment will not be communicated to the subject, investigator, or site personnel until the last subject has completed Period 2.

Efficacy and safety data obtained for subjects randomized to all doses, including doses that may have been discontinued or added based on the recommendation from the Protocol Steering Committee, will be included in the final analysis. Further details of analysis will be provided in the SAP.

15.6 Study Endpoints

15.6.1 Key Efficacy Endpoints

The primary efficacy endpoint of the study will be determined by the death of adult scabies mites, with death defined as the degradation (homogenization of internal structures and/or external anatomic structures, and increased reflectance) of the adult mite observed by RCM. Mites will be assessed at Hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28 in not less than two lesions nominated pre-treatment. The average proportion (crude mortality rate) of dead adult scabies mites per subject will be calculated as the number of dead adult scabies mites from among the live adult scabies mites identified at Baseline for each individual subject calculated at each time point measured. The proportion of subjects with 100% dead adult scabies mites from among the live adult scabies mites identified at Baseline calculated at each time point measured will also be reported.

The following are examples of key efficacy endpoints defined at the individual mite level of analysis:

- The mortality rate for adult scabies mites from among those identified at Baseline, calculated at each time point measured.
- The time-to-death of adult scabies mites from among those identified at Baseline.

15.6.2 Key Pharmacokinetic Endpoints

Exposure metrics of moxidectin will be determined by non-compartmental analysis of key moxidectin pharmacokinetic parameters or other methods as appropriate assessed up to and including Day 28.

Specific pharmacokinetic 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
- $AUC_{0\text{-t}}$: AUC from time 0 extrapolated to time t (where t = 24, 48, 72 Hours, Day 7, 14 and 28)
- C_{max}: maximum observed plasma concentration
- T_{max}: time to maximum observed plasma concentration
- $t_{1/2}$: terminal elimination half-life

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

15.6.3 Exploratory Endpoints

The exploratory endpoints of the study are:

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

15.6.4 Safety Endpoints

- Incidence and severity of treatment emergent adverse events (TEAEs)
- Incidence of serious TEAEs
- Incidence of TEAEs leading to study withdrawal and/or death
- Changes from baseline in laboratory assessments, vital signs, and physical exams

15.7 General Analytic Methods

15.7.1 Overview

The focus of the statistical analysis will be descriptive and exploratory. Statistical models for estimation and/or hypothesis testing to assess various parasitological assessments with respect to dose may be conducted; however, it is recognized that the sample size may not adequately support more complex models that may be utilized to account for the clustering of scabies mites within subjects. When this is the case it will be noted. Given the exploratory nature of the study, no adjustment for multiple comparisons will be made.

Detailed methods will be provided in the SAP.

15.7.2 Subject Disposition, Demographic and Medical History

Tables of summary data reflecting subject disposition including the number of subjects randomized, the number of subjects receiving study drug, the number of subjects in each analysis set, and the number of subjects withdrawing early including the reasons for early withdrawal will be tabulated by dose group and overall.

Summaries of baseline demographic data and medical history, and baseline infection status will also be provided.

15.7.3 Analysis of Key Efficacy Endpoints

Continuous key efficacy endpoints will be summarized via the mean, standard deviation (SD), median, minimum, maximum, and the number of subjects with observed data by dose group and overall. Categorical key efficacy endpoints will be summarized via the number and percent

(proportion) of subjects within each category. Where feasible, 95% confidence intervals will also be provided. Summary measures where the mite is the unit of analysis will be identified. Due to the possible lack of independence between scabies mites observed within the same subject, where possible, "robust" standard errors and/or estimates resulting from models accounting for the clustering will be presented along with any unadjusted estimates.

For the key efficacy endpoints, the PPAS will be used as the primary analysis set. If the FAS differs from the PPAS, sensitivity analyses using the FAS may also be conducted to assess differences between the two analysis sets.

For continuous subject level endpoints such as the average proportion of dead adult scabies mites per subject, pairwise comparisons between dose groups may be conducted using an unpaired t-test or nonparametric Wilcoxon Rank-Sum Test if the assumptions of the t-test do not appear to hold.

Binary endpoints at the subject level such as clinical cure rates may be examined via logistic regression models or chi-square tests with estimates of the relative risk and their associated 95% confidence intervals. Where appropriate exact methods will be employed.

Point estimates and confidence intervals for the mortality rates when the scabies mite is the unit of analysis will be estimated using a logistic regression model with "robust" standard errors. Additionally, the analysis of these data using a Generalized Linear Mixed Models (GLMMs) with random intercepts or a Generalized Estimating Equation (GEE) model may be employed. The time-to-death for an individual scabies mite may be analyzed using a frailty survival model.

Because of the small sample sizes, it is recognized that convergence or estimation issues may arise for some of more complex exploratory models that may be conducted.

Further details will be provided in the SAP.

15.7.4 Analysis of Pharmacokinetics

Non-compartmental analysis (NCA), using Phoenix WinNonlin version 6.4, or *post-hoc* model-based exposure estimates will be implemented for the calculation of pharmacokinetic parameters as appropriate. The C_{max} will be excluded from all estimations of elimination rate constants for NCA. 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 pharmacokinetic parameters for moxidectin in plasma will be summarized and listed by treatment group, including mean, geometric mean, SD, median, and range, as appropriate.

15.7.5 Analysis of Pharmacokinetics/Pharmacodynamics

Exposure metrics, including C_{max} and AUC, and pharmacodynamic data will be pooled across the study. The relationship between efficacy endpoints and plasma concentrations of moxidectin for all subjects in the PKPDAS will be assessed graphically using scatterplots or box plots, as appropriate to the pharmacodynamic endpoint. pharmacokinetic/pharmacodynamic analysis techniques will be applied as appropriate. For example, logistic regression or time-to-event modelling approaches may be applied to examine pharmacokinetic/pharmacodynamic where a binary pharmacodynamic outcome variable is desired. Alternatively, analysis of continuous pharmacodynamic data may use nonlinear or quantile regression response (E_{max}).

If deemed appropriate at the conclusion of the study, an existing moxidectin population-pharmacokinetic model will be updated with the pharmacokinetic data from this study to enable formal comparison of the moxidectin pharmacokinetic characteristics observed within the scabies patient population to other populations administered moxidectin. Where appropriate, this refreshed

population-pharmacokinetic model will then be linked to critical pharmacodynamic responses observed during the study to enable selection of dose regimens for future clinical studies by clinical trial simulations.

15.7.6 Analysis of Safety

15.7.6.1 Treatment Emergent Adverse Events

Subject incidence of treatment emergent adverse events (TEAEs) will be summarized by dose group and overall using the SfAS. Events will be categorized by body system and preferred term. AEs will also be summarized by severity, investigator assessment of relationship to study drug, serious events, and events leading to withdrawal or death. Line listings of all TEAEs will be provided.

15.7.6.2 Laboratory Assessments

Summary statistics at each time point and changes from Baseline will be provided by dose group and overall for laboratory assessments. For continuous assessments, means, SDs, medians, minimums and maximums will be provided. For categorical assessments, the number and percent of subjects in each category will be provided. Shift tables may also be calculated. All laboratory assessments will be included in line listings. Further details will be provided in the SAP.

15.7.6.3 Vital Signs and Physical Exams

The analysis of vital signs and physical exams will be similar to laboratory assessments.

15.7.7 Other Efficacy Analysis

Other efficacy analyses will be documented as part of the SAP.

15.7.8 Exploratory Analyses

The general analysis of the exploratory endpoints will follow similar analyses to those outlined above for the key efficacy endpoints. Further details will be provided in the SAP along with the scoring methodology for patient-reported outcome instruments.

15.7.9 Handling of Missing Data

In general, data will not be imputed except for the imputation of partial start and stop dates for AEs and concomitant medications. If an AE or medication cannot be identified as a TEAE or a concomitant medication because of a missing or partial date, the dates will be imputed using a pre-specified algorithm for the purpose of making the assignment.

Description of missing data and the potential impact on study results and interpretation particularly as it relates to key safety or efficacy assessments may be made with special attention to missing data associated with COVID-19.

Details will be provided in the SAP.

16 GENERAL STUDY ADMINISTRATION

16.1 Ethical Aspects

16.1.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the protocol, the latest version of the Declaration of Helsinki (and its amendments), and with the requirements of national drug and data protection laws of the countries in which the research is conducted.

The Sponsor and the Investigators will ensure strict adherence to the provisions of GCP and all applicable and national regulations. The International Conference on Harmonization (ICH) guidelines will apply at a minimum.

16.1.2 Informed Consent

A model informed consent form template is provided in Appendix 18.2 for the preparation of the informed consent document to be used at sites. The written informed consent document should be prepared in the language(s) of the potential subject population.

It is the responsibility of the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study prior to undertaking any study related procedures. The Investigator must also explain to the subject that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. The Investigator must use an Institutional Review Board (IRB) or IEC-approved consent form for documenting written informed consent.

16.1.3 Institutional Review Boards or Ethics Committees

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent), will be submitted to an IEC. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Investigator specifying the protocol number and version and the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IEC approval must also be submitted to the committee in accordance with institutional procedures and regulatory requirements.

When no local review board exists, the Investigator is expected to identify an appropriate review board for submission.

16.1.4 Conditions for Modifying the Protocol

Protocol modifications to ongoing studies which could potentially adversely affect the safety of participating subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated or subject selection criteria, may be made only after issue of a protocol amendment by the Sponsor and approval at the site. No prospective protocol waivers will be permitted in the study.

Protocol modifications (amendments) must be prepared by a representative of the Sponsor and initially reviewed and approved by the responsible Medical Monitor and (when applicable) the Statistician.

All protocol modifications must be submitted to the IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

In the event of an emergency, the Investigator may institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor, the Medical Monitor and the IEC.

A protocol deviation is defined as any change from the Sponsor and IEC-approved protocol, regardless of whether it has been prospectively approved by the Sponsor or IEC. Protocol deviations that avoid or reduce an immediate hazard to trial subjects do not require prior approval. Administrative changes of the protocol are defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, or on the safety of the subjects. These administrative changes will be agreed upon by the Sponsor and the Investigator, and will be documented in a memorandum. The Investigator will then notify the IEC of such administrative changes.

16.1.5 Conditions for Terminating the Study

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests.

16.2 Study Documentation, Case Report Forms and Record Keeping

16.2.1 Investigator's files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: (1) Investigator's Site File, and (2) subject clinical source documents.

The Investigator's Site File will contain the protocol/amendments, CRFs and Query Forms, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrolment log, etc. All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e. USA, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The Investigator must notify the Sponsor prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

16.2.2 Background Data

The Investigator shall supply the Sponsor, on request, with any required background data from the study documentation or clinic records. This is particularly important when CRF are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

16.2.3 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representative or to regulatory authority or health authority inspectors after appropriate notification. The verification of the CRF data may be by direct inspection of source documents (where permitted by law) or through an interview technique.

16.2.4 Case Report Forms

CRFs (paper or electronic format) must be completed for each subject enrolled, and signed by the Principal Investigator or co-Investigator. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. The CRF is essentially a data entry form and should not constitute the original, or source document.

Data collection and entry into the CRF will be completed by authorized study site personnel designated by the Investigator. Appropriate training will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the CRF for any study participants.

All data must be entered in English. The CRFs should always reflect the latest observations on the participants participating in the trial and are to be completed as soon as possible after the participant's visit. The Investigator must verify that all data entries in the CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the CRF.

The CRFs and the protocol are confidential. The CRFs remain the property of the Sponsor at all times.

16.3 Monitoring the Study

Before the start of the trial, a representative of the Sponsor or designee will contact the investigational site to ensure facilities are adequate and discuss responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements.

During the trial, a representative from the Sponsor or its designee will regularly visit the site to monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support as needed.

In accordance with ICH GCP guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

It is understood that the responsible monitor, as the Sponsor representative, will contact and visit the Investigator regularly and that he/she will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data

being entered on them. Where local regulations permit, the monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16.4 Confidentiality of Trial Documents and Subject Records

The Investigator must assure the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by the subject's initials and an identification code. The Investigator should keep a subject enrolment log showing codes, names and addresses. Documents not for submission to the Sponsor (e.g. subject's written consent forms), should be maintained by the Investigator in strict confidence.

All information concerning the study treatment and the Sponsor and its operation, 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 study and will not use it for any other purposes without written consent from the Sponsor.

16.5 Publication of Data and Protection of Trade Secrets

In accord with standard editorial and ethical practice, the Sponsor will support publication of multicenter trials only in their entirety and not as individual center data.

The Sponsor will list the study on a public database listing of clinical trials, for example, www.clinical trials.gov.

The results of this study may be published or presented at scientific meetings. If this is envisaged, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Any formal publication of the study in which input of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate the Sponsor personnel. Authorship will be determined by mutual agreement prior to the completion of the study.

16.6 Anticipated Subject Accrual and Duration of the Study

The anticipated patient accrual will be agreed at the site initiation visit. The Investigator should continually compare the actual and expected accrual rates, and make every effort to ensure that they are as closely matched as possible. If the Investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the Sponsor as early as possible.

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18 APPENDICES

18.1 Toxicity Grading Scale

The FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials is available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977

Tables from the guidance are presented for reference.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mmHg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/24 hours	4 – 5 stools or 400 – 800 g/24 hours	6 or more watery stools or > 800 g/24 hours or requires outpatient IV hydration	ER 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	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
				with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

18.2 Model Patient Information Sheet and Consent Form

Title	A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies
Protocol Number	MDGH-MOX-2001
EudraCT Number (if required)	*[Insert EudraCT Number]*
Study Sponsor	Medicines Development Limited (trading as Medicines Development for Global Health)
Coordinating Principal Investigator/ Principal Investigator	*[Insert Investigator Name]*
Associate Investigator(s) (if required by institution)	*[Associate Investigator(s)]*
Study Site	*[Site name]*

This Participant Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Consent Form (for signatures if you agree to take part)**

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

Participant Information Sheet

PART 1 WHAT DOES MY PARTICIPATION INVOLVE?

1. INTRODUCTION

You are invited to take part in this research study because you are aged 18 years or over and your doctor has diagnosed you with scabies infection. The research study is testing a new experimental medicine called moxidectin for the treatment of scabies.

This Participant Information Sheet and Consent Form tells you about the research study. It explains the treatment and tests involved. This will help you decide if you want to take part in the research. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will still receive the best possible care.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

If you decide you want to take part in the research, you will be asked to sign the Consent Form. By signing it you are telling us that you:

- Understand what you have read
- Consent to taking part in the research study

- Consent to having the tests and treatments that are described
- Consent to the use of your personal and health information as described

2. WHAT IS SCABIES?

Scabies is an infection of the skin. It is caused by tiny mites that burrow just under the surface of the skin and can cause itch, rash and skin sores. Scabies can be found all over the world: the World Health Organization has estimated that approximately 130 million people worldwide currently have scabies. Anyone can get scabies. You can become infected with the scabies mite from any infected people you have had contact with or from clothing and other surfaces.

3. WHAT ARE THE CURRENT TREATMENTS FOR SCABIES?

Scabies is treated with a cream that contains a medicine called permethrin (*as appropriate to the site: Lyclear®/Topiscab®*). Permethrin cream is applied to the skin from head to toe, left on over-night and washed off the next morning. The cream works well but if it is not applied thoroughly, some people can continue to have scabies. Scabies is also treated with another medicine available in tablet form called ivermectin. This is taken by mouth and is also very effective, but a second treatment is needed about one or two weeks after the first to kill all the mites.

4. WHY ARE YOU BEING ASKED TO PARTICIPATE IN THIS STUDY?

You are being asked to take part in what is called a Phase 2 clinical trial. We are doing this research study to find out if moxidectin can be used to treat scabies and also to find the best dose of moxidectin to treat it.

5. WHAT IS MOXIDECTIN?

Moxidectin is an experimental medicine and has not been approved for treatment of scabies anywhere in the world. However, it is believed that moxidectin may be useful as it is used in many countries to treat the scabies mite that infects animals.

Moxidectin is from a class of drugs called “macrocyclic lactones” which includes ivermectin, the treatment for scabies mentioned before. Moxidectin 8 mg as a single dose has been approved by the United States Food and Drug Administration for the treatment of river blindness (also known as onchocerciasis), a disease found in Africa and Latin America caused by a parasitic worm.

6. WHERE IS THIS STUDY BEING CONDUCTED AND HOW MANY PEOPLE ARE TAKING PART?

This study is being conducted at approximately 4 hospitals in France and Australia. Up to approximately 36 people are going to take part.

7. WHO IS BEING ASKED TO TAKE PART?

People aged 18 years old and above who are known or suspected to have scabies are being asked to take part in this research study.

8. DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

No. Your participation in the study is voluntary and it is up to you to decide whether or not to take part. If you decide to take part and later change your mind, you are free to withdraw at any time. This will not affect your future treatment, or your relationship with your local doctor or the study doctor or other staff at the clinic. Your study doctor will discuss available treatment options with you before you decide to take part in this research study. You can also discuss the options with your local doctor and anyone else you choose.

9. HOW DO I KNOW IF I CAN TAKE PART?

Your doctor and the clinic team will check if you are eligible to take part in the study, also known as screening. You will be asked questions about your health and previous treatments by the doctor and/or study team, who will also examine you and take blood tests to see if you are eligible to take part. Your doctor will explain all results and let you know if you are eligible. If not, they will discuss your alternative treatment options with you.

10. WHAT ARE THE TREATMENTS IN THE STUDY?

Because we don't know which dose of moxidectin is best to treat scabies, this study compares different doses of moxidectin. If you agree to participate and are eligible for the study, you will be allocated by chance (called "randomization") to receive either 2 mg, 8 mg or 20 mg moxidectin as a single dose. You have an equal chance of receiving any one of these three doses. During this research study, a committee of experts not directly involved in the study will review all the available information to see whether or not the doses are working. The committee could suggest that we make no changes to the study, or that we change the study by removing one of the original three doses and/or adding an extra dose. If they choose to add a dose, a 36 mg single dose of moxidectin may be included. About 6 people will be included in each group so your chance of being allocated to a group might be adjusted to allow for that. Results from the participants in each dose group will be compared to choose the dose of moxidectin that works the best to treat scabies.

This is a double-blind study, which means that neither you, your doctor/clinical staff, nor the staff from Medicines Development for Global Health will know which dose you are receiving. However, if an emergency occurred and your study doctor needed to do so, he/she can find out which treatment you are receiving.

Moxidectin will be given to you as tablets that you swallow. Because the study is blinded, everyone will be required to take the same number of tablets. The maximum number of tablets you could receive is 18 tablets. You will only take the tablets once. Moxidectin tablets contains 2 mg of moxidectin so you might take a mixture of moxidectin and placebo tablets. A placebo is a dummy tablet with no active ingredients. It looks like the real thing but is not. This is to make sure the dose is hidden.

This research study has been designed to make sure the researchers interpret the results in a fair way.

11. WHAT DOES TAKING PART IN THIS RESEARCH STUDY INVOLVE?

If you wish to take part, you will be asked to provide written consent to take part before any study assessments are performed. You should take your time, feel no pressure to take part, and ask any questions you would like to. You should also feel free to discuss this study with anyone of your choosing.

Once you have consented to take part, you will be checked for eligibility. Screening may take up to 7 days. If you are eligible, study assessments will take place over 12 weeks. During that time, you will be asked to come to the clinic 8 times. On the day you receive treatment, you will stay in the clinic for approximately 9 hours (called Day 0). You will then come back to the clinic each day for the next three days (Days 1, 2 and 3) for approximately 2 hours each time. You will then come back to the clinic on Days 7, 14 and 28, and Week 12 for approximately 1 to 2 hours. The visits and assessments are being done to answer the research questions and are not usually done to manage scabies infection.

Two different pieces of equipment will be used to look at the scabies mite in your skin:

- Looking at the location of the scabies infection with a low-power hand-held microscope called a "dermatoscope", which allows the doctor to see the scabies mite and your skin in more detail. This will be used once on the day you receive treatment, then once 3, 7, 14 and 28 days after you receive treatment. Photographs of the scabies mite will be taken with this microscope.
- Use of a higher powered microscope called a "reflectance confocal microscope". This microscope allows the doctor to look into the skin at the scabies mite using a safe, low power laser. Using this microscope causes no pain. This will be performed twice on the day you receive your treatment, once daily for the next three days, then once 7, 14 and 28 days after treatment. Photographs of the scabies mite will be taken using this microscope.

The study doctor will also map where scabies symptoms occur on your body and take close up photographs of the body areas where there is a scabies infection. Scabies symptoms can include rash, redness and scratch marks. This will be done before treatment and 7, 14 and 28 days after treatment. These photographs will be carefully taken to make sure you cannot be identified. If you have scabies mite infection on your groin, breasts and/or face, photographs here are optional: you will be asked by your doctor if you consent to have photos taken of these locations and you may decline to have these photos taken at any time.

You will also be required to give blood. The blood is taken to measure the amount of moxidectin in your blood, to monitor the safety markers in your blood, and to collect plasma for potential development of a test to diagnose scabies. On the first day of treatment blood will be taken several times. To make this easier, the study team will insert a temporary access called a cannula (a thin plastic tube placed in a vein in your arm). You will also give blood once daily for the next three days, then once 7, 14 and 28 days after treatment. About 125 mL (or about half a cup) of blood will be collected over the whole study. In comparison, a standard blood donation is about 470 mL.

You will be asked to complete several questionnaires about your symptoms and how these affect your daily life. This will take place before treatment and 7, 14 and 28 days after treatment. If you need it, an interpreter can assist you with answering these questionnaires.

More details of each assessment are provided below.

Screening (up to 7 days before study drug dosing)

Estimated duration: 3 hours

The study doctor or study team members will explain the aims of the study including the risks and benefits involved and the fact that your participation is voluntary. If you decide to be assessed for inclusion in the study, you will be asked to provide written informed consent by signing the Consent Form at the end of this document.

The study doctor will discuss the eligibility criteria with you, and then confirm that you have scabies by examining your skin with a dermatoscope and reflectance confocal microscope. If you have scabies and the minimum number of visible scabies mites required to participate, the study doctor will do a physical exam and measure your blood pressure, temperature, heart rate, breathing rate, height and weight. The study doctor will also conduct an electrocardiogram to measure the activity of your heart. You will be asked questions about your medical history, your current health and any medicines you are taking, including herbal preparations and vitamins. Blood samples will be collected using a needle and syringe (about 12 mL or about 3 teaspoons of blood) and prepared for testing for hematology and clinical chemistry (tests of general health and wellbeing also known as 'safety blood tests'). If you are a female participant, a pregnancy test will be conducted.

Your eligibility for the trial is dependent on the number of scabies mites in your skin and the results of these eligibility assessments. If you are not eligible to take part, you will be offered the current standard of care treatment for scabies. Your doctor or study team member will let you know if you are eligible for the study and discuss these options with you.

Day 0

Estimated duration: 9 hours

Before treatment

You will be asked to stop eating and drinking from midnight the night before you come to the clinic and until 2 hours after you have taken your treatment. This means you will not be allowed to eat any foods or drink, including alcohol, coffee, tea and other drinks. However, you can drink as much water as you would like. Two hours after you have taken your allocated treatment, you will be served breakfast at the clinic.

At this visit, the study doctor will examine you and measure your blood pressure, temperature, heart rate and breathing rate. You will be asked questions about your health and use of medicines since the previous visit. Blood samples will be collected using a needle and syringe (about 8 mL or about 2 teaspoons of blood) or using a cannula and prepared for testing the quantity of moxidectin in your blood and storage of a sample.

The study doctor will examine your skin with the dermatoscope and reflectance confocal microscope. The study doctor will select at least two but no more than four areas on your skin that contain scabies mites that will be examined at each visit. The study doctor will perform an assessment of your symptoms, which will involve looking at your whole body (including groin and nipple region, with your permission) and making a record of the location of symptoms. Photos will be taken of the regions showing signs and symptoms of scabies such as rash or scratch marks.

You will be asked to complete three questionnaires designed to measure how itchy you are and the impact scabies has had on your life.

After treatment

You will be required to stay in the clinic for a further 8 hours. Four more blood samples to test for the quantity of moxidectin will be taken (about 32 mL or about 8 teaspoons of blood). Once the last sample is taken, the cannula (if used) will be removed. The study doctor will do two more examinations with the reflectance confocal microscope of the areas containing scabies mites they chose before treatment. Your blood pressure, temperature, heart rate and breathing rate will also be measured once during this time. After the last blood sample and microscope assessment is performed, you may leave the clinic.

Day 1 (24 hours), 2 (48 hours), 3 (72 hours), 7, 14 and 28.

Estimated duration: 2 hours each visit

You will need to come back to the clinic at these times. At these visits, you will be asked questions about your health and use of medicines since the previous visit.

- At each visit, you will be asked questions about how you feel and your use of medicines since the previous visit.
- The study doctor may examine you and will measure your blood pressure, temperature, heart rate and breathing rate.

- Blood samples will be also taken to test for the quantity of moxidectin and to measure safety markers in your blood. Over all these visits, about 75 mL of blood will be taken (about 20 teaspoons).
- The study doctor will examine the areas of your skin selected before treatment with the reflectance confocal microscope. On Day 3, this exam will also use the dermatoscope. In addition, on Days 7, 14 and 28 only, the study doctor will perform an assessment of your symptoms, which will involve looking at your whole body (including groin and nipple region with your permission) and making a record of the location of symptoms. Photos will be taken of the regions showing signs and symptoms of scabies such as rash or scratch marks.
- Also on Days 7, 14 and 28 only, you will be asked to complete three questionnaires designed to measure how itchy you are and the impact scabies has had on your life.

Week 12

Estimated duration: 1 hour

You will be asked to come back 12 weeks after treatment for a final follow up visit. You will be asked questions about your health and use of medicines since the previous visit. The study doctor will perform a symptom-based physical examination and measure your blood pressure, temperature, heart rate, breathing rate and weight. If you are a female participant, a pregnancy test will be conducted.

12. COSTS AND COMPENSATION

There are no cost to you for taking part in this research study. All medication, tests and medical care that are part of the research study will be provided to you free of charge. The Sponsor, Medicines Development for Global Health, will pay for this.

If you are eligible for the study, and you take the treatment and complete the study, you will be compensated up to *$XXXX [dependent on the site]*. If you withdraw before the end of the study, you will be compensated as follows *[pro-rated payments description]*. Your costs for reasonable travel, parking, meals and other expenses will also be paid back to you.

If your screening results show that you are not eligible for the study or you withdraw prior to taking the study tablets, you will receive no payment. If you wish to withdraw from the study before completion, or if the study doctor decides that it is in your best interests to withdraw from the study, the amount of the payment will be adjusted based on how long you took part and which visits you completed.

13. IF WE FIND A MEDICAL CONDITION OF WHICH YOU WERE UNAWARE

If during the course of the study the study team uncovers a medical condition of which you were unaware, we will refer you to your primary care doctor for follow up and advice on next steps.

14. YOUR RESPONSIBILITIES AND RESTRICTIONS

It is desirable that your local doctor be advised of your decision to take part in this research study. If you have a local doctor, your study doctor will notify them of your taking part unless you object to this.

You will need to attend the clinic at the times and on the study days outlined above.

You should notify the study team in advance of your visits if you are experiencing symptoms that suggest a COVID-19 infection, or if you know you have been in contact with someone with COVID-19. You may be required to follow site-specific instructions to manage the risk of

COVID-19 spread, including wearing a mask and maintaining an appropriate level of social distance from other patients and clinic staff.

If you choose to take part in this study, you must observe the following restrictions:

Medicines

Whilst you are taking part in this research study, you may not be able to take some or all of the medications or treatments you have been taking for scabies or for other reasons. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research study.

In most cases you can take your regular medication. There are some exceptions:

- For the duration of the study, you must tell the study doctor or study staff about any medicines that you may be taking, including prescription or over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research study.
- You must not take any other treatments for scabies during the course of the study.
- You must not take any other treatments for parasites during the course of the study.
- You must not take any antihistamines during the study.
- You must not use any medicated topical lotions (or similar) during the study. These lotions include any that contain zinc, tar, calamine or salicylic acid.

Contraception

If you or your partner are able to become pregnant you must agree to use reliable contraception during the course of the research study and for a period of 3 months after completion of the study visits (24 weeks total). You should discuss methods of effective contraception with your study doctor.

Blood Donation

You must not donate blood or plasma during the study.

Assessment Sites

You must try to avoid scratching your skin at the places where you are infected with scabies, especially where your study doctor has chosen to examine these areas using the reflectance confocal microscope. The study doctor will show you these at the beginning of the study.

15. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

This is a research study. Therefore, it is not known if moxidectin will be useful in treating your scabies infection. We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include:

- You will have a medical visit which will include a physical examination, vital signs measurements and blood tests to determine your current state of health with respect to study criteria.
- The study doctor will closely follow up whether treatment gets rid of the scabies mite. If it does not, you will be offered other treatments as soon as possible, and you will be offered a clinic recall 1 week after to check this alternative treatment has worked.
- If you choose, you will have support to ensure your home is free of scabies mites. This may include cleaning services to help with washing sheets, towels and clothing used in the days

before treatment, placing mattresses, pillows and blankets in the sun and thoroughly vacuuming the house and furniture.

- Treatment will be offered to the members of your household and other close contacts at no additional cost. Treatment of your close contacts will help reduce the risk that you become infected again.
- Information found during this study may be helpful in developing future treatment options for scabies.

16. WHAT ARE THE POSSIBLE RISKS AND DISADVANTAGES OF TAKING PART?

Side effects

Almost all medicines cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, please speak with your study doctor.

Your safety will be closely monitored throughout the study and your study doctor will also be looking for side effects of treatment. Tell your study doctor immediately about any new or unusual symptoms that you get. Many side effects are temporary. However, sometimes side effects can be serious, long lasting or permanent. There may be side effects that the researchers do not expect or do not know about and that may be serious. Your study doctor will discuss the best way of managing any side effects with you.

Moxidectin is a new medicine and therefore all side effects are not known. Common side effects of moxidectin reported in healthy volunteers and onchocerciasis patients are listed below. In most cases, side effects were mild, went away on their own and lasted less than a week. No person who has received moxidectin has withdrawn from any clinical study due to side effects.

This list is not a complete list of possible side effects. Side effects may occur almost immediately after the drug is administered, or days later. Side effects that are unknown at this time may occur. As information becomes available, you will be told of any newly identified risks that may affect your willingness to participate in the study. Your doctor will provide further information about the events below.

Side effects in healthy volunteers

Moxidectin has been given to 260 healthy volunteers at doses between 3 mg and 36 mg. The most common side effects, reported by 3% of participants or more were:

- Headache
- Rhinitis (stuffy nose)
- Flu like symptoms
- An upset stomach (nausea and diarrhea)
- Dizziness

Most of these side effects were mild.

Side effects in patients with onchocerciasis (a parasitic worm infection present in African and Latin American regions)

The most common side effects reported in patients with onchocerciasis were those often seen when they receive a treatment for onchocerciasis. These side effects are due to allergic reactions caused by the worms dying in the skin and eyes as a result of treatment and are unlikely to be the same for people with scabies.

Side effects that occurred in more than 10% of onchocerciasis patients were:

- Changes to the proportions of white blood cells, including increases in the number of cells called eosinophils and decreases in the number of cells called lymphocytes and neutrophils
- Pruritus (itching)
- Pain (including muscle pain, joint pain, general body pain, abdominal pain and lymph node pain)
- Headache
- Tachycardia (an increased heart rate, including when people went from laying down to standing)
- Rash
- Hypotension (reduced blood pressure, including when people went from laying down to standing).
- About 5% of patients reported feeling dizzy or light-headed and needed support during a test where they lay down for 5 minutes and then stood up. This was most common 1-2 days after treatment and went away when they lay down again.
- Fever and chills
- Influenza (flu) like illness
- Cough
- Dizziness
- An upset stomach, including diarrhea, gastroenteritis and enteritis
- Reduced concentration of salt in the blood
- Swelling of the limbs

Some onchocerciasis patients had side effects in their eyes, including pain and/or discomfort, itching, blurry vision, red eyes and conjunctivitis (a bacterial infection of the eye). Between 1% and 8% of patients with onchocerciasis treated with moxidectin experienced these side effects.

Between 1% to 3% of onchocerciasis patients had changes to their liver function tests, including increases in some liver enzymes called AST, ALT and GGT and a product called bilirubin. Most of the increases were temporary.

There is a risk that patients who are infected with a parasite called *Loa loa* develop serious or even fatal brain injury after taking moxidectin. *Loa loa* is only found in certain parts of West and Central Africa including Cameroon, Democratic Republic of Congo, Gabon and Nigeria. If you have been to any of these areas you should tell the study doctor as you may need a test to confirm it is safe for you to take part in this study.

Side effects in patients with scabies

Moxidectin has not been given to people with scabies. However, one of the most common side effects of other treatments for scabies is a temporary worsening of itch over one to two weeks. This has been reported following treatment with permethrin and ivermectin.

Blood tests

Having blood taken may cause some discomfort, bruising, minor infection at the needle site or bleeding. If this happens, it can be easily treated. There is also a small risk of a fainting episode, which can occur as a reaction to having blood drawn.

Pregnancy

The effects of moxidectin on the unborn child and on the newborn baby are not known. Because of this, it is important that research study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research study. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and having a child is a possibility, you will be required to undergo a pregnancy test prior to commencing the research study and at the end of the study. If you are male, you should not father a child or donate sperm for at least 6 months after the dose of study medication.

Both male and female participants must agree to use reliable contraception during the course of the research and for a period of 6 months after you have taken the study medication. You should discuss methods of reliable contraception with your study doctor.

If you are a female participant and you do become pregnant whilst participating in the research study, you should advise your study doctor immediately. Your study doctor will withdraw you from the research study and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

If you are a male participant, you should advise your study doctor if you father a child while participating in the research study. Your study doctor will advise on medical attention for your partner should this be necessary.

17. WHAT WILL HAPPEN TO MY TEST SAMPLES?

By consenting to take part in this study, you also consent to the collection, storage and use of your blood samples. This is a mandatory part of the study. During the course of the study blood samples will be taken on 12 occasions. The total volume of blood taken for the entire study will be about 125 mL (about half a cup). In comparison, one standard blood donation is 470 mL. Your blood samples are anonymous and will only be labelled with your unique study number (but not your name).

Collected blood samples will be used to check your general health at screening and throughout the study. Your blood samples will also be used to prepare plasma (the clear liquid that carries red and white blood cells) to measure the quantity of moxidectin in your blood throughout the study. Samples of your plasma obtained for the purpose of this research study will be transferred to an analytical laboratory working on behalf of the study Sponsor to measure moxidectin in your blood. This laboratory may be located in another country to the clinic where you are assessed.

Your blood samples will not be sold by the Sponsor or any third party contractors. A sample of your plasma will also be used to look for markers of scabies infection for development of tests that could help with diagnosis of the disease. Examples of such tests include looking for biomarkers of an immune response to the scabies mite (called an antibody test). Development of such a test would make it easier for doctors to correctly diagnose scabies because it is a disease that can be confused with others. Your stored samples will be used or destroyed no later than 2 years after the completion of the study. Your samples will not be used for any genetic testing.

18. WHAT IF NEW INFORMATION ARISES DURING THIS RESEARCH STUDY?

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research study. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research study you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research study. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

19. WHAT IF I WITHDRAW FROM THIS RESEARCH STUDY?

You can withdrew from this research study at any time. If you decide to withdraw from the study, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. You may be withdrawn from the study if the doctors feel it is best for you or if you do not comply with the requirements of the study.

If you do withdraw your consent during the research study, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research study can be measured properly and to comply with local and international law. You should be aware that data collected by the Sponsor up to the time you withdraw will form part of the research study results. If you do not want them to do this, you must tell them before you join the research study.

20. COULD THIS RESEARCH STUDY BE STOPPED UNEXPECTEDLY?

Yes, this is possible. This research study may be stopped unexpectedly for a variety of reasons which may include unacceptable side effects, or for reasons made in the commercial interests of the sponsor, or by local regulatory/health authorities.

21. WHAT HAPPENS WHEN THE RESEARCH STUDY ENDS?

At the final study visit 12 weeks after treatment, you will be asked about any symptoms that might suggest a new scabies infection. If you do show signs of infection, you will be offered [*the standard of care*], and instructed how to use it by the study doctor. You will not receive further doses of moxidectin after your first treatment. You will also be asked about your health and any medications you have taken since the last visit.

Once all the participants have completed treatment in the study, the treatment blind will be broken. This means that the treatment each participant was taking and the results of the testing done can be analyzed together. The results of the analysis will be published.

PART 2 HOW IS THE RESEARCH STUDY BEING CONDUCTED?

1. WHAT WILL HAPPEN TO INFORMATION ABOUT ME?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research study. Any information obtained in connection with this research study that can identify you will remain confidential and will not be made publicly available. Your information cannot be used for any purposes except those clearly indicated within this consent form and will only be used for the purpose of this research study.

As applicable for EU GDPR regulations:

Any data transferred to destinations outside the European Economic Area (EEA) will be protected in a manner that is consistent with how personal data is protected in the EEA. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. We will only retain your personal data for

as long as necessary to fulfil the purpose for which it was collected or to comply with legal or regulatory requirements.

Your health records and any information obtained during the research study are subject to inspection (for the purpose of checking that the study is conducted correctly and to ensure the accuracy of the study information) by relevant regulatory authorities, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA), and authorized representatives of the Sponsor, Medicines Development for Global Health, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. These people are all required to maintain confidentiality by the nature of their work, or are bound by confidentiality agreements.

While participating in this study, the study doctor will replace your name with a special code that identifies you. This code, along with your study information, will be used by the study sponsor, Medicines Development for Global Health and their representatives, for the study purposes mentioned above and to help establish whether the study drug is safe and effective. Study Information, your study code, and samples collected as part of this study will be included in secure electronic trial systems. By signing the Consent Form, you authorize release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research study will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research study may be recorded in your health records.

In accordance with relevant *[country]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

A description of this clinical trial may be available on http://www.clinicaltrials.gov, as required by US laws. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

2. COMPLAINTS AND COMPENSATION

In cases of trial related injury or if you require any more information concerning the trial and your rights and obligations as a clinical trials subject you should contact the study doctor. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

Complaints

If you have a concern about any aspect of this study, you should ask to speak with the study doctor who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the *[site complaint procedure]*. Details can be obtained from the hospital.

Harm

If you suffer any injuries or complications as a result of this research study, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. The Sponsor adheres to [*local guidelines*] for an injury resulting from participation in a company

sponsored study which provides for medical treatments and/or compensation in the event of injury as a result of your participation in this trial in compliance with local applicable laws and regulations. Provided the study medication was administered in accordance with the study protocol, you will be covered by the Sponsor's insurance.

3. WHO IS ORGANIZING AND FUNDING THE RESEARCH?

This research study is being conducted by [*Investigator name*] and sponsored by Medicines Development for Global Health. The research is being funded by Medicines Development for Global Health.

Medicines Development for Global Health may benefit financially from this research study if, for example, the study assists Medicines for Global Health to obtain approval for moxidectin as a new treatment for scabies.

By taking part in this research study you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Medicines Development for Global Health.

You will not benefit financially from your involvement in this research study even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to Medicines Development for Global Health. In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Medicines Development for Global Health, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

The Sponsor of this study will pay the research unit for conducting the study. No member of the research team will receive a personal financial benefit from your involvement in this research study (other than their ordinary wages).

4. WHO HAS REVIEWED THE RESEARCH STUDY?

All research involving humans is reviewed and approved by an independent group of people called an Independent Ethics Committee (IEC), also known as [*local ethics committee name – Human Research Ethics Committee (HREC) or Comité de Protection de Personnes (CPP)*]. The Committee consists of a number of medical staff (hospital consultants, GPs, nurses and pharmacists) and lay members whose expertise is not in the field of medicine.

This study has also been reviewed and approved by the local agency responsible for the standards of safety, quality and performance of medicines.

This research will be conducted in accordance with the International Council for Harmonization Guideline for Good Clinical Practice version E6(R2), which is an international ethical and scientific quality standard developed to protect the interests of people who agree to participate in clinical studies. This research will also be conducted in accordance with any local standards that govern the conduct of clinical trials.

This clinical trial is being conducted under the regulatory requirements of [*local regulatory agency - the Australian Therapeutic Goods Administration or L'Agence nationale de sécurité du médicament et des produits de santé*].

5. FURTHER INFORMATION AND WHO TO CONTACT

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any side effects), you can contact the principal study doctor on *[phone number]* or any of the following people:

Clinical contact person (available 24 hours)

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email address]

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email address]

If you have any complaints about any aspect of the study, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing Independent Ethics Committee (IEC) approving this research and IEC Executive Officer details

Reviewing IEC name	[Name of IEC]
IEC Executive Officer	[Name]
Telephone	[IEC Executive Officer Phone number]
Email	[IEC Executive Officer Email address]

Local IEC Office contact (Single Site -Research Governance Officer)

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email address]

CONSENT FORM

Title	A Phase II, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies
Protocol Number	MDGH-MOX-2001
EudraCT Number (if required)	*[Insert EudraCT Number]*
Study Sponsor	Medicines Development Limited (trading as Medicines Development for Global Health)
Coordinating Principal Investigator/ Principal Investigator	*[Insert Investigator Name]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the study.

I voluntarily consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research study
- Other research that is closely related to this research study
- Any future research.

I voluntarily give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease and treatment for the purposes of this study. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant *(to be completed by participant)*	Date *(DD MMM YYYY)* *(to be completed by participant)*	Signature

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor†	Date *(DD MMM YYYY)*	Signature

† A senior member of the research team must provide the explanation of, and information concerning, the research study.

Note: All parties signing the consent section must date their own signature.

18.3 Summary of Protocol Amendments

18.3.1 Protocol version 2 (incorporating Amendment 1), dated 26 Aug 2019

Rationale for Amendment 1: Protocol MDGH-MOX-2001 is amended at the request of the French national competent authority (Agence Nationale du Securité du Medicament; ANSM) during their 14 Aug 2019 review letter concerning the clinical trial application for this protocol.

Table 12 Amendment 1 Administrative Protocol Amendments

Section	Original Text	Revised to Read	Rationale for Change
Page size	Nil	Nil	Paper size now letter format to reflect Sponsor style guide, pagination automatically amended accordingly
Cover page, Sponsor signature page	Version 01 07 Nov 2018	Version 2 (incorporating Amendment 1) 26 Aug 2019	Version number and date updated to indicate protocol amendment
Footer	MDGH-MOX-2001 Protocol final v01	MDGH-MOX-2001 Protocol final v2 (incorporating Amendment 1)	Version number updated to indicate protocol amendment
Footer	07 Nov 2018	26 Aug 2019	Date updated to reflect protocol amendment date
Footer	Page I – Page XII	Page 1 of 86 – Page 12 of 86	Page number format updated for reviewer clarity
Table of Contents	Nil	List of Figures	List added for document navigation for reviewer clarity
Table of Contents	Nil	List of Tables	List added for document navigation for reviewer clarity
Appendix 17.1	Table 9 Tables for Clinical Abnormalities, Table 10 Tables for Laboratory Abnormalities	A Tables for Clinical Abnormalities, B Tables for Laboratory Abnormalities	Table numbering amended to reflect format of guidance document for reviewer clarity

Table 13 Amendment 1 Formal Protocol Amendments

Section	Original Text	Revised to Read	Rationale for Change
Section 11.3.3.1 All Serious Adverse Events	Nil	[redacted]	Email to Sponsor Safety Desk added at ANSM request.

18.3.2 Protocol version 3 (incorporating Amendments 1 and 2), dated 19 Jun 2020

Rationale for Amendment 2: Protocol MDGH-MOX-2001 is amended to permit ongoing data review and provision for doses greater than 20 mg. The protocol is amended to include a Protocol Steering Committee and the addition of a 36 mg dose cohort, should there be evidence that the current maximum dose (20 mg) has inadequate efficacy.

Table 14 Amendment 2 Administrative Protocol Amendments

Section	Original Text	Revised to Read	Rationale for Change
Cover page	Medicines Development Limited (trading as Medicines Development for Global Health)	Medicines Development for Global Health	Amended to reflect Sponsor name change
Cover page	Nil	EudraCT Number: 2019-001775037	Addition of European Clinical Trials database number per convention
Cover page	2 (incorporating Amendment 1) 26 Aug 2019	3 (incorporating Amendments 1 and 2)	Protocol version and date updated to reflect amendment
Confidentiality Statement	*Sponsor*	Medicines Development for Global Health	Correction of typographical error
Study acknowledgement	Version 2 (incorporating amendment 1), 26 Aug 2019 Sally Kinrade Vice President	Version 3 (incorporating amendments 1 and 2), 19 June 2020 Mark Sullivan Managing Director	Protocol version and date updated to reflect amendment Administrative update
Footer	MDGH-MOX-2001 Protocol final v2 (incorporating Amendment 1)	MDGH-MOX-2001 Protocol final v3 (incorporating Amendments 1 and 2)	Version number updated to indicate protocol amendment
Footer	Page X of X	Page X	Page numbering format updated for reviewer clarity
Footer	26 Aug 2019	19 Jun 2020	Date updated to reflect protocol amendment date
Section numbering	14 to 17	15 to 18	Section numbering revised due to inclusion of new Section 13.
Table of Contents, List of Tables	NA	NA	Updated to incorporate new sections and tables

Table 15 Amendment 2 Formal Protocol Amendments

Section	Original Text	Revised to Read	Rationale for Change
Throughout	NA	NA	Correction of minor grammatical and/or typographical errors, text edited for clarity.
Protocol Synopsis			
Number of Subjects	Approximately 18 subjects will be enrolled	A maximum of approximately 36 subjects will be enrolled	The Protocol Synopsis is updated to reflect changes in Protocol version 3. See corresponding Protocol sections for rationale.
Number of Centers	Up to four	Approximately four	
Design Details and Dose Regimens	Three cohorts of six subjects per cohort are planned. Subjects will be randomized 1:1:1 to receive 2, 8 or 20 mg moxidectin as a single oral dose. All subjects will receive 10 tablets comprised of moxidectin 2 mg tablets and matched placebo if required to maintain the blind.	Initially, three cohorts of approximately six subjects per cohort are planned. Subjects will be randomized 1:1:1 to receive 2, 8 or 20 mg moxidectin as a single oral dose. Once approximately three subjects have been recruited to these three dose cohorts, a Protocol Steering Committee will evaluate the unblinded safety and efficacy data and recommend: • Continuation of the study with no dose modification to the target sample size of 6 subjects per cohort; or, • Stopping recruitment of one of more of the current dose cohorts; and/or, • The addition of a 36 mg dose cohort. Once the Committee has made their recommendation, randomization will continue into the same or revised dosing regimens with a final target sample size of 6 subjects per arm. Subjects may receive a maximum of 18 tablets comprised of moxidectin 2 mg	

Section	Original Text	Revised to Read	Rationale for Change
		tablets and matched placebo to maintain the blind.	
Data Safety Monitoring Board (DSMB)	As safety of single doses up to 36 mg in adults has been demonstrated in previous clinical trials, a DSMB will not be convened for this study	NA (Section deleted)	Section deleted due to inclusion of Protocol Steering Committee
Protocol Steering Committee	NA (New section)	A Protocol Steering Committee will maintain oversight on emerging efficacy and safety data to ensure that the study meets its objective to identify a well-tolerated and optimally effective dose of moxidectin for scabies.	The Protocol Synopsis is updated to reflect changes in Protocol version 3. See corresponding Protocol sections for rationale.
Exclusion Criteria 2.	Diagnosis of crusted/Norwegian scabies	Diagnosis of crusted/Norwegian scabies or scabies that, in the opinion of the Investigator, would require treatment with more than one standard of care (e.g. scabies requiring concurrent topical and oral treatment).	
Exclusion Criteria 7 [New criteria]	NA	Body Mass Index over 35 kg/m^2	
Exclusion Criteria 10 [11]	Use of systemic steroids within 14 days of Screening, or history of prolonged use of systemic and/or high-dose inhaled corticosteroids	Use of systemic steroids within 14 days of Screening, or history of prolonged use of systemic and/or high-dose inhaled corticosteroids, or use of topical steroids for 7 out of the 14 days prior to Screening	
Exclusion Criteria 12 [NA]	Received a vaccination within 28 days of Baseline	NA (Criteria deleted)	
Sample Size Determination	No formal sample size calculations were performed for this study. Dose cohorts of n = 6 are considered to be practical and adequate to provide information for the full characterization of pharmacokinetics across the dose range of 2 mg to 20 mg.	No formal sample size calculations were performed for this study. Dose cohorts of approximately n = 6 are considered to be practical and adequate to provide information for the full characterization of pharmacokinetics across the dose range.	
Statistical analyses	All statistical analyses will be prospectively described in full in a statistical analysis plan, prior to unblinding of treatment and analysis of the study data	All statistical analyses will be prospectively described in full in a statistical analysis plan which will be finalized prior to breaking the blind for the final analysis.	

Section	Original Text	Revised to Read	Rationale for Change
Table 1 footnote	safety 12-lead ECG (if not done at D3)	safety 12-lead ECG	Error corrected as the protocol does not require an ECG to be conducted at D3.
Protocol			
5.3.1.3 Toxicology	NA (New paragraph)	There are adequate nonclinical safety margins determined in oral acute (single dose) safety pharmacology and chronic (repeat dose) toxicology studies in relation to the use of moxidectin doses in humans up to a maximum of 36 mg. These margins were determined to be greater than one for the majority of studies, regardless of whether margins were calculated with dose or exposure parameters. Consistent with these safety margins, existing safety data from the clinical trials conducted to date do not suggest any dose limiting toxicities following administration of single oral moxidectin doses up to and including 36 mg (Section 5.3.2.2)	Paragraph added to provide an overview of nonclinical safety margins relative to the proposed maximum 36 mg dose in humans.
5.3.2.2.1 Overview of Safety in Healthy Volunteers	NA (New section)	See Section 5.3.2.2.1	Addition of new section to provide an expanded summary of safety of Phase I studies conducted in healthy volunteers, and to provide additional detail regarding safety outcomes in the Phase I two healthy volunteer studies which included the 36 mg dose. Additional tables (Table 3, 4 and 5) are included to provide summary safety data of healthy volunteer exposure to doses between 3 mg and 36 mg and summaries of adverse events reported in studies with the 36 mg dose.
5.3.2.2.3 Safety and Efficacy in Scabies	No patients with *S. scabiei* infestation have been treated with moxidectin	This is the first study of moxidectin in patients with *S. scabiei* infestation	Text updated to reflect the enrolment and completion of two subjects with scabies under Protocol version 2

Section	Original Text	Revised to Read	Rationale for Change
			(dated 26 Aug 2020) at the date of Protocol version 3 (19 June 2020).
5.4.2 Dose Selection	The minimal and optimal effective doses (MED and OED) of moxidectin to treat human scabies are not known. Previous clinical studies have examined the safety of single moxidectin doses up to 36 mg, which were well-tolerated in healthy volunteers. Therefore, taking into account existing moxidectin exposure margins, model-based estimations of human moxidectin pharmacokinetic and pharmacokinetic data from the porcine scabies model, single oral moxidectin doses of 2 mg, 8 mg and 20 mg per oral will be evaluated in this study in order to establish the MED and OED. A single oral dose was selected as the long terminal half-life (t1/2) of moxidectin is expected to provide adequate exposure coverage for the entire life cycle of the scabies mite and eliminate hatching mites. The lowest dose (2 mg per oral) was chosen as this dose was shown to be effective at eliminating microfilariae in onchocerciasis patients. The efficacy of the 2 mg moxidectin dose in onchocerciasis provides evidence of its activity in the skin, a target organ of both onchocerciasis microfilariae and scabies mites. The highest dose (20 mg per oral) was selected as this is similar on a weight for weight basis to the dose shown to be effective against S. scabiei in the porcine model of scabies. In this model, scabies-infected pigs were administered 300 µg/kg moxidectin per oral, equivalent to a 21 mg dose in a 70 kg human. The mid dose of 8 mg per oral was chosen as this is the approved dose for moxidectin in the treatment of onchocerciasis	The minimal and optimal effective doses (MED and OED) of moxidectin to treat human scabies are not known. Previous clinical studies have examined the safety of single moxidectin doses up to 36 mg, which were well-tolerated in healthy volunteers (Section 5.3.2.2.1). Taking the available clinical data into account as well as existing moxidectin exposure margins, model-based estimations of human moxidectin pharmacokinetic and pharmacokinetic data from the porcine scabies model, the range of doses to potentially be evaluated in the current trial will include single oral doses of moxidectin up to a maximum of 36 mg. A single oral dose was selected as the long terminal half-life (t1/2) of moxidectin is expected to provide adequate exposure coverage for the entire life cycle of the scabies mite and eliminate hatching mites. The lowest dose (2 mg per oral) was chosen as this dose was shown to be effective at eliminating microfilariae in onchocerciasis patients. The efficacy of the 2 mg moxidectin dose in onchocerciasis provides evidence of its activity in the skin, a target organ of both onchocerciasis microfilariae and scabies mites. Twenty mg per oral was initially selected as the upper dose for this study as it is similar on a weight for weight basis to the dose shown to be effective against S. scabiei in the porcine model of scabies. In this model, scabies-infected pigs were administered 300 µg/kg moxidectin per oral, equivalent to a 21	Updates were made to this section to provide the rationale for the potential inclusion of a 36 mg dose as the maximum possible dose in the study.

Section	Original Text	Revised to Read	Rationale for Change
		mg dose in a 70 kg human. Although the 20 mg dose may be effective in humans, to robustly determine the OED, additional doses up to a maximum of 36 mg may need to be evaluated. As described in Section 5.3.2.2.1, 36 mg was well tolerated in previous clinical studies and is within the established clinical and nonclinical safety margins for moxidectin	
5.4.3 Study Design Paragraph 2	Therefore, a parallel design has been selected as the doses proposed for evaluation in this study are less than the doses previously studied.	Therefore, a parallel design has been selected as the doses proposed for evaluation in this study will not exceed the doses previously studied.	Clarification that the potential single moxidectin doses in this protocol (2, 8, 20 or 36 mg) are within the doses already included in previous clinical studies of moxidectin, with maintenance of the parallel design of the study.
5.4.3 Study Design Paragraph 4	As pharmacokinetic and pharmacodynamic data will be pooled across the dose cohorts, three dose cohorts of n = 6 subjects spanning 2 to 20 mg will result in 18 individual subject pharmacokinetic exposure profiles. This is considered an adequate range of exposures to allow examination of pharmacokinetic/pharmacodynamic relationships to determine the therapeutic exposure required to effectively treat scabies infestation.	Dose cohorts of approximately 3 to 6 subjects will receive moxidectin doses of 2, 8, or 20 mg. A dose of 36 mg may be added, depending on the pharmacodynamic response observed in the study. The target sample size of the additional dose cohort will be approximately 6 subjects. As pharmacokinetic and pharmacodynamic data will be pooled across the dose cohorts, this design will result in a broad range of individual subject pharmacokinetic exposure profiles. This is considered an adequate range to allow examination of pharmacokinetic/pharmacodynamic relationships and determine the therapeutic exposure required to effectively treat scabies infestation.	Amendment of text for consistency with the design modifications in Protocol version 3 (dated 19 Jun 2020)
5.4.3 Study Design Paragraph 5	Dose cohorts of n = 6 subjects were also considered to be practical for recruitment of the study.	Dose cohorts of approximately 6 subjects were also considered to be practical for recruitment of the study.	Amendment of text for consistency with the design modifications in Protocol version 3 (dated 19 Jun 2020).

Section	Original Text	Revised to Read	Rationale for Change
7.2 Dosing Regimens	Approximately 18 subjects will be randomized 1:1:1 to one of the following treatment regimens: • Moxidectin 2 mg (n = 6) • Moxidectin 8 mg (n = 6) • Moxidectin 20 mg (n = 6)	Initially, subjects will be randomized with a target allocation ratio of 1:1:1 to one of the following single dose treatment regimens: • Moxidectin 2 mg • Moxidectin 8 mg • Moxidectin 20 mg Once approximately three subjects have been recruited to these three dose cohorts and completed their Day 14 visit, a Protocol Steering Committee (see Section 13) will evaluate the unblinded safety and efficacy data and recommend: • Continuation of the study with no dose modification to the target sample size of 6 subjects per cohort; or, • Stopping recruitment of one of more of the current dose cohorts; and/or, • The addition of a 36 mg single dose cohort. Once the Committee has made their recommendation, randomization will continue into the same or revised dosing regimens with a final target sample size of 6 subjects per cohort. It is anticipated that a maximum of 36 subjects will be included in the study.	It was determined that the primary objectives of the study would be better supported if ongoing data review and provision for doses greater than 20 mg were included in the protocol. This section has been expanded to modify the study to include a Protocol Steering Committee and the potential addition of a 36 mg dose cohort, should there be evidence that the current maximum dose (20 mg) has inadequate efficacy. The text also clarifies subject numbers targeted for enrolment in the study.
7.4 Estimated Duration of Study	The study is expected to take approximately 9 months to complete. The on-study period per subject is 13 weeks, consisting of one week for Screening and 12 weeks post-treatment	The study is expected to take approximately 18 months to complete. The on-study period per subject is 13 weeks, consisting of one week for Screening and 12 weeks post-treatment	The duration of the study has been extended due to the predicted extension of recruitment period (as opposed to changes to the Schedule of Assessments). In addition to the potential recruitment of more subjects than the 18 originally targeted, recruitment is expected to be slower than anticipated due to the impact of the COVID-19 pandemic.

Section	Original Text	Revised to Read	Rationale for Change
8.3 Exclusion Criteria	2. Diagnosis of crusted/Norwegian scabies	2. Diagnosis of crusted/Norwegian scabies or scabies that, in the opinion of the Investigator, would require treatment with more than one standard of care (e.g. scabies requiring concurrent topical and oral treatment).	Revised to clarify the exclusion of other severe forms of scabies infestations in addition to the most severe crusted/Norwegian scabies form. Revision was based on Investigator feedback.
8.3 Exclusion Criteria	NA (New criteria)	7. Body Mass Index over 35 kg/m^2.	Moxidectin has been evaluated in subjects populations (of healthy volunteers and onchocerciasis patients) with limited variability in body mass index. This exclusion criteria based on body mass index is added to limit unanticipated pharmacokinetic/pharmacodynamic variability in the exposure parameters and response of subjects to treatment.
8.3 Exclusion Criteria	7 to 10	8 to 11	Numbering of criteria updated to reflect addition of criterion.
8.3 Exclusion Criteria	10. Use of systemic steroids within 14 days of Screening, or history of prolonged use of systemic and/or high-dose inhaled corticosteroids.	11. Use of systemic steroids within 14 days of Screening, or history of prolonged use of systemic and/or high-dose inhaled corticosteroids, or use of topical steroids for 7 out of the 14 days prior to Screening.	Extensive use of topical steroids can change the presentation of scabies and could interfere with efficacy assessments. As topical steroids are readily available over the counter at current study sites, limited or occasional use is not excluded. Addition also based on Investigator feedback.
8.3 Exclusion Criteria	12. Received vaccination within 28 days of Baseline	NA (criteria removed)	Criteria removed as vaccination is not expected to interact with disease presentation or moxidectin pharmacokinetics/pharmacodynamics.
9.2 Visit Windows	Screening must be conducted after informed consent has been given, in the window of Day -7 to Day 0	Screening must be conducted after informed consent has been given, in the window of Day -7 to Day -1	Error corrected for consistency with Schedule of Assessments
9.3.1 Screening Visit	Blood samples drawn for hematology, clinical chemistry (see Section 9.4.6.1) and plasma banking (see Section 9.4.6.3)	Blood samples drawn for hematology and clinical chemistry (see Section 9.4.6.1)	Error corrected for consistency with Schedule of Assessments

Section	Original Text	Revised to Read	Rationale for Change
9.3.2.1 Pre-Treatment	If Screening was conducted more than 48 hours before Baseline, blood samples should also be collected for hematology and clinical chemistry (see Section 9.4.6.1)	If Screening was conducted more than 72 hours before Baseline, blood samples should also be collected for hematology and clinical chemistry (see Section 9.4.6.1)	Clarification to minimize need for extraneous blood draws for safety hematology and biochemistry
9.3.3 On-study Clinic Visits (Hours 24, 48 and 72, and Days 7, 14 and 28)	• Blood samples for: ○ pharmacokinetic assessment at each visit (see Section 9.4.6.3); ○ hematology and clinical chemistry to be performed at Day 7 and Day 28 (see Section 9.4.6.1); ○ plasma for banking to be performed at Day 7 and Day 28 (see Section 9.4.6.3).	• Blood samples for: ○ pharmacokinetic assessment and plasma banking at each visit (see Section 9.4.6.3); ○ hematology and clinical chemistry to be performed at Day 7 and Day 28 (see Section 9.4.6.1).	Error corrected for consistency with Schedule of Assessments
9.3.7 Modification of Scheduled Procedures due to COVID-19	NA (New section)	The safety and wellbeing of research subjects and the study team is paramount. Adherence to official public health guidance, government or site governance directives issued in response to the COVID-19 pandemic should take precedence over the procedures in this protocol. Subjects should be informed of the importance of notifying the study team in advance if they are experiencing one or more symptoms suggestive of SARS-CoV-2 infection or other infectious disease that includes respiratory symptoms, or have been in close contact with someone who is known to have contracted SARS-CoV-2. The Principal Investigator or delegate may advise the subject to present to the relevant health service for further investigation. Subjects who are unwilling or unable to attend clinic visits or complete other trial activities due to the pandemic may be asked to comply with study procedures. However, subjects are entitled to	Addition of new section to provide procedures and guidance in the event issues arise as a consequence of the ongoing COVID-19 pandemic.

Section	Original Text	Revised to Read	Rationale for Change
		withdraw from the study at any time or for any reason and their decision is to be respected. The majority of assessments in this protocol require physical attendance at the clinic. Exceptions may be made at the Investigator's discretion for assessments that are able to be conducted remotely (such as Week 12). If subjects become unable to undertake protocol required assessments due to self-isolation or have been advised to stay away from the clinic, resulting protocol deviations should be documented to enable appropriate evaluation for the study. If biospecimens are collected from subjects known to be actively infected with COVID-19, this information should be noted in the documentation that accompanies any sample transfer activities. In addition to the provisions outlined in Section 14, subjects with missing key efficacy assessments due to COVID-19 may be replaced.	
9.4.4 Vital Signs	Oral body temperature (degrees Celsius [°C])	Oral/aural body temperature (degrees Celsius [°C])	Addition of alternate methodology to take body temperature. Tympanic temperature measurements may be quicker and more comfortable than measuring temperature in the mouth.
9.4.6.1 Safety Laboratory Tests Paragraph 2	Blood samples for hematology and serum chemistry will be collected at Screening, Baseline (before dosing, if Screening samples were collected more than 48 hours before Baseline)	Blood samples for hematology and serum chemistry will be collected at Screening, Baseline (before dosing, if Screening samples were collected more than 72 hours before Baseline)	Change for consistency with Section 9.3.2.1 Pre-Treatment
Table 8 Hematology and Serum Chemistry Tests	Blood urea nitrogen	Blood urea nitrogen or urea	Addition made to include a more common standard test outside of United States-based sites. Blood urea

Section	Original Text	Revised to Read	Rationale for Change
			nitrogen and urea are both considered appropriate tests for kidney function.
9.4.6.3 Pharmacokinetic Samples and Samples for Plasma Banking	For this purpose, plasma will be prepared from blood samples and divided into two aliquots stored at -20°C.	For this purpose, plasma will be prepared from blood samples and divided into two aliquots stored at -20°C or -80°C conditions.	Deletion of temperature requirement as moxidectin in plasma samples is stable when stored at either -20°C and -80°C conditions.
10.1 Randomization Process	Potential subjects who provide written informed consent will be sequentially assigned a Screening Number prefixed by "S" (e.g. S001). A randomization scheme with equal allocation to each of the three (3) moxidectin treatment groups will be prepared in advance by an unblinded statistician otherwise independent of study conduct using a computer-generated system according to relevant SOPs. Treatment packs will be prepared according to the random code by an independent pharmaceutical packaging group and provided to participating sites. Treatment packs will be numbered for sequential allocation to eligible study subjects. Randomization will take place before dosing on Day 0, with equal random assignment to one of the following treatments: • Treatment 1: moxidectin 2 mg (n = 6) • Treatment 2: moxidectin 8 mg (n = 6) • Treatment 3: moxidectin 20 mg (n = 6) Randomization to treatment will be accomplished by sequential assignment of treatment numbers, corresponding to the pre-packaged individual drug supplies provided.	Potential subjects who provide written informed consent will be sequentially assigned a Screening Number prefixed by "S" (e.g. S001). For each site, a randomization scheme with equal allocation to each of the initial three moxidectin treatment groups will be prepared in advance by an unblinded statistician otherwise independent of study conduct using a computer-generated system according to relevant SOPs. Treatment packs will be prepared according to the randomization scheme. Randomization will take place before dosing on Day 0, with equal random assignment to one of the following treatments: • Treatment 1: moxidectin 2 mg • Treatment 2: moxidectin 8 mg • Treatment 3: moxidectin 20 mg Randomization to treatment will be accomplished by sequential assignment of treatment numbers, corresponding to the pre-packaged individual drug supplies provided. Following review of safety and efficacy data by the Protocol Steering Committee (see Section 13 for more information), one or more dose cohort(s) may be discontinued and/or a new 36 mg dose cohort added. If required, the randomization plan will be revised to	Clarification of the randomization process before and after dose modification decisions are made by the Protocol Steering Committee. Section has also been modified to allow adjustment of the randomization process to maintain a final target sample size of 6 subjects per cohort. As this may require implementation of a central randomization scheme, this provision has also been added to the section.

Section	Original Text	Revised to Read	Rationale for Change
		maintain the final target sample size of 6 subjects per cohort. The study may switch from a stratified randomization by site to a central randomization scheme for logistical reasons. This approach would allow greater control over the number of subjects randomized to each dose cohort across all sites. However, random allocation of treatment assignment will be preserved in all cases.	
10.2 Blinding	Neither the subjects nor staff administering the study drug will know the study drug being administered. To maintain the blind, each subject will receive 10 matching tablets in pre-packed bottles. 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.	Neither the subjects, staff administering the study drug nor Sponsor staff directly involved in the conduct of the study will know the dose of study drug being administered. To maintain the blind, each subject will receive the same number of tablets, regardless of dose, in pre-packed bottles. Each bottle will contain moxidectin 2 mg tablets and placebo tablets as required to maintain the blind. 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. A maximum of 18 tablets may be required to blind the doses. Investigational product will be packaged to permit this in line with Section 10.4. The Protocol Steering Committee will be unblinded. No member of the Committee will be directly involved in the day-to-day conduct of the study	Revision and clarification of the section due to the potential addition of the 36 mg dose, which will require the number of tablets increase from a total of 10 to a total of 18 moxidectin 2 mg tablets to administer while maintaining the double-blind design of the study
10.3.1 Medical Emergency Paragraph 1	No open key to the random code will be available to the study centers and Sponsor. Sealed code break envelopes will be held by the clinical site, medical monitor and/or Sponsor. The breaking of the blind will only	No open key to the random code will be available to the study centers and Sponsor. Sealed code break envelopes will be held by the clinical site, medical monitor and/or Sponsor. In an	Revision and clarification of section to align with the opinion of EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG).

Section	Original Text	Revised to Read	Rationale for Change
	be sanctioned where knowledge of the study medication treatment will affect subject management. The Medical Monitor must be consulted prior to the breaking of the blind	emergency, the Investigator or other study team member may need to break the treatment code immediately, or as quickly as possible if this is in the best interest of the trial subject. The breaking of the blind should only occur where knowledge of the study medication treatment will affect the subject's clinical management. The Medical Monitor should be consulted prior to the breaking of the blind.	
10.3.2 End of Study	The randomization code will be broken by the Study Statistician once data entry has been completed, the database locked, and the per-protocol population for analysis established and the Statistical Analysis Plan (SAP) finalized and approved. Sponsor will provide written permission to the Study Statistician prior to the breaking of the randomization code	The randomization code will be broken by the blinded Study Statistician once data entry has been completed, the database locked, and the per-protocol population for analysis established. Sponsor will provide written permission to the Study Statistician prior to the breaking of the randomization code	Minor clarifications to the responsibility and process of unblinding
10.4.2 Packaging and Labelling	Moxidectin will be supplied to the site packaged in 25 cc high density polyethylene bottles each containing 10 tablets.	Moxidectin will be supplied to the site packaged in high density polyethylene bottles	Modification to allow for increased tablet number and alternate pack size.
10.4.4 Dosage and Administration of Test Drugs Paragraph 1	Subject will receive 10 tablets for oral administration. Administration will be observed by clinic staff to ensure compliance.	Subjects may receive a maximum of 18 tablets for oral administration comprised of moxidectin 2 mg tablets and matched placebo to maintain the blind and accommodate the 36 mg dose. Administration will be observed by clinic staff to ensure compliance. This pill burden is considered reasonable for this phase of study. Each moxidectin 2 mg and placebo to match tablet is 100 mg total weight and < 1 cm in length. Eighteen (18) tablets were administered without issue in MDGH MOX 1008, where 60 healthy volunteers received 18 moxidectin 2 mg and/or matched placebo tablets per oral of the current formulation.	Amendment of section to clarify that subjects may receive up to 18 tablets to maintain the blind (increased from 10 tablets), and supplemental information provided on previous clinical experience with this number of tablets.

Section	Original Text	Revised to Read	Rationale for Change
		No acceptability or compliance issues were reported in this study and all subjects were able to (and observed to) swallow the 18 tablets.	
11.2.2 During the Study Dosing Period Paragraph 4	Subjects should not receive supportive therapies to manage their scabies symptoms, including antihistamines, or treatment with other anti-parasitic treatments up to and including Day 28.	Scabies symptoms including pruritus may persist for several weeks after successful treatment of the infestation. Subjects should not receive supportive therapies to manage their scabies symptoms or treatment with other anti-parasitic treatments (in addition to those listed above) up to and including Day 28. Should the subject report scabies symptoms that are intolerable, oral antihistamines may be used at the discretion of the Investigator.	Section amended to more clearly permit the use of antihistamines to manage intolerable or durable symptoms associated with scabies.
11.2.2 During the Study Dosing Period Paragraph 5	Topical steroids and topical preparations containing zinc, calamine, tar or salicylic acid (including medicated emollients) are prohibited after Screening up to and including Week 12.	Topical steroids and topical preparations containing zinc, calamine, tar or salicylic acid (including medicated emollients) are prohibited after Screening up to and including Day 28.	Period during which topical treatments to manage scabies symptoms are prohibited reduced from the 12-week period of the study to the 28-day efficacy period. After Day 28, there are no further efficacy assessments and the prohibition is no longer warranted.
12.3.3.1 All Serious Adverse Events	1) Complete the "Serious Adverse Event Report" 2) Send the completed "Serious Adverse Event Report" to the Sponsor Safety Desk [redacted] within 24 hours of the Investigator's knowledge of the event. Contact details for the Safety Desk can be found in the SRM. 3) For fatal or life-threatening events, also submit copies of hospital case reports, autopsy reports, and other documents when requested and applicable	1) Complete the "Serious Adverse Event Report Form" 2) Send the completed "Serious Adverse Event Report Form" to the Sponsor Safety Desk [redacted] within 24 hours of the Investigator's knowledge of the event. 3) For fatal or life-threatening events, also submit copies of hospital case reports, autopsy reports, and other documents when requested and applicable Additional detail on reporting SAEs is included in the SRM.	Clarification of serious adverse event reporting processes, including clearer reference to the reporting form and where additional contact details may be sought.

Section	Original Text	Revised to Read	Rationale for Change
13 Protocol Steering Committee	NA (New section)	See Section 13	Section added to describe the role, responsibilities and functioning of the Protocol Steering Committee.
(14.1) 15.1 Statistical Methods Paragraphs 1 and 2	The study is a randomized, double-blind proof-of-concept trial designed to describe the association between 3 moxidectin doses and various parasitological outcomes observed over a 28-day follow-up period. Subjects will continue to be followed for safety to Week 12. Following screening, eligible consenting subjects will be randomized to one of three moxidectin dose groups, 2, 8, and 20 mg, administered orally in 10 tablets. The primary objective of this proof of concept study is to identify an optimal dose of moxidectin for further study. The sample size, n = 6 per dose group, was selected to be practical and an adequate sample size for full characterization of pharmacokinetic across the dose range of 2 mg to 20 mg. Sample size was not based on formal power considerations with respect to statistical hypothesis testing, and as such, the focus of the statistical analysis will be descriptive and exploratory. Nonetheless, statistical models for estimation and hypothesis testing to assess various parasitological assessments with respect to dose may be conducted. It is recognized that the sample size may not adequately support more complex models. When this is the case it will be noted. Given the exploratory nature of the study, no adjustment for multiple comparisons will be made.	The study is a randomized, double-blind, proof-of-concept trial designed to describe the association between single moxidectin doses and various parasitological outcomes observed over a 28-day follow-up period. Subjects will continue to be followed for safety to Week 12. Following Screening, eligible consenting subjects will be randomized to one of the 3 initial moxidectin dose groups, 2, 8, or 20 mg. The randomization will be stratified by site and within each site subjects will be randomized using a 1:1:1 allocation ratio. After review of the accumulating data by the Protocol Steering Committee, the randomization scheme may be modified to accommodate the addition or deletion of doses such that the final target sample size of 6 subjects per dose retained/added after the unblinded data review is accommodated. The primary objective of this proof of concept study is to identify an optimal dose of moxidectin for further study. The target sample size, n = 6 per completed dose group, was selected to be practical and an adequate sample size for full characterization of pharmacokinetic profile across the dose ranges studied. Sample size was not based on formal power considerations with respect to statistical hypothesis testing, and as such, the focus of the statistical analysis will be descriptive and exploratory. Nonetheless, statistical	Revisions made to accommodate the potential addition of the 36 mg dose and unblinded data review by the Protocol Steering Committee.

Section	Original Text	Revised to Read	Rationale for Change
		models for estimation and hypothesis testing to assess various parasitological assessments with respect to dose may be conducted. It is recognized that the sample size may not adequately support more complex models. When this is the case it will be noted. Given the exploratory nature of the study, no adjustment for multiple comparisons or Protocol Steering Committee data reviews will be made. Given the small sample size per dose group, descriptive analyses per site may be difficult to interpret.	
(14.2) 15.2 Hypothesis	Study data will be analyzed in a descriptive manner with the objective of observing an exposure-response association between the three moxidectin dose groups and parasitological outcomes and/or observing a single exposure or dose that appears to have the "best" parasitological effect while maintaining an acceptable safety profile	Study data will be analyzed in a descriptive manner with the objective of describing an exposure-response association between the moxidectin dose groups and parasitological outcomes and/or observing a single exposure or dose that appears to have the "best" parasitological effect while maintaining an acceptable safety profile	Revision for clarification of text.
(14.3) 15.3 Sample Size Determination	The sample size chosen for this study, n = 6 subjects per dose group, was selected to be practical and an adequate sample size for full characterization of pharmacokinetic across the dose range of 2 mg to 20 mg. Sample size was not based on formal power considerations with respect to statistical hypothesis testing.	The sample size chosen for this study, approximately 6 subjects per dose group, was selected to be practical and an adequate sample size for full characterization of pharmacokinetics profile across the dose ranges studied. Sample size was not based on formal power considerations with respect to statistical hypothesis testing	Amendment of text for consistency with the design modifications in Protocol version 3 (dated 19 Jun 2020).
(14.5.1) 15.5.1 Protocol Steering Committee Data Review	NA (New section)	No formal interim analysis is planned. The Protocol Steering Committee will review unblinded safety and efficacy data as described in Section 13 and with the ability to make dose modification recommendations. The analyses to be	Addition of section to describe the functioning of the Protocol Steering Committee data review.

Section	Original Text	Revised to Read	Rationale for Change
		conducted during these interim reviews may entail review of individual subject line listings and/or aggregate data. Since the study is exploratory and not powered to conduct hypothesis testing, no adjustments to the type I error rate will be implemented. Further details will be provided in the SAP and Protocol Steering Committee Charter.	
(14.5.2) 15.5.2 Final Analysis Paragraph 1	No interim analysis is planned. For purposes of statistical analysis, this study is divided into two study periods	For purposes of final statistical analysis, this study is divided into two study periods	Part of paragraph moved to Section 15.5.1
(14.5.2) 15.5.2 Final Analysis Paragraph 3	Further details of analysis will be provided in the SAP	Efficacy and safety data obtained for subjects randomized to all doses, including doses that may have been discontinued or added based on the recommendation from the Protocol Steering Committee, will be included in the final analysis. Further details of analysis will be provided in the SAP.	Addition of text to clarify that the final statistical analysis will incorporate data reviewed by the Protocol Steering Committee and any doses modified as a result of the Protocol Steering Committee review.
(14.7.9) 15.7.9 Handling of Missing Data Paragraph 2	NA (New paragraph)	Description of missing data and the potential impact on study results and interpretation particularly as it relates to key safety or efficacy assessments may be made with special attention to missing data associated with COVID-19.	Paragraph added to clarify that data missing due to the COVID-19 pandemic may be described and assessed for impact during data analysis.
(15.1.2) 16.1.2 Informed Consent Paragraph 1	A model informed consent form template is provided in Appendix 18.2 for the Investigator to prepare the informed consent document to be used at their site. The written informed consent document should be prepared in the language(s) of the potential subject population.	A model informed consent form template is provided in Appendix 18.2 for the preparation of the informed consent document to be used at sites. The written informed consent document should be prepared in the language(s) of the potential subject population.	Clarification to align with processes at sites where the preparation of informed consent documents is a shared responsibility between Sponsor and Investigator.
(15.1.3) 16.1.3 Institutional Review Boards or Ethics Committees Paragraph 1	This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent),	This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent), will be submitted to an IEC.	Clarification to align with processes at sites where ethics committee submissions are made by parties other than the Investigator.

Section	Original Text	Revised to Read	Rationale for Change
	will be submitted, by the Investigator, to an IEC		
(15.1.3) 16.1.3 Institutional Review Boards or Ethics Committees Paragraph 2	Any modifications made to the protocol after receipt of IEC approval must also be submitted by the Investigator to the committee in accordance with institutional procedures and regulatory requirements	Any modifications made to the protocol after receipt of IEC approval must also be submitted to the committee in accordance with institutional procedures and regulatory requirements	Clarification to align with processes at sites where ethics committee submissions are made by parties other than the Investigator.
Model Patient Information Sheet and Consent Form			
Section 6 Where is this study being conducted and how many people are taking part?	This study is being conducted at approximately 4 hospitals in France and Australia. Approximately 18 people are going to take part.	This study is being conducted at approximately 4 hospitals in France and Australia. Up to approximately 36 people are going to take part.	Amended to reflect increase in subject numbers under Protocol version 3 (dated 19Jun 2020)
Section 10 What are the treatments in the study	Because we don't know which dose of moxidectin is best to treat scabies, this study compares different doses of moxidectin. If you agree to participate and are eligible for the study, you will be allocated by chance (called "randomization") to receive either 2 mg, 8 mg or 20 mg moxidectin as a single dose. You have an equal chance to receive any one of these doses. Results from the participants in each dose group will be compared to choose the dose of moxidectin that works the best to treat scabies. This is a double-blind study, which means that neither you, your doctor/clinical staff, nor the staff from Medicines Development for Global Health will know which dose you are receiving. However, if an emergency occurred and your study doctor needed to	Because we don't know which dose of moxidectin is best to treat scabies, this study compares different doses of moxidectin. If you agree to participate and are eligible for the study, you will be allocated by chance (called "randomization") to receive either 2 mg, 8 mg or 20 mg moxidectin as a single dose. You have an equal chance of receiving any one of these three doses. During this research study, a committee of experts not directly involved in the study will review all the available information to see whether or not the doses are working. The committee could suggest that we make no changes to the study, or that we change the study by removing one of the original three doses and/or adding an extra dose. If they choose to add a dose, a 36 mg single dose of moxidectin may be included. About 6 people will be included in each group so your chance of	Amendment of text for consistency with the design modifications in Protocol version 3 (dated 19 Jun 2020)

Section	Original Text	Revised to Read	Rationale for Change
	do so, he/she can find out which treatment you are receiving. Moxidectin will be given to you as tablets that you swallow. Because the study is blinded, everyone will be required to take 10 tablets. You will only take the 10 tablets once. Moxidectin tablets contains 2 mg of moxidectin so if you are allocated to either the moxidectin 2 mg or 8 mg groups, you will take a mixture of moxidectin and placebo tablets. A placebo is a dummy tablet with no active ingredients. It looks like the real thing but is not. This is to make sure the dose is hidden. Each treatment group will receive the following tablets: • 2 mg moxidectin: 1 x 2 mg moxidectin tablet and 9 x placebo tablets • 8 mg moxidectin: 4 x 2 mg moxidectin tablets and 6 x placebo tablets • 20 mg moxidectin: 10 x moxidectin tablets and no placebo tablets	being allocated to a group might be adjusted to allow for that. Results from the participants in each dose group will be compared to choose the dose of moxidectin that works the best to treat scabies. This is a double-blind study, which means that neither you, your doctor/clinical staff, nor the staff from Medicines Development for Global Health will know which dose you are receiving. However, if an emergency occurred and your study doctor needed to do so, he/she can find out which treatment you are receiving. Moxidectin will be given to you as tablets that you swallow. Because the study is blinded, everyone will be required to take the same number of tablets. The maximum number of tablets you could receive is 18 tablets. You will only take the tablets once. Moxidectin tablets contains 2 mg of moxidectin so you might take a mixture of moxidectin and placebo tablets. A placebo is a dummy tablet with no active ingredients. It looks like the real thing but is not. This is to make sure the dose is hidden.	
Section 14 Your responsibilities and restrictions Paragraph 3	NA (New paragraph)	You should notify the study team in advance of your visits if you are experiencing symptoms that suggest a COVID-19 infection, or if you know you have been in contact with someone with COVID 19. You may be required to follow site-specific instructions to manage the risk of COVID-19 spread, including wearing a mask and maintaining an	Addition of paragraph to clarify the patient's responsibilities relative to potential COVID-19 infection, and following protocols in place at sites to manage the risk of COVID-19 infection among patients and staff.

Section	Original Text	Revised to Read	Rationale for Change
		appropriate level of social distance from other patients and clinic staff.	