Medicines Development for Global Health

Clinical Study Protocol

Study Title:	A Phase 2, placebo-controlled, double-blind, randomized, dose ranging, efficacy and safety study of orally administered moxidectin in adults with scabies			
Sponsor:	Medicines Development for Global Health Limited Level 1, 18 Kavanagh Street Southbank, VIC 3006, Australia +61 3 9912 2400			
Investigational New Drug (IND) Number:	138487			
Protocol Number:	MDGH-MOX-2002			
Medical Monitor:	[redacted]			
Protocol Version/Date:	**Current**	3 (incorporating Amendment 1 and 2)	**Date**	28 Dec 2023
	Supersedes version	2 (incorporating Amendment 1)	**Dated**	24 Aug 2023

CONFIDENTIALITY STATEMENT

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

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MEDICINES DEVELOPMENT FOR GLOBAL HEALTH

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SOUTHBANK, VIC 3006, AUSTRALIA

STUDY ACKNOWLEDGEMENT

MDGH-MOX-2002

A PHASE 2, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, DOSE RANGING, EFFICACY AND SAFETY STUDY OF ORALLY ADMINISTERED MOXIDECTIN IN ADULTS WITH SCABIES

VERSION 3, 28 DEC 2023

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

[redacted]

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 in accordance with the Declaration of Helsinki (2013), the International Ethical Guidelines for Health-related Research Involving Humans (2016), the International Conference on Harmonization Good Clinical Practice guidelines (ICH E6(R2), 2016), all regional, national, and local laws and requirements, and any updates to these if issued during the course of this study.

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

1 PROTOCOL SYNOPSIS

Protocol Number:	MDGH-MOX-2002
Study Title:	A Phase 2, placebo-controlled, double-blind, randomized, dose ranging, efficacy and safety study of orally administered moxidectin in adults with scabies
Investigational Product:	Moxidectin
Indication:	Treatment of scabies due to *Sarcoptes scabiei*
Development Phase:	Phase 2
Background:	Scabies is a common ectoparasitic skin infestation caused by the mite *Sarcoptes scabiei* variant *hominis* (*S. scabiei* var. hominis). Scabies occurs in all countries, affecting people of all ages. In 2017, the disease was estimated to affect 100 to 200 million people at any time[1] Populations at greatest risk live in socioeconomically disadvantaged settings where access to healthcare is limited or where overcrowding is common. Reflecting its burden in these types of settings, scabies was formally adopted as a neglected tropical disease by the World Health Organization in 2017[2]. The characteristic symptom of scabies is itch accompanied by skin lesions and eruptions caused by a hypersensitivity reaction to the mite's presence in the stratum corneum. Although the symptoms can be variable in severity, the itch is frequently reported to be worse at night and can impact the quality of life of the patient. Burrows are pathognomonic for the disease, and secondary skin lesions include papules, vesicles and nodules which can present with erythema and excoriations. Due to the nature of the disease, post-scabietic itch and skin lesions may persist four to six weeks after effective treatment[3]. There are numerous treatment options for scabies available worldwide, the majority of which are topical options. Ivermectin 200 µg/kg is the only oral treatment for scabies in broad use globally, although it is not approved for this indication in the United States. Although current topical and oral treatments are effective when used as recommended, poor patient compliance and acceptability of topical treatments, and the frequent need to treat patients more than once regardless of whether a topical or oral option is used are barriers to optimal disease control. Therefore, a new treatment modality that enhances patient compliance and simplifies the treatment regimen is needed. Moxidectin has well-established activity against the *S. scabiei* variants responsible for infestations in livestock and companion animals. Moxidectin's partitioning into the subcutaneous fatty tissue and its relatively long half-life after a single oral dose are expected to enable a single treatment to eliminate both mites and their newly hatching offspring in the skin of scabies patients.
Study Rationale	Single moxidectin doses of 8 mg, 16 mg and 32 mg will be evaluated in this study. Selection of the 8 mg starting dose was based on observations of mite mortality at exposures associated with this dose in protocol MDGH-MOX-2001. Two-fold increasing increments of 16 mg

	and 32 mg will ensure sufficient separation in exposures between doses to support broad exploration of the exposure-response surface for the primary endpoint of Complete Cure. Single moxidectin doses up to 36 mg were well tolerated in patients aged 18 years and older with scabies in protocol MDGH-MOX-2001 and in healthy volunteers aged 18 years and older in two Phase 1 studies. This study will compare each of the three moxidectin doses to placebo in outpatients aged 18 years and older with scabies without significant comorbidities to assess the efficacy of moxidectin in achieving Complete Cure by Day 28. A placebo control is included in this trial to establish background cure rates in the absence of clear untreated control data for the disease. There is no evidence from the literature to suggest that there are safety concerns for scabies patients who receive placebo, and standard of care will be available after the Day 28 assessments. All subjects regardless of treatment assignment may experience pruritus, so supportive therapies for symptom management such as unmedicated emollient creams and antihistamines will be allowed for subjects seeking relief from symptoms. *S. scabiei* is highly contagious, and it is common for more than one member of a household to be infested. Because treatment efficacy could be affected by household members with an active but asymptomatic scabies infestation, all members of the household not enrolled in the study must receive treatment with permethrin 5% cream on the same day as the subject (index subject) receives their first dose of investigational product (IP) (Day 0). Only a single index subject from each household may be enrolled in the study.
Study Design:	Multi-country, multi-center, double-blind, parallel, randomized, placebo-controlled.
Number of Subjects:	Approximately 200 subjects.
Number of Centers:	This study will be conducted at approximately 8 to 20 sites internationally, including in the United States and Latin American region.
Design Details and Dose Regimens:	Within each region subjects will be randomized into one of 4 cohorts using an equal allocation ratio: (1) placebo (approximately n=50) (2) moxidectin 8 mg, single dose (approximately n=50) (3) moxidectin 16 mg, single dose (approximately n=50) (4) moxidectin 32 mg, single dose (approximately n=50)
Primary Efficacy Objective:	To compare the efficacy of a single oral administration of moxidectin for each of the three moxidectin doses to matching placebo with respect to the Day 28 Complete Cure rate.
Primary Safety Objective:	To compare the safety of a single oral administration of moxidectin for each of the three moxidectin doses with placebo.
Secondary Objectives:	There are no secondary objectives.

Exploratory Objectives:	The exploratory objectives of the study include but are not limited to:
	• For each of the three moxidectin doses, determine the Day 28 Complete Cure rate.
	• In each of the 4 groups determine:
	  ○ The Day 28 clinical cure rates,
	  ○ The Day 28 combined microscopic and dermatoscopic cure rates,
	  ○ The Day 28 Investigator-assessed Cure rates,
	  ○ The concordance between the Complete Cure rate and Investigator-assessed Cure rate,
	  ○ The change from Baseline in the total number of lesions at Day 28,
	• And assess:
	  ○ Secondary bacterial infection at Day 28,
	  ○ Pharmacokinetics (PK) of moxidectin in a subset of subjects.

Primary Efficacy Endpoint:	The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both: (1) Clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus). and (2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.
Primary Safety Endpoints:	The primary safety endpoints are the incidence and severity of adverse events, changes in electrocardiograms (ECG), in laboratory parameters and changes in vital signs
Secondary Efficacy Endpoints:	None
Exploratory Endpoints:	The exploratory endpoints include but are not limited to: • The proportion of index subjects demonstrating clinical cure without microscopic or dermatoscopic cure at Day 28. • The proportion of index subjects demonstrating microscopic or dermatoscopic cure without clinical cure at Day 28. • The proportion of index subjects demonstrating cure as assessed by the Investigator at Day 28. • The change from Baseline for index subjects in the total number of lesions at Day 28. • The proportion of index subjects with concordant and discordant Day 28 cure rates as assessed by the Investigator and the Complete Cure rate. • The proportion of index subjects with secondary bacterial skin infections at Day 28. • Plasma concentrations of moxidectin in a subset of index subjects selected for sparse PK sampling.

Inclusion Criteria:	1. Aged 18 years or older. 2. Provided written informed consent. 3. Diagnosis of active scabies infestation confirmed by the presence of clinical signs and symptoms (evidence of burrows or typical inflammatory/noninflammatory lesions and pruritus) and either microscopic confirmation of scabies mite(s), ova or scybala by skin scraping or dermoscopy. 4. All female subjects of childbearing potential must agree to the use of a highly effective method of birth control until 16 weeks after administration of IP.
Exclusion Criteria:	1. Diagnosis of crusted/Norwegian scabies or scabies presentation that, in the opinion of the Investigator, would require treatment with more than one standard of care treatment for scabies (e.g., scabies requiring concurrent topical and oral treatment). 2. History of chronic or recurrent dermatologic disease or skin conditions other than scabies that could interfere with the diagnosis of scabies and evaluation of cure. 3. Received any treatment with one or more scabicides within the 28 days prior to Screening, or between Screening and Baseline, including but not limited to permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil or spinosad. 4. Body mass index > 35 kg/m^2. 5. Creatinine clearance < 30 mL/min (using Cockcroft-Gault equation). 6. Both total bilirubin >1.5 x upper limit of normal (ULN) and AST > ULN. 7. Abnormal and clinically relevant findings in hematology or biochemistry assessments at Screening, or in vital signs, 12-lead ECG, or physical examination at Screening and/or Baseline, that in the opinion of the Investigator would put the subjects at increased risk from participating in the study, confound study evaluations, or may interfere with study conduct. 8. 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 in the opinion of the Investigator would put the subjects at increased risk from participating in the study, confound study evaluations, or interfere with the study conduct. 9. Use of topical steroids, systemic or high-dose inhaled corticosteroids (>500 µg per day of fluticasone propionate or equivalent for adults), or other immunomodulators within 14 days of Baseline. 10. Requiring ongoing treatment with, or received within 5 half-lives before Screening, any of the following medications that are clinical BCRP inhibitors: curcumin (turmeric) supplements, cyclosporine A, darolutamide, eltrombopag, febuxostat, fostamatinib, rolapitant and teriflunomide. 11. Received an investigational agent within 28 days of Screening (or 5 half-lives of the investigational agent, whichever is longer). 12. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin or ivermectin. 13. Known or suspected hypersensitivity to any of the components in permethrin 5% cream, to any synthetic pyrethroid or pyrethrin, or to the components of spinosad 0.9% topical suspension. 14. Known, suspected or at risk of *Loa loa* coinfection. 15. Difficulty swallowing tablets or capsules.

<table>
<tr><td></td><td>16. Pregnant or breastfeeding or planning to become pregnant from Screening until 16 weeks after treatment with IP.
17. Known or suspected alcohol or illicit substance abuse.
18. Unwilling, unlikely or unable to comply with all protocol specified assessments.
19. Previous enrolment in this study.
20. Previous moxidectin exposure within 6 months (5 half-lives) from Baseline.
21. Has household members who refuse or are unable to receive permethrin 5% cream treatment for scabies.</td></tr>
<tr><td>Investigational products</td><td>Moxidectin 2 mg tablets. Tablets will be over encapsulated.

Placebo capsules to match over encapsulated moxidectin tablets.</td></tr>
<tr><td>Dosing and Administration:</td><td>Subjects will fast for 8 hours prior to dosing and 60 minutes after dosing. Each subject will receive 16 capsules on Day 0, as shown in the table below. Matching placebo capsules will be given in the number required to match the maximum moxidectin dose and maintain the blind. The placebo cohort will receive only placebo capsules on Day 0.
<table>
<tr><th>Cohort</th><th>Number of moxidectin capsules</th><th>Number of placebo capsules</th></tr>
<tr><td>Moxidectin 8 mg</td><td>4</td><td>12</td></tr>
<tr><td>Moxidectin 16 mg</td><td>8</td><td>8</td></tr>
<tr><td>Moxidectin 32 mg</td><td>16</td><td>0</td></tr>
<tr><td>Placebo</td><td>0</td><td>16</td></tr>
</table></td></tr>
<tr><td>Duration of Study Per Subject:</td><td>Up to 17 weeks</td></tr>
<tr><td>Clinical Procedures and Assessments:</td><td>Subjects who provide voluntary written informed consent will be screened for eligibility. After obtaining written informed consent, the subject will be assessed for findings typical of scabies. A definitive diagnosis of active scabies infestation, e.g., demonstration of mites or mite products, is required for enrolment in the study. If the subject is definitively diagnosed with scabies and meets all the other inclusion and none of the exclusion criteria, they will be eligible for randomization and enrollment into the study. Only one subject will be enrolled per household; where more than one household member is screened for participation in the study, the randomized/enrolled (index) subject will be the youngest eligible member of the household.

For details of study procedures, refer to Table 1. Index subjects will undergo a thorough full-body clinical and microscopic or dermatoscopic assessment by a trained evaluator prior to randomization. They will be randomized to one of the 4 study cohorts on Day 0 after eligibility has been confirmed. Approximately 20 subjects will be randomly selected from each of the 4 cohorts for collection of sparse blood samples for moxidectin PK analysis. Blood samples will be collected from this PK subset at 3 hours (± 30 minutes) and 10 hours (± 2 hours) post dose.

Following randomization and treatment administration on Day 0, all subjects will be contacted by phone by the site study team on Day 7 to enquire about any adverse events, concomitant medications and the subject’s general health. Subjects will return to the clinic on Day 14 for routine safety follow-up including safety hematology and biochemistry tests, assessment for adverse events and concomitant medications,</td></tr>
</table>

	including to support ongoing management of pruritus. On Day 28, subjects will undergo a thorough full-body clinical and microscopic or dermatoscopic assessment by a trained evaluator in-clinic, and blood samples will be collected for the subjects in the PK subset. A complete safety review will also be conducted, including safety hematology and biochemistry tests. If at the Day 28 visit the subject has scabies mites confirmed by microscopy or dermoscopy, or their clinical presentation has significantly worsened from Day 0, the subject will receive standard of care treatment for scabies per local guidelines. All subjects will return on Day 42 for routine safety follow up including assessment for adverse events and concomitant medications. Blood samples will be collected from the PK subset on Day 42. Extended safety follow up will occur for all subjects after Day 42. All subjects will be contacted by phone by the site study team at Week 12 to enquire about any adverse events, concomitant medication and the subject's general health. A routine safety follow up visit will be completed at the end of study at Week 16 including assessment for adverse events and concomitant medications, vital signs and an ECG. If any clinically significant abnormalities are identified in serum chemistry or safety hematology tests at the Day 28 visit, additional blood tests should be completed at Week 16. All adverse events, regardless of severity, causality or seriousness must be reported from commencement of Screening until the end of the study. However, any adverse event that the Investigator believes is at least possibly related to study medication and any serious adverse events ongoing at the end of the study should be followed up until resolution or until the Investigator determines the subject's condition is stable. As subjects with scabies are expected to experience mild to severe pruritus after treatment, the use of unmedicated emollient creams and oral over-the-counter antihistamines is permitted during the study for symptom management. Scabicides and topical over the counter and prescription medications used to manage itching (i.e., containing corticosteroids, ferric oxide, crotamiton, calamine etc.) are prohibited before the Day 28 visit as these may influence or mask the effect of treatment. Subjects should be counselled that post-scabietic pruritus is common for a period of four to six weeks after treatment and that this is not indicative of treatment failure. Explanations of the physiological reasons for the itch should be carefully explained to the subject appropriate to their level of understanding. Subjects should be encouraged to contact the site regarding the choice of any concomitant medication to relieve itch prior to using any such medication. Details of family treatment can be found in the special protocol requirements section at the end of the synopsis.
Specialized Analyses:	None.
Sample Size Determination:	Although the analyses will include an adjustment for region, which may yield smaller variance estimates, the estimated powers and confidence interval widths for the unadjusted risk differences described below are expected to provide reasonable estimates of power and precision. <u>Superiority of Moxidectin to Placebo – Day 28 Complete Cure Rate</u>

	A sample size of 50 subjects per randomized treatment group will yield an approximate power of 75% for the pairwise comparisons of each moxidectin dose group to placebo assuming a placebo Day 28 Complete Cure rate of 40% or less and a moxidectin Day 28 Complete Cure rate of 70% or more. Power calculations for each pairwise comparison were conducted via a Z -test for two independent proportions with pooled variance at a two-tailed adjusted alpha of 0.019. The pairwise adjusted alpha of 0.019 is used to control the familywise error rate (FWER) at an overall two-tailed alpha of 0.05 using a large sample approximation to Dunnett's critical value for the three pairwise comparisons of each moxidectin dose group to placebo.
Statistical Analyses:	**Final Analysis and Extended Safety Follow-Up** The final analysis of efficacy and safety data collected through Day 42 will take place after the last subject has completed the Day 42 visit when PK sampling is complete in the PK subset. Following their Day 42 visit, all subjects will continue to be monitored for safety through the extended safety follow-up period to Week 16, during which the study blind will be maintained for personnel with an operational role in study management. Once the last subject has completed the extended safety follow-up period at Week 16, additional safety analyses will be conducted for data collected during the extended safety period. **Primary Efficacy Analysis: Superiority of Moxidectin to Placebo – Day 28 Complete Cure Rate** The three primary efficacy hypotheses to be tested are the comparison of the Day 28 Complete Cure rates (proportions) for each of three moxidectin dose groups to the placebo group adjusted for region. Each analysis will be conducted as a test of superiority for the marginal risk difference adjusted for region using the standardized estimator as outlined by Steingrimsson et al[4]. Statistical significance will be based on a Dunnett adjusted two-tailed alpha level of 0.019 to account for the multiplicity of the three primary efficacy analyses and maintain a FWER of 0.05. For each comparison Wald type 95% confidence intervals (CI) incorporating Dunnett's critical value will also be calculated using the bootstrapped standard error for the adjusted risk difference. The Day 28 Complete Cure status for subjects exposed to scabicides prior to their Day 28 assessment will be imputed as a non-responder (not cured) for the primary analyses using the Full Analysis Set (FAS). The FAS is defined as all randomized index subjects receiving at least one dose of investigational product. Subjects in the FAS will be analyzed in the treatment group to which they were randomized. Subjects missing Day 28 assessments due to events reasonably considered to be non-informative, e.g., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), will have their Day 28 Complete Cure rate imputed using multiple imputation. Additionally, sensitivity analyses will be conducted assessing the potential impact of missing data on the primary results. Therefore, the estimand for each hypothesis is the Day 28 Complete Cure rate of moxidectin without use of rescue medication versus the Day 28 Complete Cure rate of placebo without use of rescue medication. **Safety Analyses** Safety will be analyzed using the Safety Analysis Set (SfAS) defined as all index subjects exposed to investigational product. For the SfAS, subjects will be analyzed as belonging to the actual treatment received

	regardless of their randomized treatment group. Descriptive safety summaries for each treatment group and overall will be provided for treatment emergent adverse events, ECGs, laboratory parameters, and vital signs. Analyses for the safety data collected during the extended safety follow-up will also be conducted. Details of the above analyses will be specified in the Statistical Analysis Plan (SAP). **Exploratory Pharmacokinetic Analyses** Twenty subjects from each of the cohorts will be randomly selected for sparse PK sampling (PK subset). Listings of individual moxidectin concentration versus time data by dose and mean (± standard deviation) moxidectin concentration versus time data by dose will be reported (tabular and/or figure format).
Special protocol requirement / issues:	If more than one household member is definitively diagnosed with scabies, the index subject is defined as the youngest eligible member of the household. Household members 2 months of age and older and sexual contacts of all enrolled subjects must be treated with permethrin 5% cream on Day 0. Instructions for treatment administration of topical products and household cleaning will be provided orally and in writing. All subjects enrolled in the study will have active management of their pruritus with provision of emollient and instructions to apply liberally and as often as is required. Investigators should not enroll subjects who perceive their itch to be intolerable at Screening, for whom emollients and/or antihistamines is unlikely to provide relief, and/or who are at risk of not being able to complete the study because of intolerable pruritus.

Table 1 Overall Schedule of Assessments

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

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

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

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

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

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

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

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

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

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

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

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

2 TABLE OF CONTENTS

List of Tables

Table of Appendices

3 LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation or Acronym	Definition
°C	degrees Celsius
°F	Degrees Fahrenheit
µg	microgram
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP/ABCG2	breast cancer resistance protein
bpm	beats per minute
CI	confidence intervals
C_{max}	maximum observed plasma concentration
cm	centimeter
CRF	case report form
CSR	clinical study report
CYP	cytochrome
ECG	12-lead electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
FWER	familywise error rate
g	gram
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
h	hour
hERG	human éther-a-go-go
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ISF	Investigators' Site File
kg	kilogram
LDH	lactate dehydrogenase
max	maximum
MDGH	Medicines Development for Global Health
MedDRA	Medical Dictional for Regulatory Activities
mg	milligram
MI	multiple imputation
min	minimum
mL	milliliters
mmHg	millimeters of mercury
mRNA	mitochondrial ribonucleic acid
ng	nanogram
NTD	neglected tropical disease
PAP	Pharmacokinetic Analysis Plan
PK	pharmacokinetic
PPAS	per protocol analysis set
PSRT	Protocol Safety Review Team
RCM	Reflectance confocal microscopy
RD	risk difference
SAE	serious adverse event

Abbreviation or Acronym	Definition
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SE	standard error
SfAS	safety analysis set
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
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WOCBP	woman of childbearing potential

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 ectoparasitic mite *Sarcoptes scabiei* variant *hominis (S. scabiei* var *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[1]. Globally, scabies was responsible for 0.21% of all disability-adjusted life years from all conditions studied in the most recent Global Burden of Diseases study[5]. The highest incidence of the disease occurs in tropical climates in socioeconomically disadvantaged populations, the main risk factors for infestation being poverty and overcrowding[6]. 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)[2]. 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; 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[7].

S. scabiei is contagious, usually spread by direct skin-to-skin contact and occasionally via exposure to bedlinen 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 scabies 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 can appear within 24 to 28 hours in 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 total mite burden in typical scabies infestations per person is thought to be 10 to 15, though hyperinfestation with hundreds of mites has been reported[8,9]. 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, possibly due to an immunodeficiency and consequential inability to control the infestation[10].

A presumptive diagnosis of scabies can 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[11]. 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 scybala (fecal pellets)[11].

5.2 Current Treatment and Unmet Need

Treatment either with a topical acaricide or oral treatment with ivermectin 200 micrograms per kilogram (µg/kg) is the current standard of care for scabies[12], depending on geographic location. Topical treatments, such as permethrin 5% cream and benzyl benzoate 10 to 25% lotion, are the mainstay of treatment. They must be applied to all areas of the skin from head to toe and left on overnight before washing off. The prescribing information states that one application is generally curative but recommends that a second application may be necessary 14 days after the

first application, if there are signs that the infestation persists. 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 200 µg/kg is approved in only a few countries. As ivermectin is not ovicidal, a second dose within 7 to 14 days of the first course is often administered to ensure that hatching mites are also eliminated. 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 contribute to re-infestation of the patient.

The inability to effectively treat scabies contributes to considerable economic burden and health disparities in endemic regions[13,14]. The direct effects of the intense pruritus 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[6,15].

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 (IB). Moxidectin is unapproved for scabies in any country. Moxidectin 8 mg per oral (single dose) has been approved for use in the treatment of onchocerciasis in patients aged 12 years and older by the United States (US) 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).

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 vivo* in a porcine model of human scabies and in other natural *S. scabiei* infestations in farm and companion animals. 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 that macrocyclic lactones exert their efficacy in arachnids in a similar manner to other invertebrates, via glutamate-gated chloride channels.

5.3.1.2 Safety Pharmacology

The safety pharmacology of moxidectin has been assessed *in vitro* using the human éther-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 IB.

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 most 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 IB.

5.3.1.4 Absorption, Distribution, Metabolism and Excretion

The pharmacokinetic (PK) profile of moxidectin in rats and dogs was 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 is a substrate of breast cancer resistance protein BCRP/ABCG2 *in vitro* and in mice. Moxidectin produced weak or no inhibition of seven major human cytochrome (CYP) P450 enzymes *in vitro* but did induce CYP3A4 mitochondrial ribonucleic acid (mRNA) and activity *in vitro*. However, a subsequent clinical study showed that moxidectin was not a CYP3A4 inducer *in vivo* at an 8 mg single oral dose.

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 IB.

5.3.2 Clinical

The moxidectin clinical program encompasses nine completed single oral dose trials spanning Phases 1 to 3 and involving a total of 1904 subjects.

Across six completed Phase 1 studies, 243 healthy volunteers received moxidectin per oral at doses of 3 mg 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 healthy volunteers (protocol 3110A1-100-EU).
- A study of the relative bioavailability of a tablet and a liquid formulation of moxidectin in healthy subjects (protocol 3110A1-101-EU).
- An open-label, single-dose study to evaluate the excretion of moxidectin into the breast milk of lactating, non-breastfeeding women (protocol 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 (protocol 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 (protocol 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 (protocol MDGH-MOX-1008).

Across one Phase 1, one Phase 2 and one Phase 3 study enrolling subjects with onchocerciasis, 1141 subjects received moxidectin per oral at doses of 2 mg to 8 mg while 539 received ivermectin per oral 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 (protocol 3110A1-200-GH; Phase 2).
- A single dose, ivermectin-controlled, double blind, efficacy, safety, and tolerability study of orally administered moxidectin in subjects infected with *Onchocerca volvulus* (protocol ONCBL60801; Phase 3).
- An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in subjects aged 4 to 17 years with (or at risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years (protocol MDGH-MOX-1006).

The safety and efficacy of moxidectin in patients with *S. scabiei* var *hominis* infestation has been evaluated in a Phase 2, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in patients aged 18 years and older with scabies (protocol MDGH-MOX-2001) where 22 subjects received moxidectin per oral at doses between 2 mg and 36 mg.

5.3.2.1 Clinical Pharmacology

Moxidectin displays linear, dose-proportional PK. 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 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

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 PK analyses showed that the long $t_{½}$ was governed by tissue distribution rate-limited elimination.

There were no clinically relevant effects of age, gender, race, weight, renal function, or hepatic function on the PK of moxidectin in the original population PK model developed in healthy volunteers and patients with onchocerciasis aged 18 years and older. Body weight was identified as a key covariate in the current population PK model required to adequately fit the PK data in younger children (4 to 11 years). Administration of moxidectin in a fed state modestly slows absorption and increases bioavailability. Moxidectin has low potential for involvement as a victim or perpetrator in clinically relevant drug-drug interactions.

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.

For more information, please refer to the IB.

5.3.2.2 Clinical Safety and Efficacy

5.3.2.2.1 Overview of Safety in Healthy Volunteers

In 6 studies in healthy volunteers aged 18 years and older, moxidectin was well tolerated when given as a single dose of between 3 mg and 36 mg. There were no treatment or dose related relationships in the incidence, nature, nor 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 (ECG)/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.

One hundred and fourteen (114) healthy volunteers have been administered single moxidectin doses greater than the 8 mg single dose approved for the treatment of onchocerciasis. Of these, 20 subjects have received a single dose of 36 mg moxidectin in two Phase 1 studies, protocols 3110A1-100-EU and 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.

Protocol 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 volunteers aged 18 years and older. 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 $t_{½}$ of moxidectin. Safety laboratory analyses were undertaken, and AEs were reported throughout.

Table 2 summarizes AEs reported by all subjects from dosing to Week 12. Each treatment emergent adverse event (TEAE) 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 2 Number of Subjects (%) with Treatment-Emergent Adverse Events to Week 12 in Study MDGH-MOX-1008

Preferred Term	Treatment N (%)						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	1 (1.7)
Abdominal discomfort	0	0	0	0	0	1 (10)	1 (1.7)
Diarrhea	1 (10)	0	0	0	0	0	1 (1.7)
Medical device site reaction	1 (10)	0	0	0	0	0	1 (1.7)
Aspartate aminotransferase increased	0	0	1 (10)	0	0	0	1 (1.7)
Elevated total bilirubin	0	0	0	0	1 (10)	0	1 (1.7)
Blood cholesterol increased	1 (10)	0	0	0	0	0	1 (1.7)
Neck pain	0	0	0	0	1 (10)	0	1 (1.7)
Arthralgia (hip pain)	1 (10)	0	0	0	0	0	1 (1.7)
Pain in extremity	0	0	0	0	1 (10)	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)
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) or Grade 2 (moderate) in severity, and all AEs were transient and self-limiting. 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 aspartate aminotransferase (AST) and total bilirubin were reported in one subject (moxidectin 16 mg) at Day 22 and one subject (moxidectin 36 mg) at Week 12, respectively. Neither event was considered related to investigational product (IP) by the Investigator. Moxidectin had no statistically nor clinically significant effect on QT interval at any dose. There were also no clinically significant effects of moxidectin at any dose on heart rate, PR and QRS intervals, or abnormal diagnostic statements.

Protocol 3110A-1100-EU was a single-ascending dose, placebo controlled, double blind, safety, tolerability, and PK study of single oral doses between 3 mg and 36 mg. Moxidectin was administered as an oral solution under fed and fasted conditions. Consistent with protocol 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 one subject 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.

Adverse events and laboratory findings reported for each of the completed Phase 1 studies are further summarized in the IB.

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 in these patients. 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 (protocols 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 3). 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 no increased need for medical or therapeutic intervention for management of efficacy-related events with moxidectin when compared to ivermectin.

Table 3 Adverse Reactions Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase 3)

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 protocols 3110A1-200-GH or ONCBL60801. 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 4.

Table 4 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
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

Safety and efficacy of moxidectin in patients aged 18 years and older with scabies was evaluated in protocol MDGH-MOX-2001. Twenty-two subjects were enrolled into four cohorts to receive 2 mg, 8 mg, 20 mg, and 36 mg single doses of moxidectin per oral. All subjects had parasitologically confirmed active *S. scabiei* infestation, defined as the presence of at least two lesions, each containing at least one live (internal and/or external structures discernible by reflectance confocal microscopy [RCM]) adult *S. scabiei* var *hominis* mite. All subjects received a single dose of moxidectin on Day 0, with follow up at hours 4, 8, 24, 48 and 72 and Days 7, 14 and 28 and Week 12. The primary efficacy endpoint was death of the mites, defined as the degradation (loss of internal and/or external anatomic structures) of the adult mite by RCM.

In the 2 mg moxidectin group, no *S. scabiei* mite death was observed between Baseline and Day 28. In the 8 mg, 20 mg and 36 mg moxidectin groups, there was a clear trend for increasing *S. scabiei* mite death over time. Mite mortality was first observed within eight hours of dosing in the 8 mg moxidectin group, and by Day 2 in the 20 mg and 36 mg moxidectin groups. Complete (100%) *S. scabiei* var *hominis* mite mortality was first achieved at Day 14 in the 20 mg moxidectin group, and by Day 28 in the 8 mg and 36 mg moxidectin groups.

Moxidectin was well tolerated, with no treatment-related SAEs reported and no AEs leading to study withdrawal or resulting in death. Every subject reported at least one treatment emergent adverse event (TEAE), and a total of 57 TEAEs were reported in the study. The majority of TEAEs (74%) were considered Grade 1 (mild) in severity, with the remainder (26%) considered Grade 2 (moderate) in severity. Thirty-three (58%) of TEAEs were considered unrelated to IP, with the remaining 24 events (42%) considered related. The most common TEAEs (occurring in 2 or more subjects or occurring more than once in the same subject) are shown in Table 5.

Two SAEs were reported, both occurring in a single subject from the 36 mg moxidectin group (spontaneous miscarriage and uterine bleeding) and both events were considered unlikely related to IP by the Investigator and resolved.

Hematology and biochemistry results generally remained stable over time and similar between dose groups. There were two clinically significant safety laboratory results reported from routine assessments as TEAEs, both occurring in subjects from the 36 mg moxidectin group; hypereosinophilia (Grade 1 [mild], possibly related) and hyperphosphatemia (Grade 1 [mild], not related).

There were no clinically relevant changes in vital signs or physical examination findings observed during the study.

Table 5 Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (MDGH-MOX-2001)

	2 mg moxidectin (n=4)	8 mg moxidectin (n=4)	20 mg moxidectin (n=6)	36 mg moxidectin (n=8)	Overall (N=22)
Preferred Term	**Subjects (%)**				
Total number of subjects with ≥ 1 TEAE	4 (100)	4 (100)	6 (100)	8 (100)	22 (100)
Total number of TEAEs	9	8	15	25	57
Acarodermatitis	2 (50.0)	3 (75.0)	4 (66.7)	5 (62.5)	14 (63.3)
Pruritus	0	0	1 (16.7)	3 (37.5)	4 (18.2)
Eczema	0	2 (50.0)	0	1 (12.5)	3 (13.6)
Rash papular	1 (25.0)	0	0	1 (12.5)	2 (9.1)
Headache	1 (25.0)	0	1 (16.7)	2 (25.0)	4 (18.2)
Insomnia	1 (25.0)	0	1 (16.7)	0	2 (9.1)
Diarrhea	0	1 (25.0)	1 (16.7)	0	2 (9.1)
Nausea	0	1 (25.0)	1 (16.7)	0	2 (9.1)
Dysmenorrhea	0	0	1 (16.7)	0	1 (4.5)

5.4 Rationale

Scabies, as a neglected tropical disease, is relatively poorly characterized and has limited treatment options, the majority of which are topical. Ivermectin 200 µg/kg is the only oral therapy for scabies, but it is not approved for this indication in all regions. Although current topical and oral treatments are effective when used as recommended, poor patient compliance, acceptability of topical treatments, and the frequent need to treat patients more than once regardless of whether a topical or oral option is used are barriers to optimal disease control. A new treatment modality that enhances patient compliance and simplifies the treatment regimen is therefore needed.

5.4.1 Moxidectin

Moxidectin has well-established activity against the *S. scabiei* variants responsible for infestations in livestock and companion animals[16–19]. Moxidectin also has the potential advantage of a longer duration of exposure that may limit the need for a second dose and enable a once only, oral dosing paradigm in humans. Comparison of moxidectin and ivermectin PK in the porcine scabies model indicates that moxidectin has longer persistence in blood and skin compared to ivermectin, providing exposures that may cover the entire mite life cycle including newly hatching offspring in the skin of scabies patients[20].

The single moxidectin doses of 8 mg, 16 mg and 32 mg per oral were selected for further evaluation in this study based on the existing nonclinical and clinical safety, and exposure-response data. This dose range was well tolerated in patients aged 18 years and older with scabies in protocol MDGH-MOX-2001 and in healthy volunteers aged 18 years and older in two Phase 1 studies. Selection of the 8 mg starting dose was based on observations of mite mortality at exposures resulting from this dose in protocol MDGH-MOX-2001. Two-fold increasing increments to 16 mg and 32 mg will ensure sufficient separation in exposures between doses to support broad exploration of the exposure-response surface for the proposed primary Complete Cure endpoint.

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 protocol MDGH-MOX-2002, 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.

5.4.2 Selection of the Placebo Control

This study will compare each of the three moxidectin doses to placebo to establish background Complete Cure rates in the absence of clear untreated control data for the disease. The placebo arm will provide data on the natural course of scabies, which has been poorly defined in the literature, and address subjective elements of symptomology. Several therapies are approved and available for scabies treatment, but data supporting their use are highly variable in quality and consistency: published meta-analyses of historical scabies research has reproducibly found randomized controlled trials have greatly differed in design and execution[12,21,22], with design issues including the absence of blinding or random treatment allocation, and lack of consistency in the definition of the primary endpoint. The uncertainty in the "true" effectiveness of any potential active control poses a significant challenge when designing a comparative study, even when the treatments have been shown to be efficacious in clinical practice. Therefore, a placebo control was selected for this study because active control effect size estimates are not well-supported by the results of historical scabies randomized controlled trials. There is no increased risk to patients of temporary deferral of treatment as long as active pruritus management is undertaken and household contacts are treated. The placebo control presents the most statistically robust method to confirm moxidectin's efficacy.

A conservative estimate of the placebo control cure rate has been proposed by basing this on the two recently completed Phase 3 Natroba® (spinosad) trials which used a topical vehicle control[23]. A meta-analysis of the vehicle control cure rates from these studies, calculated using the non-responder imputation for scabicide exposure, results in a 40% Day 28 Complete Cure rate for placebo. This hypothetical Complete Cure rate is considered conservative as the topical vehicle control contained benzyl alcohol, an ingredient that may have activity against the scabies mite.

There is no evidence from the literature to suggest that there are safety concerns for scabies patients who receive placebo, and standard of care will be available after the Day 28 assessment. All subjects, regardless of treatment assignment, may experience pruritus so supportive therapies for symptom management such as unmedicated emollient creams and antihistamines will be permitted as required for subjects seeking relief from symptoms.

5.4.3 Study Design

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

Scabies occurs in all regions and populations around the world. As the number of subjects required for this protocol precludes recruitment in a single reference site and it is important to evaluate the overall treatment effect based on subjects in all regions, centers in multiple countries are planned. It is planned that centers from the US and Latin America will be included and that no center, country, or regional quotas will be imposed. The prevalence of scabies in the

US is generally considered to be low with higher prevalence observed in settings or countries with socio-economically disadvantaged or vulnerable populations, while Latin American countries are generally considered to have higher disease prevalence[5]. Unless otherwise specified, data will be pooled across regions. There is no data to suggest that the course or severity of disease differs between populations in the US and Latin American target regions, nor that there are any clinically relevant differences in intrinsic and extrinsic factors that would result in clinically meaningful differences in efficacy.

The moxidectin doses proposed for evaluation in this study are within the range of doses previously studied and no subject will receive more than a single oral dose of moxidectin. Only subjects aged 18 years and older will participate in this study as there are limited data on the pediatric use of moxidectin, which has only been administered to subjects ≥ 4 years with, or at risk of onchocerciasis, at an 8 mg single dose per oral. Only one subject will be enrolled per household; where more than one household member is screened for participation in the study, the enrolled (index) subject will be the youngest eligible member of the household.

Efficacy will be determined through assessments of Complete Cure conducted at Day 28. Complete Cure is defined as a combination of clinical cure (all clinical features of the infestation have resolved) and microscopic or dermatoscopic cure (absence of mites and/or mite products and burrows). The presence or absence of mites and/or mite products may be determined either using microscopy of material taken from the skin or dermoscopy as these methods provide the highest degree of diagnostic certainty by direct visualization of the scabies mite, eggs or scybala[11]. The most common method to collect material from the skin is by skin scraping, using a scalpel blade to remove the stratum corneum over a suspected mite. A standard light microscope is used to examine the material. Dermoscopy is performed with a handheld device that permits low-magnification (typically x10) examination of the skin. Microscopy of material collected through skin scrapings, while are 100% specific, can have variable sensitivity as it is dependent on the area selected for scraping and quality of the sample collected. Dermoscopy is less invasive than skin scraping and permits a more thorough inspection of the skin surface for "jet with contrail" signs that are suggestive of the scabies mite being present in the skin and appears to have comparable sensitivity and specificity for scabies[24]. For both methods, sensitivity improves with operator experience and flexibility is offered to ensure sites use the method with the highest sensitivity according to their expertise.

The 28-Day efficacy assessment period will also allow for assessment of clinical signs and symptoms following resolution of infestation. Scabies signs and symptoms result from a sensitization of the host to mite antigens and are known to persist for several weeks after treatment. Twenty-eight days is considered a minimum period for the resolution of all signs and 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 this indication[25]. Due to moxidectin's half-life in healthy volunteers aged 18 years and older, the last study day will be extended from Day 28 to Week 16 for the completion of additional safety assessments. To assist in determining the duration of safety follow-up, PK analyses were performed to describe the time-course of moxidectin exposures in patients aged 18 years and older with scabies. In protocol MDGH-MOX-2001, the mean maximum plasma concentration (C_{max}) was 286 ng/mL and median time to maximum plasma concentration was 3.0 hours. By Day 28, it was 4.14 ng/mL (minimum [min] 2.51 ng/mL; maximum [max] 6.12 ng/mL). The expected moxidectin concentration at Day 42 in healthy volunteers aged 18 years and older, simulated using the moxidectin population PK model, is 3.75 ng/mL (min 0.62 ng/mL; max 9.11 ng/mL). These concentrations are 12- to 18-times lower than the mean C_{max} observed in the healthy

volunteer and scabies patient populations aged 18 years and older after administration of the approved single 8 mg dose per oral and 36- to 76-times lower than the C_{max} of the 36 mg dose. Therefore, the residual exposure to moxidectin after Day 28 is considered unlikely to be pharmacologically relevant. There is currently no evidence of AEs that have been regarded as related to treatment emerging after Day 28 in the clinical safety database for single doses up to 36 mg in healthy volunteers or patients with scabies aged 18 years and older. The final analysis of efficacy and safety data collected through Day 42 will occur after the last subject has completed the Day 42 visit when PK sampling is complete in the PK subset. An extended safety follow-up will be conducted for all subjects to Week 16, corresponding to approximately 5 half-lives of moxidectin in the scabies patient population.

S. scabiei is easily spread through close contact. Assessment of treatment efficacy could be confounded by household members with an active, even if asymptomatic, scabies infestation who cause reinfections in the enrolled index case. The signs and symptoms of scabies can reappear in as little as 24 hours in cases of reinfestation and would confound the interpretation of Day 28 Complete Cure rates if they occur during the study. Limited data is available to quantify the risk of infection from household members or vice versa, but it is accepted that the risk is not zero. Presumptive treatment of household members is a conservative strategy to minimize the risk of reinfection of enrolled subjects across all the treatment arms and is a consistent approach with many available guidelines for the treatment of scabies, including those from the Centers for Disease Control and Prevention[26], which recommends that the close personal contacts of scabies patients should also be treated at the same time to prevent reinfestation of the patient and/or infestation of the contacts. Permethrin 5% cream has been selected to standardize the treatment of household members as it is a widely approved product in broad use for this population, and unlike ivermectin 200 µg/kg, can be used in infants 2 months of age and older.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives

6.1.1 Primary Objectives

The primary objectives of the study are:

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

6.1.2 Secondary Objective

There are no secondary objectives.

6.1.3 Exploratory Objectives

The exploratory objectives of the study include but are not limited to:

- For each of the three moxidectin doses, determine the Day 28 Complete Cure rate.
- In each of the 4 groups determine:
    - The Day 28 clinical cure rates,
    - The Day 28 combined microscopic and dermatoscopic cure rates,
    - The Day 28 Investigator-assessed Cure rates,
    - The concordance between the Complete Cure rate and Investigator-assessed Cure rate,
    - The change from Baseline in the total number of lesions at Day 28,
- And assess:
    - Secondary bacterial infection at Day 28,
    - Pharmacokinetics of moxidectin in a subset of subjects.

6.2 Endpoints

6.2.1 Primary Endpoints

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

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

and

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

The primary safety endpoints are the incidence and severity of adverse events, changes in electrocardiograms (ECG), in laboratory parameters and changes in vital signs.

6.2.2 Secondary Endpoints

None.

6.2.3 Exploratory Endpoints

The exploratory endpoints include but are not limited to:

- The proportion of index subjects demonstrating clinical cure without microscopic or dermatoscopic cure at Day 28.
- The proportion of index subjects demonstrating microscopic or dermatoscopic cure without clinical cure at Day 28.
- The proportion of index subjects demonstrating cure as assessed by the Investigator at Day 28.
- The proportion of index subjects with concordant and discordant Day 28 cure rates as assessed by the Investigator and the Complete Cure rate.
- The change from Baseline for index subjects in the total number of lesions at Day 28.
- The proportion of index subjects with secondary bacterial skin infections at Day 28.
- Plasma concentrations of moxidectin in a subset of index subjects selected for sparse PK sampling.

7 STUDY DESIGN

7.1 Study Design

This is a randomized, double-blind, placebo-controlled, dose ranging multinational, multi-center, parallel group, efficacy and safety study of orally administered moxidectin in patients aged 18 years and older with scabies.

7.2 Dosing Regimens

Approximately 200 index subjects will be randomized into one of four cohorts using an equal allocation ratio:

(1) placebo per oral (approximately n=50)
(2) moxidectin 8 mg, single dose per oral (approximately n=50)
(3) moxidectin 16 mg, single dose per oral (approximately n=50)
(4) moxidectin 32 mg, single dose per oral (approximately n=50)

7.3 Study Sites

This study will be conducted at approximately 8 to 20 sites internationally, including in the US and Latin American regions.

7.4 Estimated Duration of the Study

The study is expected to take approximately 12 months to complete. The on-study period per subject is approximately 17 weeks, consisting of up to 7 days for Screening and 16 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 any study-related procedures.

Subjects who meet all the inclusion and none of the exclusion criteria described in Sections 8.2 and 8.3 will be eligible for randomization and treatment. Once randomized, subjects will not be permitted to be re-randomized. Approximately 20 subjects from each of the cohorts will be randomly selected for sparse PK sampling at the time of randomization to IP.

Inclusion and exclusion criteria are to be assessed at the Screening assessment and prior to randomization.

Only one subject will be enrolled per household; where more than one household member is screened for the study, the enrolled (index) subject will be the youngest eligible member of the household.

8.2 Inclusion Criteria

A subject must meet all the following inclusion criteria:

1. Aged 18 years or older.
2. Provided written informed consent.
3. Diagnosis of active scabies infestation confirmed by the presence of clinical signs and symptoms (evidence of burrows or typical inflammatory/noninflammatory lesions and pruritus) and either microscopic confirmation of scabies mite(s), ova or scybala by skin scraping or dermoscopy.
4. All female subjects of childbearing potential must agree to the use of a highly effective method of birth control until 16 weeks after administration of IP (Section 8.4.1).

8.3 Exclusion Criteria

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

1. Diagnosis of crusted/Norwegian scabies or scabies presentation that, in the opinion of the Investigator, would require treatment with more than one standard of care treatment for scabies (e.g., scabies requiring concurrent topical and oral treatment).
2. History of chronic or recurrent dermatologic disease or skin conditions other than scabies that could interfere with the diagnosis of scabies and evaluation of cure.
3. Received any treatment with one or more scabicides within the 28 days prior to Screening, or between Screening and Baseline, including but not limited to permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil or spinosad.
4. Body mass index > 35 kg/m^2.
5. Creatinine clearance < 30 mL/min (using Cockcroft-Gault equation).
6. Both total bilirubin >1.5 x upper limit of normal (ULN) and AST > ULN.
7. Abnormal and clinically relevant findings in hematology or biochemistry assessments at Screening, or in vital signs, 12-lead ECG, or physical examination at Screening and/or Baseline, that in the opinion of the Investigator would put the subjects at increased risk from participating in the study, confound study evaluations, or may interfere with study conduct.

8. 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 in the opinion of the Investigator would put the subjects at increased risk from participating in the study, confound study evaluations, or interfere with the study conduct.
9. Use of topical steroids, systemic or high-dose inhaled corticosteroids (>500 µg per day of fluticasone propionate or equivalent for adults), or other immunomodulators within 14 days of Baseline.
10. Requiring ongoing treatment with, or received within 5 half-lives before Screening, any of the following medications that are clinical BCRP inhibitors: curcumin (turmeric) supplements, cyclosporine A, darolutamide, eltrombopag, febuxostat, fostamatinib, rolapitant and teriflunomide.
11. Received an investigational agent within 28 days of Screening (or 5 half-lives of the investigational agent, whichever is longer).
12. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin or ivermectin.
13. Known or suspected hypersensitivity to any of the components in permethrin 5% cream, to any synthetic pyrethroid or pyrethrin, or to the components of spinosad 0.9% topical suspension.
14. Known, suspected or at risk of *Loa loa* coinfection.
15. Difficulty swallowing tablets or capsules.
16. Pregnant or breastfeeding or planning to become pregnant from Screening until 16 weeks after treatment with IP.
17. Known or suspected alcohol or illicit substance abuse.
18. Unwilling, unlikely or unable to comply with all protocol specified assessments.
19. Previous enrolment in this study.
20. Previous moxidectin exposure within 6 months (5-half-lives) from Baseline.
21. Has household members who refuse or are unable to receive permethrin 5% cream treatment for scabies.

8.4 Other Study Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regards 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 IP being used in this study. Such documents may include the IB.

8.4.1 Contraception

As no adequate and well-controlled studies of moxidectin in pregnant women have been conducted, the safety of moxidectin in pregnancy has not been established. All women of child-bearing potential (WOCBP) (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. Serum pregnancy testing will be performed at Screening and repeated (urine test) pre-dosing if Baseline (Day 0) is more than 24 hours later and at Week 16 or at the End of Study visit, whichever occurs earlier.

WOCBP must agree not to attempt to become pregnant during the study until 16 weeks following IP administration. If participating in sexual activity that could lead to pregnancy, then WOCBP must agree to use a highly effective method of contraception during the study until 16 weeks following IP administration. Highly effective methods of contraception are defined as

those methods that have a failure rate of less than 1% per year when used consistently and correctly. These methods include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine devices; implantable rod; male partner who has undergone successful surgical sterilization; or abstinence as the subject's usual and preferred lifestyle.

Additional precaution is warranted for hormonal contraceptives that are sensitive CYP3A4 substrates as the clinical risk of CYP3A4 induction by moxidectin at doses higher than 8 mg is unknown. Barrier methods of contraception, such as diaphragms with spermicide or male condoms, should be used by subjects on hormonal contraception or if contraception is started within 7 days of IP administration for a minimum of 14 days after.

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.

8.4.2 Retesting and Rescreening

Subjects who have not been randomized and are determined to be ineligible due to unexpected laboratory, ECG, and/or vital signs abnormalities may have the relevant parameter(s) repeated once only. Otherwise, rescreening is not permitted.

8.5 Special Protocol Issues

8.5.1 Treatment of Contacts

S. scabiei is highly contagious, and it is common for more than one member of a household to be infested. Because Complete Cure rates could be affected by household members with an active but asymptomatic scabies infestation, all members of the household must receive treatment with permethrin 5% cream on the same day that the index subject receives their dose of IP. Instructions for treatment administration of permethrin should be provided by the clinical staff orally and in writing, and household members will be asked to confirm when the treatment is administered.

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

8.5.2 Pruritus

Scabies has a widely variable clinical presentation, ranging from mild disease with few scabies mites and few visible skin changes, to crusted scabies. Pruritus is the most commonly occurring symptom of scabies, but does not occur with the same intensity in all patients. Although some patients may report intense pruritus, several studies show the majority report pruritus as having mild to moderate intensity. Importantly from both the patient management perspective and measurement of trial outcomes, pruritus is known to have a subjective component and is vulnerable to confounding factors such as mood, environmental factors and stress.

All subjects enrolled in the study will have active management of their pruritus with provision of emollient and instructions to apply liberally and as often as is required.

Investigators should not enroll subjects who perceive their itch to be intolerable at Screening, for whom emollients and/or antihistamines is unlikely to provide relief, and/or who are at risk of not being able to complete the study because of intolerable pruritus.

9 SCHEDULE OF ASSESSMENTS AND PROCEDURES

9.1 Study Schedule of Evaluations

The schedule of assessments is presented in Table 1.

9.2 Visit Windows

Days are calculated from Day 0, which is the date of the Baseline assessments, randomization, and IP administration.

Screening may be conducted up to 7 days before Baseline (Day 0) in the window Day -7 to Day -1. All post-Baseline visits should be conducted on the specified day, whenever possible. However, when needed, the windows for each visit are:

- ± 1 day window for the Day 7 phone call,
- ± 2-day window for the Day 14 visit,
- -2 days and +4 days for the Day 28 visit,
- ± 2 day window for the Day 42 visit,
- ± 7 day window for the Week 12 phone call and Week 16 visit.

9.3 Study Procedures

The study procedures to be conducted are listed below. Further detail on 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 samples will be performed at an accredited laboratory. Refer to the SRM and/or laboratory instruction manual for information on sample collection and shipment of all required study samples.

Additional visits and/or assessments may be conducted as clinically indicated. All abnormal clinically significant hematology or biochemistry values should be confirmed by repeat testing as soon as possible, preferably within 3 calendar days of receipt of results unless such a delay is not consistent with good medical practice.

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

Subjects will be screened up to 7 days before Day 0 (Baseline) to determine eligibility for participation in the study. Screening assessments may be conducted on different days during the screening period 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).
- Scabies diagnosis based on a combination of clinical findings and microscopic or dermatoscopic confirmation (see Section 9.4.9). At Screening, dermoscopy is the preferred methodology for identification of mites, eggs, and/or scybala and to confirm the presence of burrows in the skin at Screening.
- Medical history (see Section 9.4.2).
- A complete physical examination (see Section 9.4.3) including:
  - assessment of all appropriate body systems.
  - measurement of height and weight.
- Vital signs (see Section 9.4.4).
- Concomitant medication assessment (see Section 11).

- Blood samples drawn for hematology and clinical chemistry (see Section 9.4.6).
- Serum pregnancy test for women of childbearing potential (see Section 9.4.7).

Results of all Screening tests must be available and reviewed prior to the subject's Day 0 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 for a minimum of 8 hours (preferably overnight) prior to the Day 0 visit. Water may be consumed *ad libitum.*

9.3.2 Day 0 (Baseline)

The following assessments will be performed before randomization:

- Confirmation of eligibility for the study.
- Vital signs (see Section 9.4.4).
- Assessment of clinical signs of scabies infestation, including inflammatory and non-inflammatory lesions, and assessment of presence of mites, eggs, and scybala (see Section 9.4.9).
- A 12-lead electrocardiogram (ECG) after the subject has been in the supine position for approximately 10 minutes. The Investigator/designee must review the ECG result before the subject is randomized (see Section 9.4.5).
- If the Baseline visit is more than 24 hours after screening, WOCBP must have another pregnancy test (urine) (see Section 9.4.7).
- AE assessment (see Section 12).
- Concomitant medication assessment (see Section 11).

If the subject continues to meet all the inclusion and none of the exclusion criteria, they will be randomized, and IP will be administered with water. Treatment will be observed by site staff (see Section 10.4.4) and the subject should continue to fast for 60 minutes post-dose. If feasible, subjects should remain in clinic during this time for monitoring for AEs and concomitant medication use.

A subset of approximately 20 subjects per group will be selected for collection of blood samples for assessment of moxidectin PK (PK subset). Blood samples will be collected at the following timepoints after IP administration on Day 0 (see Section 9.4.8):

- 3 hours (± 30 minutes),
    - Subjects in the PK subset will have a 12-lead ECG conducted at the 3-hour timepoint before PK sample collection.
- 10 hours (± 2 hours).

The subjects selected for the PK subset may remain at the site or be instructed to return to the site for the two post-dose PK sample collection at 3 hours (± 30 minutes) and 10 hours (± 2 hours). All other subjects can be discharged approximately 60 minutes post dose, if clinically indicated. All subjects should be provided with emollient and instructions for control of their pruritus.

9.3.3 Day 7

All subjects will be contacted by phone on Day 7 ± 1 day. Through open questioning, any adverse events (see Section 12) and concomitant medication (see Section 11) should be recorded.

Subjects should be reminded of the options available to them to manage any symptoms of pruritus.

9.3.4 Day 14

Subjects will return to the clinic on Day 14 ± 2 days. The following assessments will be performed and documented:

- A symptom-directed physical examination (see Section 9.4.3), which will include review of scabies signs and symptoms.
- Vital signs (see Section 9.4.4).
- Blood samples drawn for hematology and clinical chemistry (see Section 9.4.6).
- AE assessment (see Section 12).
- Concomitant medication assessment (see Section 11).

Subjects may still be positive for *S. scabiei* var. *hominis* by microscopy or dermoscopy at this time and may still be showing the clinical signs of scabies infestation, including pruritus. Subjects should be provided with additional emollient as required. Refer to Section 11.2 for concomitant medication options for management of pruritus.

9.3.5 Day 28

Subjects will return to the clinic on Day 28 (-2 days or +4 days). The following assessments will be performed and documented:

- Assessment of clinical signs of scabies infestation, including inflammatory and non-inflammatory lesions, and either microscopic or dermatoscopic confirmation of the presence of mites, eggs and/or scybala (see Section 9.4.9).
- A symptom-directed physical examination (see Section 9.4.3).
- Vital signs (see Section 9.4.4).
- Blood samples drawn for hematology and clinical chemistry (see Section 9.4.6).
- Blood sample collection for PK assessment will be collected from the PK subset of subjects (see Section 9.4.8).
- AE assessment (see Section 12).
- Concomitant medication assessment (see Section 11).

If the subject is positive for *S. scabiei* var. *hominis* by microscopy or dermoscopy, or if their clinical presentation has significantly worsened from Day 0, they should receive standard of care treatment per local guidelines (see Section 11.3).

9.3.6 Day 42

Subjects will return to the clinic on Day 42 ± 2 days. The following assessments will be performed and documented:

- A symptom directed physical examination (see Section 9.4.3).
- Vital signs (see Section 9.4.4).

- Blood sample collection for PK assessment will be collected from the PK subset of subjects (see Section 9.4.8).
- AE assessment (see Section 12).
- Concomitant medication assessment (see Section 11).

9.3.7 Week 12

All subjects will be contacted by phone on Week 12 ± 7 days. Through open questioning, any adverse events (see Section 12) and concomitant medication (see Section 11) should be recorded.

9.3.8 Week 16 (Follow Up and Study Conclusion)

Subjects will return to the clinic on Week 16 ± 7 days. The following assessments will be performed and documented:

- A symptom directed-physical examination (see Section 9.4.3).
- Vital signs (see Section 9.4.4).
- A 12-lead ECG after the subject has been in the supine position for approximately 10 minutes (see Section 9.4.5).
- If there were clinically relevant laboratory abnormalities at Day 28 that are unresolved, blood samples for hematology and/or clinical chemistry should be drawn (see Section 9.4.6).
- Pregnancy test (urine) for WOCBP (see Section 9.4.7).
- AE assessment (see Section 12).
- Concomitant medication assessment (see Section 11).

9.3.9 Unscheduled Visits

Subjects may attend the clinic outside of the standard visit schedule as clinically indicated. In addition to providing the required clinical care for their reason for presenting, the following should be performed:

- AE assessment (see Section 12).
- Recording of concomitant medications (see Section 11).
- A modified physical examination as clinically indicated (see Section 9.4.3).

9.3.10 Early Withdrawal

9.3.10.1 Withdrawal from the Study

Subjects should be encouraged to continue in the study until the end of study visit at Week 16. 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:

- A symptom directed physical examination (see Section 9.4.3).
- Assessment of clinical signs of scabies infestation, including inflammatory and noninflammatory lesions, and assessment of presence of mites, eggs, and scybala (see Section 9.4.9).
- Vital signs (see Section 9.4.4).
- Pregnancy test (urine) for WOCBP (see Section 9.4.7).
- AE assessment (see Section 12).

- Recording of concomitant medications (see Section 11).

9.3.11 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 coronavirus disease (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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or any 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 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.

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. 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. Deviations due to SARS-CoV-2 will be identified as such in the protocol deviation record.

If specimens are collected from subjects known to be actively infected with SARS-CoV-2, this information should be noted in the documentation that accompanies any sample transfer.

9.4 Details of Scheduled Assessments

9.4.1 Demographic Data

Demographic data will be recorded in the clinic notes and case report form (CRF) at Screening and include sex, race, ethnicity, and date of birth (note: only month and year of birth will be recorded in the CRF).

9.4.2 Medical History

Medical history will be recorded in the clinic notes and CRF at Screening and include any diagnosed medical conditions and/or current conditions, and significant medical or surgical history. It will include a review of all major body systems including the skin. A detailed history of any previous scabies infestations and treatments will also be collected for each subject.

After Screening, any worsening of Baseline conditions detected during medical history review must be recorded in the subject's clinic notes as well as reported as an AE in 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 document the subject's clinical status and determine study eligibility.

A symptom-based physical examination will be conducted as clinically indicated after Screening. The examination will be informed by prior findings, concurrent conditions, signs and

symptoms, and any AEs. A full physical examination should be performed if clinically indicated.

Findings will be recorded in the subject's notes and CRF. Post-Baseline, any new abnormalities or worsening of Baseline conditions must be recorded as AEs.

Body weight (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

Vital signs will be recorded in the subject's study records and CRF. Vital signs should be assessed prior to blood sample collection.

The following vital signs will be measured after the subject has been supine or semi-supine for 5 minutes:

- Respiratory rate (breaths per minute)
- Pulse rate (beats per minute [bpm])
- Blood pressure (millimeters of mercury [mmHg])

Body temperature may be measured orally or aurally and be reported in degrees Celsius [°C]).

Vital signs may be measured at other times as clinically indicated with clinically significant abnormalities reported as AEs.

9.4.5 Electrocardiograms

Twelve-lead ECGs will be performed before blood collection after the subject has been supine for approximately 10 minutes. ECGs will be performed in triplicate at Baseline (before randomization). After IP administration, another ECG will be performed at 3 hours (±30 minutes) for the subjects in the PK subset. At Week 16, ECGs will be performed for all subjects. Repeat measurements will be performed if there are any abnormalities observed or artifacts are present. All ECG recordings will be reviewed by the Investigator or nominee and retained in the subject's study records.

9.4.6 Safety Laboratory Tests

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 relevant local or national authority(ies). The processing of all biological specimens will be in accordance with relevant institutional Standard Operating Procedures (SOPs). Refer to the SRM for detailed instructions on sample collection, handling, and shipping, when a central laboratory is used.

Blood samples for hematology and serum chemistry will be collected at Screening, Day 14, and Day 28. Subjects with clinically significant abnormalities should have a repeat sample within 3 days. If there are ongoing clinically significant laboratory abnormalities from Day 28, laboratory tests will also be performed at Week 16.

Samples will be collected for the laboratory tests shown in Table 6.

Table 6 Laboratory Tests

Hematology	**Serum clinical chemistry**
White blood cell count (WBC) with differential	Alanine aminotransferase (ALT)
Red blood cell count	Aspartate aminotransferase (AST)
Hemoglobin	Alkaline phosphatase (ALP)
Hematocrit	Direct and Total Bilirubin
Mean corpuscular hemoglobin	Creatinine
Mean cell hemoglobin concentration	Creatine Kinase
Mean cell volume	Electrolytes (Sodium, Potassium, Chloride, Bicarbonate)
Platelets	Gamma-glutamyl transferase (GGT)
	Lactate dehydrogenase (LDH)
	Urea

Creatinine clearance should be calculated using the Cockcroft-Gault formula:

For male subjects:

$$\frac{(140 - age[years]) \times weight\ (kg)}{0.814 \times creatinine\ (\mu mol/L)}$$

For female subjects:

$$\frac{0.85 \times (140 - age[years]) \times weight\ (kg)}{0.814 \times creatinine\ (\mu mol/L)}$$

9.4.7 Pregnancy Testing

A serum pregnancy test will be performed for all women of childbearing potential at Screening. A negative pregnancy test result is required prior to IP administration. If Baseline is more than 24 hours after Screening, a urine pregnancy test must be conducted prior to dosing. A urine pregnancy test will also be performed at the Week 16 or End of Study visit.

9.4.8 Pharmacokinetic Sampling

Blood samples for assessment of moxidectin concentrations in plasma will be collected from subjects in the PK subset. The PK subset will include approximately 20 subjects selected from each study arm. To ensure the study drug allocation remains blinded, subjects from all arms of the study will be sampled. At the end of the study, only the samples from subjects allocated to one of the three moxidectin doses will be analyzed.

Blood samples from the selected subjects will be collected post-dose at 3 hours (± 30 minutes) and 10 hours (± 2 hours) on Day 0, and on Day 28 and Day 42. All samples will be collected as close to the scheduled timepoint as possible. Actual time of sample collection will be recorded in the subject clinic notes and CRF.

Directions for processing and shipping the plasma samples can be found in the SRM.

9.4.9 Scabies Assessments

At Screening, active scabies infestation will be confirmed by the presence of clinical signs and symptoms (evidence of burrows, typical inflammatory/noninflammatory lesions) as well as microscopic examination of skin scrapings or dermoscopy to demonstrate the presence of scabies mite(s), eggs and/or scybala. At Screening, dermoscopy is the preferred methodology for identification of mites, eggs, and/or scybala and to confirm the presence of burrows in the skin.

On Day 0 (prior to randomization) and on Day 28, subjects will be assessed for the presence of scabies mites, eggs, scybala, burrows, inflammatory/noninflammatory lesions and pruritus. Apart from burrows, primary and secondary signs of scabies infestation visible on the skin can include papules, vesicles, nodules, erythema, and excoriations.

The procedure for conducting scabies assessments on Day 0 and Day 28 is:

- Signs and symptoms of scabies infestation will be mapped according to pre-specified anatomical body regions.
- The presence or absence of mites, eggs or scybala will be confirmed by either microscopy of material taken from the skin via skin scraping, or by dermoscopy. If skin scraping is performed, material should be collected from skin showing burrows or lesions or from previously affected sites if signs have resolved. The method used, whether microscopy or dermoscopy, will be recorded in the subject's source notes and CRF.
- Dermoscopy will be used to confirm the presence or absence of burrows,
- Lesions will be counted, and nodules noted if present,
- Subjects will be reviewed for evidence of pruritus,
- Secondary bacterial infections will be noted if present (note that secondary bacterial infections are not included in the assessment of Complete Cure).

Separately, an Investigator Assessment of Cure will also be completed at Day 28. Based on the subject's clinical presentation, the Investigator will determine whether:

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

These data will be recorded in the subject's study records and CRF.

10 INVESTIGATIONAL PRODUCT

10.1 Randomization Process

A unique screening number will be sequentially allocated to each subject who provides written informed consent. Subjects who fail screening and are approved to be rescreened will retain their original screening number.

Subject eligibility will be confirmed before randomization. On Day 0, eligible subjects will be randomized using an Interactive Response Technology (IRT) system and assigned a unique Subject Number. The unblinded pharmacist at each site will dispense the IP corresponding to the assigned Subject Number.

Within the IRT system, the randomization of subjects to treatment will be stratified by region (e.g., US and Latin America). Within each region, a permuted block randomization algorithm reflecting an equal allocation ratio among the 4 treatment cohorts of 1:1:1:1 will be derived. The algorithm within each region will be independent and may consist of randomly varying block sizes. Block sizes will not be revealed to sites or Sponsor personnel involved in the conduct of the study. The algorithm will be generated by an unblinded statistician who is otherwise independent of the study. The random selection will be stratified by region and treatment and performed using the IRT system.

Approximately 200 subjects will be randomized targeting a sample size of 50 subjects per cohort across regions. A subset of approximately 20 subjects will be randomly selected from each arm to provide sparse blood samples for PK analyses. To ensure the study drug allocation remains blinded, subjects from all arms of the study will be sampled. Further details on the randomization procedure, treatment dispensing, and accountability are provided in the SRM.

10.2 Blinding

Clinic staff, subjects, operational Sponsor personnel and delegates will be blinded as to which treatment each subject receives until the last subject has completed their Week 16 visit. To maintain the blind, each subject will receive the same number of capsules, regardless of dose. Any break of the study blind, inadvertent or otherwise, will be reported to the Sponsor without revealing the actual treatment assignment, as soon as possible. The site will nominate an unblinded pharmacist to dispense the investigational medication per the randomization received from the IRT system. Once all subjects have completed Day 42, the final analysis of efficacy and safety data collected through Day 42 will be conducted. For these analyses, the blind will be broken once data through Day 42 have been cleaned, queries resolved, and the data through Day 42 has been “frozen/locked”. The blind break will not be added to the clinical trial database but only applied to the Day 42 analysis files. Neither the individual blind break information (e.g., individual treatment assignments) nor the results will be provided to Investigators, study subjects, the clinical management team, or Medical Monitor involved in day-to-day study operations. These individuals will remain blinded until subjects complete the extended safety follow up with the Week 16 visit and the extended safety data has been cleaned and the clinical trial database locked. Further details will be specified in the Statistical Analysis Plan.

10.3 Method of Unblinding

10.3.1 Medical Emergency

The IRT system will provide the option for an Investigator to break the blind. 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 IP treatment will affect the subject's clinical management. If a code break must occur, the Investigator or designee should advise the study Medical Monitor as soon as possible. Details for contacting the Medical Monitor will be provided in the SRM.

If the blind is broken, the reason and date, identity of the person who authorized the code break, and the date the Sponsor was informed must be documented in the subject's study file. This must be countersigned by the Investigator.

10.4 Investigational products

10.4.1 Supply

All IPs will be supplied by the Sponsor. The IPs to be administered in this clinical trial are encapsulated moxidectin 2 mg tablets, and placebo capsules.

Moxidectin tablets contain 2 mg of moxidectin supplied as 100 mg white to pale yellow, uncoated, oval-shaped tablets. Moxidectin tablet components are provided in Table 7.

Table 7 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

Each moxidectin tablet will be over encapsulated in a Size #1, opaque, white, hypromellose (hydroxypropyl methylcellulose) hard shell capsule. Each capsule will be backfilled with inert excipient powder (microcrystalline cellulose).

Matching placebo capsules will be filled with microcrystalline cellulose only.

10.4.2 Packaging and Labelling

IP will be supplied to the site packaged in bulk in high density polyethylene bottles. Each bottle will be labelled in an unblinded manner. IP 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 national and international regulations and requirements and will include at a minimum:

- Sponsor name
- Protocol number
- Product name
- Product strength
- Route of administration
- Lot number
- Expiry date or retest date
- 'For Clinical Trial Use Only'
- 'Caution: New Drug - Limited by Federal (or United States) law to investigational use'

Any additional specific requirements will be included according to local laws.

10.4.3 Storage and Handling

The Investigator is responsible for ensuring (directly or via delegation) that the IP is received, stored, and dispensed, in accordance with the protocol and only to subjects enrolled in the study.

Prior to dispensing, IP 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. IP should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as per the US Pharmacopeia (20 to 25°C [68 to 77 degrees Fahrenheit, °F], with protection from light and exposure to moisture. Do not freeze. Temperature excursions are permitted to 30°C (86°F).

IP must only be received, dispensed and accounted for by designated unblinded study staff delegated appropriately to fulfil this role by the Investigator. Any change in unblinded staff must be approved by the Sponsor prior to them assuming a role. Site staff may move from blinded to unblinded roles but will not be permitted to perform any blinded role if they were previously designated as an unblinded staff member.

10.4.4 Dosage and Administration of Investigational products

Only subjects randomized in the study may receive IP.

Subjects will receive 16 capsules for oral administration on Day 0 comprised of moxidectin, and/or matched placebo to maintain the blind and accommodate the 32 mg moxidectin dose (Table 8). Administration on Day 0 will be observed by clinic staff to ensure compliance.

Table 8 Capsule Numbers per Dose

Cohort	Study Day	Number of moxidectin capsules	Number of placebo capsules
Moxidectin 8 mg	Day 0	4	12
Moxidectin 16 mg	Day 0	8	8
Moxidectin 32 mg	Day 0	16	0
Placebo	Day 0	0	16

The pill burden is considered acceptable for this Phase 2 study. Eighteen tablets were administered to subjects in protocol numbers MDGH-MOX-1008 and MDGH-MOX-2001 and all subjects were able to (and observed to) swallow the 18 tablets with no acceptability nor compliance issues reported.

The dose of IP will be administered on Day 0 after fasting for at least 8 hours. Subjects will be required to swallow the capsules with water. Subjects should continue to fast for 60 minutes post-dose. Clear liquids may be consumed *ad libitum*.

10.4.5 Dispensing and Accountability

All IP supplied is only for use in this clinical study and must not be used for any other purpose. The Investigator is responsible for ensuring that the IP is dispensed in accordance with this protocol. The Investigator or designee is responsible for maintaining accurate records for all IP dispensed and returned. The inventory and dispensing logs must be available for inspection by the study monitor. IP supplies, including partially used or empty bottles must be accounted for by the Investigator or designee and verified by the study monitor.

Drug supplies, including unused, partially used, or empty bottles, will either be returned by the Investigator or designee to Sponsor or their agent, or destroyed on site if written approval to do so is given by Sponsor and appropriate facilities and procedures are available. Records shall be maintained by the Investigator of any such alternate disposition of the IP. 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 IP. Such records shall be submitted to the Sponsor.

11 CONCOMITANT 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 study will also be recorded. This includes details of any medication related to the occurrence of an AE.

11.1 Prior to Study Entry

As per the Exclusion Criteria in Section 8.3 the following are prohibited.

- Use of scabicides within the 28 days prior to Screening, including but not limited to permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil or spinosad. Note that this includes the use of ivermectin for any approved or unapproved indication.
- Systemic or high-dose inhaled corticosteroids (>500 µg/day of fluticasone propionate or equivalent) or other immunomodulators within 14 days of Baseline.
- Use of topical steroids within 14 days of Baseline.
- Requiring ongoing treatment with, or received within 5 half-lives before Screening, any of the following medications that are clinical BCRP inhibitors: curcumin (turmeric) supplements, cyclosporine A, darolutamide, eltrombopag, febuxostat, fostamatinib, rolapitant and teriflunomide.

11.2 During the Study Dosing Period

11.2.1 General Considerations

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

All concomitant medications, including vitamin supplements and herbal remedies, must be recorded in the appropriate section of the CRF. All changes in medication will be recorded. If the indication for a concomitant medication meets the definition of an AE, the AE will be recorded in the source documents and CRF.

11.2.2 Permitted Concomitant Medications for Pruritus Management

Investigators should be aware and subjects will be advised that post-scabietic pruritus is to be expected for a period of four to six weeks after treatment, reflecting the persistence of mite antigens even after infection has been resolved, and should be counselled that this is not indicative of treatment failure. Explanations of the physiological reasons for the itch should be carefully explained to the subject appropriate to their level of understanding.

Unmedicated emollient creams and oral over-the-counter antihistamines are permitted for relief and management of pruritus. Unmedicated emollient creams will be provided to subjects and the Investigator will inform subjects that that cream and antihistamines are permitted at any time as required for management of pruritus and should be applied liberally and frequently. Subjects should be encouraged to contact the site regarding the choice of any other concomitant medication to relieve itch prior to using any such medication.

11.2.3 Prohibited Medications

The Investigator will inform subjects of the following prohibited medications which may interfere with efficacy evaluations by masking the effect of treatment:

- subjects must not receive treatment with any scabicide, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad, between Screening and Day 28. Note that this includes the use of ivermectin for any approved or unapproved indication.
- subjects must not use topical over the counter or prescription medications used to manage itching (i.e., containing corticosteroids, ferric oxide, crotamiton, calamine etc.) between Day 0 and Day 28.
- subjects must also be advised to avoid contact with any treatments taken by their close personal contacts.

Pruritus management outlined in Section 11.2.2 should be actively followed. However, although scabicides are prohibited medications prior to the Day 28 visit, subject wellbeing is the priority. As this is a single dose treatment study, withdrawing from treatment is not applicable. If scabicides are required for the subject's wellbeing, the subject does not need to withdraw from the study for the Investigator to provide scabicides and subjects should continue on-study if they receive scabicides prior to Day 28 (Section 14). An excessive rate of scabicide administration prior to Day 28 can render the study difficult to interpret. The exposure to scabicides prior to Day 28 will be considered a major protocol deviation and subjects will be considered non-responders for the primary analysis (Section 15.6.8).

11.3 After Day 28

If subjects are positive for scabies mites by microscopy or dermoscopy at Day 28, or their clinical presentation has significantly worsened from Day 0, the subject will be given treatment with a scabicide. In the United States, permethrin 5% cream or spinosad 0.9% lotion should be used according to labelled instructions. In other regions such as Latin America, approved standard of care therapy per local guidelines may be used.

In addition to emollients and over-the-counter antihistamines, subjects may use topical over the counter or prescription medications used to manage itching (i.e., containing corticosteroids, ferric oxide, crotamiton, calamine etc.) after Day 28.

11.4 Special Dietary Requirements

There are no special dietary requirements.

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 patient or clinical investigation subject administered an IP (whether it is the experimental product or control) and which does not necessarily have a causal relationship with the IP. 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 IP. 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 phlebotomy). Adverse events newly occurring, or increasing in severity, frequency, or distribution, after initial exposure to IP will be considered as TEAEs.

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 IP period of the study), should be recorded as an AE, in the source records and the CRF.

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 IP administration, that do not worsen.
- the disease being studied unless signs and symptoms are more severe than expected for the disease.
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- overdose of either IP 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 IP, outcome and action taken with IP. 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, shown in Appendix 1. For AEs not specifically identified in those grading tables, the grades presented in Table 9 should be applied.

Table 9 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 IP should be assessed using the definitions presented in Table 10.

Table 10 Assessment of Relationship of Adverse Events to Investigational 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 IP is such that IP 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 IP.
Probable	The AE follows a reasonable temporal sequence from the time of IP administration, abates upon discontinuation of the IP 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 IP administration, abates upon discontinuation of the IP and/or reappears when IP 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 IP, then an alternative explanation should be provided. Grading and causality of adverse events must be performed by a medical practitioner delegated to the study.

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. However, any AE that the Investigator believes is at least possibly related to IP 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.
- persistent or significant disability/incapacity.
- congenital anomaly/birth defect in the offspring of a subject who received IP.

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 and of itself.
- All deaths, regardless of cause, must be reported to the Sponsor for subjects on study and for deaths occurring within 30 days of last IP dose or within 30 days of last study evaluation, whichever is longer.
- "Occurring at any dose" does not imply that the subject is receiving IP 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 IP, are as follows:

1) Complete the "Serious Adverse Event Report Form"
2) Send the completed "Serious Adverse Event Report Form" to the study Safety Desk 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, including the contact details of the Safety Desk, 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 in the concomitant medication section of the subject's CRF.

12.3.3.2 Investigator Reporting Requirements for Serious Adverse Events

A SAE may qualify for reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the IP and is unexpected (Suspected Unexpected Serious Adverse Reaction [SUSAR]) based upon the current IB. In this case, for multi-center studies, all Investigators will receive a formal notification describing the SAE.

Where this is required by local authorities, and in accordance with the local institutional policy, the Investigator should notify the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of SAEs according to their policies.

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 IP period of the study), or until the Investigator determines that the subject's condition is resolved or stable, or up to 28 days after the last dose of IP, whichever is longer. For SAEs, the Investigator must make every effort to observe subjects until the SAE has either resolved, subsided, stabilized, the event is otherwise explained, or the subject is lost to follow up. 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 but will be recorded in the subject Medical History. 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 IP 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. Abnormal laboratory values should 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 1. Where parameters are not addressed within this Toxicity Grading Scale, laboratory abnormalities should be assessed as "Clinically Significant" or "Not Clinically Significant". Laboratory abnormalities that occur without related clinical symptoms and signs should generally not be recorded as AEs 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.

All abnormal clinically significant values should be confirmed by repeat testing as soon as possible, preferably within 3 calendar days of receipt of results and prior to dose interruption or discontinuation, unless such a delay is not consistent with good medical practice.

For the purpose of monitoring and managing abnormalities, the Baseline value is defined as the last value prior to the administration of the first dose of IP.

Any laboratory test result that meets the criteria for a SAE will be reported as per Section 12.3.3.

12.6 Guidance for Dose Modification or Discontinuation of Treatment

Dose modification or discontinuation of treatment is not applicable in this study.

12.7 Warnings and Precautions

For information regarding precautions and AEs with the investigational drug, the Investigator is referred to the IB.

12.8 Risks for Women of Childbearing Potential or During Pregnancy

The risks of treatment with moxidectin during pregnancy have not been evaluated. WOCBP must agree not to attempt to become pregnant. If participating in sexual activity that could lead to pregnancy, WOCBP must agree to use a highly effective method of contraception during the study and for 16 weeks following last IP administration.

Additional precaution is warranted for hormonal contraceptives that are sensitive CYP3A4 substrates as the clinical risk of CYP3A4 induction by moxidectin at doses higher than 8 mg is unknown. Barrier methods of contraception, such as diaphragms with spermicide or male condoms, should be used by subjects on hormonal contraception or if contraception is started within 7 days of IP administration for a minimum of 14 days after.

12.9 Procedures to be Followed in the Event of Pregnancy

Subjects must be instructed to inform the Investigator immediately if they become pregnant during the study period and for 16 weeks following last IP administration. 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 the Clinical Pregnancy Notification Form provided by the Sponsor for reporting the occurrence and outcome of pregnancies.

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

13 SAFETY OVERSIGHT

The Investigator and designated staff and the Medical Monitor will be responsible for safety monitoring of all study participants and for alerting the Sponsor in accordance with Section 12.

13.1 Routine Reviews by Principal Investigator

The Investigator will be responsible for continuous close safety monitoring of all subjects, and for alerting the Medical Monitor if concerns arise or if criteria for expedited submission of safety data are met.

13.2 Routine Reviews by Medical Monitor and Protocol Safety Review Team

The Medical Monitor will complete routine and ongoing review of safety data as line listings.

The Protocol Safety Review Team (PSRT), comprised of the Medical Monitor, Statistician, and other Sponsor representatives as appropriate, will be closely involved in safety oversight of the study, as described in the PSRT charter. The PSRT may seek additional medical opinion from the Investigators or independent expert medical opinion as dictated by the occurrence of certain events. The Statistician, with assistance of the data management staff, will prepare periodic blinded safety reports for review by the PSRT, which may include but are not limited to AEs related to IP, SAEs, and discontinuations due to AEs. The PSRT will remain blinded in accordance with the provisions described in the PSRT charter.

In addition to safety data reviews, the PSRT may elect to discuss trial conduct issues that impact study integrity and participant safety. These may include, but are not limited to, data quality, critical monitoring findings, progress of enrollment, IP, research specimens, etc. The Investigator or Medical Monitor will also notify the PSRT of *ad hoc* safety reviews whenever they are aware of SAE(s) or AE(s) that meet criteria specified in the PSRT 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 Week 16 or the End of Study Visit (whichever occurs earlier) will be followed in accordance with Section 12.

14.2 Criteria for Premature Withdrawal from Treatment or the Study

Withdrawal from treatment is not relevant in this single dose 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. Study withdrawal is not required for the Investigator to provide scabicides to the subject prior to Day 28, and subjects should continue on-study if this does occur. The Investigator also has the right to withdraw subjects from the study in the event of concurrent illness, AEs, pregnancy, after a prescribed procedure, protocol violations, administrative reasons, or other reasons. The reasons for withdrawal of the subject must be recorded on the CRF.

Withdrawal of subject consent, either explicit or implicit, should be recorded in the subject's clinic records and the CRF as appropriate.

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 the Study

Should a subject decide to withdraw completely 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 included in a complete final evaluation which should be conducted at the time of the subject withdrawal. If applicable, and with the subject's agreement, any AEs or SAEs still ongoing at the time of subject withdrawal should be followed in accordance with Section 12.

14.4 Replacement of Withdrawn Subjects

Randomized subjects who withdraw from the study will not be replaced.

14.5 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 IP that indicates a change in the risk/benefit profile of the IP, 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.
If 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).

15 STATISTICAL ANALYSIS

15.1 General Analytic Overview

The study is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of a single oral administration of moxidectin for each of the three moxidectin doses compared to matching placebo with respect to the Day 28 Complete Cure rate in subjects with scabies aged 18 years and older.

The primary safety objective is to compare the safety of a single oral administration of moxidectin for each of the three moxidectin doses with placebo. Safety will be described by the AE profile focusing on TEAEs, defined as AEs occurring or worsening after exposure to IP. Additional safety analyses will examine laboratory assessments, vital signs, and physical exam results.

Approximately 200 eligible subjects will be randomized to one of 4 cohorts with a 1:1:1:1 allocation ratio:

(1) placebo per oral (approximately n=50)
(2) moxidectin 8 mg, single dose per oral (approximately n=50)
(3) moxidectin 16 mg, single dose per oral (approximately n=50)
(4) moxidectin 32 mg, single dose per oral (approximately n=50)

The randomization will be stratified by region.

The final analysis for efficacy and safety data will take place after the last subject has completed their Day 42 assessments. An extended safety follow-up period will continue for collection of safety data after the Day 42 visit through to Week 16. The blind will be maintained during the extended follow up as described in Section 10.2. The safety data collected during this extended follow-up period will be analyzed separately once the last subject has completed their Week 16 visit and is described in Section 15.6.4.5.

General statistical methods of analysis are described below with more detailed descriptions to be provided in the Statistical Analysis Plan (SAP). A separate Pharmacokinetic Analysis Plan (PAP) may be used to describe population-PK and PK/pharmacodynamic analyses. Both the SAP and PAP will be finalized prior to breaking the blind for the Day 42 analysis. Any changes to the statistical analysis plan made after the blind break will be identified in the clinical study report (CSR).

15.2 Sample Size Determination

Except as otherwise indicated, data will be pooled across regions. Although the analyses will include an adjustment for region, which may yield smaller variance estimates, the estimated powers and confidence interval (CI) widths for the unadjusted risk differences described below are expected to provide reasonable estimates of power and precision.

15.2.1 Superiority of Moxidectin to Placebo – Day 28 Complete Cure Rate

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

at an overall two-tailed alpha of 0.05 using a large sample approximation to Dunnett's critical value for the 3 pairwise comparisons of each moxidectin dose group to placebo.

15.3 Analysis Sets

15.3.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized index subjects receiving IP. Subjects in the FAS will be analyzed according to the treatment group to which they were randomized. The FAS will be the primary analysis set for the primary efficacy analyses.

15.3.2 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will include all index subjects exposed to IP without any major protocol deviations that could confound the assessment and/or interpretation of the analytic results. 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, the PPAS will be used for sensitivity analyses.

15.3.3 Safety Analysis Set

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

15.3.4 Pharmacokinetic Analysis Set

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

15.4 Final Analysis and Extended Safety Follow-Up

There will be no interim analyses. The blinded data will be continuously monitored for safety in accordance with Section 13. All blinded data will be monitored for data integrity.

The final analysis of efficacy and safety data collected through Day 42 will take place after the last subject has completed the Day 42 visit.

Following their Day 42 visit, all subjects will continue to be monitored for safety through the extended safety follow-up period to Week 16, during which the study blind will be maintained, see Section 10.2. Once the last subject has completed the extended safety follow-up period at Week 16, all data collected after the Day 42 visit will be cleaned and the clinical trial database will be locked. The blind will be broken and additional safety analyses conducted for the extended safety period.

15.5 Study Endpoints

15.5.1 Primary Efficacy Endpoint

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

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

and

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

15.5.2 Secondary Endpoints

There are no secondary endpoints.

15.5.3 Exploratory Endpoints

Exploratory endpoints include but are not limited to:

- The proportion of index subjects demonstrating clinical cure without microscopic or dermatoscopic cure at Day 28.
- The proportion of index subjects demonstrating microscopic or dermatoscopic cure without clinical cure at Day 28.
- The proportion of index subjects demonstrating cure as assessed by the Investigator at Day 28.
- The proportion of index subjects with concordant and discordant Day 28 cure rates as assessed by the Investigator and the Complete Cure rate.
- The change from Baseline for index subjects in the total number of lesions at Day 28.
- The proportion of index subjects with secondary bacterial skin infections at Day 28.
- Plasma concentrations of moxidectin in a subset of index subjects selected for sparse PK sampling.

15.5.4 Safety Endpoints

- Incidence and severity of TEAEs.
- Incidence of serious TEAEs.
- Incidence of TEAEs leading to study withdrawal and/or death.
- Changes from Baseline in ECGs, laboratory assessments and vital signs.

15.6 Statistical Methods

15.6.1 Subject Disposition, Demographic and Medical History

Tables of summary data reflecting subject disposition will be produced, including the number of subjects screened and the number and percent of screened subjects randomized. Additionally, the number and percent of randomized subjects receiving IP in each analysis set, and the withdrawals from the study (including reasons for early withdrawal) will be tabulated by dose group and overall.

Summaries of Baseline demographic data, medical history and scabies infestation status will also be provided. Unless otherwise noted, the Baseline assessment is defined as the last non-missing measurement prior to the initial exposure to IP.

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

The three primary efficacy hypotheses to be tested are the comparison of the Day 28 Complete Cure rates (proportions) for each of three moxidectin dose groups to the placebo group adjusted for region. Each analysis will be conducted as a test of superiority for the marginal risk difference (RD) adjusted for region using the standardized estimator as outlined by Steingrimsson et al.[4] The standardized estimator estimates the average treatment effect using logistic regression with treatment group and region as main effects and Day 28 Complete Cure as the outcome variable. Predicted probabilities for Day 28 Complete Cure for each treatment

group are generated for all subjects regardless of their actual randomized treatment group using their actual region values. The predicted probability of Day 28 Complete Cure for each treatment group across all subjects are then averaged and the difference in these averages is the standardized estimator for the marginal risk difference adjusted for region. Although the randomization is stratified by region to provide balance among the four treatment groups, by adjusting for region in the analysis it is anticipated that the results could yield a smaller variance which may increase precision and statistical power.

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

As supportive analyses, the Day 28 Complete Cure rates for each moxidectin group and placebo as well as the RD and 95% CIs for each pairwise comparison, will be calculated within each region. Any significance tests of the risk difference conducted within region will be viewed as supportive and exploratory due to the potential lack of power.

The Day 28 Complete Cure status for subjects exposed to scabicides prior to their Day 28 assessment will be imputed as a non-responder (not cured) for the primary analyses using the FAS. Subjects missing Day 28 assessments due to events reasonably considered to be non-informative, i.e., SARS-CoV-2, will have their Day 28 Complete Cure rate imputed using multiple imputation (MI). Details of the imputation model and MI methods, as well as alternative approaches should the MI yield unreliable imputations due to overprediction or other issues, will be outlined in the SAP.

The estimand for each of the primary efficacy hypotheses outlined above is the comparison of the Day 28 Complete Cure rate of moxidectin without use of rescue medication versus the Day 28 Complete Cure rate of placebo without use of rescue medication. Rescue medication is defined as any scabicide, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad used between Day 0 and Day 28. Rescue medication does not include products used to manage the symptoms of scabies.

As a sensitivity analysis the above primary efficacy analysis will be repeated using the PPAS as well as a completers analysis which will exclude any subject with a missing Day 28 Complete Cure assessment. Additional, sensitivity analyses will be conducted assessing the potential impact of missing data on the primary efficacy results and will be described in more detail within the SAP.

15.6.3 Additional Efficacy Analyses

Additional efficacy analyses of the exploratory endpoints will be detailed in the SAP.

15.6.4 Analysis of Safety

Safety will be analyzed using the SfAS with descriptive summaries of the incidence of TEAEs, vital signs, physical exams, clinical laboratory assessments, and concomitant medications. Summary data will be provided for each treatment cohort and overall. No safety data will be

imputed except for partial dates with the goal of determining if an AE is treatment emergent or if a medication is concomitant. The details of the algorithm for missing or partial start/end dates will be provided in the SAP. Line listings of all AEs will be provided, and those occurring during screening and not considered treatment emergent may be provided separately. Safety data collected during the extended safety follow-up period will be analyzed as outlined in Section 15.6.4.5 below.

15.6.4.1 Treatment Emergent Adverse Events

Subject incidence of TEAEs will be summarized using the Medical Dictionary of Regulatory Activities (MedDRA) system by organ class and preferred term. Summaries for severity, Investigator assessment of relationship to IP, serious TEAEs and TEAEs leading to death or study withdrawal will be provided. Events will be categorized by body system and preferred term. Event incidence will also be provided. Line listings of all TEAEs will be provided.

15.6.4.2 Laboratory Assessments

Summary statistics at each time point and changes from Baseline and/or shift tables may be provided. All laboratory assessments will be included in line listings.

15.6.4.3 ECGs, Vital Signs and Physical Exams

The analysis of ECGs, vital signs and physical exams will be conducted similarly to laboratory assessment analyses.

15.6.4.4 Prior and Concomitant Medications

Descriptive summaries of the number and percent of subjects taking prior or concomitant medications will be tabulated separately by medication class and standardized medication name. Prior and concomitant medications will also be provided in separate line listings.

15.6.4.5 Safety Follow-Up

The analysis of TEAEs collected during the extended safety follow-up after Day 42 will be similar to those described in Sections 15.5.4, and 15.6.4.1. Should the number of TEAEs reported during the extended follow-up not warrant aggregate summaries, then the data will be reported as line listings only. Interpretation of these extended safety data will be compared and contrasted to the safety data collected through Day 42 including continuing TEAEs that resolved or continued during the extended safety follow-up. The collection of concomitant medications continuing, ending or starting during the extended safety follow-up will also be described. Vital signs, physical exams and pregnancy test results will be listed along with any laboratory or ECG assessments taken.

15.6.5 Administration of Investigational Product

Summary tables will be provided reflecting IP compliance. All IP administration data will be presented in line listings.

15.6.6 Exploratory Analyses

The general analyses of exploratory endpoints will be detailed in the SAP.

15.6.7 Exploratory Pharmacokinetic Analyses

Approximately 20 subjects from each of the cohorts will be selected for sparse PK sampling (PK subset). Listings of individual moxidectin concentration versus time data by dose and mean

(± standard deviation) moxidectin concentration versus time data by dose will be reported in tabular and/or figure format.

15.6.8 Handling of Missing Data

For the Day 28 Complete Cure rate endpoint, subjects exposed to rescue medication (scabicides, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad) prior to the Day 28 assessment will be imputed as a non-responder. Subjects with missing Day 28 Complete Cure assessments for reasons deemed as non-informative will have their Day 28 value imputed using MI. Details of the imputation model and MI methods, as well as alternative approaches should the MI yield unreliable imputations due to overprediction or other issues, will be outlined in the SAP. For missing Day 28 Complete Cure status due to reasons other than scabicide exposure, the determination of whether they should be imputed as a non-responder or imputed using MI will be conducted and documented prior to breaking the blind by the study team.

Partial or missing start and stop dates for AEs and medications will be made with the objective of determining whether the event was treatment emergent, or the medication was concomitant. The algorithm for imputing partial/missing dates will be detailed in the SAP.

Table summaries, figures, and/or listings will be provided to describe the frequency, pattern, and reasons for missing data for the Day 28 Complete Cure rate by randomized treatment group. Summaries of the use of prohibited scabicides and, if feasible, the time-to-first scabicide exposure may also be provided.

Line listings that include data which were imputed for an analysis will include both the observed value and the imputed value.

15.6.9 Subgroup Analyses

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

- Region
- Age
- Gender
- Race
- Ethnicity
- Method of parasitological assessment at Baseline (microscopy or dermoscopy)

Safety summaries for TEAEs may also be provided for the following subgroups:

- Age
- Gender
- Race
- Ethnicity

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 2 for the preparation of the informed consent document to be used at sites.

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 IRB/IEC (and if applicable, regulatory agency)-approved consent form for documenting written informed consent.

The informed consent documents should be prepared in the language(s) of the potential subject population(s).

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 IRB/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 IRB/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 Medical Monitor and (when applicable) the Statistician.

All protocol modifications must be submitted to the IRB/IEC and regulatory authority 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, the IRB/IEC, and regulatory agency if required.

A protocol deviation is defined as any change from the Sponsor and IRB/IEC-approved protocol, regardless of whether it has been prospectively approved by the Sponsor or IRB/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 IRB/IEC, and regulatory agency if required, 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 ensure 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 Records

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. This includes physical and electronic records. These records should be classified into two separate categories, the Investigators' Site File (ISF), and subject clinical source.

The ISF will contain study essential documents including the protocol/amendments, IRB/IEC and regulatory authority approvals with correspondence, informed consent forms, drug records, staff curriculum vitae and authorization forms, screening and enrolment logs, and other appropriate documents and correspondence.

Subject clinical source records include, for example, subject hospital/clinic records, physician's and nurse's notes, appointment books, original laboratory reports, ECGs, X- ray, pathology and special assessment reports, consultant letters, etc. All clinical study records must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region 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. Records will be retained for longer if required according to local regulations.

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 of or all 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 documents are illegible or when errors in data transcription in to the CRF 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 investigator agrees to allow direct inspection of source documents and CRFs.

16.2.4 Case Report Forms

CRFs must be completed for each subject enrolled and signed by the Investigator or delegate. 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 in the CRF.

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 subjects.

All data must be entered in English. The CRFs should always reflect the latest observations on the subjects participating in the trial and are to be completed as soon as possible after the subject'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.

A representative from the Sponsor or its designee will visit the site at regular intervals throughout the study to verify the adherence to the protocol, ethical, and regulatory requirements, the completeness, consistency, and accuracy of the data being entered in the CRF, and to provide information and support as needed.

It is understood that the responsible monitor, as the Sponsor representative, will contact and visit the Investigator regularly and that they 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. In accordance with ICH GCP guidelines, the study monitor must have direct access to the Investigator's source documentation to verify the data recorded in the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during 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 their study 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. Investigators, site study staff, the Sponsor, and their representatives and delegates, agree to adhere to all applicable data protection requirements for collection, use, or storage of personal data.

All information concerning the IP 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.

As required by US law, a description of this clinical trial has been made available on https://clinicaltrials.gov. The Sponsor may also enter the study on other public listings of clinical trials.

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 for review at least 30 days 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.

Overall study recruitment is expected to take approximately 6 months.

16.7 Reporting of Study

This protocol will be submitted to the US FDA by the Sponsor prior to study commencement, under Investigational New Drug (IND) Application 138487. The Sponsor will provide annual safety updates on this study to the US FDA as required under the IND, and to other regulatory agencies as required. Upon completion of this study, the Sponsor intends to submit the final CSR to the US FDA and other regulatory agencies as required.

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18 APPENDICES

Appendix 1 Toxicity Grading Scale

The 2007 FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials tables are presented here 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 to 5 cm	5.1 to 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 to 5 cm and does not interfere with activity	5.1 to 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 to 38.4 100.4 to 101.1	38.5 to 38.9 101.2 to 102.0	39.0 to 40 102.1 to 104	> 40 > 104
Tachycardia - beats per minute	101 to 115	116 to 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 to 54	45 to 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mmHg	141 to 150	151 to 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	91 to 95	96 to 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 to 89	80 to 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 to 20	21 to 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 to 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 to 3 loose stools or < 400 g/24 hours	4 to 5 stools or 400 to 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 to 134	130 to 131	125 to 129	< 125
Sodium – Hypernatremia mEq/L	144 to 145	146 to 147	148 to 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 to 5.2	5.3 to 5.4	5.5 to 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 to 3.6	3.3 to 3.4	3.1 to 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 to 69	55 to 64	45 to 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random mg/dL	 100 to 110 110 to 125	 111 to 125 126 to 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 to 26	27 to 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 to 1.7	1.8 to 2.0	2.1 to 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 to 8.4	7.5 to 7.9	7.0 to 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 to 11.0	11.1 to 11.5	11.6 to 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 to 1.5	1.1 to 1.2	0.9 to 1.0	< 0.9

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Phosphorous – hypophosphatemia mg/dL	2.3 to 2.5	2.0 to 2.2	1.6 to 1.9	< 1.6
CPK – mg/dL	1.25 to 1.5 x ULN***	1.6 to 3.0 x ULN	3.1 to 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 to 3.1	2.5 to 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 to 6.0	5.0 to 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 to 2.0 x ULN	2.1 to 3.0 x ULN	3.1 to 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 to 2.5 x ULN	2.6 to 5.0 x ULN	5.1 to 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 to 1.25 x ULN	1.26 to 1.5 x ULN	1.51 to 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.0 to 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 to 210	211 to 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.1 to 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 mEg/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 to 12.0	9.5 to 10.9	8.0 to 9.4	< 8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease to 1.5	1.6 to 2.0	2.1 to 5.0	> 5.0
Hemoglobin (Male) - g/dL	12.5 to 13.5	10.5 to 12.4	8.5 to 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease to 1.5	1.6 to 2.0	2.1 to 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 to 15,000	15,001 to 20,000	20,001 to 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 to 3,500	1,500 to 2,499	1,000 to 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 to 1,000	500 to 749	250 to 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 to 2,000	1,000 to 1,499	500 to 999	< 500
Eosinophils - cell/mm^3	650 to 1500	1501 to 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 to 140,000	100,000 to 124,000	25,000 to 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 to 1.10 x ULN**	1.11 to 1.20 x ULN	1.21 to 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 to 1.2 x ULN	1.21 to 1.4 x ULN	1.41 to 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 to 500	501 to 600	> 600	--
Fibrinogen decrease - mg/dL	150 to 200	125 to 149	100 to 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 to 10	11 to 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.

Appendix 2 Model Patient Information Sheet and Consent Form

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Title	A Phase 2, placebo-controlled, double-blind, randomized, dose ranging, efficacy and safety study of orally administered moxidectin in adults with scabies
Protocol Number	MDGH-MOX-2002
Study Drug	Moxidectin, Placebo
Study Sponsor	Medicines Development for Global Health Limited
Principal Investigator	*[Insert Investigator Name]*
Associate Investigator(s) (if required by institution)	*[Associate Investigator(s)]*
Study Site	*[Site name]*

This document has two parts:

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

Participant Information Sheet

1. INTRODUCTION

You are invited to take part in this clinical research study because you are aged 18 years or over and your doctor has diagnosed that you have 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 study. Participation in this study is voluntary. If you don't want to take part, you don't have to. You will still receive the best available care.

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

If you decide you want to take part in the study, 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 and follow study procedures that are described
- Consent to the use of your personal and health information as described

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

2. WHAT IS THE PURPOSE OF THIS STUDY?

Scabies is an infection caused by tiny mites called *Sarcoptes scabiei* that burrow just under the surface of the skin and can cause itch, rash and skin sores. Scabies is very common; anyone can get scabies. You can become infected with the scabies mite from other people who have scabies, and sometimes from sharing clothing or bedding.

There are other treatments for scabies, generally a cream or a tablet taken by mouth. The creams that treat scabies need to be carefully applied to the whole body and applying the cream can be difficult. If the cream is not applied thoroughly, some people can continue to have scabies. The tablets treat scabies well, but the drug (ivermectin) clears your body quickly, which means you may have to take treatment twice, one to two weeks apart.

In this study we are testing a drug called moxidectin. Moxidectin has already been approved by the United States Food and Drug Administration for the treatment of a different disease called river blindness (also known as onchocerciasis), which is caused by a parasitic worm.

Moxidectin has not been approved for treatment of scabies anywhere in the world but has been used widely in animals for many years to treat mites very similar to the one that causes scabies in people. This study is to test if moxidectin can treat scabies in people.

This multinational study is being conducted at approximately 8 to 20 hospitals and clinics. Approximately 200 people will be enrolled in this study.

3. DO I HAVE TO TAKE PART IN THIS CLINICAL STUDY?

No. Your participation in the study is entirely voluntary and it is up to you to decide whether 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 all available treatment options with you before you decide whether to take part in this clinical study.

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

Your study doctor and the clinic team will check if you meet the requirements to take part in the study, also known as eligibility. This visit is your Screening Visit. You will be asked questions about your health and previous scabies treatments by the study doctor and/or study team, who will also examine you and take blood tests to see if there are any reasons why you should not take part. Your study doctor will explain all the results and let you know if you are eligible to go into the study. If you are not eligible, the study doctor will discuss your alternative treatment options with you and provide treatment if this is the correct thing to do.

5. WHAT ARE THE TREATMENTS IN THE STUDY?

Because we don't know if moxidectin works to treat scabies, or which dose is best, this study is going to compare different doses of moxidectin to placebo. A placebo looks the same as moxidectin but does not contain any medicine.

If you agree to take part and are eligible for the study, you will be allocated by chance (called "randomization") to receive either 8 mg, 16 mg or 32 mg of moxidectin, or placebo. These treatments are called 'study drugs' in the rest of this document. You have an equal chance of receiving any one of these study drugs, and three out of every four participants will receive moxidectin, which is a 75% chance.

This is a double-blind study, which means that neither you, your study doctor/study team, or the staff from the sponsor, Medicines Development for Global Health will know if you are receiving moxidectin 8mg, 16 mg, 32 mg, or placebo. However, if an emergency occurs and your study doctor needs to find out which treatment you are receiving this can be done.

Study drug will be given to you as capsules that you swallow. So that no one can tell what dose you are receiving, everyone will take 16 capsules on Day 0. You might be taking all moxidectin, a mixture of moxidectin and placebo capsules, or you may be taking all placebo capsules. This is to make sure the dose is hidden. The reason for this is to make sure that all the people who take part in the trial and all the results are not affected by what people, including doctors treating you, believe about the study drug.

6. WHAT DOES TAKING PART IN THIS CLINICAL STUDY INVOLVE?

If you agree to take part in this study, you will be given detailed information about the study drugs, the study, and any other relevant information by study staff and asked to provide written consent (which is the document you are now reading) to take part. 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.

If you agree to take part in this study, everyone who lives in the same house as you will need to use a treatment for scabies. This is a cream that contains a drug called permethrin. This is because scabies is easily transmitted from person to person, so you could become re-infected by a family member. Your doctor will supply this cream for them to use and ask if they agree to use it. If some of the people you live with do not agree to use the cream or can't use the cream, you will not be able to participate in this study. You must make sure that you don't come into contact with the cream when it's used by the people in your household. There is no cost to you or your family for the cream.

Once you have agreed to take part and signed the consent form, you will have some screening tests to check if there is any reason you should not take part in the study. Screening may be up to 7 days before you take the study drug. If you are eligible (that is, there is no reason that the study doctor can see why you should not take part in the study, you will be invited to take part in the study. The study assessments will take place over 16 weeks. During that time, you will be asked to come to the clinic for 5 times; on Day 0, Day 14, Day 28, Day 42 and Week 16 for the study doctor to assess your scabies. The visit on Week 16 is the last visit for the study and there are no more visits after that. The study doctor and/or study team will contact you by phone on Day 7 and Week 12 to ask about any changes in your health. The study will last approximately 17 weeks from the date you sign this informed consent form (up to 7 days for screening plus 16 weeks for follow up).

On the Day 0 visit, you might be randomly chosen by a computer to check how much study drug is in your body after taking it. Not everyone will be asked to take part in this part of the study. If you are chosen for this assessment, you will be asked to give extra blood samples on Day 0, Day 28 and Day 42. Because we do not know whether you will be chosen for these extra blood tests, you should allow enough time to stay at the clinic for 10 hours on Day 0.

Screening Visit

The following tests and checks will be performed;

- Your age and month and year of birth, gender, race, and ethnicity will be recorded.

- You will be asked about previous medical history, your current health, and any medications you are taking.
- You will undergo a physical examination including measuring your height and weight.
- Your blood pressure, heart rate, breathing rate and body temperature will be measured.
- A blood sample will be collected for safety tests, and assessment of your general health.
- If you are female and able to have children, a pregnancy test will be done on your blood sample.
- We will check your scabies infection using one of the following methods:

  Looking at the location of the scabies infection with a low-power hand-held microscope called a "dermoscope", which allows the doctor to see the scabies mite and your skin in more detail.

  Or

  Taking a small sample of the top layer of your skin (called a skin scraping) which will be examined under a microscope. The test is performed by a qualified person who use a metal blade to scrape across the skin.

This visit will take approximately *2 hours*.

If the screening tests confirm that there is no reason that you should not take part in this study, the study team will contact you to book the Day 0 visit.

It is important that you do not take any other treatment for scabies while you are waiting for your results. If you do, you must tell the study doctor before receiving any study drug. This is for your safety.

Day 0 Visit

You must fast (no food, but water is allowed) for about 8 hours before this visit and should continue to fast for 60 minutes after you take the study drug. The study staff will check if there has been any change to your health or medications since the screening assessments. The following tests and checks will be performed:

- Your blood pressure, heart rate, breathing rate, body temperature will be measured;
- Body weight may be measured if it has been over 24 hours since your screening visit;
- The study staff will perform an electrocardiogram (ECG) to record your heart's electrical activity and rhythm.
- If you are female, and able to have children, a urine pregnancy test will be performed (but only if it has been over 24 hours since the last pregnancy test);
- The study doctor will do a skin examination to review your symptoms and look for scabies mites. This will involve looking at your whole body (including groin and nipple region) and making a record of the location of symptoms. The study doctor will look at your skin again with the dermoscope or do skin scrapings;
- The study doctor may ask to take photos of your skin. You may refuse to have the photos taken and refusal will not affect you taking part in the study. Photos will only be identified by your study number and no identifying features will be included, such as eyes or full face;
- You will be given 16 capsules of study drug to take. The study staff will watch you take the tablets and check that you have swallowed them all by looking in your mouth. The capsules

must be taken with a full glass of water (around 240 mLs), and you must stay at the clinic and not eat anything for another 60 minutes after you take them;
- You will be asked about any changes in your health and well-being since your last study visit, and any medications you may have taken;
- You will be given a skin cream called an emollient, this cream does not contain any medicine that treats scabies but may decrease any itching. You can apply this cream as often as you need to;
- If you are selected for the extra blood tests measuring how much study drug is in your body, the following additional tests will be performed:
    - the study team will collect a blood sample between 2.5 hours to 3.5 hours after you take study drug.
    - the study team will perform an electrocardiogram (ECG) to record your heart's electrical activity and rhythm between 2.5 hours to 3.5 hours.
    - Another blood sample will be collected between 8 hours to 12 hours after you take study drug.
- You will be given a scabies cream and instructions to take home for the people you live with to use. Your household members must use the cream on the same day that you take your study drug.

This visit will take up to *3 hours*. If you are selected for additional blood sample collection the visit may take up to 12 hours.

On study visits

The study staff will contact you by telephone on Day 7 and at Week 12 to ask about your health and any medication you have taken. You will need to come back to the clinic on Day 14, Day 28, Day 42 and Week 16. At these visits, you will be asked questions about your health any medications you have used.

- The study doctor may examine you and will measure your blood pressure, temperature, heart rate and breathing rate;
- Blood samples will be collected for safety tests, and assessment of your general health;
- You will be asked about any changes in your health and well-being since your last study visit, and any medications you may have taken;
- On Day 28 the study doctor will repeat the scabies assessments (skin examination) described in the section above;
- If you were chosen to take part in additional blood collection to measure the amount of study drug in your body on Day 0 visit, the study team will collect blood samples on Day 28 and Day 42;
- On Week 16 visit, if you are female, and able to have children, a urine pregnancy test will be performed.
- On Week 16 visit the study doctor or study nurse will perform an electrocardiogram (ECG) to record your heart's electrical activity and rhythm.

The Day 14, Day 42 and Week 16 visits will take up to 2 hours, and the Day 28 visit up to 3 hours.

The Week 16 visit will be your last study visit.

7. COSTS AND COMPENSATION

There is no cost to you for taking part in this clinical study. All medication, tests and medical care that are part of the clinical study are free of charge. You will also be reimbursed for any reasonable travel, parking, and meals associated with the study visits.

8. YOUR RESPONSIBILITIES AND RESTRICTIONS

You will need to attend the study clinic at the times and on the study days outlined above and as requested by your study doctor or study nurse.

You should notify the study team in advance of your visits if you are experiencing COVID-19 symptoms, 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 social distancing from other patients and clinic staff.

Medicines

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 clinical study

In most cases you can take your regular medication. Please check with your study doctor.

Medications called “CYP3A4 substrates” such as benzodiazepines, hormonal contraceptives, opioid painkillers such as fentanyl or methadone, some antihistamines or statins could interact with moxidectin. If you are taking any of these, your study doctor may discuss extra precautions with you.

There are some exceptions:

- You should not take any other treatments for scabies during the study, including ivermectin tablets or permethrin cream. Ivermectin can be used for other reasons than scabies, and you should not use it for any reason. You must avoid touching the cream your household members are given at the beginning of the stud, this includes touching their skin after they have applied the cream.
- You should not use any medicated creams or lotions, or any medications for itchiness during the study. The reason we ask you not to take other treatments is because we will not be able to tell whether your scabies has been treated by moxidectin or by the other treatment you took, and that will make our study results less clear.
- Your itching could continue after you are given study drug, this is because your body reacts to the faeces (poop) of the mite, and the reaction takes some time to resolve even after the mite dies. Please contact your study doctor at any time if you are having trouble with itching or any other issues, such as not sleeping due to itching, they will be able to give you treatment and suggest some things that will help you manage the itching.

If the study doctor sees scabies mites at Day 28, or your symptoms are worse, your study doctor may give you additional scabies treatment to use.

It is very important that you receive the care that is most suitable for you and this is a decision made between you and your study doctor, taking into account many things. It is very important

that you and your study doctor recognize that you are a volunteer and your safety and comfort is of primary importance at all times.

Contraception

If you are able to become pregnant you must agree not to try to become pregnant and agree to use a highly effective method of contraception during the whole 16 weeks of the clinical study. Your doctor will discuss highly effective methods of contraception with you, which can include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) (a pill, pessary or patch);
- Progestogen-only hormonal contraception associated with inhibition of ovulation (a tablet, injection or an implant under the skin);
- Intrauterine device or intrauterine hormone-releasing system (an IUD, maybe called a coil);
- Bilateral tubal occlusion (tubes tied or sterilized);
- Sexual abstinence, defined as completely refraining from heterosexual intercourse if it is your preferred and usual lifestyle;
- If you have a male vasectomized partner (vasectomy, the snip), provided that they are your only sexual partner and they have received medical confirmation that no sperm are present.

If you start contraception within 7 days of taking the study drug, you should use additional barrier methods of contraception such as a male or female condom or diaphragm for at least 2 weeks after your dose of study drug.

Contraception will be provided to you free of charge for as long as you are in the study, if you withdraw from the study, you should still use contraception as prescribed/recommended for 16 weeks after you take the study drug.

9. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

This is a research study, and it is not yet known if moxidectin will be effective in treating scabies infection. We cannot guarantee or promise that you will receive any benefits from this clinical research study. Possible benefits may include close follow up of your condition and receiving treatment at Day 28 if required. All of your tests and visits will be free of charge and all of your results will be available to you and can be sent to your family doctor to add to your health record if you wish.

Results from this study will provide important information for any research developing future treatment options for scabies, whether the results are positive or negative.

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

Medicines have side effects. You may have none, some or all 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, you can contact your study doctor at any time.

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 mild, do not last long and clear up by themselves. Sometimes side effects can be serious, long lasting or permanent. There may be side effects that the study staff do not expect or do not know about and that may be serious. This is one of the reasons we are doing a clinical study and why it is important that you tell your study

doctor about anything that may be affecting you, even if you think it is not important. Your study doctor will be able to assess any symptoms you have and discuss the best way of managing any side effects with you.

Side effects of Moxidectin

Moxidectin is a new medicine and therefore not all side effects are known. Common side effects of moxidectin reported in healthy volunteers and patients with river blindness or scabies 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 243 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

Side effects in patients with river blindness

Moxidectin has been given to almost 10,000 people in clinical trials for river blindness. The most common side effects in patients with river blindness are caused by an allergic reaction to the presence of dead worms in the person's body, the reactions are worse in people who carry high numbers of worms and less in people who have low numbers of worms.

As this is a different disease to scabies, it is unlikely that you will have the same reactions.

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

- Changes to the proportions of white blood cells
- Itching
- Pain (including muscle pain, joint pain, general body pain, abdominal pain and lymph node pain)
- Headache
- An increased heart rate, including when people went from laying down to standing
- Rash
- reduced blood pressure, including when people went from laying down to standing.
- Fever and chills
- Influenza (flu) like illness
- Cough
- Dizziness or lightheadedness

- An upset stomach, including diarrhea, gastroenteritis and enteritis
- Reduced concentration of salt in the blood
- Swelling of the limbs

If you feel dizzy or light-headed, you should lie down until the symptom goes away and you feel better.

Less common side effects (in between 1% and 8% of patients) occurred in the in the eyes, including pain and/or discomfort, itching, blurry vision, red eyes and conjunctivitis (a bacterial infection of the eye).

Rare side effects (1% to 3% of patients) had changes to their liver function tests. 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 was given to 22 people with scabies in a research study completed in February 2022. The most common side effects were itchy, dry, and red skin, itchy rash on skin, and headache. Events were mild, lasted a short time and most resolved completely. Overall moxidectin was well tolerated by all participants in that study.

Side Effects of Permethrin

This the cream that is supplied to your household members. The main side effect of permethrin cream is itchy skin (in 7% of patients). Less common side effects may include a burning feeling, numbness, rash, redness, stinging, swelling, or tingling.

Blood tests

Having blood taken may cause some minor pain, 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. Please tell your study doctor if you have ever felt faint or fainted while have a blood sample taken.

Pregnancy

The effects of moxidectin on the unborn child and on the newborn baby are not known. Because of this, it is important that clinical study participants are not pregnant or breast-feeding and do not become pregnant during the clinical study. If you are female and having a child is a possibility, you will be required to have a pregnancy test before taking the study drug and at the end of the study. Female participants, who are able to become pregnant, must agree to use highly effective contraception during the whole 16 weeks of the study.

If you do become pregnant while you are in the clinical study, you should tell your study doctor immediately. Your study doctor will advise on further medical attention should this be necessary.

11. WHAT WILL HAPPEN TO MY TEST SAMPLES?

By agreeing to take part in this study, you also agree to the collection, storage and use of your blood samples. This is a required part of the study. During the study blood samples will be taken on 4 occasions. The total amount of blood taken for the entire study will not be more than *xx mL*. Your blood samples will only be labelled with your unique study number and will not contain any information that can identify you personally.

The blood samples collected during the study are for assessment of your health status and safety and will be tested locally. These samples will be destroyed following analysis according to local laboratory policies.

The blood test required to determine the level of study drug in your body can only be performed by a specialized laboratory. These blood samples will be sent to a laboratory in America where they will be analyzed. All samples will be de-identified and nobody at the laboratory will be able to find out your personal details. These samples will be destroyed following analysis according to the laboratory policies.

12. WHAT IF NEW INFORMATION ARISES DURING THIS CLINICAL STUDY?

Sometimes during a clinical study, new information becomes available about the study drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you how this might affect you and whether you want to continue in the clinical 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 clinical study you will be asked to sign an updated consent form. New information may be more important for people who need to take repeated doses of moxidectin, as your study treatment is only given once at the beginning of the study, it may not require you to do anything, but continuing your follow up appointments would still be important for your safety and monitoring of your scabies infection.

13. WHAT IF I WITHDRAW FROM THIS CLINICAL STUDY?

You can withdraw from this clinical study at any time. If you decide to withdraw from the study, please notify a member of the clinical team before you withdraw. This notice will allow that person or the clinical 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 clinical 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 clinical 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 clinical study results. If you do not want them to do this, you must tell them before you join the clinical study.

As your study treatment is only given once at the beginning of the study, continuing your follow up appointments would still be important for both your safety and for monitoring of your scabies infection.

You can also agree to continue to be followed up but not have all tests performed, this is something you should discuss carefully with the study doctor as all of the tests are for your safety and to provide safety information for people who may receive moxidectin in the future.

14. COULD THIS CLINICAL STUDY BE STOPPED UNEXPECTEDLY?

Yes, this is possible. This clinical study may be stopped unexpectedly for a variety of reasons which may include unacceptable side effects, or for decisions made by the sponsor, or by local regulatory/health authorities. Your study doctor will discuss any information relating to the stopping of the study with you as soon as possible. It may be that even though the study has been stopped, it is still important that you continue your follow up visits for the study. Your study doctor will discuss this with you if this is the case.

15. WHAT HAPPENS WHEN THE CLINICAL STUDY ENDS?

At the final study visit, 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 the end of the study.

Once all the participants have completed treatment and follow up in the study, the treatment blind will be broken. This means that the treatment each participant was given and the results of the testing that was done can be analyzed together. The results of the analysis will be published in a medical journal. Your study doctor will tell you what treatment you received during the study and also tell your local doctor, if you have given permission for the study team to contact them. Your study doctor can also discuss the results of the study with your or you can request a copy of the study results when they are published, it may be several months or a couple of years before the information is published.

16. WHAT WILL HAPPEN TO INFORMATION ABOUT ME?

By signing the consent form you agree that the study doctor and relevant clinical staff can collect and use personal information about you for the clinical study. Any information obtained in connection with this clinical study that could 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 clinical study.

Your health records and any information obtained during the 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) and *country agency*, and authorized representatives of the Sponsor, Medicines Development for Global Health, the clinic where you are enrolled in the clinical study , *[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.

The information from the study may be published or sent to regulatory authorities or health insurers in your country or other countries where regulatory approval or payment for the medication is required. Your identity will not be released except with your permission, unless necessary for the vital interests of your safety.

By signing this consent form, you are giving permission for the processing and use of your personal information for this study. You are also giving permission for the processing of your personal information or any part of it to be transferred to people and organizations (mentioned above) outside your country, where personal data protection laws may be different to those in your own country. If your personal information is accessed or processed outside of your

country, the Sponsor will ensure that the privacy and confidentiality of your information is protected according to the data protection laws and regulations applicable in your country. You may use your rights under your local data protection laws to access and correct your personal information or ask for it to be deleted. You can object to any further processing of your information by applying to your study doctor.

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 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.

Your medical files may be reviewed at the study site or remotely (outside of the study site, if allowed by site and applicable regulation) by authorized study personnel as indicated above in order to check the information and verify the study procedures, without breaking your confidentiality. If your medical files are reviewed remotely, the records will include your study subject number but will not include your name or other directly identifiable information, unless these records will be reviewed directly through the study site's secure electronic medical records portal. A requirement of the study is to keep your data for at least 15 years and possibly longer.

Whether your medical files are reviewed at the study center or remotely for the purposes of the study, your records will be kept secure during this process.

It is anticipated that the results of this clinical 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 clinical study may be recorded in your health records.

In accordance with privacy and other relevant laws in your country, you have the right to request access to your information collected and stored by the study doctor. 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 study will 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. *A description of the clinical study will also be available on <add reference to national register if applicable>.*

17. COMPENSATION FOR INJURY

Any compensation payable for any injury caused to you by taking part in this study will be in line with local guidelines. The Sponsor will pay for the cost of medical treatment for any injury that is directly due to treatment with the study drug or a study procedure (that has been performed as described in the study protocol). The Sponsor will not compensate you where the injury has happened because a procedure has not been carried out as described in the protocol or where the study doctor or their team has acted negligently.

The Sponsor has an insurance policy to cover compensation for any personal injury resulting from you taking the study drug, provided such personal injury is not due to fault or negligence of the study doctor or their team.

If you have medical insurance, please check with your insurance company that taking part in this study will not affect your policy.

18. WHO IS ORGANIZING AND FUNDING THE STUDY?

This clinical study is being sponsored, and funded, by Medicines Development for Global Health.

Medicines Development for Global Health may benefit financially from this clinical 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 clinical 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 clinical 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 clinical 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.

Study doctor will receive reimbursement for study activities which are carried out as part of the clinical trial from Medicines Development for Global Health. No member of the clinical study team at site will receive a personal financial benefit from the participant's involvement in this clinical study (other than their ordinary wages).

19. WHO HAS REVIEWED THE CLINICAL STUDY?

All clinical studies involving humans are reviewed and approved by an independent group of people called an Institutional Review Board (IRB) or Independent Ethics Committee (IEC), to protect your safety, rights, well-being and dignity. This study has been reviewed and has been given a favorable opinion by *Ethics Committee.*

This study has also been reviewed and approved by *CA name*, the agency responsible for the standards of safety, quality and performance of medicines in *Country*.

This study 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 study will also be conducted in accordance with any local standards that govern the conduct of clinical studies in the country where you take part in the study.

20. FURTHER INFORMATION AND WHO TO CONTACT

The person you may need to contact will depend on the nature of your question(s).

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 your 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 clinical study 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 (As applicable)

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

CONSENT FORM

Title	A Phase 2, placebo-controlled, double-blind, randomized, dose ranging, efficacy and safety study of orally administered moxidectin in adults with scabies
Protocol Number	MDGH-MOX-2002
Study Drugs	Moxidectin, Placebo
Study Sponsor	Medicines Development for Global Health Limited
Principal Investigator	*[Insert Investigator Name]*
Associate Investigator(s) (if required by institution)	*[Associate Investigator(s)]*
Study Site	*[Site name]*

Declaration by Participant

I have read and understand the Participant Information Sheet for the above study and have had enough time to think about taking part.

I understand the purposes, procedures and risks of this clinical study described in this information sheet.

I voluntarily agree to be part of this clinical study, to follow the study procedures and to provide the information the study doctor, nurses or other staff members ask from me.

I voluntarily give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[site]* 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 study as described and understand that I am free to withdraw at any time during the study without giving a reason and without affecting my future health care.

I understand that I will be given a copy, for my own records, of this document after it has been personally signed and dated by both me and the study doctor.

	DD/MMM/YYYY	00:00 AM/PM	
Name of Participant (to be completed by participant)	**Date** (to be completed by participant)	**Time of signature** (by participant)	**Signature** (to be completed by participant)

Declaration by Study Doctor / Delegate

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

	DD/MMM/YYYY	00:00 AM/PM	
Name of Study Doctor	**Date**	**Time of Signature**	**Signature**

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

Appendix 3: Summary of Protocol Amendment 1

Protocol Amendment Number: 1

Date of Protocol Amendment: 24 Aug 2023

Previous Protocol Version: 1, dated 06 Apr 2023

Resultant/Current Protocol Version: 2, dated 24 Aug 2023

Protocol MDGH-MOX-2002 is amended following receipt of communication from the Consejo Nacional de Bioética en Salud (CONABIOS) dated 12 Jul 2023 and the study May Proceed communication from the United States Food and Drug Administration dated 08 Aug 2023.

Section	Original Text	Revised to Read	Rationale for Change
Administrative Updates			
Cover page	Protocol version/date: Current Final Date: 06 Apr 2023	Protocol version/date: Current 2 (incorporating Amendment 1) Date: 24 Aug 2023	Protocol version and date updated to reflect amendment
Study acknowledgement	Version 1, 06 Apr 2023	Version 2, 24 Aug 2023	Protocol version and date updated to reflect amendment
Footer	MDGH-MOX-2002 Protocol version 1 Final	MDGH-MOX-2002 Protocol version 2 Final Incorporating Amendment 1	Document name and version updated to reflect protocol amendment
Footer	06 Apr 2023	24 Aug 2023	Document date updated to reflect protocol amendment
Section Numbering	N/A	Section 8.5.2 Section 9.3.8 to Section 9.3.11 Section 11.2 Section 15.6.4.5	Section numbering revised due to inclusion of new sections

Section	Original Text	Revised to Read	Rationale for Change
Table of Contents	NA	NA	Updated to incorporate new sections and revised page numbering
References	NA	NA	Reference list updated to align with body text
Throughout	NA	NA	Correction of minor typographical and/or typographical errors throughout, or text edits for clarity
Formal Protocol Amendments			
Protocol Synopsis			
Exploratory Endpoint	The average change from Baseline for index subjects in the total number of lesions at Day 28.	The change from Baseline for index subjects in the total number of lesions at Day 28.	Updated to keep the endpoint consistent with the protocol body
Inclusion Criteria # 4	All female subjects of childbearing potential must agree to the use of a highly effective method of birth control until 3 months after administration of IP.	All female subjects of childbearing potential must agree to the use of a highly effective method of birth control until 16 weeks after administration of IP.	Duration of contraception and duration of period where female subjects agree to use highly effective method of birth control to align with extended safety follow-up at Week 16
Exclusion Criteria #12 Protocol body text Section 8.3	Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin.	Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin or ivermectin.	Sensitivity to macrocyclic lactones or excipients used in the formulation of ivermectin added to accommodate potential use of ivermectin as scabicidal treatment in regions where it is an accepted standard of care as specified in Section 11.3.

Section	Original Text	Revised to Read	Rationale for Change
Exclusion Criteria #13 Protocol body text Section 8.3	NA	Known or suspected hypersensitivity to any of the components in permethrin 5% cream, to any synthetic pyrethroid or pyrethrin, or to the components of spinosad 0.9% topical suspension.	New exclusion criteria added for sensitivity to the components of permethrin 5% cream or spinosad 0.9% lotion to accommodate potential use of these products as scabicidal treatment in the United States as specified in Section 11.3.
Exclusion Criteria numbering 12 onwards, Protocol body text Section 8.3	12, 13, 14, 15, 16, 17, 18, 19, 20	12, 13, 14, 16, 17, 18, 19, 20, 21	Incremental numbering due to addition of new exclusion criteria # 13
Exclusion Criteria #15, Protocol body text Section 8.3	Pregnant or breastfeeding or planning to become pregnant from Screening until 3 months weeks after treatment with IP.	Pregnant or breastfeeding or planning to become pregnant from Screening until 16 weeks after treatment with IP.	Pregnant or breastfeeding or planning to become pregnant from Screening until 16 weeks after treatment with IP to align with extended safety follow-up at Week 16
Duration of Study Per Subject	Up to 91 days (13 weeks).	Up to 17 weeks	On-study period revised to reflect addition of Week 16 visit
Clinical Procedures and Assessments Statistical Analyses, Paragraph 2	Approximately 15 subjects will be randomly selected from each of the 4 cohorts for collection of sparse blood samples for moxidectin PK analysis.	Approximately 20 subjects will be randomly selected from each of the 4 cohorts for collection of sparse blood samples for moxidectin PK analysis.	Number of subjects in the PK subset increased from 15 to 20 for collection of additional exposure-response data
Clinical Procedures and Assessments: Paragraph 3, Paragraph 4	Following randomization and treatment administration on Day 0, all subjects will be contacted by phone by the site study team on Day 7 and Day 14 to enquire about any adverse events, concomitant medications and the subject's general health. Subjects will return	Following randomization and treatment administration on Day 0, all subjects will be contacted by phone by the site study team on Day 7 to enquire about any adverse events, concomitant medications and the subject's general health. Subjects will return	Details of visits and visit procedures updated to reflect addition of Week 16 extended safety follow-up visit and Day 14 visit revised to occur in-clinic for review of safety and provision of additional concomitant medications

Section	Original Text	Revised to Read	Rationale for Change
	to the clinic on Day 28 and will undergo a thorough full-body clinical and microscopic or dermatoscopic assessment by a trained evaluator, and blood samples will be collected for the subjects in the PK subset. A complete safety review will also be conducted, including safety hematology and biochemistry tests. If at the Day 28 visit the subject has scabies mites confirmed by microscopy or dermoscopy, or their clinical presentation has significantly worsened from Day 0, the subject will receive standard of care treatment for scabies. All subjects will return on Day 42 and Day 84 for routine safety follow up including assessment for adverse events and concomitant medications. If any clinically significant abnormalities are identified in liver function tests or safety hematology tests at the Day 28 visit, additional blood tests should be completed at Day 84. Blood samples will be collected from the PK subset on Day 84.	to the clinic on Day 14 for routine safety follow-up including safety hematology and biochemistry tests, assessment for adverse events and concomitant medications, including to support ongoing management of pruritus. On Day 28, subjects will undergo a thorough full-body clinical and microscopic or dermatoscopic assessment by a trained evaluator in-clinic, and blood samples will be collected for the subjects in the PK subset. A complete safety review will also be conducted, including safety hematology and biochemistry tests. If at the Day 28 visit the subject has scabies mites confirmed by microscopy or dermoscopy, or their clinical presentation has significantly worsened from Day 0, the subject will receive standard of care treatment for scabies per local guidelines. All subjects will return on Day 42 for routine safety follow up including assessment for adverse events and concomitant medications. Blood samples will be collected from the PK subset on Day 42. Extended safety follow up will occur for all subjects after Day 42. All subjects will be contacted by phone by the site study team at	(e.g., emollients) for pruritus management if required.

Section	Original Text	Revised to Read	Rationale for Change
		Week 12 to enquire about any adverse events, concomitant medication and the subject's general health. A routine safety follow up visit will be completed at the end of study at Week 16 including assessment for adverse events and concomitant medications, vital signs and an ECG. If any clinically significant abnormalities are identified in serum chemistry or safety hematology tests at the Day 28 visit, additional blood tests should be completed at Week 16.	
Clinical Procedures and Assessments: Paragraph 6	As subjects with scabies often experience severe pruritus, the use of unmedicated emollient creams and oral over-the-counter antihistamines is permitted during the study for symptom management. Scabicides and topical over the counter and prescription medications used to manage itching (i.e., containing corticosteroids, ferric oxide, crotamiton, calamine etc.) are prohibited during the study as these may influence or mask the effect of treatment.	As subjects with scabies are expected to experience mild to severe pruritus after treatment, the use of unmedicated emollient creams and oral over-the-counter antihistamines is permitted during the study for symptom management. Scabicides and topical over the counter and prescription medications used to manage itching (i.e., containing corticosteroids, ferric oxide, crotamiton, calamine etc.) are prohibited before the Day 28 visit as these may influence or mask the effect of treatment.	Text added to clarify management of pruritus.
Statistical Analyses, Paragraph 1	NA	**Final Analysis and Extended Safety Follow-Up** The final analysis of efficacy and safety data collected through	Overview of general analytic strategy added to describe data analysis at Day 42 and Week 16.

Section	Original Text	Revised to Read	Rationale for Change
		Day 42 will take place after the last subject has completed the Day 42 visit when PK sampling is complete in the PK subset. Following their Day 42 visit, all subjects will continue to be monitored for safety through the extended safety follow-up period to Week 16, during which the study blind will be maintained for personnel with an operational role in study management. Once the last subject has completed the extended safety follow-up period at Week 16, additional safety analyses will be conducted for data collected during the extended safety period.	
Statistical Analyses	**Safety Analyses** Safety will be analyzed using the Safety Analysis Set (SfAS) defined as all index subjects exposed to investigational product. For the SfAS, subjects will be analyzed as belonging to the actual treatment received regardless of their randomized treatment group. Descriptive safety summaries for each treatment group and overall will be provided for treatment emergent adverse events, ECGs, laboratory parameters, and vital signs.	**Safety Analyses** Safety will be analyzed using the Safety Analysis Set (SfAS) defined as all index subjects exposed to investigational product. For the SfAS, subjects will be analyzed as belonging to the actual treatment received regardless of their randomized treatment group. Descriptive safety summaries for each treatment group and overall will be provided for treatment emergent adverse events, ECGs, laboratory parameters, and vital signs. Analyses for the safety data collected during the extended	Overview of general analytic strategy added to describe data analysis at Day 42 and Week 16.

Section	Original Text	Revised to Read	Rationale for Change
		safety follow-up will also be conducted.	
Special protocol requirement / issues: Paragraph 2, Paragraph 3	NA	All subjects enrolled in the study will have active management of their pruritus with provision of emollient and instructions to apply liberally and as often as is required. Investigators should not enroll subjects who perceive their itch to be intolerable at Screening, for whom emollients and/or antihistamines is unlikely to provide relief, and/or who are at risk of not being able to complete the study because of intolerable pruritus.	Provision of emollients to subjects for pruritus management and guidance added to clarify the management of pruritus.
Table 1	NA	Overall schedule of Assessments Table updated to reflect the revised visit schedule and procedures.	Overall schedule of Assessments Table updated to reflect the revised visit schedule and procedures.
Body Text			
Section 5.4.2 (Paragraph 1)	This study will compare each of the three moxidectin doses to placebo to establish background Complete Cure rates in the absence of clear untreated control data for the disease. The placebo arm will control for spontaneous change (natural history of the disease and regression to the	This study will compare each of the three moxidectin doses to placebo to establish background Complete Cure rates in the absence of clear untreated control data for the disease. The placebo arm will provide data on the natural course of scabies, which has been poorly defined in the literature, and address subjective elements of	Supplementary rationale provided to justify the choice of a placebo control design when existing treatments for scabies are approved.

Section	Original Text	Revised to Read	Rationale for Change
	mean), and subjective elements of diagnosis.	symptomology. Several therapies are approved and available for scabies treatment, but data supporting their use are highly variable in quality and consistency: published meta-analyses of historical scabies research has reproducibly found randomized controlled trials have greatly differed in design and execution, with design issues including the absence of blinding or random treatment allocation, and lack of consistency in the definition of the primary endpoint. The uncertainty in the “true” effectiveness of any potential active control poses a significant challenge when designing a comparative study, even when the treatments have been shown to be efficacious in clinical practice. Therefore, a placebo control was selected for this study because active control effect size estimates are not well-supported by the results of historical scabies randomized controlled trials. There is no increased risk to patients of temporary deferral of treatment as long as active pruritus management is undertaken and household contacts are treated. The placebo control presents the most statistically robust method to confirm moxidectin’s efficacy.	

Section	Original Text	Revised to Read	Rationale for Change
Section 5.4.3 (Paragraph 5)	Due to moxidectin's half-life in healthy adult volunteers, the last study day will be extended from Day 28 to Day 84 for the completion of additional safety assessments.	Due to moxidectin's half-life in healthy adult volunteers, the last study day will be extended from Day 28 to Week 16 for the completion of additional safety assessments.	Study duration revised to reflect addition of Week 16 visit.
Section 5.4.3 (Paragraph 5)	NA	The final analysis of efficacy and safety data collected through Day 42 will occur after the last subject has completed the Day 42 visit when PK sampling is complete in the PK subset. An extended safety follow-up will be conducted for all subjects to Week 16, corresponding to approximately 5 half-lives of moxidectin in the scabies patient population.	Supplementary rationale provided to justify primary efficacy and concurrent safety data analysis at the completion of Day 42 visits, and clarification of extended safety follow-up period.
Section 7.4	The study is expected to take approximately 12 months to complete. The on-study period per subject is approximately 91 days, consisting of up to 7 days for Screening and 84 days post-treatment.	The study is expected to take approximately 12 months to complete. The on-study period per subject is approximately 17 weeks, consisting of up to 7 days for Screening and 16 weeks post-treatment.	On-study period revised to reflect addition of Week 16 visit
Section 8.1, Section 9.3.2 (Paragraph 3), Section 9.4.8, Section 10.1, Section 15.6.7	Approximately fifteen subjects from each of the cohorts will be randomly selected for sparse PK sampling at the time of randomization to IP.	Approximately 20 subjects from each of the cohorts will be randomly selected for sparse PK sampling at the time of randomization to IP.	Number of subjects in the PK subset increased from 15 to 20 for collection of additional exposure-response data
Section 8.2 (Inclusion Criteria 4), Section 8.4.1 (Paragraph 2),	All female subjects of childbearing potential must agree to the use of a highly effective method of birth	All female subjects of childbearing potential must agree to the use of a highly effective method of birth	Duration of contraception and duration of period where female subjects agree the use of a highly

Section	Original Text	Revised to Read	Rationale for Change
Section 12.8 (Paragraph 2), Section 12.9 (Paragraph 1)	control until 3 months after administration of IP.	control until 16 weeks after administration of IP.	effective method of birth control extended to align with extended safety follow-up at Week 16
Section 8.5.2	NA	Scabies has a widely variable clinical presentation, ranging from mild disease with few scabies mites and few visible skin changes, to crusted scabies. Pruritus is the most commonly occurring symptom of scabies, but does not occur with the same intensity in all patients. Although some patients may report intense pruritus, several studies show the majority report pruritus as having mild to moderate intensity. Importantly from both the patient management perspective and measurement of trial outcomes, pruritus is known to have a subjective component and is vulnerable to confounding factors such as mood, environmental factors and stress. All subjects enrolled in the study will have active management of their pruritus with provision of emollient and instructions to apply liberally and as often as is required. Investigators should not enroll subjects who perceive their itch to be intolerable at Screening, for whom emollients and/or antihistamines is unlikely to	Section added to clarify the management of pruritus

Section	Original Text	Revised to Read	Rationale for Change
		provide relief, and/or who are at risk of not being able to complete the study because of intolerable pruritus.	
Section 9.2	All post-Baseline visits should be conducted on the specified day, whenever possible. However, when needed, the windows for each visit are: • ± 1 day window for the Day 7 phone call, • ± 2-day window for the Day 14 phone call, • -2 days and +4 days for the Day 28 visit, • ± 2 day window for the Day 42 visit; and, ± 7 day window for the Day 84 visit	All post-Baseline visits should be conducted on the specified day, whenever possible. However, when needed, the windows for each visit are: • ± 1 day window for the Day 7 phone call, • ± 2-day window for the Day 14 visit, • -2 days and +4 days for the Day 28 visit, • ± 2 day window for the Day 42 visit, ± 7 day window for the Week 12 phone call and Week 16 visit	Details of visits and visit windows updated to reflect addition of Week 16 extended safety follow-up.
Section 9.3.2 (Last paragraph)	All other subjects can be discharged approximately 60 minutes post dose, if clinically indicated.	All other subjects can be discharged approximately 60 minutes post dose, if clinically indicated. All subjects should be provided with emollient and instructions for control of their pruritus.	Text added to include provision of emollients to subjects for pruritus management clarified.
Section 9.3.3 (second paragraph)	NA	Subjects should be reminded of the options available to them to manage any symptoms of pruritus.	Provision of emollients to subjects for pruritus management clarified.
Section 9.3.4	All subjects will be contacted by phone on Day 14 ± 2 days. Through open questioning, any	Subjects will return to the clinic on Day 14 ± 2 days. The following	Day 14 visit revised to occur in-clinic for review of safety and provision of additional emollients

Section	Original Text	Revised to Read	Rationale for Change
	adverse events (see Section 12) and concomitant medication (see Section11) should be recorded.	assessments will be performed and documented: • A symptom-directed physical examination (see Section 9.4.3), which will include review of scabies signs and symptoms. • Vital signs (see Section9.4.4). • Blood samples drawn for hematology and clinical chemistry (see Section9.4.6). • AE assessment (see Section 12). • Concomitant medication assessment (see Section 11). Subjects may still be positive for S. scabiei var. hominis by microscopy or dermoscopy at this time and may still be showing the clinical signs of scabies infestation, including pruritus. Subjects should be provided with additional emollient as required. Refer to Section 11.2 for concomitant medication options for management of pruritus.	for pruritus management if required.
Section 9.3.6 (Third bullet)	NA	Blood sample collection for PK assessment will be collected from the PK subset of subjects (see Section 9.4.8).	Terminal phase PK sample collection moved to Day 42 due to Day 84 (Week 12) visit conversion to a phone call.

Section	Original Text	Revised to Read	Rationale for Change
Section 9.3.7	Subjects will return to the clinic on Day 84 ± 7 days. The following assessments will be performed and documented: • A symptom directed-physical examination (see Section 9.4.3). • Vital signs (see Section 9.4.4). • A 12-lead ECG after the subject has been in the supine position for approximately 10 minutes (see Section 9.4.5). • Pregnancy test (urine) for WOCBP (see Section 9.4.7) • Blood sample collection for PK assessment will be collected from the PK subset of subjects (see Section 9.4.8) • If there were clinically relevant laboratory abnormalities at Day 28 that are unresolved, blood samples for hematology and/or clinical chemistry should be drawn (see Section 9.4.6) • AE assessment (see Section 12) Concomitant medication assessment (see Section 11)	All subjects will be contacted by phone on Week 12 ± 7 days. Through open questioning, any adverse events (see Section 12) and concomitant medication (see Section 11) should be recorded.	Day 84 visit nomenclature amended to Week 12 for consistency with nomenclature of extended safety follow up at Week 16. Day 84/Week 12 visit converted to phone call for adverse event and concomitant medication questioning as end-of-study visit now occurring at Week 16. End-of-study assessments (ECG, hematology/safety biochemistry, pregnancy testing) now occurring at Week 16.

Section	Original Text	Revised to Read	Rationale for Change
Section 9.3.8	NA	**Week 16 (Extended Follow Up and Study Conclusion)** Subjects will return to the clinic on Week 16 ± 7 days. The following assessments will be performed and documented: A symptom directed-physical examination (see Section 9.4.3). Vital signs (see Section 9.4.4). A 12-lead ECG after the subject has been in the supine position for approximately 10 minutes (see Section 9.4.5). If there were clinically relevant laboratory abnormalities at Day 28 that are unresolved, blood samples for hematology and/or clinical chemistry should be drawn (see Section 9.4.6). Pregnancy test (urine) for WOCBP (see Section 9.4.7). AE assessment (see Section 12). Concomitant medication assessment (see Section 11)	Week 16 extended safety follow up added to align with duration of moxidectin 5 half-lives in scabies patients.
Section 9.3.10.1 (First sentence)	Subjects should be encouraged to continue in the study until the end of study visit at Day 84.	Subjects should be encouraged to continue in the study until the end of study visit at Week 16.	On-study period revised to reflect addition of Week 16 visit.
Section 9.4.5	At Day 84, ECGs will be performed for all subjects.	At Week 16, ECGs will be performed for all subjects.	Day 84/Week 12 visit converted to phone call and all End-of-study assessments (ECG,

Section	Original Text	Revised to Read	Rationale for Change
			hematology/safety biochemistry, pregnancy testing) now occurring at Week 16.
Section 9.4.6 (Paragraph 2, last sentence)	laboratory tests will also be performed at Day 84	laboratory tests will also be performed at Week 16	End-of-study assessments (ECG, hematology/safety biochemistry, pregnancy testing) now occurring at Week 16.
Section 9.4.7 (Last sentence)	A urine pregnancy test will also be performed at the Day 84 or End of Study visit.	A urine pregnancy test will also be performed at the Week 16 or End of Study visit.	End-of-study assessments (ECG, hematology/safety biochemistry, pregnancy testing) now occurring at Week 16.
Section 9.4.8 (Paragraph 2, first sentence)	Blood samples from the selected subjects will be collected post-dose at 3 hours (± 30 minutes) and 10 hours (± 2 hours) on Day 0, and on Day 28 and Day 84	Blood samples from the selected subjects will be collected post-dose at 3 hours (± 30 minutes) and 10 hours (± 2 hours) on Day 0, and on Day 28 and Day 42	Terminal phase PK sample collection moved to Day 42 due to Day 84 (Week 12) visit conversion to a phone call.
Section 10.2	Clinic staff, subjects, operational Sponsor personnel and delegates will be blinded as to which treatment each subject receives. To maintain the blind, each subject will receive the same number of capsules, regardless of dose. Any break of the study blind, inadvertent or otherwise, will be reported to the Sponsor without revealing the actual treatment assignment, as soon as possible. The site will nominate an unblinded pharmacist to dispense the investigational medication per the randomization received from the IRT system. The Sponsor will	Clinic staff, subjects, operational Sponsor personnel and delegates will be blinded as to which treatment each subject receives until the last subject has completed their Week 16 visit. To maintain the blind, each subject will receive the same number of capsules, regardless of dose. Any break of the study blind, inadvertent or otherwise, will be reported to the Sponsor without revealing the actual treatment assignment, as soon as possible. The site will nominate an unblinded pharmacist to dispense the investigational medication per the randomization	Text added to clarify maintenance of blinding of personnel with an operational role in the study through to study completion (Week 16) in light of the addition of database lock and analysis of efficacy and safety data collected to Day 42. See rationale for changes to Section 15 for further detail.

Section	Original Text	Revised to Read	Rationale for Change
	provide unblinded monitors and unblinded study team members as appropriate. It is anticipated that the study will remain blinded until the completion of the study and following database lock in preparation for the final analysis. The Sponsor will provide written permission to the Study Statistician to break the randomization code.	received from the IRT system. Once all subjects have completed Day 42, the final analysis of efficacy and safety data collected through Day 42 will be conducted. For these analyses, the blind will be broken once data through Day 42 have been cleaned, queries resolved, and the data through Day 42 has been "frozen/locked". The blind break will not be added to the clinical trial database but only applied to the Day 42 analysis files. Neither the individual blind break information (e.g., individual treatment assignments) nor the results will be provided to Investigators, study subjects, the clinical management team, or Medical Monitor involved in day-to-day study operations. These individuals will remain blinded until subjects complete the extended safety follow up with the Week 16 visit and the extended safety data has been cleaned and the clinical trial database locked. Further details will be specified in the Statistical Analysis Plan.	
Section 11.2.2	NA	Investigators should be aware and subjects will be advised that post-scabietic pruritus is to be expected for a period of four to six weeks after treatment, reflecting the persistence of mite antigens even after infection has been resolved,	Section added to clarify permitted concomitant medications for pruritus management prior to Day 28.

Section	Original Text	Revised to Read	Rationale for Change
		and should be counselled that this is not indicative of treatment failure. Explanations of the physiological reasons for the itch should be carefully explained to the subject appropriate to their level of understanding. Unmedicated emollient creams and oral over-the-counter antihistamines are permitted for relief and management of pruritus. Unmedicated emollient creams will be provided to subjects and the Investigator will inform subjects that cream and antihistamines are permitted at any time as required for management of pruritus and should be applied liberally and frequently. Subjects should be encouraged to contact the site regarding the choice of any other concomitant medication to relieve itch prior to using any such medication.	
Section 11.2.3	NA	Pruritus management outlined in Section 11.2.2 should be actively followed. However, although scabicides are prohibited medications prior to the Day 28 visit, subject wellbeing is the priority. As this is a single dose treatment study, withdrawing from treatment is not applicable. If scabicides are required for the subject's health and wellbeing, the subject does not need to withdraw	Section added to clarify prohibited concomitant medications prior to Day 28 and administration of scabicides.

Section	Original Text	Revised to Read	Rationale for Change
		from the protocol for the Investigator to provide such medication to the subject and subjects should continue on-study if they receive scabicides prior to Day 28 (Section 14). An excessive rate of scabicide administration prior to Day 28 can render the study difficult to interpret. The exposure to scabicides prior to Day 28 will be considered a major protocol deviation and subjects will be considered non-responders for the primary analysis (Section 15.6.8).	
Section 11.3	If subjects are positive for scabies mites by microscopy or dermoscopy at Day 28, or their clinical presentation has significantly worsened from Day 0, the subject will be given standard of care therapy per local guidelines.	If subjects are positive for scabies mites by microscopy or dermoscopy at Day 28, or their clinical presentation has significantly worsened from Day 0, the subject will be given treatment with a scabicide. In the United States, permethrin 5% cream or spinosad 0.9% lotion should be used according to labelled instructions. In other regions such as Latin America, approved standard of care therapy per local guidelines may be used. In addition to emollients and over-the-counter antihistamines, subjects may use topical over the counter or prescription medications used to manage itching (i.e. containing corticosteroids, ferric	Clarification of text to ensure that scabicides with supported efficacy data are used to treat subjects after Day 28 (if required) in accordance with labelled instructions or local guidelines as applicable to the regions where the study is being conducted.

Section	Original Text	Revised to Read	Rationale for Change
		oxide, crotamiton, calamine etc.) after Day 28.	
Section 14.1	A subject will be deemed to have completed the study once all trial procedures have been conducted. Any AEs or SAEs still ongoing at Day 84 or the End of Study Visit (whichever occurs earlier) will be followed in accordance with Section 12.	A subject will be deemed to have completed the study once all trial procedures have been conducted. Any AEs or SAEs still ongoing at Week 16 or the End of Study Visit (whichever occurs earlier) will be followed in accordance with Section 12.	Details of AE follow up updated to reflect addition of Week 16 extended safety follow-up.
Section 14.2 (Paragraph 1)	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.	Withdrawal from treatment is not relevant in this single dose 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. Study withdrawal is not required for the Investigator to provide scabicides to the subject prior to Day 28, and subjects should continue on-study if this does occur.	Section clarified to confirm that withdrawal from treatment is not relevant as this is a single dose study. Section clarified to confirm withdrawal of subjects from the study is not required for subjects to receive scabicides prior to Day 28.
Section 15.1 (Paragraph 5)	NA	The final analysis for efficacy and safety data will take place after the last subject has completed their Day 42 assessments. An extended safety follow-up period will continue for collection of safety data after the Day 42 visit through to Week 16. The blind will be maintained during the extended	Overview of general analytic strategy added to describe data analysis at Day 42 and Week 16, and general provisions for maintenance of study blind during the study.

Section	Original Text	Revised to Read	Rationale for Change
		follow up as described in Section 10.2. The safety data collected during this extended follow-up period will be analyzed separately once the last subject has completed their Week 16 visit and is described in Section 15.6.4.5.	
Section 15.1 (Last Paragraph)	General statistical methods of analysis are described below with more detailed descriptions to be provided in the Statistical Analysis Plan (SAP). A separate Pharmacokinetic Analysis Plan (PAP) may be used to describe population-PK and PK/pharmacodynamic analyses. Both the SAP and PAP will be finalized prior to breaking the blind for the Final analysis	General statistical methods of analysis are described below with more detailed descriptions to be provided in the Statistical Analysis Plan (SAP). A separate Pharmacokinetic Analysis Plan (PAP) may be used to describe population-PK and PK/pharmacodynamic analyses. Both the SAP and PAP will be finalized prior to breaking the blind for the Day 42 analysis	Overview of general analytic strategy added to describe data analysis at Day 42.
Section 15.4	NA	The final analysis of efficacy and safety data collected through Day 42 will take place after the last subject has completed the Day 42 visit. Following their Day 42 visit, all subjects will continue to be monitored for safety through the extended safety follow-up period to Week 16, during which the study blind will be maintained, see Section 10.2. Once the last subject has completed the extended safety follow-up period at Week 16, all data collected after the Day 42 visit will be cleaned and the clinical trial	Interim analysis section changed to Final analysis to describe the general analytic strategy for final analysis and analysis of safety data collected during the extended safety follow-up period to Week 16.

Section	Original Text	Revised to Read	Rationale for Change
		database will be locked. The blind will be broken and additional safety analyses conducted for the extended safety period.	
Section 15.6.4 (Last sentence)	NA	Safety data collected during the extended safety follow-up period will be analyzed as outlined in Section 15.6.4.5 below.	Reference provided to describe statistical methods used for analysis of safety data collected during the extended safety follow-up period to Week 16.
Section 15.6.4.5	NA	The analysis of TEAEs collected during the extended safety follow-up after Day 42 will be similar to those described in Sections 15.5.4 and 15.6.4.1. Should the number of TEAEs reported during the extended follow-up not warrant aggregate summaries, then the data will be reported as line listings only. Interpretation of these extended safety data will be compared and contrasted to the safety data collected through Day 42 including continuing TEAEs that resolved or continued during the extended safety follow-up. The collection of concomitant medications continuing, ending or starting during the extended safety follow-up will also be described. Vital signs, physical exams and pregnancy test results will be listed along with any laboratory or ECG assessments taken.	Addition of section to describe the statistical methods used for analysis of safety data collected during the extended safety follow-up period to Week 16.

Section	Original Text	Revised to Read	Rationale for Change
Section 15.6.8 (First sentence)	For the Day 28 Complete Cure rate endpoint, subjects exposed to rescue medication (scabicides) prior to the Day 28 assessment will be imputed as a non-responder.	For the Day 28 Complete Cure rate endpoint, subjects exposed to rescue medication (scabicides, including permethrin, ivermectin, benzyl benzoate, sulfur, lindane, crotamiton, malathion, tea tree oil, or spinosad) prior to the Day 28 assessment will be imputed as a non-responder.	Clarification to define rescue medication as scabicides added.

Appendix 4: Summary of Protocol Amendment 2

Protocol Amendment Number: 2

Date of Protocol Amendment: 28 Dec 2023

Previous Protocol Version: 2, dated 24 Aug 2023

Resultant/Current Protocol Version: 3, dated 28 Dec 2023

Protocol MDGH-MOX-2002 version 2 is amended to correct the wording of primacy efficacy endpoint to keep it consistent with the assessments intended to evaluate the endpoint.

Section	Original Text	Revised to Read	Rationale for Change
Administrative Updates			
Cover page	Protocol version/date: Current 2 (incorporating Amendment 1) Date: 24 Aug 2023 Supersedes version: 1 dated 06 Apr 2023	Protocol version/date: Current 3 (incorporating Amendment 1 and 2) Date: 28 Dec 2023 Supersedes version: 2 (incorporating Amendment 1) dated 24 Aug 2023	Protocol version and date updated to reflect amendment

Section	Original Text	Revised to Read	Rationale for Change
Study acknowledgement	Version 2, 24 Aug 2023	Version 3, 28 Dec 2023	Protocol version and date updated to reflect amendment
Footer	MDGH-MOX-2002 Protocol version 2 Final Incorporating Amendment 1	MDGH-MOX-2002 Protocol version 3 Final Incorporating Amendment 1 and 2	Document name and version updated to reflect protocol amendment
Footer	24 Aug 2023	28 Dec 2023	Document date updated to reflect protocol amendment
Table of Contents	NA	NA	Updated to revised page numbering
Throughout	NA	NA	Formatting and spelling updates/corrections
Appendix 1 Toxicity Grading scale	NA	NA	Replaced the "-" with "to" for the reference ranges for all parameters for clarity.
Formal Protocol Amendments			
Protocol Synopsis			
Study Rationale	Single moxidectin doses up to 36 mg were well tolerated in adults with scabies in protocol MDGH-MOX-2001 and in healthy adult volunteers in two Phase 1 studies. This study will compare each of the three moxidectin doses to placebo in adult outpatients with scabies without significant comorbidities to assess the efficacy of moxidectin in achieving Complete Cure by Day 28.	Single moxidectin doses up to 36 mg were well tolerated in patients aged 18 years and older with scabies in protocol MDGH-MOX-2001 and in healthy volunteers aged 18 years and older in two Phase 1 studies.	Updated to clarify the patient population and permit enrolment of patients aged 18 years and older in the region where 18 to 21 year olds are considered minors.

Section	Original Text	Revised to Read	Rationale for Change
		This study will compare each of the three moxidectin doses to placebo in outpatients aged 18 years and older with scabies without significant comorbidities to assess the efficacy of moxidectin in achieving Complete Cure by Day 28.	
Exploratory Objectives	The exploratory objectives of the study include:	The exploratory objectives of the study include but are not limited to:	Updated to clarify that additional exploratory objectives may be considered
Primary Efficacy Endpoint	The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both: (1) Clinical cure: all signs of scabies have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus. and (2) Microscopic or dermatoscopic cure demonstrating the absence of scabies mites, eggs, and/or scybala, and negative dermoscopy for burrows.	The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both: (1) Clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus). and (2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.	Updated to keep the endpoint consistent with the assessments intended to evaluate the endpoint.
Exploratory Endpoints	The exploratory endpoints of the study include:	The exploratory endpoints of the study include but are not limited to:	Updated to clarify that additional exploratory objectives may be considered

Section	Original Text	Revised to Read	Rationale for Change
Body Text			
Section 5.3.2	The safety and efficacy of moxidectin in patients with S. scabiei var hominis infestation has been evaluated in a Phase 2, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in adults with scabies (protocol MDGH-MOX-2001) where 22 subjects received moxidectin per oral at doses between 2 mg and 36 mg	The safety and efficacy of moxidectin in patients with S. scabiei var hominis infestation has been evaluated in a Phase 2, randomized, double-blind, parallel group dose finding study of single oral doses of moxidectin in patients aged 18 years and older with scabies (protocol MDGH-MOX-2001) where 22 subjects received moxidectin per oral at doses between 2 mg and 36 mg	Clarification of patient population
Section 5.3.2.1	There were no clinically relevant effects of age, gender, race, weight, renal function, or hepatic function on the PK of moxidectin in the original population PK model developed in adults.	There were no clinically relevant effects of age, gender, race, weight, renal function, or hepatic function on the PK of moxidectin in the original population PK model developed in healthy volunteers and patients with onchocerciasis aged 18 years and older. For more information, refer to the IB.	Clarification of patient population Added IB reference at the end of paragraph for details of clinical pharmacology.
Section 5.3.2.2 Paragraph 1	In 6 studies in healthy adult volunteers, moxidectin was well tolerated when given as a single dose of between 3 mg and 36 mg.	In 6 studies in healthy volunteers aged 18 years and older, moxidectin was well tolerated when given as a single dose of between 3 mg and 36 mg.	Clarification of patient population.

Section	Original Text	Revised to Read	Rationale for Change
Section 5.3.2.2 Paragraph 3	Protocol 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.	Protocol 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 volunteers aged 18 years and older.	Clarification of patient population.
Section 5.3.2.2.3 Paragraph 1	Safety and efficacy of moxidectin in adults with scabies was evaluated in protocol MDGH-MOX-2001.	Safety and efficacy of moxidectin in patients aged 18 years and older with scabies was evaluated in protocol MDGH-MOX-2001.	Clarification of patient population.
Section 5.4.1 Paragraph 2	This dose range was well tolerated in adults with scabies in protocol MDGH-MOX-2001 and in healthy adult volunteers in two Phase 1 studies.	This dose range was well tolerated in patients aged 18 years and older with scabies in protocol MDGH-MOX-2001 and in healthy volunteers aged 18 years and older in two Phase 1 studies.	Clarification of patient population.
Section 5.4.3 Paragraph 1	This study also aims to assess the safety of three strengths of single moxidectin doses in adults with scabies.	This study also aims to assess the safety of three strengths of single moxidectin doses in patients aged 18 years and older with scabies.	Clarification of patient population.
Section 5.4.3 Paragraph 3 and throughout Paragraph 5	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 subjects ≥ 4 years with, or at risk of onchocerciasis, at an 8 mg single dose per oral.	Only subjects aged 18 years and older will participate in this study as there are limited data on the pediatric use of moxidectin, which has only been administered to subjects ≥ 4 years with, or at risk of onchocerciasis, at an 8 mg single dose per oral. 'Adult' is replaced with 'Patients aged 18 years and older'.	Clarification of patient population and permit enrolment of patients aged 18 years and older in the region where 18 to 21 year olds are considered minors.

Section	Original Text	Revised to Read	Rationale for Change
Section 6.1.3	The exploratory objectives of the study include:	The exploratory objectives of the study include but are not limited to:	Updated to clarify that additional exploratory objectives may be considered
Section 6.2.1 and Section 15.5.1	The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both: (1) Clinical cure: all signs of scabies have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus. and (2) Microscopic or dermatoscopic cure demonstrating the absence of scabies mites, eggs, and/or scybala, and negative dermoscopy for burrows.	The primary efficacy endpoint is the proportion of index subjects achieving Complete Cure at Day 28. Complete Cure is defined as demonstration of both: (1) Clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/noninflammatory lesions and pruritus). and (2) Microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermoscopy for burrows.	Updated to keep the endpoint consistent with the assessments intended to evaluate the endpoint.
Section 6.2.3	The exploratory endpoints include:	The exploratory endpoints include but are not limited to:	Updated to clarify that additional exploratory endpoints may be considered
Section 7.1	This is a randomized, double-blind, placebo-controlled, dose ranging multinational, multi-center, parallel group, efficacy and safety study of orally administered moxidectin in adults with scabies	This is a randomized, double-blind, placebo-controlled, dose ranging multinational, multi-center, parallel group, efficacy and safety study of orally administered moxidectin in patients aged 18 years and older with scabies	Clarification of patient population.

Section	Original Text	Revised to Read	Rationale for Change
Section 9.4.9	• Secondary bacterial infections will be noted if present	• Secondary bacterial infections will be noted if present (note that secondary bacterial infections are not included in the assessment of Complete Cure).	Clarification added as secondary bacterial infections are not considered under the definition of Complete Cure as they are not a routine sign of scabies infestation.
Section 15.1	The study is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of a single oral administration of moxidectin for each of the three moxidectin doses compared to matching placebo with respect to the Day 28 Complete Cure rate in adult subjects with scabies	The study is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of a single oral administration of moxidectin for each of the three moxidectin doses compared to matching placebo with respect to the Day 28 Complete Cure rate in subjects with scabies aged 18 years and older.	Clarification of patient population.
Section 15.5.3	Exploratory endpoints include:	Exploratory endpoints include but are not limited to:	Updated to clarify that additional exploratory endpoints may be considered.