Clinical Study Protocol

Study Title:	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.			
Sponsor:	Medicines Development for Global Health			
Investigational New Drug (IND) No (If applicable):	IND 126876			
Protocol Number:	MDGH-MOX-1006			
Medical Monitor:	Dr Jolanta Airey Consultant Clinical Development Physician SJA Consulting Services, Australia [redacted]			
Protocol Version/Date:	**Current:**	Final v1.5 (incorporating Amendments 1, 2, 3, 4 and 5)	**Date:**	03 Jul 2020
	Prior version:	Final v1.4 (incorporating Amendments 1, 2, 3 and 4)	**Date:**	21 Jan 2020

CONFIDENTIALITY STATEMENT

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

Until publication of this protocol following approval by applicable Regulatory Authorities and Ethics Committees, any unpublished information contained in this document is the property of, or under the control of Medicines Development for Global Health and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and any applicable Regulatory Authority or Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational product described in the protocol. Prior to publication, you will not disclose any of the information to others without written authorization from Medicines Development for Global Health, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

MEDICINES DEVELOPMENT FOR GLOBAL HEALTH

LEVEL 1, 18 KAVANAGH STREET

SOUTHBANK, VICTORIA 3006, AUSTRALIA

STUDY ACKNOWLEDGEMENT

MDGH-MOX-1006

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.

V1.5, incorporating Amendments 1, 2, 3, 4 and 5, 03 Jul 2020

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

[redacted]		15 Jul 2020 Date

INVESTIGATOR STATEMENT

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

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

[redacted]		[redacted]
Principal Investigator's (PI) Name (Printed)		Signature
		[redacted]
		Date (dd mmm yyyy)

STUDY SYNOPSIS (Project Summary)

Protocol Number:	MDGH-MOX-1006
Study Title:	An open-label study of the safety and pharmacokinetics 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.
Investigational Product:	Moxidectin
Indication:	Treatment of onchocerciasis
Development Phase:	Phase I
Background:	Moxidectin, a macrocyclic lactone of the milbemycin class, has broad activity against filarial and ectoparasitic diseases. Moxidectin has been shown in clinical trials to be well tolerated when administered as a single dose of between 2 and 36 milligrams (mg). A Phase III clinical trial completed in adults and adolescents (aged 12 years and over) with onchocerciasis demonstrated that moxidectin 8 mg provided superior skin microfilariae suppression compared to ivermectin (Mectizan®; Merck & Co., Inc.), the current standard of care for onchocerciasis. Moxidectin 8 mg as a single oral dose is approved by the United States Food and Drug Administration (US FDA) for the treatment of onchocerciasis due to *Onchocerca (O.) volvulus* in patients aged 12 years and over. The optimal dose of moxidectin to treat onchocerciasis in children less than 12 years of age is not known. The pharmacokinetics of moxidectin in children and adolescents aged 4 to 17 years is also not known. This study minimizes the number of children and the number of invasive procedures for each child. In-center stays with a parent or guardian will be implemented to reduce the travel required and maximize their access to support during study procedures. Efficacy has been demonstrated in the Phase III study and does not form an objective of this study. As such, skin snipping to determine skin microfilariae density is not included in this study. To balance risks in study participation with potential individual benefit from treatment, participants will be recruited from an area where onchocerciasis is endemic. Pharmacokinetic results are not anticipated to be affected by infection status. Potential adverse events (AEs) associated with effective treatment of onchocerciasis are expected to be manageable and transient.

Rationale:	To characterize the pharmacokinetics and safety of moxidectin in children (aged 4 to 11 years) and adolescents (aged 12 to 17 years) and to enable determination of an optimal dose for treatment of children 4 to 11 years.
Design:	Prospective, age-stratified, adaptive, open-label, single-dose pharmacokinetic and safety study of moxidectin in children and adolescents aged 4 to 17 years with, or at risk of, infection with *O. volvulus*.
Number of Subjects:	Approximately 27 with approximately 9 subjects per cohort (to a maximum of 63, depending on pharmacokinetic outcomes).
Number of Centers:	One site – School of Public Health, University of Health and Allied Sciences (UHAS) Research Centre, formerly the Onchocerciasis Chemotherapy Research Centre (OCRC) research facility, Volta Region, Ghana.
Primary Objective:	Identify an optimal dose of moxidectin for the treatment of children aged 4 to 11 years with onchocerciasis.
Secondary Objectives:	Evaluate the safety and pharmacokinetics of a single dose of moxidectin in children and adolescents aged 4 to 17 years.
Primary Endpoints:	Dose(s) for children aged 4 to 11 years will be selected based on non-compartmental exposure metrics including area under the concentration time curve (AUC) assessed up to and including Day 28 and a population pharmacokinetic model.
Secondary Endpoints:	Safety endpoints include the incidence and severity of AEs, physical examination findings, changes in vital signs, and laboratory safety parameters at all time points in the study. Pharmacokinetic parameters of moxidectin in children and adolescents aged 4 to 17 years, including maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), and other pharmacokinetic parameters will be determined by non-compartmental analysis or other methods, as appropriate.

Inclusion Criteria:	1. Aged 4 to 17 years, inclusive: Cohort I: 12 to 17 years; Cohort II: 8 to 11 years; Cohort III: 4 to 7 years. 2. Live in a region designated by the World Health Organization (WHO) as endemic for *O. volvulus* infection (World Health Organization 2019). Specifically, participants will be recruited from the Kpassa sub-district of the Nkwanta North district. The specific communities will include Wii, Jagri-Do, and Azua, where mass drug administration with ivermectin for onchocerciasis commenced in October 2017; 3. Willing and able to remain at the research center from Screening up to Day 7; 4. Provision of parental or guardian written informed consent and child assent / lack of expression of 'deliberate objection' (as appropriate for age); 5. Females of childbearing potential must commit to using a highly effective method of contraception as per local family planning guidelines from Baseline (pre-treatment on Day 0) until approximately 6 months (Week 24) after treatment with study drug.
Exclusion Criteria:	1. History of serious medical or psychiatric condition which, in the opinion of the investigator, would put the subject at increased risk by participating in the study or jeopardize study outcomes; 2. Known or suspected concurrent clinically significant renal, cardiac, pulmonary, vascular, metabolic (thyroid disorders, adrenal disease), immunological disorders or malignancy, congenital heart disease, chronic lung disease; 3. Has received an investigational product within 28 days, or 5 half-lives, of Baseline, whichever is longer; 4. Has received ivermectin or any other anti-helminthic treatments within 28 days of Baseline; 5. Has received a vaccination within 7 days of Baseline; 6. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin; 7. Poor venous access; 8. Unable to swallow tablets (flat oval, 8.0 millimeters (mm) x 4.5 mm x 3.0 mm); 9. Weight: Cohort I (12 to 17 years): < 30 kg Cohort II (8 to 11 years): < 18 kg Cohort III (4 to 7 years): < 12 kg 10. Clinically relevant laboratory abnormalities at Screening, including: o Hemoglobin < 9.5 grams per deciliter (g/dL) o Neutrophil (granulocyte) count < 1.5 x 10^9/L o Platelet count < 110 x 10^9/L o Alanine aminotransferase (ALT) > 1.5 times the upper limit of normal range (ULN)

	○ Total bilirubin > 1.5 times ULN 11. Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV) positive; 12. Known or suspected malaria or other ongoing viral, bacterial, or plasmodium infection at Screening and/or Baseline; 13. *Loa loa* co-infection; 14. Unwilling, unlikely or unable to comply with all protocol specified assessments; 15. For females of child-bearing potential, pregnant or breastfeeding, or planning to become pregnant; 16. Previous enrolment in this study; 17. Is a sibling of another child already enrolled in this study.
Investigational Product:	Moxidectin oral tablets 2 mg.
Comparator:	None
Design Details and Dose Regimens:	Each subject will receive a single oral dose of moxidectin. Three age-defined cohorts will be recruited: i. Cohort I (12 to 17 years, n = 9) will receive moxidectin 8 mg (4 x 2 mg tablets) ii. Cohort II: (8 to 11 years, n = 9) will receive moxidectin 8 mg (4 x 2 mg tablets) A sentinel group of three subjects will be enrolled in Cohort II. If safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled. Once all Cohort I and II subjects complete Day 28, a Data and Safety Monitoring Board (DSMB) will review safety and pharmacokinetic data to recommend if Cohort III is enrolled, and if so, the dose of moxidectin to be administered. iii. Cohort III: children 4 to 7 years, inclusive (n = 9) will receive a single oral dose of moxidectin at a dose to be determined from analyses of Cohorts I and II. Initially, a sentinel group of 3 subjects will be enrolled. If safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled. If for Cohorts II and III, the starting dose results in at least 3 of the subjects having moxidectin exposures above the target range, a revised dose will be determined in decrements of 2 mg and the Cohort will be repeated with at least 9 new subjects enrolled at the new dose. If for Cohort III, the starting dose results in at least 3 subjects having moxidectin exposures below the target range, a revised dose will be determined in increments of 2 mg to a maximum dose of 8 mg.

Duration of Treatment Per Subject:	Approximately 28 weeks total: up to 30 days prior to Day 0 for consent and pre-screening, up to 7 days prior to Day 0 for Screening, 7 days in-center and 23 weeks outpatient follow up post-treatment.
Study Procedures:	Consent and assent (or lack of expression of 'deliberate objection', as appropriate for age) will be obtained in the village setting and may be obtained up to 30 days prior to Baseline. After obtaining written informed consent from the parent(s)/guardian(s) and assent (or determining lack of expression of 'deliberate objection') from the child (see Section 14.1.2 for details), children meeting eligibility criteria that are able to be evaluated in the village, will be invited to attend the research center for further screening, together with one parent or guardian. Transport by car to and from the research center will be provided. Screening procedures will be completed at the research center from Day -7 to Day -1 to determine eligibility to participate. On the morning of Day 0 the Baseline assessment and confirmation of eligibility will be completed. Subjects meeting all of the inclusion and none of the exclusion criteria will receive treatment and be monitored post-treatment throughout the day. They will remain in the research center until Day 7, and then return to the center at Days 14 and 28, and at Week 12 for pharmacokinetic sample collection and safety review and at Week 24 for a final safety review. For further details of clinical study procedures, please refer to schedule of assessments as presented in Table 1. Additional visits and/or assessments may be conducted as clinically indicated. These data will be captured in the Case Report Form (CRF) as unscheduled visits, as appropriate.
Contraindications to Further Dosing:	Not applicable on an individual subject basis as all subjects will receive a single dose only. Dosing of additional subjects in the study will be guided by the DSMB.
Safety Parameters:	Physical examinations. Vital signs: Respiratory rate, pulse rate, temperature, blood pressure. Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count and RBC morphology (if abnormal), white blood cell and differential white blood cell count, platelet count. Clinical chemistry: aspartate aminotransferase (AST), ALT, gamma-glutamyl transferase (GGT), amylase, creatine kinase, total protein, albumin, direct and total bilirubin, sodium, potassium, chloride, bicarbonate, phosphorus, blood urea nitrogen (BUN), creatinine.

Specialized Tests and Analyses:	Plasma pharmacokinetic samples will be collected at Screening (to avoid an extra blood collection time point pre-dose) then at Hours 1, 2, 4, 8, 24 and 72 and Days 7, 14 and 28 and Week 12 post dose. Testing for HIV, hepatitis B surface antigen and hepatitis C virus will be conducted at Screening. Loiasis will be assessed by daytime blood smear, if required.
Sample Size Determination:	No formal sample size determination has been undertaken. Approximately 9 subjects in each Cohort at a given dose is considered to be an adequate sample size for full characterization of the pharmacokinetics of a single dose of moxidectin.
Statistical Analyses:	No formal hypothesis testing will be performed in this study. Analyses will be descriptive. All planned analyses, including non-compartmental pharmacokinetics, population pharmacokinetic modelling and safety analyses, will be described in a Statistical Analysis Plan (SAP) that will be finalized prior to commencing data analysis. At the conclusion of analysis of data for Cohorts I and II, the existing population pharmacokinetic model will be updated with these data and formal simulations of AUC from time 0 extrapolated to infinity ($_{0\text{-inf}}$) and C_{max} will be performed by age, and other possible covariates to support ongoing dose decisions and initiation of Cohort III. At the end of the study, the population pharmacokinetic model will be updated with data from all cohorts to support the dose rationale for children.
Data and Safety Monitoring Board (DSMB):	A DSMB of independent experts has been established, with a charter that defines in detail its roles and responsibilities. The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II and advise the sponsor on the dose with which Cohort III will be initiated. The DSMB will also meet as required during the study. The DSMB will receive any reported Serious Adverse Events (SAEs) throughout the study. The DSMB will recommend to the Sponsor whether the trial may continue as planned or if the trial should be modified or stopped. Any decision to modify or stop the study will be communicated to investigators, and regulatory agencies by the Sponsor. Ethics Committees will be notified by the investigator according to their requirements.

Special Protocol Requirements or Issues:	The study will be conducted in an area(s) endemic for *O. volvulus* and currently participating in implementation of ivermectin treatment. The study will recruit subjects in communities in the Volta Region of Ghana familiar with clinical research and the research center in Hohoe where the in-center period of the study will be conducted, since participants in the Phase III study of moxidectin were recruited from these villages. This will facilitate understanding of the study and enable parents/guardians, as well as children, to provide appropriate informed consent and assent for study participation.

Table 1: Table of Assessments

Assessment	Consent & Pre-screening	Screening	On-Study Period											Exit Evaluation			
			In-center										Outpatient				
	D-30 to D-1	D-7 to D-1	D0						D1 (H24)	D2 (H48)	D3 (H72)	D7	D14	D28	W12	W24 (or Unscheduled / Early Withdrawal visit)
			Pre-Dose / BL	H0	H1	H2	H4	H8								
Allowable assessment window					±10M	±10M	±30M	±1H	±2H	±2H	±2H	±1D	±2D	±4D	±14D	±28D
Informed consent / assent	X															
Inclusion/exclusion criteria	X	X	X													
Medical history	X	X														
Physical examination [a]		X														
Targeted physical examination [a]			X		(X)	(X)	(X)	(X)	X	X	X	X	X	X	X	X
Vitals signs [b]		X	X		X	(X)	(X)	X	X	X	X	X	X	X	X	X
Height		X														
Body weight		X												X		X[i]
Arm circumference		X														
12-lead ECG		X			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Hematology [c,g]		X										X		X	X	(X)
Clinical chemistry [c,g]		X										X		X	X	(X)
Pregnancy test [d]		X												X	X	X[i]
Pharmacokinetic blood sampling [g]		X			X	X	X	X	X		X	X	X	X	X	
Screening for co-infections [f]		X														
Moxidectin administration [h]				X												
Adverse events	X<----------->X															
Concurrent medications	X<----------->X															

Abbreviations: X = required; (X) = as clinically indicated; M = minutes; H = hour; D = day; W = Week; ECG = electrocardiogram; BL = Baseline.

a. A full physical examination at Screening, a targeted physical examination (informed by concurrent conditions, signs, symptoms and adverse events) at all subsequent time points.

b. Blood pressure, pulse, temperature and respiratory rate will be measured lying semi-supine for 5 mins. Unscheduled recordings will be performed if clinically indicated.

c. Blood samples (approx. 2 milliliter (mL) total) for hematology and biochemistry testing will be drawn within 3 days prior to the Baseline visit (Day 0) and results available prior to dosing.

d. Serum pregnancy testing will be conducted at Screening and urine pregnancy testing for all other time points for female subjects who are of child-bearing potential (may be conducted at unscheduled visits as clinically indicated).

f. Testing for Human Immunodeficiency Virus (HIV), hepatitis B, and hepatitis C. *Loa loa* testing only for subjects who have a history of residence in an endemic area.

g. Application of topical local anesthetic is recommended prior to obtaining blood samples via cannula or needle.

h. Study drug dosing will be after an overnight fast. Breakfast may be given 2 hours after dosing (and following the H2 blood sample collection).

i. Not required at unscheduled visits unless clinically indicated.

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ABBREVIATIONS

Abbreviation	Definition
%	percent/percentage
<	less than
>	greater than
≤	less than or equal to
≥	equal or greater to
°C	degrees Celsius
°F	degrees Fahrenheit
μg	microgram(s)
μL	microliter(s)
μmol	micromole(s)
μM	micromolar
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	AUC from time 0 extrapolated to infinity
$AUC_{0\text{-}last}$	AUC from time 0 extrapolated to the last observed concentration
BL	Baseline
BUN	blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CL	apparent plasma clearance
CL/F	apparent plasma clearance, fasting
CLd2	clearance from the second compartment
cm	centimeter(s)
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRF	case report form
$cumAUC_{0\text{-}t}$	cumulative AUC from time 0 extrapolated to time t (where t = 24, 48, and 72 hours)
CYP	cytochrome
D	day
DAIDS	Division of AIDS
dL	deciliter
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ESPEN	Expanded Special Project for Elimination of Neglected Tropical Diseases
fL	femtoliter(s)
g/dL	grams per deciliter

Abbreviation	Definition
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GHS	Ghana Health Service
H or h	hour
HIV	human immunodeficiency virus
HV	healthy volunteers
IC_{50}	half maximal inhibitory concentration
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug
IQR	interquartile range
IU	international units
kg	kilogram(s)
L	liter(s)
LAR	legally acceptable representative
LC	liquid chromatography
LD_{50}	lethal dose, 50% fatalities in test sample
M	minute
MDGH	Medicines Development for Global Health
mg	milligram(s)
mL	milliliter(s)
mm	millimeter(s)
mmHg	millimeters of mercury
mmol/L	millimoles per liter
MS	mass spectrometry
N or n	number
ng	nanogram(s)
NOAEL	no observed adverse effect level
O. volvulus	*Onchocerca volvulus*
OCRC	Onchocerciasis Chemotherapy Research Centre
OV16 lgG4	Onchocerca volvulus 16 antigen immunoglobulin G4
pg	picogram(s)
P-gp	P-glycoprotein
PI	Principal Investigator
QTc	corrected QT (interval)
QTcB	QTc – Bazett's correction formula
QTcF	QTc – Fridericia's correction formula
RBC	red blood cell
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
SRM	study reference manual
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T_{max}	time to maximum observed plasma concentration
UHAS	University of Health and Allied Sciences
ULN	upper limit of normal range
US	United States
US FDA	United States Food and Drug Administration
Vc	central volume of distribution
Vp2	volume of distribution of the second peripheral compartment
W	week
WHO	World Health Organization

2 STUDY CONTACTS

The study will be conducted at the School of Public Health, University of Health and Allied Sciences (UHAS) Research Centre, formerly the Onchocerciasis Chemotherapy Research Centre (OCRC) research facility, Volta Region, Ghana.

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

3 INTRODUCTION

3.1 Onchocerciasis

Onchocerciasis (river blindness) is a serious, debilitating, and stigmatizing parasitic disease caused by the helminth *O. volvulus*. It is recognized as an important public health issue by health authorities worldwide and is listed by the WHO (African Programme for Onchocerciasis Control 2015) and US FDA (The Henry J. Kaiser Family Foundation 2015) as one of the neglected tropical diseases for which new treatments are sought.

Onchocerciasis is endemic in sub-Saharan Africa (Zoure et al. 2014). More than 200 million people are considered to be at risk of infection (World Health Organization 2018). Onchocerciasis is the second leading cause of infectious blindness (after trachoma) and the fourth leading cause of preventable blindness worldwide. In addition to substantial ocular and cutaneous morbidity, excess mortality of visually impaired and non-impaired individuals with heavy onchocercal infection accounted for 5% of deaths in the Onchocerciasis Control Program (a WHO-managed international collaboration that ran from 1974 to 2002) area in West Africa (Prost and Vaugelade 1981, Pion et al. 2002, Little et al. 2004).

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

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

3.2 Current Treatment and Unmet Need

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

treatment of onchocerciasis is a single oral dose of ivermectin 150 micrograms (µg) per kilogram (kg). In Africa, the most commonly used retreatment interval is during mass drug administration is 12 months. The aim of these community-directed ivermectin treatment programs is to achieve control of the disease as a public health problem in affected communities (Uniting to Combat Neglected Tropical Diseases 2012). Ultimately, the WHO and onchocerciasis endemic countries are working towards elimination of onchocerciasis where feasible.

Despite the positive impact of ivermectin treatment, onchocerciasis is still a cause of significant morbidity. Suboptimal responses to ivermectin have been observed in several populations in Africa over several years and have been reported in the literature in both ivermectin-naïve and ivermectin-experienced patients (African Programme for Onchocerciasis Control 2015, Awadzi et al. 2004a, Awadzi et al. 2004b, Ardelli et al. 2005, Osei-Atweneboana et al. 2007, Basanez et al. 2008, Pion et al. 2011, Bakajika et al. 2013, Coffeng et al. 2013, Awadzi et al. 2014). Ivermectin recipients in the Phase III study also provide further evidence of this (Opoku et al. 2018). Adolescents (12 to 17 years of age) with pre-treatment microfilariae densities of between 10.51 and 74.21 microfilariae per mg of skin were treated in the Phase III study (n = 77). Fifteen (15) of 24 (62.5%) ivermectin treated adolescents did not achieve zero skin microfilariae density at any time point (Month 1, Month 6, Month 12 and/or Month 18) compared with 1 of 53 (1.9%) moxidectin treated adolescents. Two-thirds of these subjects were enrolled in the Volta region of Ghana (see Section 3.4.3 for further detail).

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

Moxidectin is a macrocyclic lactone of the milbemycin class. It is derived (semi-synthetic) from the actinomycete *Streptomyces cyanogriseus*.

3.3.1 Nonclinical

3.3.1.1 Pharmacology

The mechanism by which moxidectin exhibits its effect against *O. volvulus* is not known. The primary pharmacology of moxidectin is proposed to be through binding to the glutamate-gated chloride channels. Moxidectin also binds to gamma-aminobutyric acid (GABA) receptors and/or adenosine triphosphate-binding cassette transporters. This leads to increased permeability, influx of chloride ions, hyperpolarization and muscle paralysis (Arena et al. 1995, Martin et al. 2002, Yates et al. 2003). Additionally, there is a reduction in parasite motility (Tompkins et al. 2010) and reduced excretion of immunomodulatory proteins of both male and female adult worms (Wolstenholme and Rogers 2005, Geary and Moreno 2012, Wolstenholme et al. 2016). Studies also suggest that while moxidectin is not effective in killing the adult worms, it does reduce adult worm fertility (Bourguinat et al. 2007, Stitt et al. 2011).

Moxidectin exhibits anthelminthic activity across the nematode and arthropod phyla (Geary and Moreno 2012) and has demonstrated efficacy in a number of *Onchocerca* species, including *O. ochengi* in cattle (Trees et al. 2000), *O. cervicalis* in horses (Monahan et al. 1995, Mancebo et al. 1997), as well as *Dirofilaria immitis* in dogs (Nolan and Lok 2012). Moxidectin was not macrofilaricidal in the *Onchocerca ochengi* model in cattle (Trees et al. 2000).

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

3.3.1.2 Nonclinical Safety

3.3.1.2.1 Safety Pharmacology

The safety pharmacology of moxidectin has been studied using a panel of *in vitro* and *in vivo* pulmonary, neurofunctional and cardiac assessments. Moxidectin did not show significant binding activity to 64 different biological receptors in the NovaScreen assay. The inhibitory concentration for a 50% decrease (IC_{50}) in the human ether-a-go-go-related gene current was calculated at > 10 micromolar (µM) (6.4 µg/milliliter (mL)) moxidectin.

Moxidectin caused mild neurofunctional and respiratory effects in rats as well as a mild reduction in heart rate relative to baseline in dogs. Oral administration of 1.0 mg/kg moxidectin to beagle dogs resulted in a statistically significant decrease in heart rate, but no consistent changes in systolic, diastolic or mean arterial blood pressure. There were no effects on the ECG, including the corrected QT (QTc) interval.

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

3.3.1.2.2 Toxicology

The nonclinical toxicology profile of moxidectin is characterized by low acute toxicity, consisting mostly of transient central nervous system (CNS)-related clinical signs. Decreased body weight and/or body weight gain were also common findings, which were attributed to a change in consumption of food. In single and repeat dose toxicity studies with moxidectin, transient CNS signs were reported in mice, rats and dogs. There was no target organ toxicity in any of the studies based on evaluation by 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.

Macrocyclic lactones are known to interact with GABA-A receptors, expressed in nematodes and in the mammalian CNS. There was no histological evidence for direct neurotoxicity in nonclinical studies, but transient neurobehavioral effects were noted. Entrance into the brain is restricted by the P-glycoprotein (P-gp) efflux transporter, while toxicity is mediated through the brain GABA-A receptors. In P-gp-deficient mice, moxidectin was less toxic than ivermectin (lethal dose in 50% (LD_{50}) was 0.46 and 2.3 micromoles (μmol)/kg for ivermectin and moxidectin, respectively), had a lower brain-to-plasma concentration ratio and entered into the brain more slowly than ivermectin (Menez et al. 2012). Higher brain concentrations are required for moxidectin toxicity than ivermectin which causes a greater potentiation of GABA action. Differences in the accumulation of ivermectin and moxidectin in the brain and in the interaction of ivermectin and moxidectin with GABA-A receptors account for differences in neurotoxicity seen in nonclinical studies (Menez et al. 2012).

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

3.3.1.2.3 Juvenile Nonclinical Safety

The toxicity profile and toxicokinetics of moxidectin in juvenile dogs was evaluated in a pivotal single-dose oral (capsule) study. Moxidectin was administered to juvenile (11 weeks old) dogs at doses up to 3 mg/kg. There were no deaths and clinical observations related to the CNS (i.e. tremors, ataxia, abnormal posture, decreased motor activity, salivation, emesis, ptosis, and disorientation) were observed in all juvenile dogs in the highest dose group (3 mg/kg). The CNS-related clinical observations were not considered adverse because the findings were transient (occurring only within 24 hours after dosing and not during the remainder of the 12-week observation period) and because the dogs did not require medical treatment. There were no moxidectin-related clinical signs at lower doses, and no other parameters were affected by moxidectin. Therefore, the no observed adverse effect level NOAEL) in juvenile dogs was 3 mg/kg.

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

3.3.1.3 Absorption, Distribution, Metabolism and Excretion

Moxidectin is a Biopharmaceutics Classification System Class 2 compound with high permeability and low solubility, which is not affected by pH.

The pharmacokinetics 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. Moxidectin is minimally metabolized *in vivo*. Moxidectin has also been shown to be a weak substrate of breast cancer resistance protein 1 (Perez et al. 2009). Moxidectin produced weak or no inhibition of seven major human cytochrome (CYP) P450 enzymes *in vitro* but did induce CYP3A4 messenger ribonucleic acid and enzyme activity *in vitro*. However, a subsequent clinical study showed that moxidectin was not a CYP3A4 inducer *in vivo* (Section 3.3.2.1).

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

3.3.2 Clinical

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

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

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

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

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

3.3.2.1 Clinical Pharmacology

Moxidectin displays linear, dose-proportional pharmacokinetics. Following a single oral moxidectin dose (ranging from 3 mg to 36 mg, tablet or solution) administered to fasting healthy volunteers, the non-compartmentally-derived apparent moxidectin plasma clearance (CL/F) ranged from 2760 to 3506 mL/h in healthy volunteers and 3500 mL/h in patients and the mean $t_{½}$ ranged from 485 to 1139 hours (approximately 20 to 47 days). Moxidectin was rapidly absorbed; the median T_{max} in a fasted state was 3 to 4 hours post-dose. Moxidectin has a large apparent volume of distribution, and rapid decline of moxidectin concentrations occurred within 48 hours of dose administration in all studies, and, thereafter, plasma concentrations declined slowly in accordance with the long $t_{½}$. Population pharmacokinetic analyses showed that the long $t_{½}$ was governed by tissue distribution rate-limited elimination.

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

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

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

3.3.2.2 Clinical Safety & Efficacy

3.3.2.2.1 Overview of Safety in Healthy Volunteers

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

AE and laboratory findings reported for each of the completed Phase I studies are summarized in the Investigator's Brochure.

3.3.2.2.2 Overview of Safety and Efficacy in Patients with Onchocerciasis

The safety of moxidectin has been evaluated in patients with onchocerciasis. Signs and symptoms associated with microfilarial death, sometimes referred to as the "Mazzotti reaction" were commonly observed. These reactions are caused by an immunologically-mediated reaction to the death of microfilariae and manifest as pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia. Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision, photophobia, changes in visual acuity, hyperemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment.

In the two studies conducted in onchocerciasis patients (3110A1-200-GH and ONCBL60801), the profile of AEs reported for moxidectin was similar to the profile in ivermectin recipients. In these studies, the most commonly occurring events were pruritus, edema, headache, hypotension and compensatory tachycardia, rash and urticaria, myalgia, arthralgia, pyrexia and chills, lymphadenopathy, paresthesia and asthenia (see Table 2). These events were transient and self-limiting, generally occurring and resolving within the first week of treatment. In general, there was a transient (first 48 hours) increase in the number of moxidectin subjects reporting efficacy-associated AEs compared to ivermectin. There was not an increased need for medical or therapeutic intervention for management of efficacy-related events with moxidectin when

compared to ivermectin. Given that the spectrum of symptoms and severity were similar, the guidance to patients and physicians are otherwise unchanged compared to ivermectin for onchocerciasis patients.

Table 2: Treatment-emergent Adverse Events Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III)

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

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

There was no pattern indicating a temporal association with treatment or with body system of SAEs occurring in either the 3110A1-200-GH or the ONCBL60801 studies. In both studies, there were no SAEs regarded by the investigator (or Sponsor) as being treatment related. Treatment-emergent SAEs (occurring during the first 180 days post-dose) are shown in Table 3.

Table 3: 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.

The efficacy of moxidectin was demonstrated in two adequate and well-controlled trials comparing moxidectin and ivermectin as part of US FDA marketing approval activities. In both trials, moxidectin was superior to ivermectin in decreasing the number of *O. volvulus* microfilariae in the skin 12 months post-treatment. Both trials also demonstrated that more moxidectin-treated patients had no detectable microfilariae in skin samples 12 months post-treatment.

Further details can be found in the Investigator's Brochure.

3.4 Background Rationale

3.4.1 Study Rationale (Study Goals and Objectives)

Moxidectin was superior to ivermectin in suppressing skin and ocular microfilariae in the Phase III study, in more patients, to a greater extent and for longer. It is anticipated that the improved efficacy of moxidectin will be important in the control and elimination of onchocerciasis. Therefore, the purpose of this study is to determine an optimal pediatric dose of moxidectin for use in children with onchocerciasis aged 4 to 11 years to achieve exposure in the range observed in adults administered a dose of 8 mg. This will allow the use of moxidectin across the communities affected by this disease, including in mass drug administration programs for onchocerciasis control and elimination.

3.4.2 Age Rationale

This study will evaluate moxidectin in children aged 4 years and older. As infection rates in children under 4 years of age have been shown to be comparatively low in meso- and hyperendemic areas, the WHO and the African Program for Onchocerciasis Control previously recommended a lower age limit of 4 years for use of moxidectin in onchocerciasis control (World Health Organization 2008).

This study also includes adolescents aged 12 to 17 years, noting that this age range was enrolled into the Phase III study. Although safety and efficacy were evaluated in this age group in the Phase III study, pharmacokinetic data were not collected. This study will permit the characterization of the pharmacokinetics of moxidectin in adolescents, as well as assess pharmacokinetics and safety in children (aged 4 to 11 years).

3.4.3 Design Rationale

The study employs an adaptive approach using modelled and experimental data, allowing the use of pharmacokinetic modelling assumptions for dose selection. Non-compartmental pharmacokinetic and safety data analyses will occur in an ongoing manner during the study. Pharmacokinetic data will be used to confirm or adjust the population pharmacokinetics modelling and, ultimately, the dosage. This design should minimize the number of children required to determine a dose with similar exposures to an 8 mg dose in adolescents and adults, and the number of invasive procedures and inconvenience for each child. There is a considerable body of data available on the use of moxidectin in humans, including children aged 12 to 17 years of age. Moxidectin was well tolerated at all doses studied. In healthy volunteers, the safety profile was similar to placebo and no treatment-related laboratory or clinical toxicities were identified. In onchocerciasis patients, the nature, incidence and severity of adverse events associated with moxidectin efficacy was similar to ivermectin, and there were no serious adverse events due to efficacy and no treatment-related serious adverse events in any patient (Section 3.3.2.2).

The requirement for inclusion of a control group(s) was assessed in the context of available standard therapies, the adequacy of evidence to support the chosen design and desired outcomes, and ethical considerations regarding the protection of children in clinical investigations.

Inclusion of a placebo control was regarded as inappropriate for this patient population as it is not required for the study to meet its objectives (identification of an optimal moxidectin dose for children 4 to 11 years of age) and would expose children receiving placebo to greater than minimal risk (due to the collection of multiple blood samples for pharmacokinetic analysis) without the possibility of a direct benefit. Similarly, the Sponsor's decision not to include an active comparator was considered in the context of risks to benefit ratio for individual subjects. The Sponsor believes, and has supporting pharmacokinetic modeling data, that comparison of MDGH-MOX-1006 study data to existing modeling data from adults will be sufficient to distinguish between an optimal and suboptimal dose of moxidectin based on pharmacokinetic parameters. Not including an active comparator group also reduces the number of children required to participate in the study.

Microfilariae density assessment by skin snip, the gold standard diagnostic method for *O. volvulus* infection, has not been included in this study as the efficacy of moxidectin has already been demonstrated in completed Phase II and III studies (see Section 3.3.2.2) and is not an objective of the study. Additionally, this diagnostic method is invasive and can potentially scar skin at the sampling sites, which is not considered to be appropriate or ethical in the context of this study. In the absence of skin snip assessments to confirm infection with *O. volvulus*, the study will recruit children from an area designated as endemic for *O. volvulus* infection and undergoing ivermectin mass drug administration. This ensures the relevance of the clinical investigation to the intended study population. Specifically, subjects will be recruited from communities located in the Nkwanta district, northern Volta region, Ghana, an area assessed as endemic for onchocerciasis by the WHO (World Health Organization 2019). In recognition of the prevalence of onchocerciasis in this region, community-directed treatment with ivermectin commenced in October 2017 with ongoing 6-monthly rounds of treatment planned.

O. volvulus 16 antigen immunoglobulin G4 (Ov16 IgG4) positivity determined using the Ov16 IgG4 antibody rapid format card test was originally included as an eligibility criterion in order to provide a benefit to study participants, since it was assumed that a positive test would indicate that the participant had been exposed to *O. volvulus*. However, this criterion has now been eliminated for the following reasons:

- Recently-published results of a WHO external advisory committee review of large-scale evaluation of different assays for detecting Ov16 IgG4 antibodies in different settings and countries has identified significant discrepancies between the results obtained with different assays and concerns about both false positive and false negative results (World Health Organization 2020).
- The concerns about false positive and false negative results, together with the fact that Ov16 IgG4 antibody testing is designed to be a surveillance tool for onchocerciasis elimination programs in the late and post-control stages and not an individual diagnostic (Abbott 2020), indicate that it will not be possible to reliably identify individual children who have been exposed to *O. volvulus* using the Ov16 IgG4 antibody test. In addition, the Ov16 IgG4 antibody test is not registered in Ghana and is consequently an investigational diagnostic.

- While the study presents a minor increase over minimal risk to the participating children, it can be justified on the basis that it is not possible to gather the necessary data in adults and the study is being conducted in a region designated as endemic for *O. volvulus*, where children are at risk of *O. volvulus* infection. Consequently, the participants represent the population which will benefit from the identification of a paediatric dose that will allow children younger than 12 years to be included in moxidectin-based elimination strategies.

Pharmacokinetic results are not anticipated to be affected by infection status. Potential AEs associated with effective treatment of onchocerciasis are expected to be manageable and transient based on the prior experience in the Phase II and Phase III study. Since the Phase III study was recruited from the villages from which the participants in the current study will be recruited, a number of members of these communities will be familiar with clinical studies and biological sample collection.

Protocol MDGH-MOX-1006 is specifically designed to determine the optimal dose of moxidectin for onchocerciasis treatment in the 4- to 11-year-old age group. The inclusion of adolescents 12 to 17 years of age will provide additional pharmacokinetic data for inclusion in the population pharmacokinetic model used to predict drug exposures across all age groups and to support dose selection for children aged 4 to 11 years. Some study participants may have skin microfilariae and moxidectin treatment will be of benefit to these individuals. In recognition that the study involves a minor increase over minimal risk to children without known direct benefit to individual subjects (i.e. without confirmation of *O. volvulus* microfilarial burden pre-treatment), the Sponsor points to (1) engagement with the investigator, (2) confirmation that the study design is acceptable based on protocol review by local and regional independent experts on the DSMB, (3) protocol amendments based on local (UHAS), country (Ghana Health Service (GHS)) and independent (WHO) ethics committee review and (4) protocol amendment following Ghana Food and Drugs Administration review prior to study conduct. The study is also being conducted under United States Food and Drug Administration IND 126876 and in accordance with the requirements of the United States (US) Code of Federal Regulations, including Title 21 Sections 50.52, 50.53 and 50.55.

3.4.4 Dose Rationale

The proposed dose is 8 mg (4 x 2 mg tablets) for adolescents (aged 12 to 17 years) and children aged 8 to 11 years. These doses have been chosen with consideration of exposure multiples of nonclinical studies in both adult and juvenile animals, and based on clinical pharmacokinetics and population pharmacokinetics modelling data.

As determined in clinical studies, including a large Phase III study (Section 3.3.2.2.2), moxidectin has a substantial safety margin for both AUC and C_{max}, supported by both nonclinical and clinical studies. In single ascending dose clinical studies, there was no evidence of clinically relevant safety findings after administration of moxidectin (oral liquid and tablet formulations) at dosages of up to 36 mg to healthy adult subjects (Section 3.3.2.2.1). Additionally, moxidectin 8 mg administered to 55 adolescents in the Phase III study was well tolerated. For children aged 8 to 11 years, population pharmacokinetics modelling has determined that the C_{max} and AUC values resulting from an 8 mg dose will also be within existing exposure safety multiples and the dose of moxidectin will not exceed 8 mg for any subject. These data are further described below.

3.4.4.1 Nonclinical Dose Rationale

From nonclinical data, the exposure risk has been determined by examining data from species that are sensitive to the toxicological effects of moxidectin.

Moxidectin in dogs has a lower NOAEL and longer half-life than in rodents, and the same NOAEL has been identified in adult and juvenile dogs. Compared to adult dogs, juvenile dogs dosed at 3 mg/kg, the highest dose tested and equivalent to 23 times a single oral 8 mg dose in adult humans (0.13 mg/kg in a 60 kg person) had higher C_{max} but lower AUC values in both sexes. For juvenile dogs C_{max} was elevated by 1.5-fold in males and 1.3-fold in females while for AUC values the ratios were 0.44 for males and 0.77 for females. The exposure in dogs at the 3 mg/kg NOAEL (see Section 3.3.1.2.3) when compared with that in adult humans at an 8 mg dose provides an estimated safety margin of at least 7-fold for pediatric subjects.

In a neurofunctional and pulmonary study in male rats, the NOAEL was 5 mg/kg, with corresponding C_{max} of 1116 ng/mL, which was above the previously measured C_{max} in adults and predicted C_{max} to be reached in the pediatric study if all age groups received a dose of 8 mg (Table 4).

In two-year carcinogenicity studies in mice and rats (Section 3.3.1.2.2), there was no evidence of tumorigenicity in mice administered a mean dietary dose of 8.7 mg/kg/day moxidectin (approximately equivalent to 5 times the recommended human dose of 8 mg based on body surface area comparison) or rats administered a mean dietary dose of 6.1 mg/kg/day moxidectin (approximately equivalent to 7 times the recommended human dose based on body surface area comparison).

Moxidectin administered orally to pregnant rats or pregnant rabbits during the period of organogenesis was not associated with significant embryo-fetal developmental effects at doses of approximately 15 times (rats) or 24 times (rabbit) the 8 mg dose based on body surface area.

Daily parental oral administration of dietary moxidectin to rats for 70 days prior to mating, and through mating, gestation, and lactation in a pre- and post-natal three generation study was associated with decreased survival and body weights for first-generation offspring without maternal toxicity at moxidectin doses approximately 1.3-times the recommended human dose based on body surface area comparison (>1.1 mg/kg/day). However, daily dietary moxidectin did not produce maternal toxicity or adverse effects for first- and second-generation offspring at doses approximately equivalent to the recommended human dose based on body surface area comparison (0.82 mg/kg/day). Offspring were assessed for survival, body weights, and fertility; developmental milestones were not assessed in this study.

3.4.4.2 Population Pharmacokinetic Modelling

Concentration-time profiles were simulated from a previously developed population pharmacokinetic model of moxidectin. In brief, the model was built using pharmacokinetic data from healthy adult volunteers and adult patients infected with *O. volvulus*. The model comprises three compartments with an n-transit absorption process and first-order elimination. To allow the potential to extrapolate to other populations, the model incorporated allometry where consistent with the observed data (central volume of distribution [Vc/F]), inter-compartmental clearance between the central and second peripheral compartments [CLd2/F] and volume of distribution of the second peripheral compartment [Vp2/F]). The model includes effects of food and formulation on absorption and relative bioavailability. The model also stipulates that females have larger values of clearance from the second compartment (CLd2/F) and Vp2/F than males; subjects with larger values of body mass index have increased Vp2/F (stratified by

Phase I and Phase II). As the population pharmacokinetic model does not include covariates of age or body size to assess effects on the total clearance, it was not able to establish differences in AUC by dose in pediatrics. However, for a given dose and AUC, the C_{max} did alter, due to covariate effects impacting the volume parameters (i.e. body weight).

The outcomes of the simulation predicted that children have a similar exposure (AUC) to adults and that, for a given dose, smaller body size was associated with higher values of C_{max} (Table 4).

Specifically, the simulation model predicted that adolescents 12 to 17 years receiving 8 mg of moxidectin may achieve similar exposures (AUC) to adults receiving 8 mg, with a higher C_{max} (median 82.5 nanograms (ng) /mL vs. 56.8 ng/mL in *O. volvulus* infected adults). For children aged 8 to 11 years (as well as children 4 to 7 years), exposures are also predicted to be similar to adults, while median C_{max} is predicted to be 116 ng/mL (maximum 214 ng/mL). This is well within the safety margins of moxidectin in humans; in adults, moxidectin has been studied up to a median C_{max} of 244 ng/mL and a maximum of 473 ng/mL. The full pharmacokinetic report has been provided for reference (see Appendix 16.2).

Table 4: Summaries of C_{max} and AUC_{inf} for Children 4 to 11 years (8 mg), Adolescents 12 to 17 years (8 mg) and Adult *O. volvulus*-infected Individuals and Healthy Volunteers (8 mg, 16 mg, 36 mg) Emerging from the Population Pharmacokinetic Model Used to Determine the Starting Dose for Children 8 to 11 Years

Age Cohort (Dose)	C_{max} (ng/mL)				AUC_{inf} (ng*h/mL)		
	Mean	SD	Median	IQR	Mean	10th Percentile	90th Percentile
4 to 7 years (8 mg)	157	35.8	156	47.2	2478*	1317*	3858*
8 to 11 years (8 mg)	118	25.2	116	33.8	2475	1316	3854
12 to17 years (8 mg)	83.5	17.2	82.5	23.9	2471	1314	3849
Adults (Oncho, 8 mg)	57.6	11.7	56.8	15.9	2466	1312	3844
Adults (HV; 8 mg)	55.6	12.0	54.3	16.4	3471	1899	5210
Adults (HV; 16 mg)	111	24.0	109	32.7	6942	3798	10420
Adults (HV; 36 mg)	250	54.1	244	73.6	15620	8546	23445

The predicted mean and 10th and 90th percentile AUC_{inf} for children 4 to 7 years will be re-estimated after pharmacokinetic data for 8 to 11 years and adolescents 12 to 17 years are available to update the model as a basis for determining the first dose for children 4 to 7 years to be proposed to the DSMB (see Section 13.5.3). Adults = 18+ years, Oncho = *O. volvulus* infected, HV = healthy volunteers, IQR = interquartile range, AUC_{inf} = AUC from time 0 extrapolated to infinity, SD = Standard Deviation.

To date, the population pharmacokinetic model used for the simulations has not been verified with pharmacokinetic data from children or adolescents. See Section 13.5.3 for a summary of planned addition of pharmacokinetic and demographic data from Cohorts I to III to the population pharmacokinetic model.

3.4.4.3 Consideration of Dose Format (Ability of Children to Swallow Dose)

Tablets are the most common dosage form used in onchocerciasis-endemic regions in both children and adults. The moxidectin tablet presentation (dimensions 8.0 mm x 4.5 mm x 3.0 mm, total weight 100 mg) is smaller than or comparable to tablets which children in this region routinely swallow, including biltricide, albendazole, mebendazole, azithromycin, and ivermectin. However, it is acknowledged that this study may exclude otherwise eligible children due to their inability to swallow tablets (see Section 7.3.3 for guidance on evaluation of ability to swallow tablets).

The Sponsor is currently exploring alternative moxidectin presentations, including chewable and liquid formats.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives

The primary objective of this study is to identify an optimal dose of moxidectin for the treatment of children aged 4 to 11 years with onchocerciasis.

A secondary objective is to evaluate the safety and pharmacokinetics of a single dose of moxidectin in children and adolescents aged 4 to 17 years.

4.2 Endpoints

Dose(s) for children aged 4 to 11 years will be selected based on non-compartmental exposure metrics including AUC assessed up to and including Day 28 and a population pharmacokinetic model.

Pharmacokinetic parameters of moxidectin in children and adolescents aged 4 to 17 years, including C_{max}, T_{max}, and other pharmacokinetic parameters will be determined by non-compartmental analysis or other methods, as appropriate.

The safety endpoints include the incidence and severity of AEs, physical examination findings, changes in vital signs, and laboratory safety parameters at all time points in the study.

5 STUDY DESIGN

5.1 Study Design

This is a prospective, age-stratified, adaptive, open-label, single-dose pharmacokinetic and safety study of moxidectin in children and adolescents aged 4 to 17 years with, or at risk of, onchocerciasis infection.

5.2 Number of Subjects

The expected recruitment is 27 subjects enrolled in 3 Cohorts (approximately 9 subjects per cohort), with subjects allocated to cohorts on the basis of their age at Screening. However, an additional 4 cohorts (i.e. up to a maximum of 36 additional subjects) may be enrolled if required to achieve pharmacokinetic parameters within the required range.

5.3 Cohorts and Dosing Regimens (Methodology)

Cohorts I and II will be recruited concurrently.

The dose regimen is:

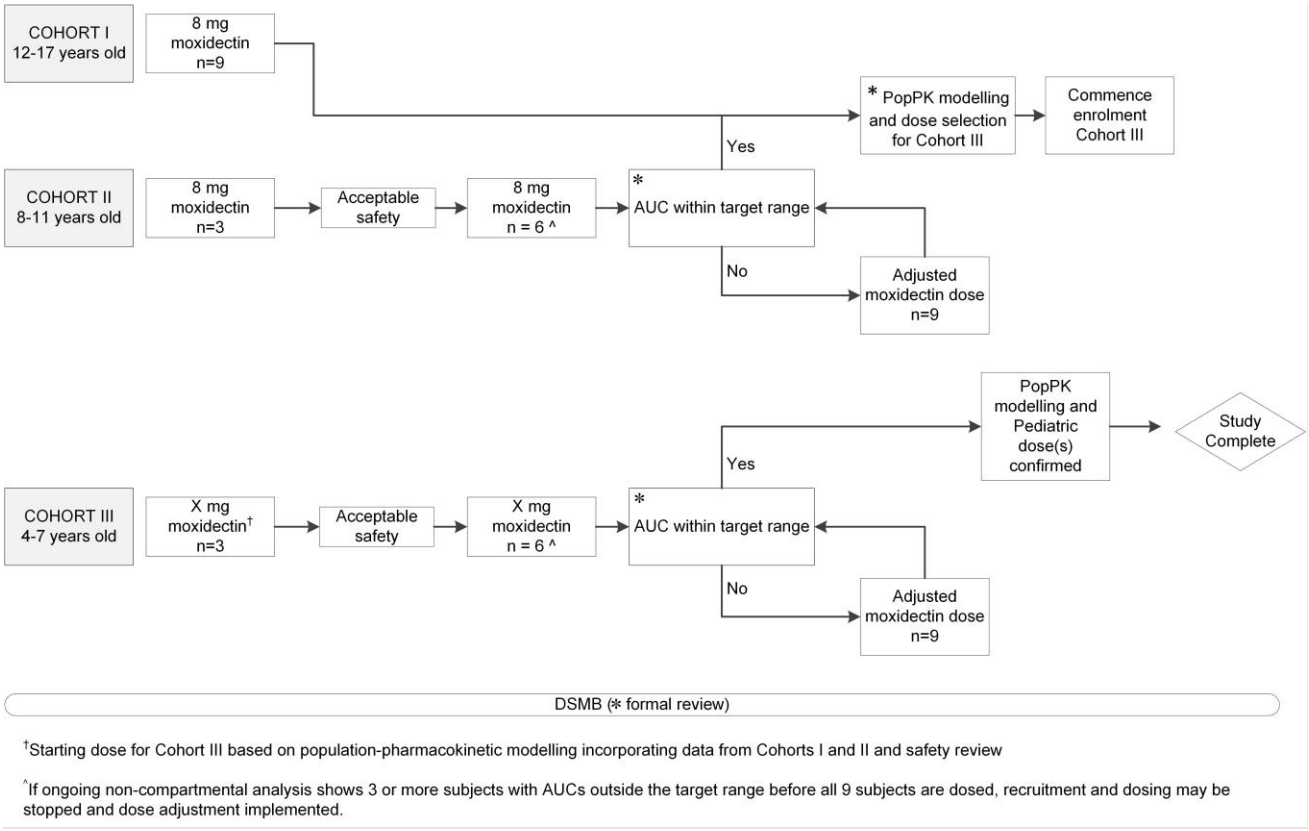
Cohort I: (n = 9 subjects aged 12 to 17 years, inclusive): a single oral dose of moxidectin 8 mg.

Cohort II: (n = 9 subjects aged 8 to 11 years, inclusive): a single oral dose of moxidectin 8 mg.

A sentinel group of three subjects will be enrolled in Cohort II. If the investigator considers, based on their experience with onchocerciasis treatments, that safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled. If safety concerns arise in the sentinel group, the DSMB will review the data and make a recommendation to continue dosing as planned, or to modify or stop dosing.

Once all Cohort I and II subjects complete Day 28, a safety and non-compartmental pharmacokinetic data review will be performed by the DSMB (See Section 11). If 3 or more of the 9 subjects in Cohort II have moxidectin exposures above the target range, defined as AUCs to Day 28 greater than the predicted 90th percentile mean AUC (see Table 4), a reduced dose of moxidectin will be selected for dosing of additional subjects in the Cohort II age range. The new dose will be in decrements of 2 mg, reflecting the 2 mg moxidectin tablet format used in the study. If Cohort II pharmacokinetic analyses for 9 subjects (per dose and cohort) cannot be calculated due to the availability of results from too few samples, additional subjects may be enrolled at that dose. The process is outlined in Figure 1.

Figure 1: Enrolment and Dosing Decision Tree



†Starting dose for Cohort III based on population-pharmacokinetic modelling incorporating data from Cohorts I and II and safety review

^If ongoing non-compartmental analysis shows 3 or more subjects with AUCs outside the target range before all 9 subjects are dosed, recruitment and dosing may be stopped and dose adjustment implemented.

Upon successful completion of Cohort II and selection of a starting dose for Cohort III based on pharmacokinetic modelling with inclusion of Cohort I and II data and consideration of all predicted pharmacokinetic parameters, and DSMB recommendation (see Section 11), Cohort III will be enrolled.

Cohort III (n = 9, subjects aged 4 to 7 years, inclusive) will receive a single oral dose of moxidectin at the recommended dose level.

Initially, a sentinel group of 3 subjects will be enrolled. If safety up to and including Day 3 in these subjects is considered acceptable, based on the investigator's experience with onchocerciasis treatments, the additional 6 subjects will be enrolled. If safety concerns arise in the sentinel group, the DSMB will review the data and make a recommendation to continue dosing as planned, or to modify or stop dosing.

Once all Cohort III subjects complete Day 28, a safety and pharmacokinetic data review will be performed by the DSMB. If 3 or more of the 9 Cohort III subjects have moxidectin exposures to

Day 28 below or above the target range, defined as AUCs less than the 10th percentile or greater than the 90th percentile mean AUC predicted by the population pharmacokinetic model, a revised dose of moxidectin will be determined in increments or decrements of 2 mg (maximum dose 8 mg) and Cohort III will be repeated with at least 9 new subjects enrolled at the new dose. If 3 or more of the 9 subjects enrolled at the new dose have moxidectin exposures outside the target range, the moxidectin dose may be adjusted once more and Cohort III repeated for a second time with at least 9 further subjects.

Subsequent to the enrolment of the initial group of 3 subjects in each of Cohort II and Cohort III, additional subjects will be enrolled in groups of at least 3. This is for operational and social reasons (to ensure subjects have other children to spend their time with while in the research clinic so they don't feel lonely).

5.4 Study Sites

This will be a single center study. The study will be conducted at the School of Public Health, UHAS Research Centre, formerly the OCRC research facility, Volta Region, Ghana, which was the site for the Phase II and III studies of moxidectin. The Investigator was a Co-investigator on the Phase II study and the Principal Investigator (PI) on the Phase III study and thus has substantial experience with moxidectin.

5.5 Estimated Duration of the Study

The on-study period per subject is approximately 28 weeks in total: up to 30 days for Pre-screening (including consent/assent) and Screening (including up to 7 days in the research center for Screening) prior to Baseline (pre-treatment on Day 0) and 7 days stay in the research center and 23 weeks outpatient follow-up post-treatment.

It is anticipated that the total duration of the study will be up to 15 months, including 6 months for recruitment in the event that more than one cohort per age group is required and for data analysis and reporting.

5.6 Expansion in Children 4 to 11 years, Inclusive

Once an appropriate dose (or doses if required) has been identified, it is intended that an expansion study in children 4 to 11 years of age, inclusive, will be conducted. A protocol amendment will be generated to allow enrolment of further subjects in an expansion cohort for this study in order to further evaluate safety and potentially add further pharmacokinetic data. In

addition, or alternatively, children in these age groups may be included in treatment protocols for community studies with intensified safety monitoring requirements such as daily AE assessment in the immediate post-dose period and with DSMB oversight.

6 STUDY POPULATION

6.1 Selection of Subjects

Study recruitment will occur in villages in the Kpassa sub-district of the Nkwanta North district, including Wii, Azua and Jagri-Do (for ethically relevant considerations relating to the choice of these communities see Section 14.1.2).

The nature of the study and the possible risks will be explained to all potential subjects and their parent(s)/guardian(s) (legally acceptable representative, LAR) and communities. Written informed consent will be obtained from each child's parent(s)/guardian(s) and assent will be obtained from each child (as and if appropriate for age) prior to performing any study -related procedures. For children too young or immature to give assent, the investigator will search for indication of 'deliberate objection' as per commentary to the Council for International Organizations of Medical Sciences (CIOMS) Guideline 17 (Council for International Organizations of Medical Sciences (CIOMS) 2016) (this is subsequently considered to be implied in the use of the term 'assent'). The consent/assent process is described in Section 14.1.2.

After obtaining written informed consent/assent, children will, where possible, be assessed in the village setting against eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.2 and Section 6.3. This is intended to minimize the number of potentially ineligible children who travel to the study site to determine eligibility. Those who continue to be eligible for the study will receive transportation to the research center together with a parent or guardian for the remaining Screening assessments.

Eligibility will be determined at Screening unless specified below. Subjects who meet all inclusion and none of the exclusion criteria will be eligible for participation in the study.

6.2 Inclusion Criteria

The criteria for entry into the study are:

1. Age 4 to 17 years, inclusive:

   Cohort I: 12 to 17 years;

   Cohort II: 8 to 11 years;

   Cohort III: 4 to 7 years.

2. Live in a region designated by the WHO as endemic for *O. volvulus* infection (World Health Organization 2019). Specifically, participants will be recruited from the Kpassa sub-district of the Nkwanta North district. The specific communities will include Wii, Jagri-Do, and Azua where mass drug administration with ivermectin for onchocerciasis commenced in October 2017;
3. Willing and able to remain at the research center from Screening up to Day 7;
4. Provision of parental or guardian written informed consent and child assent / lack of expression of 'deliberate objection' (as appropriate for age);
5. Females of childbearing potential must commit to using a highly effective method of contraception as per local family planning guidelines from Baseline (pre-treatment on Day 0) until approximately 6 months (Week 24) after treatment with study drug;

6.3 Exclusion Criteria

The criteria for exclusion from the study are:

1. History of serious medical or psychiatric condition which, in the opinion of the investigator, would put the subject at increased risk by participating in the study or jeopardize study outcomes;
2. Known or suspected concurrent clinically significant renal, cardiac, pulmonary, vascular, metabolic (thyroid disorders, adrenal disease), immunological disorders or malignancy, congenital heart disease, chronic lung disease;
3. Has received an investigational product within 28 days, or 5 half-lives, of Baseline, whichever is longer;
4. Has received ivermectin or any other anti-helminthic treatments within 28 days of Baseline;
5. Has received a vaccination within 7 days of Baseline;
6. Known or suspected hypersensitivity to macrocyclic lactones or excipients used in the formulation of moxidectin;
7. Poor venous access;
8. Unable to swallow tablets (flat oval, 8.0 millimeters (mm) x 4.5 mm x 3.0 mm);
9. Weight:
    - Cohort I (12 to 17 years): < 30 kg
    - Cohort II (8 to 11 years): < 18 kg
    - Cohort III (4 to 7 years): < 12 kg

10. Clinically relevant laboratory abnormalities at Screening, including:
    - Hemoglobin < 9.5 g/dL
    - Neutrophil (granulocyte) count < 1.5 x 10^9/L
    - Platelet count < 110 x 10^9/L
    - ALT > 1.5 times ULN
    - Total bilirubin > 1.5 times ULN
11. Hepatitis B, Hepatitis C, or HIV positive;
12. Known or suspected malaria or other ongoing viral, bacterial, or plasmodium infection at Screening and/or Baseline;
13. *Loa loa* co-infection;
14. Unwilling, unlikely or unable to comply with all protocol specified assessments;
15. For females of child-bearing potential, pregnant or breastfeeding, or planning to become pregnant;
16. Previous enrolment in this study;
17. Is a sibling of another child already enrolled in this study.

6.4 Other Study Eligibility Criteria Considerations

In order to assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the current Investigator's Brochure and other documentation provided by the Sponsor for detailed information regarding warnings, precautions, contraindications, AEs, and other relevant data pertaining to the drug product being used in this study. The investigator should also consult with the Medical Monitor as necessary.

6.4.1 Contraception

Female subjects of child-bearing potential (post-commencement of menarche and physically able to bear children) must have a negative pregnancy test (with a sensitivity of at least 50 International Units (IU)/mL) performed at Screening (serum) and at Day 28, Week 12 and Week 24 (urine) as indicated in Table 1.

In addition, they must agree not to attempt to become pregnant and must commit to using a highly effective method of birth control (failure rate of less than 1% when used consistently and correctly) in accordance with local family planning guidelines, for approximately 6 months (to the Week 24 visit) following study drug administration.

Reliable methods of contraception include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal;
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable;
- intrauterine device;
- sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from intercourse during the entire period of the study. Compliance with the commitment to sexual abstinence will be evaluated at the Day 14, Day 28, Week 12 and Week 24 visits by asking subjects whether they have been abstinent. In addition, a pregnancy test will be carried out for all girls of child-bearing capacity as described above, regardless of the chosen method of contraception.

Counselling and provision of contraceptives (if needed) will be carried out by the staff of the Family Planning Unit of the Hohoe Municipal Hospital.

6.4.2 Rescreening

Subjects with clinically relevant laboratory abnormalities that are exclusionary may be re-tested once, within the screening window, under the same subject identifier. Rescreening for other reasons is not permitted.

7 SCHEDULE OF ASSESSMENTS AND PROCEDURES

7.1 Study Schedule of Evaluations

The schedule of assessments is presented in Table 1.

7.2 Visit Windows

Consent/assent may be obtained up to 30 days prior to the day of planned study drug administration (Day 0) and before any study-specific procedures are conducted. Screening (with the exception of initial assessment of eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1) must be conducted in the window of Day -7 to Day -1.

All visit dates are calculated from Day 0, the date of the Baseline (pre-dose) assessment and study drug administration. Hours are calculated from the time of administration of moxidectin.

Assessments should be performed within the specified time window (Table 5):

Table 5: Allowable Visit Windows

Time point	Window
Hours 1 and 2	± 10 minutes
Hour 4	± 30 minutes
Hour 8	± 1 hour
Hours 24, 48 and 72	± 2 hours
Day 7	± 1 day
Day 14	± 2 days
Day 28	± 4 days
Week 12	± 14 days
Week 24	± 28 days

7.3 Study Procedures / Assessment Periods

For further details on timing of clinical procedures, please refer to Table 1.

Additional visits and/or assessments may be conducted as clinically indicated. These data will be captured in the CRF as unscheduled visits, as appropriate.

Study procedures will be conducted in the presence and with the help of the parent/guardian who accompanies the subject to the research center, as per the wishes of the accompanying parent/guardian and child.

7.3.1 Consent/Assent

The process for obtaining informed consent and assent is described in Section 14.1.2.

7.3.2 Pre-Screening (Screening Conducted in the Community)

Subjects for whom informed consent/assent has been obtained as described in Section 14.1.2 will be evaluated for eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1. These evaluations will be conducted between Day 30 and Day -1 and may also be performed in the research center during Screening.

7.3.3 Screening

Subjects who pass pre-screening and their parent or guardian will be invited to attend the research center for Screening. Screening must be conducted between Day -7 and Day -1.

As subjects will be recruited from villages not proximal to the study center, they and their parents/guardians will be provided with accommodation for the duration of their stay in a newly renovated dormitory-style ward on the campus of the Hohoe Municipal Hospital. The dormitory ward has four separate rooms and each group of parents/guardians with their children can choose how to occupy these. A registered nurse will be on duty at all times. The dormitories have comfortable beds with mattresses and sheets and there is also a recreational area with large screen television and an outdoor space. The subjects and their parents/guardians will be provided with three meals daily.

Unless already completed at Pre-screening, the following assessments / study requirements will be performed and documented:

- Medical history, including medication history and evaluation of ability to swallow tablets (see Section 7.4.1)
- A complete physical examination including assessment of all appropriate body systems and evaluation of venous access to determine study eligibility (see Section 7.4.1)
- Vital signs (blood pressure, pulse, temperature and respiratory rate) measurement after lying semi-supine for 5 minutes (see Section 7.4.1)
- Body height and weight measurement (see Section 7.4.1)
- Measurement of upper arm circumference as an indicator of lean body weight (see Section 7.4.1)
- 12-lead safety ECG (see Section 7.4.2)
- Collection of blood samples for testing:

  - Pharmacokinetic analysis (plasma) (see Section 7.4.3.2)
  - Hematology and clinical chemistry (see Section 7.4.3.1)
  - Serum pregnancy test for females of childbearing potential (see Section 7.4.3.4)
  - HIV, hepatitis B surface antigen, hepatitis C virus (see Section 7.4.3.3)
  - *Loa loa* infection (if relevant; see Section 7.4.3.3)
- AE assessment (see Section 10.2.1)
- Concurrent medication assessment (see Section 9)

All required test results must be available before eligibility can be confirmed.

The ability of children to swallow tablets will be assessed by the investigator based on discussion with the child and their parent(s)/guardian(s) of the child's previous experience with taking tablets of a similar size (see Section 3.4.4.3). Parent(s)/guardian(s) and the child will be shown a tablet of a similar size to moxidectin as an example.

Eligible girls of child-bearing potential and their accompanying parent/guardian will have a discussion with a family planning nurse about the need for contraception and the different options available, and will be provided with a contraceptive as needed, as described in Section 6.4.1.

If the subject is ineligible for the study, the investigator will discuss the reason for ineligibility with the subject and their parent(s)/guardian(s). If the subject is ineligible to participate in the study due to a clinically significant laboratory abnormality or medical condition, including a positive test for HIV, hepatitis B or hepatitis C, referral will be made to an appropriate GHS treatment facility for follow-up. Transport for the subject and their parent/guardian to return to their village will be arranged for the day following Screening.

7.3.4 Day -1

Subjects will be required to fast overnight (from after dinner, which will be served at approximately 19:00) prior to dosing (see Section 8.5.1). Water may be consumed *ad libitum* during that time.

7.3.5 Day 0 (Baseline, Dosing and Post-Dose Assessment)

7.3.5.1 Pre-dose

The following will be performed and documented pre-dose:

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- Final confirmation of eligibility. Only subjects continuing to meet all of the inclusion criteria and none of the exclusion criteria will be dosed with moxidectin

7.3.5.2 Dosing

Administration of moxidectin tablets to fasted subjects (see Section 8.5.1) and recording of time (Hour 0). If a subject vomits within 30 minutes of taking the dose of moxidectin, the subject will be assessed as described in Section 12.2.

7.3.5.3 Post-Dose

The subject must be assessed throughout the post-dosing period with specific assessments at Hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 30 minutes) and 8 post-dose (± 1 hour).

The following assessments/study requirements will be performed and documented post-dose:

- Vital signs measurement at Hours 1 and 8, and, if clinically indicated, at Hours 2 and 4 (see Section 7.4.1)
- Targeted physical examination (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood samples (plasma) at Hours 1, 2, 4 and 8 hours for moxidectin concentration determination (see Section 7.4.3.2)
- Provision of a meal 2 hours post dose, after Hour 2 blood sample collection.
- Continuous AE assessment (see Section 10.2.1)
- Continuous concurrent medications assessment (see Section 9)

Subjects will remain in the research center.

7.3.6 Day 1 (24 hours)

The following will be performed and documented at Hour 24 (± 2 hours):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood sample (plasma) for moxidectin concentration determination (see Section 7.4.3.2)

- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

Subjects will remain in the research center.

7.3.7 Day 2 (48 hours)

The following will be performed and documented at Hour 48 (± 2 hours):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Adverse event assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

Subjects will remain in the research center.

7.3.8 Day 3 (72 hours)

The following will be performed and documented at Hour 72 (± 2 hours):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood sample (plasma) for moxidectin concentration determination (see Section 7.4.3.2)
- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (See Section 9)

Subjects will remain in the research center.

7.3.9 Day 7

The following will be performed and documented at Day 7 (± 1 day):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood samples for hematology and clinical chemistry and moxidectin concentration determination (see Sections 7.4.3.1 and 7.4.3.2)

- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

Subjects will be discharged from the research center after these assessments. Subjects may remain if clinically indicated and any ongoing AEs should be managed as required.

7.3.10 Day 14 Visit

The following will be performed and documented at Day 14 (± 2 days):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood sample for moxidectin concentration determination (see Section 7.4.3.2)
- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

7.3.11 Day 28 Visit

The following will be performed and documented at Day 28 (± 4 days):

- A targeted physical examination (see Section 7.4.1)
- Body weight measurement (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood samples for hematology and clinical chemistry and moxidectin concentration determination (see Sections 7.4.3.1 and 7.4.3.2)
- Urine pregnancy test for females of child-bearing potential (see Section 7.4.3.4)
- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

7.3.12 Week 12 Visit

The following tests will be performed and documented at Week 12 (± 14 days):

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)

- Collection of blood samples for hematology and clinical chemistry and moxidectin concentration determination (see Sections 7.4.3.1 and 7.4.3.2)
- Urine pregnancy test for females of child-bearing potential (see Section 7.4.3.4)
- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

7.3.13 Week 24, Exit Evaluation

The following will be performed and documented at Week 24 (± 28 days) or upon early withdrawal if agreed by the subject:

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Weight measurement (see Section 7.4.1)
- Collection of blood samples for clinically indicated hematology and/or clinical chemistry (see Section 7.4.3.1)
- Urine pregnancy test for females of child-bearing potential (see Section 7.4.3.4)
- AE assessment (see Section 10.2.1)
- Concurrent medications assessment (see Section 9)

These procedures should be conducted in the case of that a subject withdraws from the study prior to Week 24. This is the final study visit.

7.3.14 Unscheduled Visits

The following should be performed and documented at unscheduled visits as clinically indicated:

- A targeted physical examination (see Section 7.4.1)
- Vital signs measurement (see Section 7.4.1)
- 12-lead ECG if clinically indicated (see Section 7.4.2)
- Collection of blood samples for clinically indicated hematology and/or clinical chemistry (see Section 7.4.3.1)
- Urine pregnancy test for females of child-bearing potential (see Section 7.4.3.4)
- AE assessment (see Section 10.2.1)

- Concurrent medications assessment (see Section 9)

7.4 Details of Scheduled Assessments

7.4.1 Demographic Data, Medical History, Physical Examination, Vital Signs

Demographic data will include sex, date of birth, height (in centimeters [cm]), upper arm circumference (in cm) and weight (in kg), as well as history of living in a *Loa loa* endemic area.

The medical history will include any significant diagnosed medical conditions or surgical history and medication history.

A complete physical examination (including head, eyes, ears, nose, throat, lungs, lymph nodes, heart, abdomen and skin) and body weight and height measurements will be conducted at Screening to determine study eligibility.

A targeted physical examination based on prior findings and reported AEs will be performed on Day 0 pre-dose and at all subsequent visits. Targeted physical examinations may also be performed at Hours 1, 2, 4 and 8 on Day 0 and at unscheduled visits as clinically indicated.

Body weight measurement will be repeated at the Day 28 and Week 24/Early Withdrawal visits and may be performed at unscheduled visits if clinically indicated.

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

- Body temperature (degrees Celsius; °C)
- Respiratory rate (breaths per minute)
- Pulse rate (beats per minute)
- Blood pressure (millimeters of mercury [mmHg])

Vital signs will be assessed in association with other signs and symptoms detected upon physical examination for potential clinical significance and determination of study eligibility and AEs. Vital signs normal reference ranges as published in the American Heart Association Pediatric Advanced Life Support Guidelines 2015 and Canadian Paediatric Society Position Statement on Temperature Measurement in Paediatrics 2013 (Canadian Paediatric Society 2013, American Heart Association 2016) and as summarized in Appendix 16.3 may be used to assist a diagnosis.

7.4.2 Electrocardiograms

Standard 12-lead ECGs will be recorded at Screening and at physician discretion during the study. The ECG recordings will be performed once the subject has been resting semi-supine for at least 10 minutes and will be measured in triplicate over approximately 3 minutes. The following parameters will be reported: QRS, QT, QTcB (Bazett's correction formula), QTcF (Fridericia's correction formula), RR and PR intervals. Repeat measurements will be performed if there are any identified clinical abnormalities observed or artifacts are present. All ECG recordings will be reviewed by the investigator or nominee and a clinical assessment documented in the research center notes [(normal, abnormal (not clinically significant) or abnormal (clinically significant)]. Any new clinically significant findings after Baseline will be reported as AEs.

7.4.3 Blood and Urine Samples

The following blood samples are to be collected:

- A 0.5 mL sample of blood for hematology assessments and 1.5 mL for biochemistry assessments at each of Screening, Days 7 and 28, and Week 12 (total 8 mL across all visits) and at other visits if clinically indicated (see Section 7.4.3.1)
- 1.5 mL for pharmacokinetic analysis at each of Screening, Hours 1, 2, 4, 8 and 24, Days 3, 7, 14, and 28 and Week 12 (total 16.5 mL across all visits) (see Section 7.4.3.2)
- up to 5 mL for testing for HIV, hepatitis B surface antigen, and hepatitis C virus RNA and, if required, *Loa loa* testing (see Section 7.4.3.3)
- up to 4 mL for serum pregnancy testing at Screening (see Section 7.4.3.4)

Planned blood sample collection will be no more than 33.5 mL for females requiring pregnancy testing (≥ 12 years and ≥ 30 kg) and 29.5 mL for all other subjects. The maximum blood sample collection in any 4-week period for any subject is 30 mL (when pregnancy testing is required). For a child of 4 to 7 years weighing an allowable minimum 12 kg, the blood volume required in any 4 week period (26 mL) is less than the recommended maximum 3% of blood volume of 28 mL and the maximum amount drawn within a single day (8.5 mL) is less than the recommended maximum 1% of blood volume of 9.6 mL (2001/20/EC 2008, Zisowsky et al. 2010)

The first 24 hours after dosing requires a number of samples for pharmacokinetic analysis to be collected, in order to appropriately characterize moxidectin pharmacokinetics. The use of an intravascular catheter to facilitate venous access for sample collection during that time is recommended. In addition, an effective topical anesthetic for application to the skin prior to each application of a needle for blood sample collection is also strongly recommended.

A single mid-stream urine sample will be collected from female participants of childbearing potential for pregnancy testing at Day 28, Week 12 and Week 24 / Early Withdrawal visits and, if clinically required, at unscheduled visits as (See Section 7.4.3.4).

7.4.3.1 Safety Laboratory Tests

Blood will be collected at scheduled time points and, if clinically indicated, at unscheduled visits, for safety laboratory testing. A maximum of 2 mL per visit will be collected at the scheduled time points at Screening, Days 7 and 28 and Week 12 (8 mL total; see Section 7.4.3 for evaluation of blood volumes collected relative to guidance on blood collection in children).

The handling and processing of hematology and clinical chemistry will be in accordance with the site's usual processes. These tests will all be performed at the site's local laboratory with equipment and test kits able to accurately analyze small sample volumes. Normal reference ranges for clinical chemistry and hematology for Ghanaian children (Dosoo et al. 2014) will be used in this study. These reference ranges are included in Appendix 16.4 to the protocol.

Samples will be collected for the following tests at a minimum:

Hematology: Hemoglobin, hematocrit, RBC count and RBC morphology, white blood cell and differential white blood cell count, platelet count.

Chemistry: AST, ALT, GGT, amylase, creatine kinase, total protein, albumin, direct and total bilirubin, sodium, potassium, chloride, bicarbonate, phosphorus, BUN, creatinine.

Other parameters may be tested if clinically indicated.

7.4.3.2 Pharmacokinetic Samples

Plasma will be prepared from 1.5 mL blood collected (with samples for safety testing as appropriate) at Screening and post-dose at Hours 1, 2, 4, 8, 24 and 72, Days 7, 14 and 28 and Week 12 (16.5 mL in total; see Section 7.4.3 for evaluation of blood volumes collected relative

to guidance on blood collection in children). Plasma will be divided into two aliquots of at least 250 µL (unless insufficient sample available) and stored at -20°C. A single sample at each time point for each subject will be sent to Frontage Laboratories (Exton, Philadelphia, United States of America) for determination of moxidectin plasma concentration in a fully validated liquid chromatography (LC) with mass spectrometry (MS) LC/MS/MS method used in previous studies. The remaining samples will be stored as back-up during the study, should these be required.

Details of the laboratory, and collection, processing, storage and shipping information for the samples will be described in the SRM.

Any remaining samples after analysis and completion of the study will be destroyed.

7.4.3.3 Testing for Other Infections

Testing for the presence of infection with HIV, chronic hepatitis B and C will be conducted at Screening using commercially available rapid test kits as per the manufacturer's instructions.

Subjects who have resided in an area endemic for *Loa loa* will be tested for presence of infection. Instructions on sample collection and testing will be provided in the SRM.

The volume of blood required for testing is detailed in Section 7.4.3. For information on referrals in case of positive tests, see Section 7.3.3.

Testing for other infections (e.g. malaria) will be conducted as per investigator judgement in case of clinical suspicion.

7.4.3.4 Pregnancy Test

A serum pregnancy test will be performed at Screening for all females of child-bearing potential. Subjects with a positive result are not eligible for the study.

At Day 28, Week 12 and Week 24 / Early Withdrawal (and at unscheduled visits as clinically indicated), a urine pregnancy test will be performed.

Commercially available rapid test kits will be used as per the manufacturer's instructions.

7.4.3.5 Handling and Processing of Biological Specimens

Blood and urine specimens collected during the trial may contain harmful pathogens. All personnel involved in collecting and handling biological specimens should follow appropriate

precautionary procedures for handling biohazardous materials as currently recommended by the national regulatory authority. The processing of all biological specimens will be in accordance with relevant institutional Standard Operating Procedures (SOPs).

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

8 INVESTIGATIONAL PRODUCT

8.1 Randomization Process

The study is not randomized.

8.2 Blinding

The study is open label.

8.3 Treatment Allocation

Treatment is allocated based on aged-based treatment cohorts.

A Screening identification (ID) number will be allocated to each subject for whom parental/guardian informed consent and child assent (as appropriate for the age group, see Section 14.1.2) is provided. The Screening ID is a number prefixed with "S" starting with S001. It is allocated in sequence. If a subject fails Screening, the Screening ID number will not be reused.

All subjects eligible for the study will also receive a Subject ID number. It is comprised of a cohort number (1, 2 or 3) and within each cohort, a sequential, ascending 3-digit ID number (beginning with 001, 002, 003). Together these will provide a unique subject identifier (e.g. 1001, 1002, 2001). Each subject will retain the same Subject ID for the duration of the study and the number will not be reused.

8.4 Supply, Packaging and Labelling

Moxidectin 2 mg tablets will be supplied by the Sponsor. Moxidectin will be supplied as oval-shaped solid tablets for oral administration containing 2 mg of moxidectin, packaged in white high-density polyethylene bottles with polypropylene cap, desiccant sachet, rayon coil (filler) and induction sealed containing 500 tablets. Moxidectin 2 mg tablets will be shipped by the Sponsor prior to study start and in accordance with all applicable country and regulatory requirements.

Bottle labelling will include at least the following:

- Sponsor name and address
- Moxidectin name, strength, and formulation
- Batch number
- Protocol number

- Storage temperature and conditions

Details of the expiry or re-test date will be provided either on the label or in separate study documentation. A Certificate of Analysis will be provided and retained on file at site.

8.5 Storage and Handling

Moxidectin 2 mg tablets should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 20 to 25°C (68 to 77°F), with protection from light and moisture. Do not freeze. Temperature excursions are permitted to 30°C (86°F) for up to 12 months. Unless otherwise labelled, the full contents of the container should be used within 7 days or unused contents discarded. To ensure the stability of the drug product and proper product identification, moxidectin 2 mg tablets should be administered directly from the container in which they are supplied.

Only subjects enrolled in the study (i.e. those for whom eligibility has been confirmed on Day 0, see Section 13.3) may receive moxidectin 2 mg tablets. Prior to dispensing, moxidectin 2 mg tablets 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 laws. The PI or authorized designee will ensure these requirements are met.

The PI is responsible for ensuring that moxidectin is dispensed in accordance with the protocol and only to subjects enrolled in the study. Authorized study personnel will dispense moxidectin according to the dose specified for the relevant cohort.

8.5.1 Dosage and Administration of Moxidectin Tablets

No subject will receive more than 8 mg of moxidectin (4 x 2 mg tablets).

Each enrolled subject will receive a single oral dose of moxidectin, according to their age cohort:

- Cohort I (12 to 17 years of age) will receive moxidectin 8 mg (4 x 2 mg tablets);
- Cohort II (8 to 11 years of age) will receive moxidectin 8 mg or an adjusted (lower) dose based on data from the group treated with an 8 mg dose (see Section 5.3);
- Cohort III (4 to 7 years of age) will receive a dose of moxidectin to be determined based on the population pharmacokinetic modelling, including data obtained from Cohorts I and II.

The appropriate number of tablets for an individual dose will be dispensed for each subject from the moxidectin supplied.

The dose of moxidectin will be administered on Day 0 after fasting for not less than 6 hours. Subjects will be required to swallow moxidectin tablets with approximately 250 mL of water. A visual mouth check will be conducted post-dosing to ensure all tablets have been swallowed. Each subject must continue to fast for 2 hours post-dose. Water may be consumed *ad libitum* during that time.

8.5.2 Dispensing and Accountability

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

The PI or designee is responsible for maintaining accurate records for all moxidectin received, stored, dispensed, and returned. The inventory and dispensing logs must be available for inspection by the study monitor. Moxidectin supplies, including any partially used or empty bottles, must be accounted for by the PI or designee and verified by the study monitor.

At the end of the study, moxidectin may be returned to the Sponsor (or designee), or, if pre-approved in writing by the Sponsor and Ghana Food and Drugs Authority, sent for safe destruction at an approved local facility. Records shall be maintained in the study site file. 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 responsible for disposal of the test substance. A copy of such records shall be submitted to the Sponsor.

9 CONCURRENT MEDICATIONS AND TREATMENTS

Throughout the 24-week duration of the study, subjects may not receive treatment with ivermectin.

Any concurrent medications administered, including vaccinations, vitamin supplements and herbal remedies or traditional medicines, must be recorded in source documents and the appropriate section of the CRF.

10 ADVERSE EVENTS AND TOXICITY MANAGEMENT

10.1 Safety Parameters

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

10.2 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing events which 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 AEs. AEs may also include complications that occur as a result of protocol-mandated procedures (e.g. invasive procedures such as biopsies).

Any AE with an onset date after investigational product administration up to the last day on study (including the follow-up, off study medication period of the study), should be recorded as an AE on the appropriate CRF page(s).

An AE **does not** include:

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

10.2.1 Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the source documents and the appropriate CRF page, including the date of onset and resolution, severity, relationship to investigational product, outcome and action taken with investigational product.

AEs should be recorded, and severity graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017. This is provided in Appendix 16.5 and is available at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The relationship to investigational product therapy should be assessed using the definitions provided in Table 6.

Table 6: Relationship to Investigational Product Assessment Terms

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

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

10.2.2 Adverse Event Reporting Period

All AEs, regardless of severity, causality or seriousness must be reported to the Sponsor, from commencement of Pre-screening until the end of the study or 28 days after the administration of study medication, whichever is later. However, any AE that the investigator believes is at least possibly related to study medication should be reported regardless of time elapsed from the dose.

All AEs, including SAEs and deaths, will be reported to the reviewing Ethics Committees according to their specified timelines.

10.3 Serious Adverse Events

A SAE is defined as follows:

Any AE that results in any of the following outcomes:

- death;
- life-threatening situation;
- inpatient hospitalization or prolongation of existing hospitalization;
- persistent or significant disability/incapacity; or
- congenital anomaly/birth defect in the offspring of a subject who received investigational product.

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

- intensive treatment in an emergency room or at home for allergic bronchospasm;
- blood dyscrasias or convulsions that do not result in hospitalization; and/or
- development of drug dependency or drug abuse.

10.3.1 Clarification of (Serious) Adverse Events

Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the investigational product.

All deaths, regardless of cause, must be reported to the Sponsor for subjects on study and for deaths occurring within 30 days of investigational product dose or within 30 days of last study evaluation, whichever is longer.

"Occurring at any dose" does not imply that the subject is receiving investigational product at the time of 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.

10.3.2 Serious Adverse Event Reporting Requirements

10.3.2.1 All Serious Adverse Events

The Sponsor has requirements for expedited reporting of SAE's 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 causal relationship, are as follows:

- complete the "Serious Adverse Event Report" and
    - send to the Safety Desk within 24 hours of the investigator's knowledge of the event by emailing to:

      sae@medicinesdevelopment.com
    - for fatal or life-threatening events, also provide copies of hospital case reports, autopsy reports, and other documents when requested and applicable

The Safety Desk 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 subject's CRF.

10.3.2.2 Investigator Reporting Requirements for SAEs

Per Ghana Food and Drugs Authority guidelines, the investigator should report all SAEs to the Authority within 48 hours. Where required by local regulations, and in accordance with the local institutional policy, the investigator should also notify the EC of SAEs within the required timelines.

10.4 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 or until the investigator determines that the subject's condition is stable, whichever is longer. The Sponsor may request that certain AEs be followed until resolution.

10.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs

All laboratory values must be reviewed by the investigator as soon as practical after the data are available.

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

Any laboratory test result that meets the criteria for a SAE (refer to Section 10.3) should be recorded as an AE, the AE page of the CRF completed and a SAE form also completed in order to provide the Sponsor with additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken and resolution.

10.6 Toxicity Management

AEs and abnormal laboratory values, if appropriate, should be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Section 10.2.1).

Laboratory abnormalities should be assessed as "Clinically Significant" or "Not Clinically Significant".

For the purpose of monitoring toxicities, the baseline value is defined as the last value prior to the administration of the dose of moxidectin. All management (as described in Sections 10.3 and 10.4) is based on changes from this value.

10.7 Guidance for Dose Modification or Discontinuation of Treatment

There will be no dose modification for individual subjects, since this is a single dose study.

Discontinuation of treatment is not applicable in a single dose study.

10.8 Warnings and Precautions

For information regarding precautions and AEs observed after treatment with moxidectin, whether related or unrelated to treatment, the investigator is referred to the Investigator's Brochure for moxidectin.

10.9 Risks for Women of Childbearing Potential or During Pregnancy

The risks of treatment with moxidectin during pregnancy have not been evaluated in humans. For information on the risk assessed in animal studies, see Section 3.3.1.2.2 and the Investigator's Brochure for moxidectin. Females of childbearing potential will be asked to agree to use a highly effective birth control regimen (see Section 6.4.1) while participating in the study and for approximately 6 months (Week 24) following dosing with the Investigational Product.

10.10 Procedures to be Followed in the Event of Pregnancy

The subject and their parent(s)/guardian(s) must be instructed to inform the investigator IMMEDIATELY if the subject or, if male, their partner, becomes pregnant during the study period. Contact information is provided on the study information sheet and the participant identification card each subject will receive. Subjects can also choose to ask the community coordinator (see Section 14.1.2.1) to contact the study team.

The investigator should report all pregnancies to the Sponsor or designee within 48 hours of becoming aware of the pregnancy.

In the event of pregnancy in a subject, the investigator will advise the subject to attend all ante-natal visits and refer them to the appropriate GHS ante-natal service. Monitoring of the subject should continue until conclusion of the pregnancy (i.e. the investigator will ask the pregnant subject to contact the study team in case the GHS ante-natal service informs her of any abnormal finding). The outcome of the pregnancy should be reported to the Sponsor. Post-natal follow-up assessments of the health of the baby will be conducted by a pediatrician at least annually up to 2 years of age. In the event of a pregnancy in the partner of a subject, the investigator should seek informed consent from the partner to report the outcome of the pregnancy to the Sponsor and conduct follow-up assessments of the baby as described above for pregnant study subjects.

All abnormal GHS ante-natal service findings and results of follow-up assessments of babies will be reported to the Sponsor.

11 DATA AND SAFETY MONITORING BOARD (DSMB)

A DSMB has been established with a charter that defines in detail its roles and responsibilities.

The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II and recommend a starting dose for Cohort III. The DSMB will also meet as required during the study. The DSMB will also receive any reported SAEs throughout the study.

The DSMB will recommend to the Sponsor whether the trial may continue as planned or if the trial should be modified or stopped. Any decision to modify or stop the study will be communicated to investigators and regulatory agencies by the Sponsor. ECs will be notified by the PI according to their requirements.

12 SUBJECT COMPLETION / WITHDRAWAL

12.1 Subject Completion

A subject will be deemed to have completed the study once all trial procedures have been conducted. Any AEs or SAEs still ongoing at the time of the Exit Evaluation will be followed in accordance with Section 10.

12.2 Criteria for Premature Withdrawal from Treatment or the Study

Participation in this study is voluntary. Please see Section 14.1.2 for further details on voluntary participation and informed consent and assent.

Subjects (or their parent(s)/guardian(s)) also have the right to withdraw themselves (or their child/ward) from the study at any time for any reason. The PI must make every reasonable effort to understand the reason for the withdrawal and, if possible, retain the subject in the study if their concerns can be addressed.

If a subject vomits in the 30 minutes after taking the dose of moxidectin, all Day 0 assessments should be completed, and the subject should be withdrawn from the study. Any AEs or SAEs still ongoing at the time of withdrawal will be followed in accordance with Section 10.

The PI also has the right to withdraw subjects from the study for safety reasons (e.g. in the event of concurrent illness, AEs, or pregnancy), protocol non-compliance, or administrative or other reasons (see Section 12.6).

An excessive rate of withdrawals from the study can render the study difficult to interpret. In particular, missing data could significantly impact on the interpretation of the results; therefore, unnecessary withdrawal of subjects from the study (e.g. based on misconceptions) should be avoided.

The reasons for withdrawal of the subject must be recorded on the CRF (if given; if a reason is not given, this will be recorded).

12.3 Withdrawal of Subjects from Moxidectin

This is a single dose study, so treatment withdrawal is not relevant.

If a subject is unable to take a full dose of Investigational Product (unable to swallow all required tablets) they should remain on study and be followed up according to protocol.

12.4 Withdrawal of Subjects from the Study

Should a subject and their parent(s)/guardian(s) and/or the investigator decide on the withdrawal of a subject from the study, all efforts will be made to complete and report the observations as thoroughly as possible.

The PI or delegate should contact the subject through a personal visit or through contact with a responsible relative to determine, if possible, the reason for withdrawal. A complete final evaluation should be made at the time of the subject withdrawal, with an explanation of the reason for the withdrawal. Where possible, subjects should be followed until any AEs are resolved or abnormal laboratory tests have returned to normal.

12.5 Replacement of Withdrawn Subjects

Any subjects who discontinue a clinical study of their own and/or their parent(s)/guardian(s) volition or are withdrawn by the PI are defined as “withdrawals”. Replacement subjects (up to a total study maximum of 63 participants treated) may be enrolled into the study at the request of the Sponsor to ensure adequate pharmacokinetic time points are obtained.

12.6 Premature Termination of the Study

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

- New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the investigational product, such that the risk/benefit is no longer acceptable for subjects participating in the study;
- Significant violation of GCP that compromises the ability to achieve the primary study objective or compromises subject safety.
- In the event that data obtained for Cohorts I or II does not enable determination of a starting dose for Cohort III, or Cohorts I to III data does not enable determination of an optimal dose.

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

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

13 DATA MANAGEMENT CONSIDERATIONS AND STATISTICAL ANALYSIS

13.1 Hypothesis

No formal hypothesis testing will be performed in this study. Analyses will be descriptive only. All planned analyses will be presented in a SAP.

13.2 Sample Size Determination

Cohorts of nine (9) subjects each is considered to be an adequate sample for full characterization of moxidectin pharmacokinetics and for dose selection based on achieving exposures within the acceptable range at the same dose. If one third of subjects or more is above or below the target $AUC_{0\text{-}inf}$ range, then a new dose will be chosen and a further 9 subjects will be targeted for recruitment.

13.3 Enrolment and Randomization

Subjects are considered enrolled after informed consent has been obtained and eligibility has been confirmed on the morning of Day 0. The study is not randomized.

Subject disposition will be described according to the numbers of subjects screened (not enrolled), enrolled (not treated) and treated. Screen failure data will be included in the database only as necessary to determine the number of subjects screened but not enrolled and the reason(s) for ineligibility.

13.4 Analysis Populations

The pharmacokinetic analysis population will include all subjects who receive moxidectin and provide a minimum number of samples for the determination of plasma pharmacokinetic parameters.

A subject will be included in the pharmacokinetic population if they have at least the following:

1) Samples taken at Hours 4, 24 and 72; and
2) One sample on either Day 14 or Day 28.

Subjects in this population will be used for all pharmacokinetic summaries. Subjects in this population will be analyzed according to the dose received.

Note that any deviation from the full sampling schedule (i.e., less samples) may compromise the accuracy of pharmacokinetic calculations, and thus may inhibit the ability to make dosing decisions for subsequent (e.g. younger) cohorts. As such, it is strongly recommended to adhere

to the full pharmacokinetic sampling schedule as best as possible, unless non-adherence is required to safeguard subject safety.

The safety population will include all subjects who receive at least 2 mg of study drug. Subjects in this population will be used for demographic and safety summaries. Subjects in this population will be analyzed according to the dose received (actual amount of investigational product swallowed).

13.4.1 Demographic and Baseline Characteristics

Demographic and baseline information including key medical conditions, will be summarized and tabulated by cohort. The purpose of these summaries is (1) to characterize the study population, and (2) to identify any baseline imbalances of clinical significance that may require consideration in the evaluation of safety and pharmacokinetics.

13.4.2 Data Analysis Methods

No formal hypothesis testing will be performed in this study. Analyses will be descriptive only. All planned analyses will be presented in a SAP that will be finalized prior to commencing the final data analysis.

13.5 Statistical and Analytical Plan

A detailed SAP in which all aspects of data analysis will be defined will be prepared prior to undertaking the final analysis and database lock. The SAP will be submitted to regulatory authorities prior to database lock, as required.

13.5.1 Analysis of Demographics

Demographic and other baseline characteristics will be described by age Cohort and dose and for the total population.

13.5.2 Analysis of Pharmacokinetics

Non-compartmental pharmacokinetic analyses will be conducted on emerging pharmacokinetic data from the study, to evaluate whether the dose taken will ensure subjects have AUC values anticipated to be within the range expected to be safe and efficacious based on Phase II and III studies in adults and adolescents.

Phoenix WinNonlin version 6.4, will be implemented for the calculation of pharmacokinetic parameters including $AUC_{0\text{-}inf}$ to ensure subjects fall within the pre-determined acceptable exposure range, and C_{max}.

Specific pharmacokinetic parameters for moxidectin in plasma will include:

- $AUC_{0\text{-}last}$:: AUC from time 0 extrapolated to the last observed concentration;
- $AUC_{0\text{-}inf}$: AUC from time 0 extrapolated to infinity;
- cumulative AUC from time 0 extrapolated to time t (where t = 24, 48, and 72 hours) ($cumAUC_{0\text{-}t}$);
- C_{max}: maximum observed plasma concentration;
- T_{max}: time to maximum observed plasma concentration;
- $t_{½}$: terminal elimination half-life.

Additional pharmacokinetic parameters, including CL, volume of distribution, and others may be determined as appropriate.

The C_{max} will be excluded from all estimations of elimination rate constants for non-compartmental analysis. The elimination rate constant will be estimated if a given subject has more than two concentration values in the terminal portion of the curve and R-square greater than 0.95. Computed pharmacokinetic parameters for moxidectin in plasma will be summarized and listed for moxidectin, including mean, geometric mean, standard deviation, median, and range, as appropriate.

13.5.3 Population Pharmacokinetics

The pharmacokinetic and demographic data from Cohorts I and II (adolescents and older children) will be used to update the existing population pharmacokinetic model for moxidectin. Covariate effects for central volume, systemic clearance and peripheral compartments will be explored and the updated model will be used to forecast $AUC_{0\text{-}inf}$ and C_{max} values by dose for Cohort III (children 4 to 7 years) to support dose selection.

At the end of the clinical trial, the population pharmacokinetic model will be updated once more with all available adult and pediatric pharmacokinetic data to assist in providing robust dose recommendations across the age range of 4 to 11 years.

The population pharmacokinetic model updates will be conducted with the non-linear mixed effects modeling software NONMEM. For the first update, parameter estimates from the existing population pharmacokinetic model will be re-estimated using pharmacokinetic and demographic data from adults and Cohorts I and II. Standard diagnostic procedures will be employed to evaluate model fit. Any modifications to the existing structure of the model (e.g., parameterization of covariate effects) will be guided by these diagnostic procedures. The final model from this first update will be assessed using advanced procedures to ensure acceptable structural and simulation properties.

For the second (last) model update, the modeling and evaluation procedures described above will be repeated using all available pharmacokinetic and demographic data (i.e., adults and Cohorts I, II and III).

Full details of the population pharmacokinetic modeling and simulation procedures will be provided in a SAP.

13.5.4 Analysis of Safety

All subjects receiving any dose of moxidectin will be included in the safety analyses.

AEs, concomitant medications and laboratory data will be listed and summarized by Cohort and/or by dose if more than one dose level is evaluated in an age group.

AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE, based on preferred terminology defined by Medical Dictionary for Regulatory Activities (Version 13.1, or later), will be counted only once for a given subject. A summary of the number and percent of subjects with the following treatment emergent AEs will be displayed:

- All AEs
- Drug-related AEs
- Severe AEs
- SAEs

All the laboratory values will be classified by grade. Changes over time in laboratory parameters will be explored. Grade 3 and 4 laboratory abnormalities will also be summarized.

13.6 Pharmacokinetic Assessments for Dose Determinations

Non-compartmental pharmacokinetic analyses will occur in an ongoing manner during the study. Based on these analyses, if 3 or more subjects enrolled in Cohort II or III have moxidectin exposures below or above the target range, defined as AUCs less than the 10^{th} percentile or greater than the 90^{th} percentile mean AUC predicted by the population pharmacokinetic model, then the dose will be modified and 9 new subjects will be enrolled into that age cohort at the new dose. The intention is to provide pharmacokinetic and safety data in each cohort for a minimum of 9 subjects at a dose that is considered optimal to provide therapeutic exposures.

If the required pharmacokinetic parameters for 9 subjects (per dose and cohort) cannot be calculated due to the availability of results from too few samples, additional subjects may be enrolled at that dose. Pharmacokinetic data from 9 subjects at the dose(s) selected for each cohort will be obtained.

The first dose level to be proposed to the DSMB for administration in children aged 4 to 7 years (Cohort III) (and subsequent dose levels, if applicable, see Section 5.3) will be selected following additional population pharmacokinetic modelling with allometric scaling including data obtained from Cohorts I and II.

14 GENERAL STUDY ADMINISTRATION

14.1 Ethical Aspects (Ethical and Safety Considerations)

14.1.1 Local Regulations/Declaration of Helsinki

The PI 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 Ghana.

The Sponsor and the investigators will ensure strict adherence to the provisions of GCP and all applicable local and national regulations and those of applicable regulatory agencies, including the Ghana Food and Drugs Authority and the US FDA. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines will apply at a minimum.

14.1.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from parents/guardians and assent from potential subjects (or to look for expressions of 'deliberate objection' in younger children, as appropriate for their age and level of maturity) after adequate explanation of the aims, methods, objectives and potential hazards of the study prior to undertaking any study related procedures. The investigator should also explain that the potential subjects and their parent(s)/guardian(s) are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The anticipated potential risks of participation and the safety profile of moxidectin in adults and children at least 12 years of age with onchocerciasis are described in Sections 3.3.2.2, 3.4.3 and 10.9.

Information about the study and the written informed consent and assent documents will be presented in the language(s) of the potential subject population. The investigator must utilize ethics committee approved consent and assent forms, in relevant local language(s), for informing the potential subjects and their parents/guardians and documenting written informed consent and assent. The ethics committees responsible for review and approval of these documents are described in Section 14.1.5.

Both parents or guardians (unless one is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of

the child (reason for sole parent/guardian consent must be documented)) of potentially eligible children will provide written (signature or thumbprint) and witnessed informed consent for their child/ward.

Informed assent will be obtained from all children ≥ 12 years and will be considered for children from 7 years onward. Children who do not provide assent, including those aged 4 to 6 years and those aged 7 to 11 years who may not be mature enough to give assent (as judged jointly by their parent(s)/guardian(s) and investigator) will be assessed for expressions of 'deliberate objection' (i.e. expressions of disapproval or refusal), as per CIOMS guidelines (Council for International Organizations of Medical Sciences (CIOMS) 2016). Refusal to provide assent or an expression of deliberate objection by a child/adolescent must be respected even if the parents have given consent for their participation in the study. The investigator will consider the child ineligible and record this on the informed consent provided by the parent(s)/guardian(s).

All children will be informed about the study in the presence of their parent(s)/guardian(s) and an independent witness. The independent witness will confirm that the child and the parent(s)/guardian(s) have understood the information provided and document this on the consent/assent form.

14.1.2.1 Informing Communities about the Study

Information about the study will be shared with community leaders and members within the location(s) where recruitment for the study is planned to take place. The initial approach will be to explain the study, the informed consent and assent procedure, and the information document to the Municipal Assembly, which performs government business at the local level. Next the chiefs, elders, and/or opinion leaders will be informed and educated, followed by whole communities, if the elders do not object. During the community meeting, a 'community coordinator' will be selected. This will be a community member that the community thinks will best serve as a link between the subjects and the study team. Finally, the community will propose an impartial witness or witnesses for the informed consent/assent procedure.

14.1.2.2 Informing Potential Subjects and their Parents/Guardians

Obtaining informed consent and assent for pediatric subjects in rural communities in areas endemic for onchocerciasis poses challenges to the investigator in dealing with two vulnerable

groups in order to enroll a single subject for the study. One group is the parents/guardians permitting their children/wards to participate, and the other group is the even more vulnerable potential subjects, who may or may not be able to give informed assent.

The parents/guardians are considered vulnerable because the social, economic, and educational gap between the investigator and the rural population is such that they are likely to consider any proposal by a physician to be in their best interest and to accept it with little or no dissent. Moreover, many subjects may not have had access to modern clinical medicine and will be transported from their villages into the alien environment of the clinic to participate in assessment procedures that would normally be unduly invasive for them.

In order to address these factors, recruitment will occur in villages from which participants in the Phase III study of moxidectin and another study conducted by the PI were recruited. Thus, potential subjects and their parents/guardians themselves, or people they can talk to, are likely to have first-hand experience in research study participation and procedures, the research center and moxidectin treatment, and will be able to better understand the information provided about the study during the informed consent process.

Furthermore, the following informed consent procedure is planned:

1. The process will take place in the community in order to remove any pressures imposed by its occurrence in the possibly unfamiliar research center environment.
2. Initial information will be provided at a community meeting, which will allow meeting participants to benefit from the questions asked by other meeting participants. This will be followed by discussions with individual parent(s)/guardian(s) and their child/ward.
3. Study information will be conveyed in the local language. The English version of the informed consent/assent information and forms will be translated and authenticated by a reputable individual or agency. Four different information and/or consent/assent documents are provided:
    i. an adolescent (12 to 17 years) and parent/guardian information sheet and assent and consent form written in language that is understandable to a child of 12 years of age (see Appendix 16.6);

ii. a separate parent/guardian information sheet and consent/assent form for parents of children aged 4 to 11 (see Appendix 16.7), also written in language understandable to children aged 12 years and including two consent/assent forms:
    1. one for parents/guardians and children <12 years who are providing assent (includes written parent/guardian consent and child assent);
    2. one for parents/guardians of children considered too immature to provide assent (includes written parent/guardian consent and documentation of assessment of expression of 'deliberate objection'; consent will be obtained before discussion of the study with the child);

iii. a simpler study information sheet for children aged 7 to 11 years considered mature enough to provide assent (see Appendix 16.8); and

iv. an even simpler information sheet for children 4 to 6 years or older children considered too immature to provide assent (see Appendix 16.9).

4. Every effort has been made to ensure that all aspects of the study and all elements regarded as essential for informed consent/assent are specified in the information documents. These are presented in chronological order and supplemented by images and schematic diagrams to facilitate comprehension.
5. Understanding of the information provided about the study will be assessed using a short questionnaire consisting of a series of open and closed questions in the local language for parents/guardians, adolescents and children considered mature enough to give assent to answer. The questions to be asked are included at the end of the information documents, with space provided for recording responses and any questions asked by the child or parent(s)/guardian(s) (refer to Appendices 16.6, 16.7 and 16.8).
6. An impartial, literate local resident agreed to by the potential subject and their parent(s)/guardian(s) (impartial witness) must be present when study information is provided and discussed, and must countersign the consent/assent form to attest to the fact that the information has been given to and understood by the parent(s)/guardian(s) and child.

7. The informed consent/assent forms must be signed/thumbprinted in 2 originals, one of which must be given to the parent(s)/guardian(s) in front of the impartial literate witness on the same day that the informed consent/assent is given.
8. At each subsequent study visit, the investigator should verbally confirm the continued consent/assent of the subject and that they are free to withdraw from the study at any time for any reason.

14.1.2.3 Informing Children Too Young/Immature to Give Assent.

Information about the study, primarily based on pictures (Appendix 16.9) will be presented to children aged 4 to 6 years as well as older children considered not mature enough to provide assent in the joint judgement of the parent(s)/guardian(s) and the investigator.

Early on in the presentation and discussion, a tablet similar in size and shape to moxidectin tablets will be shown and the child and their parent(s)/guardian(s) will be asked whether they think the child can swallow such tablets. If a child or their parent(s)/guardian(s) states that they cannot swallow a tablet of that size and shape, there will be no further discussion. Subsequently children will be told about the need to take blood and venous access will be assessed. If a child has poor venous access, there will be no further discussion.

It is acknowledged that this constitutes evaluation of exclusion criteria 7 and 8 before the child has been presented with all information about the study and had the opportunity to express 'deliberate objection' to all other elements of the study. This sequence was chosen since it does not include an invasive procedure or confidential health information and obtaining all other information about the study has no value for a child who will be excluded on the basis that they cannot swallow the tablets or have poor venous access.

14.1.3 Compensation

All study-related costs, including study medication, laboratory tests, contraceptives counselling and provision, and medical care will be provided free of charge. In addition, transportation will be provided to and from the study center, and accommodation and food will be provided for each (potential) subject and their accompanying parent/guardian while at the study center.

The parent/guardian who accompanies the child to the study site will be compensated for loss of earnings according to the number of nights they are required to stay. The amount paid for each night's stay will approximate to "by day" earnings of individuals in the village communities,

currently forty (40.00) Ghanaian Cedi per day. In addition, treatment-emergent adverse events occurring during the study will be treated in accordance with local treatment requirements and as clinically indicated without cost.

14.1.4 Provision for Study Visits During School Time

If the child is at the study center during school time, a teacher will be employed to provide educational activities and/or oversee homework during their stay to compensate for school time missed.

14.1.5 Ethics Committees

This protocol and any accompanying material provided to the potential subject and their parents/guardian (such as information sheets with descriptions of the study used to obtain informed consent/assent) will be submitted by the investigator to the Research Ethics Committee of the UHAS and the GHS Ethics Review Committee. Furthermore, the protocol will be submitted to the WHO Ethics Review Committee. Approval from all three ethics committees will be obtained before starting the study and must be documented in a letter to the investigator (or the WHO Responsible Officer submitting the protocol to the WHO Ethics Review Committee) specifying the protocol number and version and the date on which the committee met and the date it granted the approval.

14.1.6 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 consultation between an appropriate representative of the Sponsor and the PI.

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

All protocol modifications must be submitted to the ethics committees (UHAS, GHS and WHO, see Section 14.1.5) in accordance with local requirements and to regulatory bodies (Ghana Food and Drugs Authority and US FDA) as required. Approval must be granted before changes can be implemented.

In the event of an emergency, the investigator may institute any medical procedures deemed appropriate without a formal protocol amendment being granted. However, all such procedures must be promptly reported to the Sponsor, the Medical Monitor and the ethics committees.

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. Any administrative changes must be agreed upon by the Sponsor and the PI and must be documented in a memorandum. The PI (or WHO Responsible Officer) will then notify the ethics committees of such administrative changes.

14.1.7 Conditions for Terminating the Study

Both the Sponsor and the PI 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 PI will assure that adequate consideration is given to the protection of the subject's interests.

14.1.8 Blood Volumes Sampled Relative to Maximum Recommended Volumes

Please refer to Section 7.4.3.

14.1.9 Informing Study Subjects and Communities about the Study Results

Once the final data from the study are available and a decision on further evaluation of moxidectin has been made, each community will be visited. The study subjects and their parents, as well as other interested community members, will be informed about the study results and any future activities to be undertaken to enable the use of moxidectin for control and elimination of onchocerciasis in endemic countries. Age appropriate information documents to be used for this purpose will be submitted for review and approval by the responsible ethics committees.

14.1.10 Implementation of the Study in the context of the COVID-19 Pandemic

All activities required for successful implementation of the study were reviewed, ranging from community mobilization and information (Section 14.1.2.1), informing potential participants and their parents/guardians about the study (Section 14.1.2.2) and obtaining parental informed consent and adolescent/child assent (Sections 7.3.1 and 14.1.2), through to screening in the village of residence, transport to and from the research center, treatment and follow up (Sections 7.3.2 to 7.3.14).

The objective of this review was to determine whether changes in the standard methodology and approach could be identified that would minimize contact with research participants so that the study can be conducted during the pandemic in a way that minimizes risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Further, it sought to determine whether the changes could potentially result in an overall positive benefit-risk ratio through 1) education of the population in the villages where participants will be recruited regarding coronavirus disease 2019 (COVID-19) and measures to minimize the risk of transmission, and 2) contribution to screening for COVID-19 cases via referral of suspect cases to the Nkwanta North COVID-19 Rapid Response Team.

Specifically, the review of the activities evaluated:

- the extent to which processes can be conducted with physical distancing and the operational measures required to comply with national directives;
- the extent to which those involved will have already undergone education on COVID-19 and the precautions required to minimize SARS-CoV-2 transmission and, as a result, whether the study team will need to provide initial information on COVID-19, or can build on previous information provided by the Ghana Ministries of Communication and Health via the radio and television;
- how screening for suspected COVID-19 cases through temperature measurement and assessment of other symptoms, followed by referral of suspected cases to the Nkwanta North or Hohoe COVID-19 Rapid Response Team can be conducted at the beginning of all protocol-planned activities; and
- additional measures that need to be taken to minimize the risk of SARS-CoV-2 transmission during all activities where the physical distancing advised by the GHS (currently ≥6 feet) is not possible.

Per the GHS Ethics Review Committee guidelines effective 7 May 2020, the measures that will be taken to adhere to current national directives on physical distancing and to protect the safety of participants, their communities and the study team are outlined below. As national, Nkwanta North COVID-19 Rapid Response Team or Hohoe COVID-19 Rapid Response Team directives evolve during the course of the pandemic (e.g. regarding the number of people allowed to

participate in meetings or the physical distance to be kept), these measures will be adapted accordingly.

All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the Nkwanta North COVID-19 Rapid Response Team or Hohoe COVID-19 Rapid Response Team, as applicable, based on where the protocol-planned activities take place.

14.1.10.1 Informing Communities About the Study

Measures to minimize the risk of transmission of SARS-CoV-2 will be implemented as follows.

14.1.10.1.1 District Directors, Disease Control Officers and Local Health Center Staff

- Those involved in meetings to discuss the study will have already undergone education on COVID-19, have procedures in place for screening for COVID-19 symptoms before entering the buildings where meetings are held and will be wearing masks.
- Meetings will be arranged so that the government-advised maximum group size applicable at the time is not exceeded.
- Offices/meeting rooms will be set up in compliance with government-advised physical distancing and procedures will be in place to refer anybody with COVID-19 symptoms to the Nkwanta North COVID-19 Rapid Response Team designated local health facility/COVID-19 team.
- Documents distributed at the meetings will be left with meeting participants.

14.1.10.1.2 Chiefs, Elders and Opinion Leaders

- By the time meetings with chiefs, elders and opinion leaders are initiated, most participants are likely to have received information about COVID-19 provided by the government via radio or television.
- Meetings will be arranged so that the government-advised maximum group size applicable at the time is not exceeded.
- Meetings will be set up an open space, church or school, with the study team ensuring that seating meets the current government-advised maximum group size and physical

distancing requirements for individuals who do not live together. The study team will use megaphones to ensure they can be heard.

- The study team will measure the temperature of all participants using non-contact thermometers and ask about other symptoms of COVID-19, as well as any COVID-19 tests. Suspected COVID-19 cases will be excluded from the meeting and asked to self-isolate to the extent possible. The study team will inform the COVID-19 Rapid Response Team, so that the suspected cases can receive the appropriate evaluation and follow-up.
- The study team will provide cloth masks for all meeting participants and ensure availability of soap and water (or hand sanitizer) for hand washing/sanitizing. This will ensure that all meeting participants wash/sanitize their hands before entering and on leaving the meeting space, and wear masks throughout the meeting.
- The study team will initiate the meeting with a demonstration of the proper use and cleaning of cloth masks and information on COVID-19 symptoms, how to minimize the risk of infection and the need to call the Nkwanta North COVID-19 Rapid Response Team if they or somebody they know experience symptoms.
- Documents and cloth masks will be left with participants.

14.1.10.1.3 Village Communities, Potential Participants and Their Parents

In addition to the procedures described in Section 14.1.10.1.2 for screening for COVID-19 symptoms, physical distancing, hand washing, wearing of masks, and provision of general information on COVID-19 and minimizing the risk of infection, the following measures will be implemented:

- By the time meetings are initiated with village communities, many, but not all community meeting participants are likely to have heard the information about COVID-19 provided by the government via radio or television.
- Meetings will be arranged in an open space, church or school so that seating arrangements can meet the government-advised maximum group size and physical distancing requirements for individuals who do not live together that are applicable at the time. To achieve this, meetings may be arranged at the sub-village level, including

with family groups who are interacting on a daily basis, or even by arranging meetings for individual family groups. The village coordinator (Section 14.1.2.1), a literate witness (Section 14.1.2) and a translator will always be present, together with up to five study team members.

14.1.10.2 Obtaining Informed Consent/Assent

Meetings to accomplish the final steps in informing potential participants and their parents/guardians about the study and obtain informed consent/assent will include the child/adolescent and their parents/guardian, the village coordinator, the witness, the translator and the investigator.

In addition to procedures described in Sections 14.1.10.1.2 and 14.1.10.1.3 for screening for COVID-19 symptoms, physical distancing, hand washing, wearing of masks, and provision of general information on COVID-19 and minimizing the risk of infection, the following measures will be implemented:

- Suspected cases of COVID-19 identified by symptom screening will be excluded from meetings. If the suspect case is a village coordinator, witness or translator, they will be replaced. If the suspect case is a child or parent/guardian, the child and parent/guardian will be asked whether they want to be contacted about study participation once they have tested negative or recovered from COVID-19, as applicable.

14.1.10.3 Pre-screening in Villages

In addition to procedures described in Sections 14.1.10.1 and 14.1.10.2 for screening for COVID-19 symptoms, physical distancing, hand washing, wearing of masks, and provision of general information on COVID-19 and minimizing the risk of infection, the following measures will be implemented:

- Study team members will wear medical-grade masks and wash/sanitize hands between interactions with different participants involving physical contact.
- Waiting areas for pre-screening participants will be set up to ensure government-required physical distancing between different child/parent/guardian pairs.
- While the COVID-19 pandemic is ongoing, as many protocol-planned screening activities as possible that do not require medical or laboratory examinations (see

Sections 6.1, 6.2 and 6.3) will be conducted in the villages to minimize the number of potential screen failures and their accompanying parent/guardian being transported to the UHAS research center for screening:

14.1.10.4 Transport Between Villages and the UHAS Research Center

In addition to procedures described in Sections 14.1.10.1, 14.1.10.2 and 14.1.10.3 for screening for COVID-19 symptoms, physical distancing, hand washing, wearing of masks, and provision of general information on COVID-19 and minimizing the risk of infection, the following measures will be implemented:

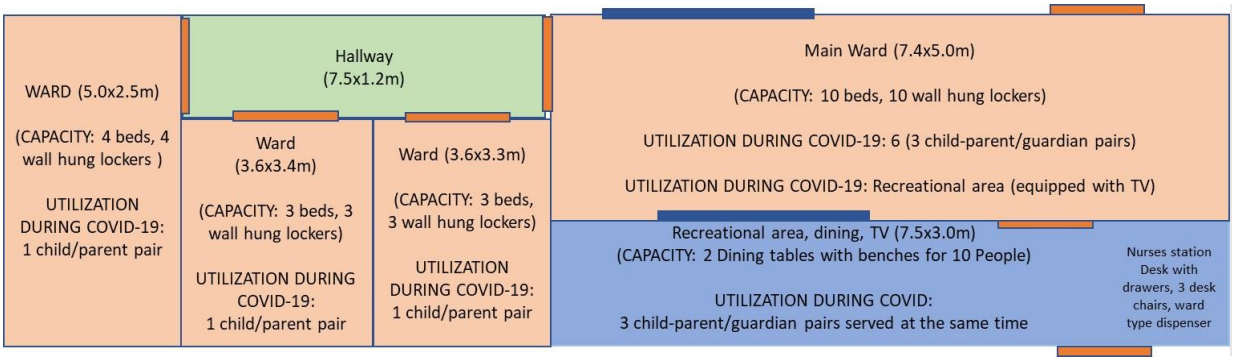
- To the extent possible, children/adolescents and accompanying parents/guardians being transported together to the Center will be selected so they are in frequent contact with each other during their daily lives.
- Only children/adolescents and their parents/guardians who pass COVID-19 screening will be allowed to travel to the Research Center.
- The number of passengers per vehicle will be limited to 8 (including 1 driver and 1 coordinator).
- Before entering the vehicle, everybody with wash/sanitize their hands and put on face masks.
- The standard cleaning of vehicles between trips will be expanded to include use of bleach or other SARS-CoV-2-suitable disinfectants.

14.1.10.5 Accommodation in the UHAS Research Center

- The standard welcome and introduction to the Research Center will be expanded to include a demonstration on the proper use and cleaning of cloth masks, and information on measures such as wearing of masks, regular hand-washing and physical distancing between people who do not normally live in the same house that will be adopted by both participants and the study team to minimize the risk of COVID-19 infection.
- The number of child/adolescent and parent/guardian pairs per ward and eating at the same time will be reduced as shown in Figure 2.

- The normal cleaning routine (morning, evening) will be expanded to three times a day (morning, mid-day, evening) and toilets and washrooms will be cleaned using bleach or other SARS-CoV-2-effective disinfectants every 3 hours during the day.

Figure 2: Capacity and Utilization of Participant and Parent/Guardian Wards and Recreational Areas During the COVID-19 Pandemic



14.1.10.6 Protocol-Planned Examinations

- Each morning, study participants and their accompanying parent/guardian will undergo temperature measurement and be questioned about other signs and symptoms of COVID-19. Individuals meeting suspected case criteria will be isolated and the Hohoe COVID-19 Rapid Response Team will be notified.
- Staff will wear medical-grade masks during all examinations involving physical contact and wash hands between interaction with different study participants.
- Children/adolescent and parents/guardians will wear cloth masks (provided and washed on a daily basis by the Research Center).
- All equipment will be disinfected between examination of different study participants.
- The normal cleaning routine (morning, evening) of all examination rooms will be expanded to three times a day (morning, mid-day, evening).
- Laboratory samples will be taken by staff wearing medical-grade masks and gloves and will be handled according to standard biosafety precautions.

14.2 Study Documentation, Case Report Forms and Record Keeping

14.2.1 Investigator Files and Retention of Documents

The PI is responsible for maintaining adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents

should be classified into two separate categories: (1) Investigator Site File, and (2) subject clinical source documents. The PI must ensure members of the study team are aware of and adhere to these requirements, by implementation of adequate training and according to relevant site SOPs.

The Investigator Site File will contain the protocol/amendments, completed CRFs and data clarification forms (or electronic (e)CRF data queries and audit trails), EC and governmental/regulatory authority approvals with correspondence, informed consent/assent forms, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence. Subject clinical source documents may include subject hospital/research center records, physician and nurse's notes, appointment books, original laboratory reports, ECG tracings etc.

All essential documents should be retained for at least 25 years after the end of the clinical trial. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the investigator/institution as to when these documents no longer need to be retained. The PI must notify the Sponsor prior to destroying any clinical study records.

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

If the PI cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the PI and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the PI 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 off-site.

14.2.2 Background Data

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

14.2.3 Audits and Inspections

The PI should understand and agree that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representative or to regulatory authority or health authority inspectors after appropriate notification. The verification of the CRF data will be by direct inspection of source documents.

14.2.4 Case Report Forms

CRFs (eCRFs) must be completed for each subject enrolled and signed by the PI. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.

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

The CRF is essentially a data entry form and should not be considered to constitute an original, or source, document.

All data must be entered in English.

The CRFs should always reflect the latest observations on the subjects participating in the trial; therefore, the CRFs are to be completed as soon as possible after the subject's visit. The PI 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, as well as the protocol, are confidential. The CRFs remain the property of the Sponsor at all times.

14.3 Monitoring the Study

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

During the trial, the designated Study Monitor will regularly visit the site to monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide

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

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

The PI agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. The SRM will include Study Monitor and back up contact details in the event they have queries or require assistance.

14.4 Confidentiality of Trial Documents and Subject Records

The PI must assure the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. Documents not for submission to the Sponsor (e.g. subject's written consent/assent forms), should be maintained by the PI in strict confidence.

On CRFs or other documents submitted to the Sponsor or designee, subjects should not be identified by their names, but by subject ID. The PI must keep a subject enrolment log showing identification codes and participant names. This log must be made available to the Study Monitor but not provided to the Sponsor.

All information concerning the study treatment shall remain the sole property of the Sponsor. The PI 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.

14.5 Publication of Data (Dissemination of Results)

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

In accord with standard editorial and ethical practice, the Sponsor will support initial publication of analyses and conclusions from the entirety of trial data only.

The results of this study may be published or presented at scientific meetings. Per local regulatory guidelines, publication will only proceed 30 days after the Sponsor receives Ghana Food and Drug Authority's acknowledgement of receipt of the final study report. Sponsor-

initiated publications and/or presentations will be agreed upon between the PI and Sponsor. PI-initiated publications and/or presentations will be provided for review by the Sponsor at least 30 days prior to submission to allow the Sponsor to provide comments based on information from other studies that may not yet be available to the PI.

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 PI and the appropriate Sponsor personnel. Authorship will be determined by mutual agreement in accordance with International Committee of Medical Journal Editors recommendations. Additional authors will be agreed prior to journal submission.

14.6 Anticipated Subject Accrual and Duration of the Study

The anticipated subject accrual to the study will be up to a maximum total of 63 subjects on study for 28 weeks, recruited over a 35-week period. Duration of study is expected to be approximately 15 months. The PI 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 PI anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the Sponsor as early as possible.

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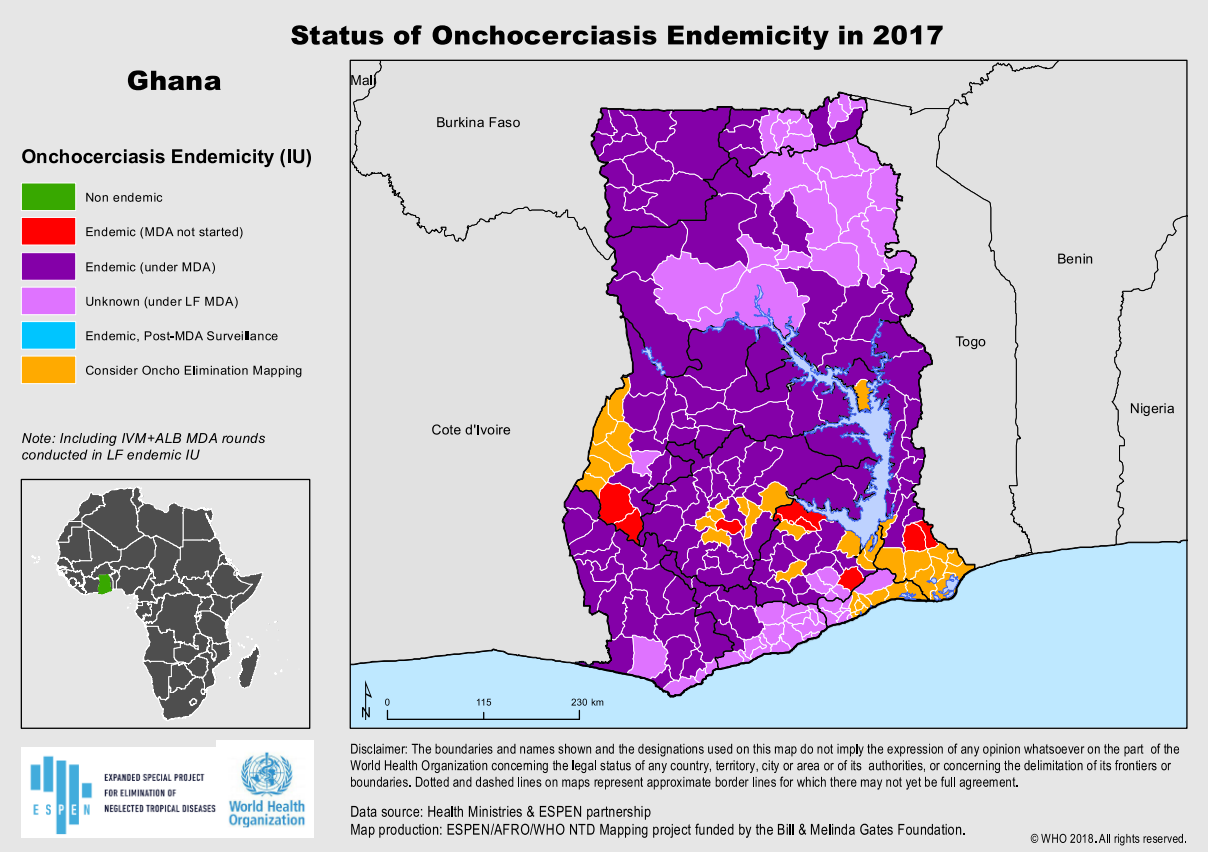
16 APPENDICES

16.1 World Health Organization Designation of Onchocerciasis Endemicity

Figure 3: Onchocerciasis Endemicity (2017) and Status of Onchocerciasis Therapeutic Mass Drug Administration Coverage (2016) in Ghana



16.2 Population Pharmacokinetic Simulation of Moxidectin to Determine Initial Dosing Recommendations for Subjects in Study MDGH-MOX-1006 (d3 Medicine Report, 9 Dec 2016, and Statistical Appendix, 26 Nov 2019)

d3 Medicine, A Certara Company

Report (Confidential)

Population Pharmacokinetics Simulation of Moxidectin to Determine Initial Dosing Recommendations for Participants in Study MDGH-MOX-1006

Sponsor	Medicines Development for Global Health
Document Issued	09 Dec 2016

1 List of Abbreviations

AUC	Area under the curve
BMI	Body mass index
CDTI	Community-directed treatment with ivermectin
CL/F	Clearance from the central compartment
CL_{d2}/F	Inter-compartmental clearance between the central and second peripheral compartments
Cmax	Maximum concentration
PK	Pharmacokinetic
SAP	Statistical analysis plan
V_c/F	Volume of distribution of the central compartment
V_{p2}/F	Volume of distribution of the second peripheral compartment
WHO	World Health Organization

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2 Introduction

Onchocerciasis is a skin and eye disease caused by the parasitic worm *Onchocerca volvulus*. The disease is transmitted to humans through the bite of a black fly (genus *Simulium*) [1]. Once matured in the human body, the adult female worm (macrofilaria) produces larval worms (microfilariae) that distribute in the skin and eye [1]. Microfilariae can cause serious skin conditions and visual impairment that may lead to irreversible blindness [2, 1]. Onchocerciasis is commonly known as "river blindness" since the black flies that transmit the disease live near fast-running rivers and streams in inter-tropical zones (mostly in sub-Saharan Africa) [1]. The World Health Organization (WHO) has listed onchocerciasis as a neglected tropical disease for which new treatments are sought [3]. Substantial effort is being made to control onchocerciasis due to its severe health and economic burden [1, 2].

The current control strategy for onchocerciasis is community-directed treatment with ivermectin (CDTI). This strategy is currently implemented in mesoendemic and hyperendemic areas [2]. Although the microfilaricidal effect of ivermectin typically results in a rapid decrease in skin microfilarial load, the microfilariae may begin to reappear in the skin three to six months after treatment [2]. Multiple doses of ivermectin have been reported to lead to a reduction in microfilarial load [4, 5, 6, 7, 8, 9].

A possible alternative to ivermectin is moxidectin. Moxidectin is an anthelmintic drug developed by Fort Dodge Animal Health [2]. It is used for prevention of canine heartworm and treatment of internal and external parasites in sheep, horses and cattle [2]. Currently, moxidectin is being developed in collaboration with the WHO as a treatment for onchocerciasis in humans [2].

A population pharmacokinetic (PK) model of moxidectin has been developed using PK data from healthy adult volunteers [10, 11] and adult patients infected with *Onchocerca volvulus* [12, 13]. The model accounted for the effects of food, formulation and body composition [13]. Importantly, the model was built with the intention of extrapolation to other populations, including paediatrics [13]. As such, this model has the potential to aid determination of dosing strategies for future studies of moxidectin in children, such as Study MDGH-MOX-1006. Study MDGH-MOX-1006 is a Phase 1 study in children and adolescents 4-17 years old, where dosing regimens for children 4-11 years have not yet been established. Adolescents 12-17 years participating in Study MDGH-MOX-1006 will receive a single oral dose of 8 mg, which was shown in Study ONCBL60801 (Phase 3) to be efficacious and well-tolerated in this group.

3 Objectives

The objectives of this work were to:

1. Predict (by population PK simulation) the range of exposures achieved with a single 8 mg oral dose of moxidectin in adolescents 12-17 years.

2. Use available data sources, including demographic data from the adolescents who participated in Study ONCBL60801, to facilitate simulations to support initial dosing recommendations of moxidectin for children 4-11 years who will participate in Study MDGH-MOX-1006.

4 Methods

4.1 Model for Simulation

Concentration-time profiles were simulated from a previously developed population PK model of moxidectin [13]. In brief, the model was built using PK data from healthy adult volunteers [10, 11] and adult patients infected with *Onchocerca volvulus* [12]. The model comprises three compartments with an n-transit absorption process and first-order elimination (Figure 1). To allow the potential to extrapolate to other populations, the model incorporated allometry [14] where consistent with the observed data (central volume of distribution $[Vc/F]$, inter-compartmental clearance between the central and second peripheral compartments $[CL_{d2}/F]$ and volume of distribution of the second peripheral compartment $[V_{p2}/F]$ [13]). The model includes effects of food and formulation on absorption and relative bioavailability (Figure 1, Table 1). The model also stipulates that females have larger values of CL_{d2}/F and V_{p2}/F than males; subjects with larger values of body mass index (BMI) have increased V_{p2}/F (stratified by Phase 1 and Phase 2; Figure 1, Table 1). See [13] for full details of the population PK model.

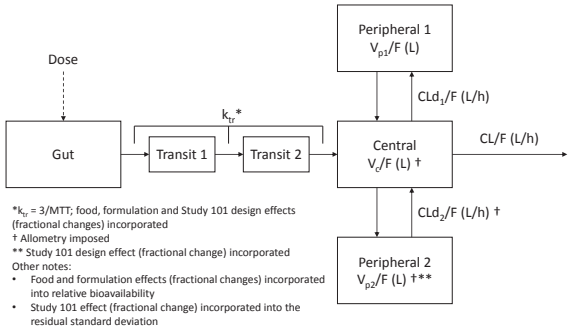

Figure 1. Schematic of the population PK model of moxidectin. ktr = transit rate constant, CL/F = apparent clearance, V_c/F = apparent volume of distribution of the central compartment, CLd_1/F = apparent inter-compartmental clearance between the central and first peripheral compartments, V_{p1}/F = apparent volume of distribution of the first peripheral compartment, CLd_2/F = apparent inter-compartmental clearance between the central and second peripheral compartments, V_{p2}/F = apparent volume of distribution of the second peripheral compartment.

Table 1. Parameter estimates from the final population PK model of moxidectin

Parameter	Estimate	%RSE	BSV	%RSE
MTT (h)	1.65	5.1	0.187	13.3
CL/F (L/h)	3.63	5.6	0.162	11
V_c/F (L/70 kg)	129	4.4	0.0528	16.1
CL_{d1}/F (L/h)	5.06	4.7		
V_{p1}/F (L)	246	7		
CL_{d2}/F (L/h/70 kg)	2.97	7.3	0.128	14.9
V_{p2}/F (L/70 kg)	1080	5.8	0.188	11.3
Phase 1 effect* on CL/F	0.694	20.1		
Phase 1 effect* on V_c/F	0.839	32.1		
Phase 1 effect* on CL_{d1}/F	0.843	40.5		
Phase 1 effect* on V_{p1}/F	0.479	11.5		
Phase 1 effect* on CL_{d2}/F	1.87	15.4		
Phase 1 effect* on V_{p2}/F	1.3	38.5		
Food effect* on MTT	2.12	12.1		
Food effect* on relative bioavailability	1.39	17.4		
Formulation effect* on MTT (fixed)	0.292	0		
Formulation effect* on relative bioavailability	1.21	13.5		
Sex effect* on CL_{d2}/F	1.52	26.4		
Sex effect* on V_{p2}/F	1.64	23.9		
Phase 1 BMI effect** on V_{p2}/F	1.56	23.6		
Phase 2 BMI effect** on V_{p2}/F	0.598	58		
Study 3110A1-101-EU effect* on MTT (fixed)	0.477	0		
Study 3110A1-101-EU effect* on V_{p2}/F	1.19	45.9		
Proportional error (SD; %)	22.6	1.1		
Study 3110A1-101-EU effect* on proportional error	0.855	13.9		

%RSE=Percent relative standard error; BSV=Between-subject variance,
*Fractional change; **Exponent from power function; SD=Standard deviation

4.2 Simulation Procedure

The simulation procedure resembled the proposed study design of Study MDGH-MOX-1006. The following single oral doses of moxidectin under fasted conditions were evaluated: 2 mg, 4 mg, 6 mg and 8 mg. For each dose, the simulation procedure was as follows:

1. Two virtual age cohorts were generated: 4-7 years and 8-11 years. For the 8 mg dose, an additional adolescent cohort (12-17 years) was generated. The 4-7 years and 8-11 years cohorts each consisted of 9 virtual individuals (4 females, 5 males). The adolescent cohort (8 mg only) consisted of 12 virtual individuals (6 female, 6 male; i.e., one male and one female for each age). Within each age cohort, individual weights, heights and body mass index (BMI) were simulated based on observed demographic profiles from Study ONCBL60801 (restricted to subjects from Ghana; ≥12 years) and WHO growth charts (children 5-11 years, with consideration of children 12-17 years) [15]. Demographic data from Study 3110A1-GH-200 [12] were also used to investigate and establish demographic profiles.

2. Each individual's (simulated) demographic data (i.e., sex, weight and BMI) were used in conjunction with the population PK model (Section 4.1) to simulate a corresponding moxidectin concentration-time profile. To facilitate calculation of PK exposure metrics (see step 3 below), an intensive PK sampling design (hourly up to 4 days post-administration; every 4.5 days up to 12 months post-administration) was specified for each individual.

3. For each individual, the area under the curve (AUC) and maximum concentration (Cmax) was derived from their simulated PK profile.

This process was repeated 1000 times. Therefore, for each dose, there were 9×1000 simulated PK profiles (and corresponding PK exposure metrics) for the 4-7 years and 8-11 years cohorts; 12×1000 profiles and exposure metrics for the adolescent cohort (8 mg only).

For purposes of comparison, an additional 1000 moxidectin PK profiles were simulated for each of the following scenarios in adults:

- Typical adult male (weight=58.2 kg, BMI=20.7 kg/m^2 [13]), single oral 8 mg dose, fasted conditions.
- Typical adult female (weight=59.7 kg, BMI=23.9 kg/m^2 [13]), single oral 8 mg dose, fasted conditions.
- Typical healthy adult male (weight=74.6 kg, BMI=23 kg/m^2 [16]), single oral 8 mg dose, fasted conditions.
- Typical healthy adult male (weight=74.6 kg, BMI=23 kg/m^2 [16]), single oral 16 mg dose, fasted conditions.

- Typical healty adult male (weight=74.6 kg, BMI=23 kg/m^2 [16]), single oral 36 mg dose, fasted conditions.

The AUC and Cmax were derived for each simulated profile (thus resulting in 1000 AUCs and Cmaxs for each adult cohort above).

4.3 Evaluations of Simulations

For each dose, the resulting simulated PK profiles and exposure metrics were summarised graphically (stratified by age cohort for children and adolescents; all together for adults). Specifically, the 10th, 50th and 90th percentiles of the simulated moxidectin concentrations over time were derived and presented for adults (to exhibit/confirm the simulation model); distributions of the simulated PK exposure metrics for all age cohorts were displayed via boxplots. Numerical summaries of the PK exposure metrics (again stratified by age cohort for children and adolescents; all together for adults) were also presented. These graphical and numerical summaries were compared across doses and age cohorts.

5 Software

The simulations were performed in R [17] using the `mrgsolve` package [18]. Summaries of the simulations were conducted in R [17].

6 Changes to the planned analyses

There were three changes to the planned analyses as specified in the statistical analysis plan (SAP) [19]:

- The PK sampling schedule for the simulations was originally specified as hourly up to 4 days post-administration and daily up to 365 days post-administration [19]. The schedule specified in Section 4.2 was employed to avoid unnecessary computational expense.

- The simulations for healthy adults, which were not specified in the SAP [19], were derived to provide additional means for comparison.

- The 10th, 50th and 90th percentiles of the simulated moxidectin concentrations over time were computed and exhibited for adults only (originally planned for all age cohorts [19]). This was done to restrict the graphical and numerical summaries to the most relevant simulated metrics for decision making, which were Cmax and AUC.

7 Results

7.1 Demographic Profiles

Figure 2 displays the relationship between height and weight (by sex) assumed for the simulations.

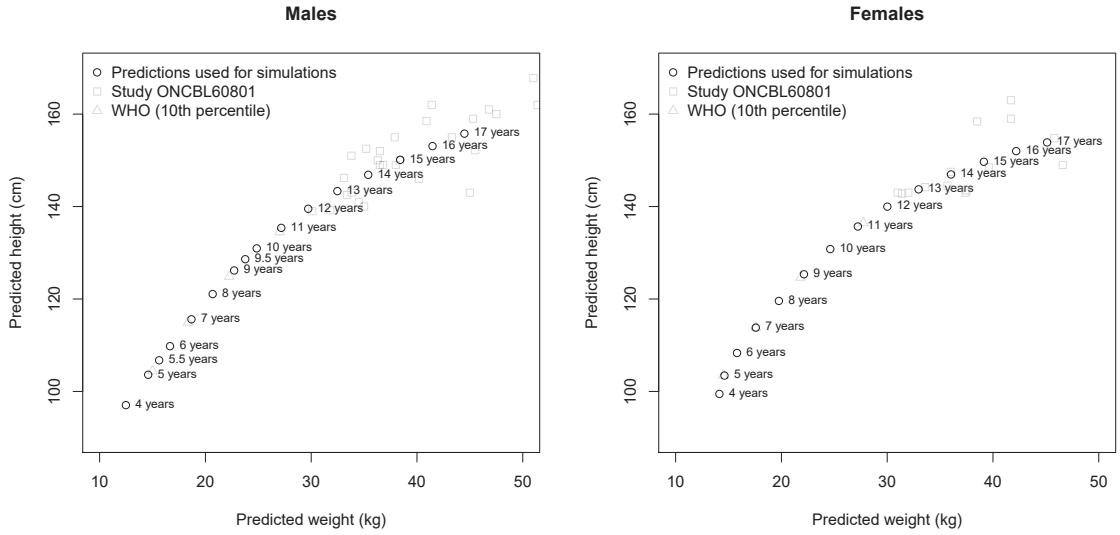

Figure 2. Relationship between height and weight assumed for the simulations. The black open circles represent the data used in the simulations, the gray open squares indicate the observed data from Study ONCBL60801 and the gray open triangles represent data from WHO growth charts (10^{th} percentile).

7.2 Simulations

Figure 3 displays the simulated PK profiles for adults (with observed PK data from Study 3110A1-GH-200 [12]) and healthy volunteers (with observed PK data from Study 3110A-EU-1005 [11]). The simulations were consistent with the observed data.

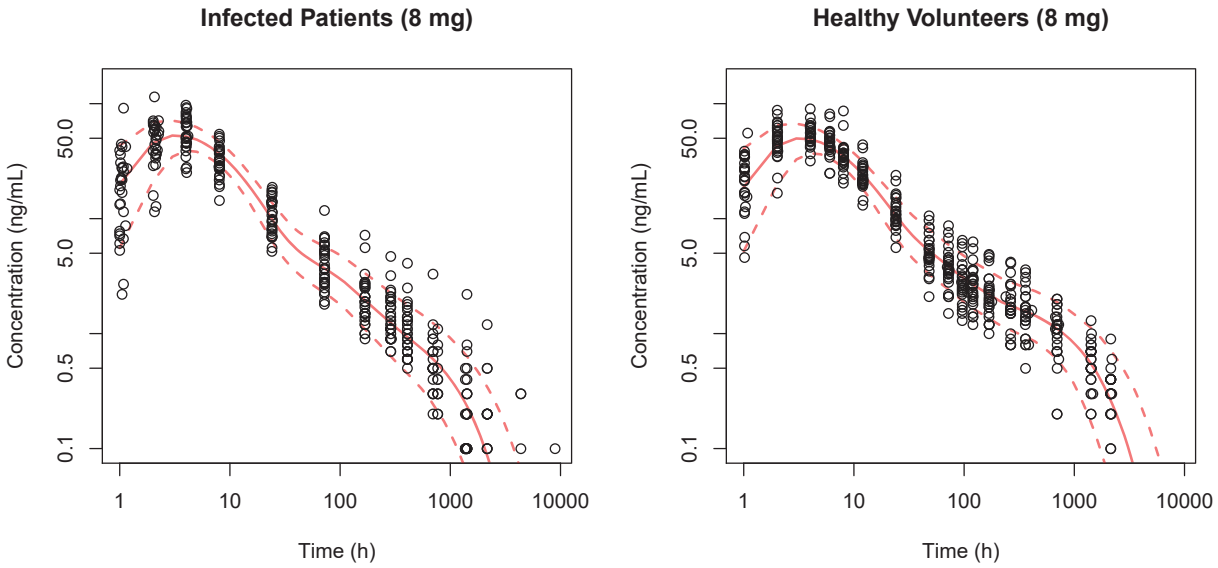

Figure 3. Simulated PK profiles for adults and healthy volunteers. In both plots, the solid red line indicates the median of the simulations and the dashed red lines represent the 10^{th} and 90^{th} percentiles of the simulations. The open black circles indicate observed PK data from Study 3110A1-GH-200 (8 mg only; left panel) and Study 3110A1-EU-1005 (8 mg, fasted; right panel).

Figure 4 displays the predicted Cmax and AUC for children 4-11 years (8 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (HV; 8 mg, 16 mg, 36 mg). Tables 2 and 3 report the corresponding numerical summaries. The 4-7 years, 8-11 years and 12-17 years cohorts had very similar exposure (AUCs) to adults; this was due to all groups receiving the same dose and clearance from the central compartment (CL/F) not being influenced by weight. Younger age (i.e., smaller body size) was associated with higher values of Cmax; this was due to all groups receiving the same dose and allometric scaling of V_c/F. In particular, the median predicted Cmax for adolescents was 80.9 ng/mL, which was approximately 47% greater than in adults.

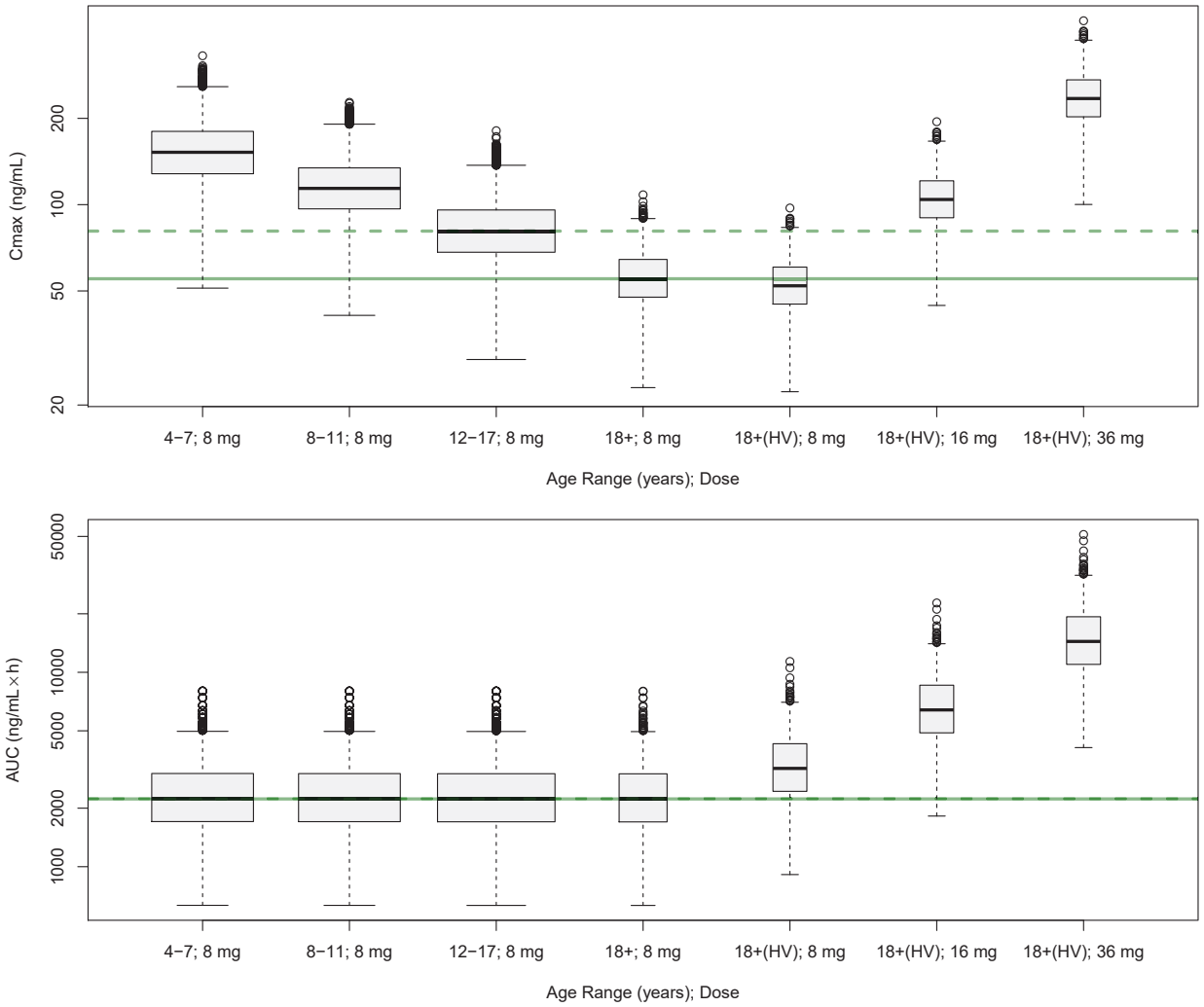

Figure 4. Summaries of simulated exposure metrics for children 4-11 years (8 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg). Within each plot, the green solid line indicates the median for adults (8 mg) and the green dashed line indicates the median for the adolescents (8 mg).

Table 2. Summaries of simulated Cmax (ng/mL) for children 4-11 years (8 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (8 mg)	156	39.4	152	52	51.1	331
8-11 years (8 mg)	117	28.3	114	37.7	41.1	228
12-17 years (8 mg)	83.2	20.8	80.9	27.6	28.8	181
18+ (8 mg)	56.6	12.5	55.1	16.8	23	108
18+ (HV; 8 mg)	53.3	11.5	52.1	15.6	22.3	97.4
18+ (HV; 16 mg)	107	23.1	104	31.1	44.5	195
18+ (HV; 36 mg)	240	51.9	235	70	100	438

Table 3. Summaries of simulated AUC (ng/mL*h) for children 4-11 years (8 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (8 mg)	2450	1020	2240	1310	633	8020
8-11 years (8 mg)	2450	1020	2240	1310	632	8020
12-17 years (8 mg)	2440	1020	2240	1310	632	8010
18+ (8 mg)	2440	1010	2230	1300	632	8010
18+ (HV; 8 mg)	3490	1430	3200	1850	911	11400
18+ (HV; 16 mg)	6970	2860	6410	3700	1820	22800
18+ (HV; 36 mg)	15700	6430	14400	8320	4100	51200

Figure 5 displays the predicted Cmax and AUC for children 4-11 years (2 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (HV; 8 mg, 16 mg, 36 mg). Tables 4 and 5 report the corresponding numerical summaries. The AUCs were influenced only by dose since weight did not impact CL/F. Hence, the 4-7 and 8-11 years cohorts exhibited similar AUCs, which were approximately 25% of the simulated exposures for adults. For a given dose, younger age groups exhibited higher values of Cmax; this was due to allometric scaling of V_c/F.

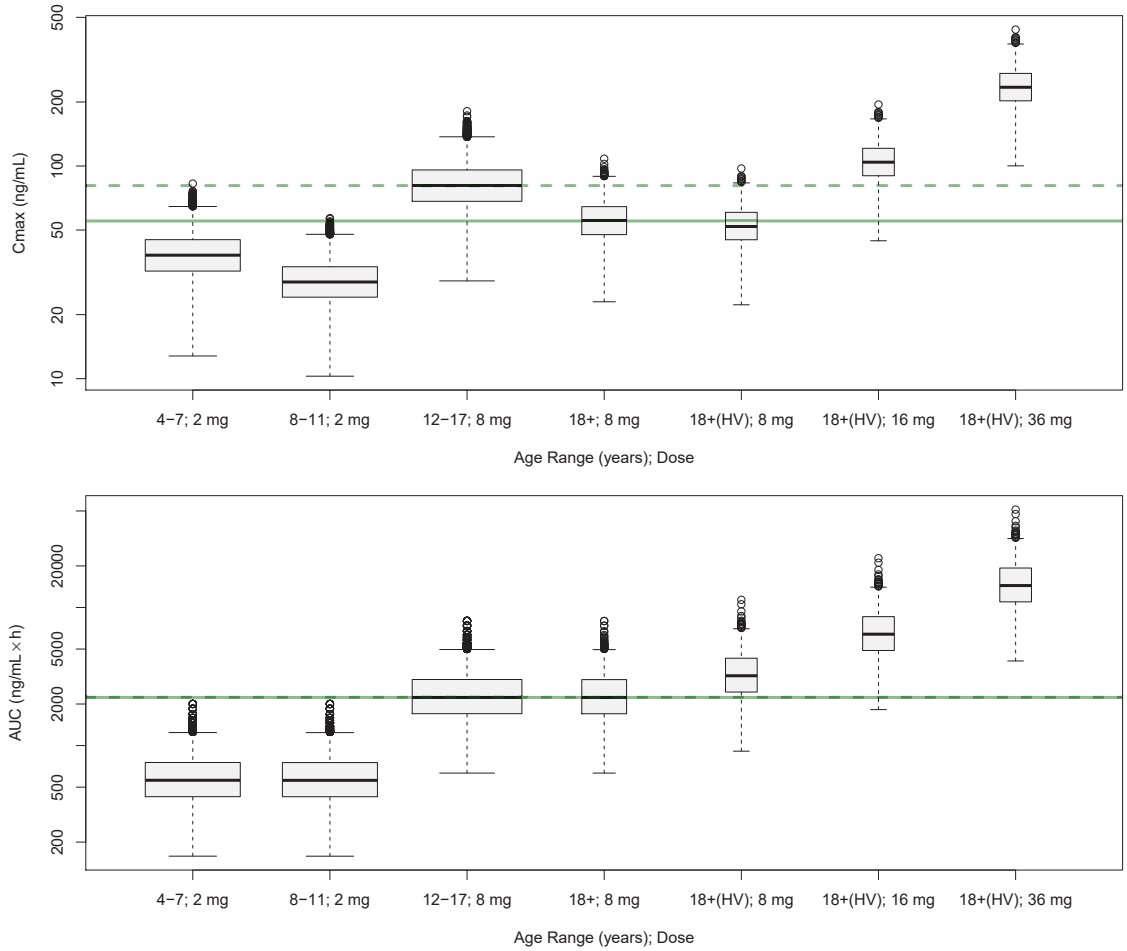

Figure 5. Summaries of simulated exposure metrics for children 4-11 years (2 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg). Within each plot, the green solid line indicates the median for adults (8 mg) and the green dashed line indicates the median for the adolescents (8 mg).

Table 4. Summaries of simulated Cmax (ng/mL) for children 4-11 years (2 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (2 mg)	38.9	9.84	38.1	13	12.8	82.7
8-11 years (2 mg)	29.2	7.07	28.5	9.42	10.3	56.9
12-17 years (8 mg)	83.2	20.8	80.9	27.6	28.8	181
18+ (8 mg)	56.6	12.5	55.1	16.8	23	108
18+ (HV; 8 mg)	53.3	11.5	52.1	15.6	22.3	97.4
18+ (HV; 16 mg)	107	23.1	104	31.1	44.5	195
18+ (HV; 36 mg)	240	51.9	235	70	100	438

Table 5. Summaries of simulated AUC (ng/mL*h) for children 4-11 years (2 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (2 mg)	612	255	561	328	158	2010
8-11 years (2 mg)	611	255	560	327	158	2000
12-17 years (8 mg)	2440	1020	2240	1310	632	8010
18+ (8 mg)	2440	1010	2230	1300	632	8010
18+ (HV; 8 mg)	3490	1430	3200	1850	911	11400
18+ (HV; 16 mg)	6970	2860	6410	3700	1820	22800
18+ (HV; 36 mg)	15700	6430	14400	8320	4100	51200

Figure 6 displays the predicted Cmax and AUC for children 4-11 years (4 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (HV; 8 mg, 16 mg, 36 mg). Tables 6 and 7 report the corresponding numerical summaries. The AUCs were influenced only by dose since weight did not impact CL/F. Hence, the 4-7 and 8-11 years cohorts exhibited similar AUCs, which were approximately half of the simulated exposures for adults. For a given dose, younger age groups exhibited higher values of Cmax; this was due to allometric scaling of V_c/F.

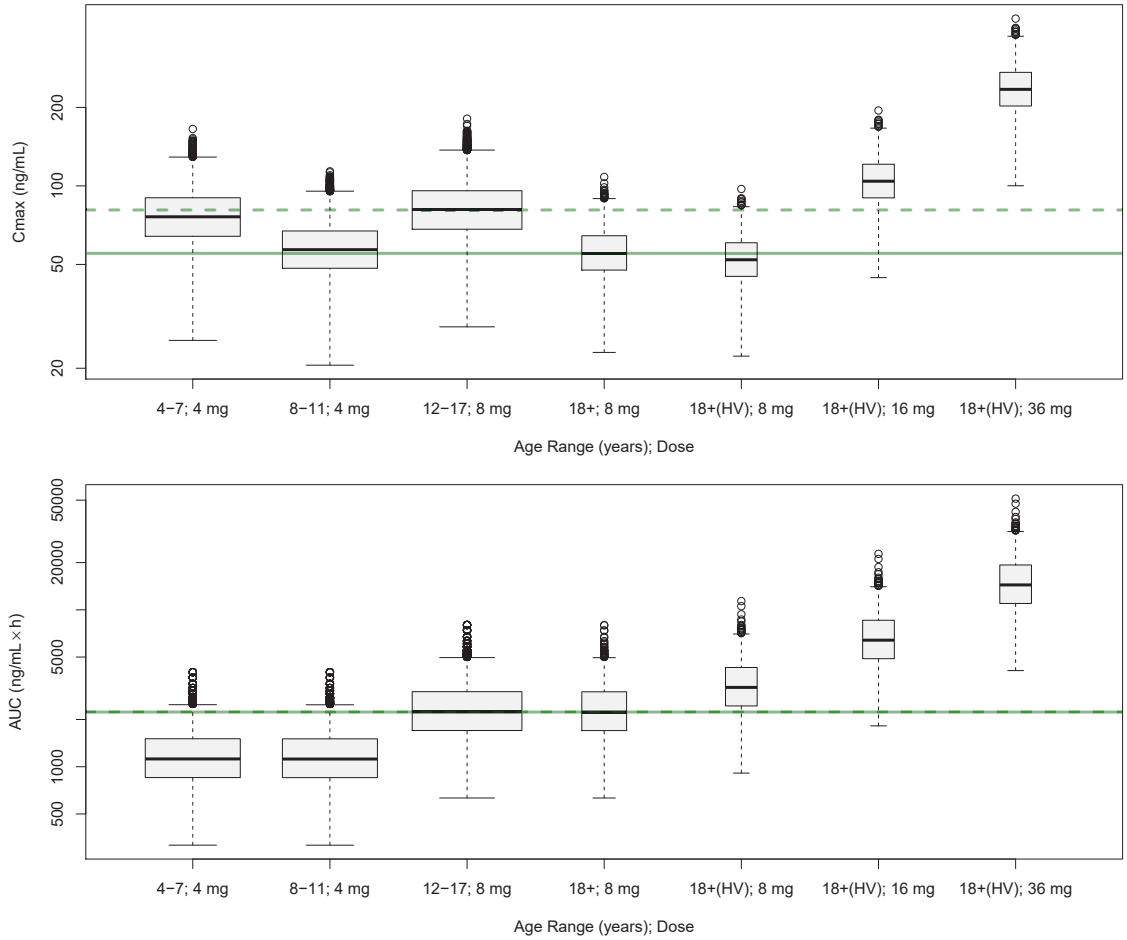

Figure 6. Summaries of simulated exposure metrics for children 4-11 years (4 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg). Within each plot, the green solid line indicates the median for adults (8 mg) and the green dashed line indicates the median for the adolescents (8 mg).

Table 6. Summaries of simulated Cmax (ng/mL) for children 4-11 years (4 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (4 mg)	77.9	19.7	76.1	26	25.6	165
8-11 years (4 mg)	58.4	14.1	57	18.8	20.5	114
12-17 years (8 mg)	83.2	20.8	80.9	27.6	28.8	181
18+ (8 mg)	56.6	12.5	55.1	16.8	23	108
18+ (HV; 8 mg)	53.3	11.5	52.1	15.6	22.3	97.4
18+ (HV; 16 mg)	107	23.1	104	31.1	44.5	195
18+ (HV; 36 mg)	240	51.9	235	70	100	438

Table 7. Summaries of simulated AUC (ng/mL*h) for children 4-11 years (4 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (4 mg)	1220	510	1120	655	316	4010
8-11 years (4 mg)	1220	509	1120	654	316	4010
12-17 years (8 mg)	2440	1020	2240	1310	632	8010
18+ (8 mg)	2440	1010	2230	1300	632	8010
18+ (HV; 8 mg)	3490	1430	3200	1850	911	11400
18+ (HV; 16 mg)	6970	2860	6410	3700	1820	22800
18+ (HV; 36 mg)	15700	6430	14400	8320	4100	51200

Figure 7 displays the predicted Cmax and AUC for children 4-11 years (6 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (HV; 8 mg, 16 mg, 36 mg). Tables 8 and 9 report the corresponding numerical summaries. The AUCs were influenced only by dose since weight did not impact CL/F. Hence, the 4-7 and 8-11 years cohorts exhibited similar AUCs, which were approximately 75% of the simulated exposures for adults. For a given dose, younger age groups exhibited higher values of Cmax; this was due to allometric scaling of V_c/F.

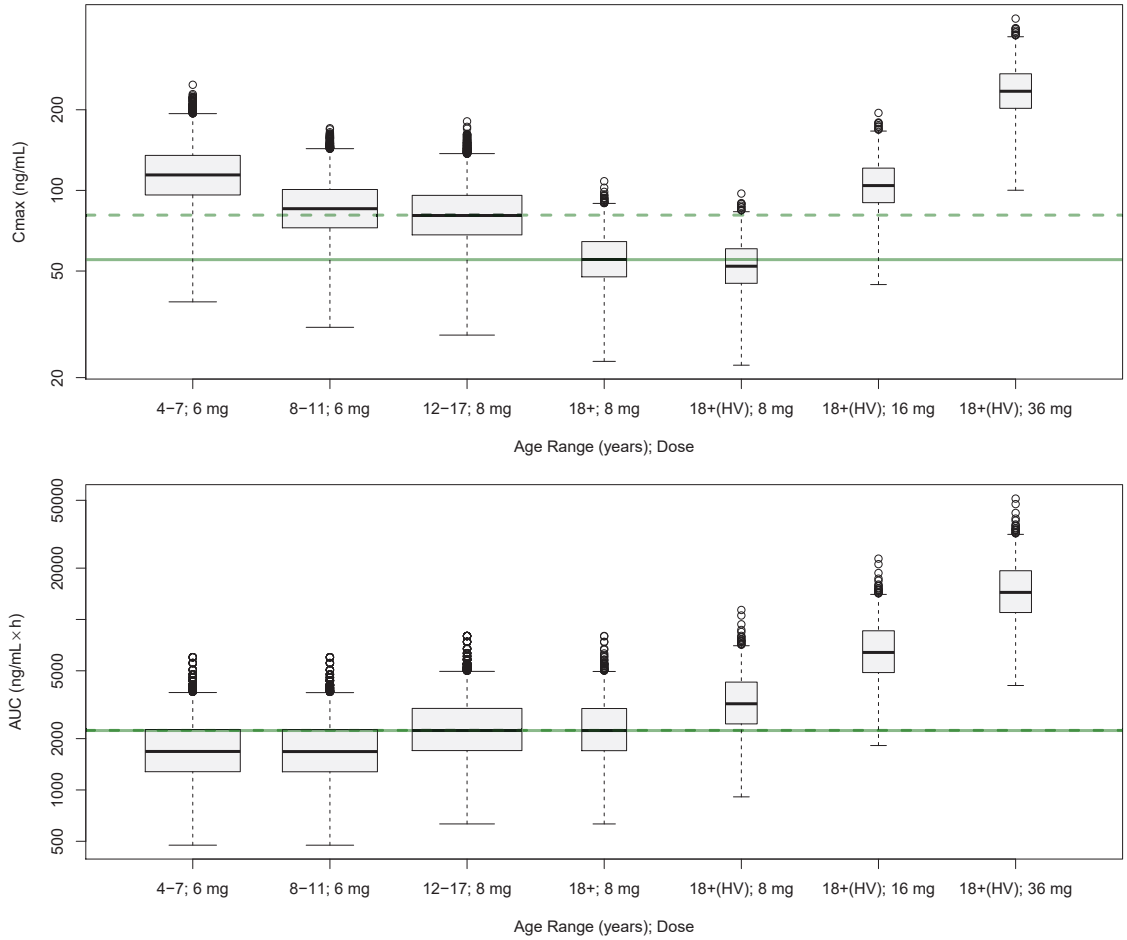

Figure 7. Summaries of simulated exposure metrics for children 4-11 years (6 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg). Within each plot, the green solid line indicates the median for adults (8 mg) and the green dashed line indicates the median for the adolescents (8 mg).

Table 8. Summaries of simulated Cmax (ng/mL) for children 4-11 years (6 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (6 mg)	117	29.5	114	39	38.4	248
8-11 years (6 mg)	87.5	21.2	85.5	28.3	30.8	171
12-17 years (8 mg)	83.2	20.8	80.9	27.6	28.8	181
18+ (8 mg)	56.6	12.5	55.1	16.8	23	108
18+ (HV; 8 mg)	53.3	11.5	52.1	15.6	22.3	97.4
18+ (HV; 16 mg)	107	23.1	104	31.1	44.5	195
18+ (HV; 36 mg)	240	51.9	235	70	100	438

Table 9. Summaries of simulated AUC (ng/mL*h) for children 4-11 years (6 mg), adolescents 12-17 years (8 mg), adults (8 mg) and healthy volunteers (8 mg, 16 mg, 36 mg)

Age Cohort (Dose)	Mean	SD	Median	IQR	Min	Max
4-7 years (6 mg)	1840	764	1680	983	474	6020
8-11 years (6 mg)	1830	764	1680	981	474	6010
12-17 years (8 mg)	2440	1020	2240	1310	632	8010
18+ (8 mg)	2440	1010	2230	1300	632	8010
18+ (HV; 8 mg)	3490	1430	3200	1850	911	11400
18+ (HV; 16 mg)	6970	2860	6410	3700	1820	22800
18+ (HV; 36 mg)	15700	6430	14400	8320	4100	51200

8 Discussion

The simulation model predicted that adolescents 12-17 years receiving 8 mg of moxidectin may achieve similar exposure (AUC) to adults receiving 8 mg, with a higher Cmax (≈81 ng/mL vs. ≈55 ng/mL in adults). The simulations also suggested that for a given dose, smaller body size was associated with higher values of Cmax; this was due to allometric scaling of V_c/F. AUC was conditional on dose but not body size; this was due to weight not impacting CL/F.

The findings of the present simulation study reflect the features of the simulation model. The model was built with the intention of extrapolating to other populations, including paediatrics [13]. Hence, the model incorporated allometry [14] where consistent with the observed data (V_c/F, CL_{d2}/F and V_{p2}/F [13]). This led to younger (smaller) children achieving a higher Cmax for a given dose. However, since allometry was not incorporated into CL/F (due to no evidence of a relationship between weight and CL/F for infected patients or healthy volunteers [13]), the predicted AUCs were not influenced by weight or body size (only dose). The lack of a clear relationship between CL/F and weight was also observed in a study of moxidectin in dogs; the results suggested that CL/F was similar between adults and juveniles [2]. Since moxidectin may not be entirely consistent with allometric principles, the simulations presented in this report should be used in conjunction with clinical experience and judgement in regards to determination of initial dosing recommendations for children participating in Study MDGH-MOX-1006.

There are some caveats to this simulation study. To date, the population PK model used for the simulations has not been verified with PK data from children or adolescents. Also, this simulation study cannot make any formal (i.e., analytical) evaluations of safety (only expected PK profiles and exposures).

9 Conclusions

The simulations suggested that for a given dose, moxidectin exposure may be similar across age groups (including adults), however, Cmax may be higher in younger age groups. The predicted (simulated) values of Cmax and AUC for all doses and ages considered in this simulation study corresponded to doses that were well-tolerated in healthy volunteers (i.e., $\leq$ 36 mg).

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STATISTICAL APPENDIX

TITLE	Supplementary Simulations of Moxidectin Pharmacokinetics in Pediatric Patients
STUDY DRUG	Moxidectin
SPONSOR	Medicines Development for Global Health
PREPARED BY	Kris Jamsen, Ph.D. Craig Rayner, Pharm.D, MBA Certara Inc.
	Sally Kinrade, Ph.D. Medicines Development for Global Health
DOCUMENT NUMBER	MDGH-MOX-1006-SA
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CERTARA REFERENCE NO:	MDGH-MOX-1006-SA-001

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1 OBJECTIVES

The objectives of this work were to:

1) Update the results of the original moxidectin pharmacokinetics simulation study [1] by using the most recent, final population pharmacokinetic (PK) model of moxidectin [2].
2) Provide additional summaries of simulated moxidectin exposure measures to support the protocol for the pediatric study (Study MDGH-MOX-1006).

2 METHODS

The methods of the current simulation study were similar to those from the previous simulation study [1]. Key differences are:

- The final population PK model of moxidectin, incorporating PK data from Study 1008, was used for the current simulations. The previous simulation study used the final population PK model that was developed before data from Study 1008 were available. Details of the final model are described elsewhere [2].
- For each onchocerciasis patient age group (4-7 years, 8-11 years, 12-17 years and adults), moxidectin PK profiles were generated for 1000 virtual patients (500 male and 500 female), where corresponding individual exposure metrics (maximum concentration, or Cmax, and area under the concentration time curve, or AUC) were derived. Similarly to the previous work, patients 12-17 or 18+ years old received 8 mg (established doses for these groups); patients 4-7 or 8-11 years old received 2, 4, 6 or 8 mg.
- For healthy subjects, moxidectin PK profiles were generated for 1000 virtual males, where corresponding individual Cmax and AUC were derived. Similarly to the previous report, healthy subjects received 8, 16 or 36 mg.
- For each (virtual) population and corresponding dose(s) described above, Cmax and AUC were summarized by the mean, standard deviation (SD), median, inter-quartile range (IQR), 10^{th} percentile, 90^{th} percentile, minimum and maximum.

Further details of the simulation methodology are described in the previous simulation report [1].

3 RESULTS

Table 3-1 and Table 3-2 display summaries of the simulated exposures, where the 4-7 and 8-11 year-old patient groups received 8 mg and all other populations received their pre-defined doses.

Table 3-1 Summaries of simulated Cmax (ng/mL) assuming an 8 mg dose in the 4-7 and 8-11 year-olds and the pre-defined doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (8 mg)	157	35.8	156	47.2	112	203	83.2	308
8-11 years (8 mg)	118	25.2	116	33.8	86.3	151	64.1	214
12-17 years (8 mg)	83.5	17.2	82.5	23.9	62.4	106	45.4	141
18+ (8 mg)	57.6	11.7	56.8	15.9	43.4	72.5	31.2	93.7
18+ HV (8 mg)	55.6	12	54.3	16.4	41.2	71.7	21.6	105
18+ HV (16 mg)	111	24	109	32.7	82.5	143	43.3	210
18+ HV (36 mg)	250	54.1	244	73.6	186	323	97.3	473

Table 3-2 Summaries of simulated AUC (ng.h/mL) assuming an 8 mg dose in the 4-7 and 8-11 year-olds and the pre-defined doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (8 mg)	2478	1087	2278	1383	1317	3858	568.7	8254
8-11 years (8 mg)	2475	1086	2275	1381	1316	3854	568.4	8255
12-17 years (8 mg)	2471	1085	2271	1380	1314	3849	568.1	8250
18+ (8 mg)	2466	1080	2267	1373	1312	3844	567.9	8180
18+ HV (8 mg)	3471	1445	3292	1725	1899	5210	842.3	12970
18+ HV (16 mg)	6942	2889	6583	3450	3798	10420	1685	25940
18+ HV (36 mg)	15620	6501	14810	7762	8546	23440	3790	58370

Table 3-3 and Table 3-4 display summaries of the simulated exposures, where the 4-7 and 8-11 year-old patient groups received 2 mg and all other populations received their pre-defined doses.

Table 3-3 Summaries of simulated Cmax (ng/mL) assuming a 2 mg dose in the 4-7 and 8-11 year-olds and the pre-defined doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (2 mg)	39.2	8.94	38.9	11.8	28	50.9	20.8	76.9
8-11 years (2 mg)	29.4	6.31	29.1	8.45	21.6	37.7	16	53.5
12-17 years (8 mg)	83.5	17.2	82.5	23.9	62.4	106	45.4	141
18+ (8 mg)	57.6	11.7	56.8	15.9	43.4	72.5	31.2	93.7
18+ HV (8 mg)	55.6	12	54.3	16.4	41.2	71.7	21.6	105
18+ HV (16 mg)	111	24	109	32.7	82.5	143	43.3	210
18+ HV (36 mg)	250	54.1	244	73.6	186	323	97.3	473

Table 3-4 Summaries of simulated AUC (ng.h/mL) assuming a 2 mg dose in 4-7 and 8-11 year-olds and the pre-defined doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (2 mg)	619.5	271.7	569.5	345.8	329.3	964.6	142.2	2064
8-11 years (2 mg)	618.6	271.5	568.6	345.4	328.9	963.4	142.1	2064
12-17 years (8 mg)	2471	1085	2271	1380	1314	3849	568.1	8250
18+ (8 mg)	2466	1080	2267	1373	1312	3844	567.9	8180
18+ HV (8 mg)	3471	1445	3292	1725	1899	5210	842.3	12970
18+ HV (16 mg)	6942	2889	6583	3450	3798	10420	1685	25940
18+ HV (36 mg)	15620	6501	14810	7762	8546	23440	3790	58370

Table 3-5 and Table 3-6 display summaries of the simulated exposures, where the 4-7 and 8-11 year-old patient groups received 4 mg and all other populations received their pre-defined doses.

Table 3-5: Summaries of simulated Cmax (ng/mL) assuming a 4 mg dose in 4-7 year-olds and the pre-specified doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (4 mg)	78.3	17.9	77.8	23.6	56.1	102	41.6	154
8-11 years (4 mg)	58.9	12.6	58.1	16.9	43.1	75.4	32	107
12-17 years (8 mg)	83.5	17.2	82.5	23.9	62.4	106	45.4	141
18+ (8 mg)	57.6	11.7	56.8	15.9	43.4	72.5	31.2	93.7
18+ HV (8 mg)	55.6	12	54.3	16.4	41.2	71.7	21.6	105
18+ HV (16 mg)	111	24	109	32.7	82.5	143	43.3	210
18+ HV (36 mg)	250	54.1	244	73.6	186	323	97.3	473

Table 3-6: Summaries of simulated AUC (ng.h/mL) assuming a 4 mg dose in 4-7 year-olds and the pre-specified doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (4 mg)	1239	543.5	1139	691.5	658.7	1929	284.4	4127
8-11 years (4 mg)	1237	542.9	1137	690.7	657.9	1927	284.2	4128
12-17 years (8 mg)	2471	1085	2271	1380	1314	3849	568.1	8250
18+ (8 mg)	2466	1080	2267	1373	1312	3844	567.9	8180
18+ HV (8 mg)	3471	1445	3292	1725	1899	5210	842.3	12970
18+ HV (16 mg)	6942	2889	6583	3450	3798	10420	1685	25940
18+ HV (36 mg)	15620	6501	14810	7762	8546	23440	3790	58370

Table 3-7 and Table 3-8 display summaries of the simulated exposures, where the 4-7 and 8-11 year-old patient groups received 6 mg and all other populations received their pre-defined doses.

Table 3-7: Summaries of simulated Cmax (ng/mL) assuming a 6 mg dose in 4-7 year-olds and the pre-specified doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (6 mg)	117	26.8	117	35.4	84.1	153	62.4	231
8-11 years (6 mg)	88.3	18.9	87.2	25.3	64.7	113	48.1	160
12-17 years (8 mg)	83.5	17.2	82.5	23.9	62.4	106	45.4	141
18+ (8 mg)	57.6	11.7	56.8	15.9	43.4	72.5	31.2	93.7
18+ HV (8 mg)	55.6	12	54.3	16.4	41.2	71.7	21.6	105
18+ HV (16 mg)	111	24	109	32.7	82.5	143	43.3	210
18+ HV (36 mg)	250	54.1	244	73.6	186	323	97.3	473

Table 3-8: Summaries of simulated AUC (ng.h/mL) assuming a 6 mg dose in 4-7 and 8-11 year-olds and the pre-specified doses in the other populations

	Mean	SD	Median	IQR	10th perc.	90th perc.	Min	Max
4-7 years (6 mg)	1858	815.2	1709	1037	988	2894	426.5	6191
8-11 years (6 mg)	1856	814.4	1706	1036	986.8	2890	426.3	6191
12-17 years (8 mg)	2471	1085	2271	1380	1314	3849	568.1	8250
18+ (8 mg)	2466	1080	2267	1373	1312	3844	567.9	8180
18+ HV (8 mg)	3471	1445	3292	1725	1899	5210	842.3	12970
18+ HV (16 mg)	6942	2889	6583	3450	3798	10420	1685	25940
18+ HV (36 mg)	15620	6501	14810	7762	8546	23440	3790	58370

4 CONCLUSIONS

The results are consistent with the previous simulation study [1], suggesting that 8 mg may be an appropriate initial dose for the first pediatric cohort of Study MDGH-MOX-1006 (8-11 years).

5 REFERENCES

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16.3 Vital Signs Reference Values for Children

Pediatric vital signs reference ranges are provided in Table 7 (Canadian Paediatric Society 2013, American Heart Association 2016).

Table 7: Vital Signs Reference Ranges for Children

Parameter	Normal Reference Range (low to high)		
Age	**3 to 5 years**	**6 to 11 years**	**12 to 15 years**
Heart rate (beats/minute)			
Awake rate	80 to 120	75 to 118	60 to 100
Sleeping rate	65 to 100	58 to 90	50 to 90
Respiratory rate (breaths/minute)	20 to 28	18 to 25	12 to 20
Systolic pressure (mmHg)	89 to 112		110 to 131
6 to 9 years		97 to 115	
10 to 11 years		102 to 120	
Diastolic pressure (mmHg)	46 to 72		64 to 83
6 to 9 years		57 to 76	
10 to 11 years		61 to 80	
Temperature, ear (°C)	35.8 to 38	35.8 to 38	35.8 to 38

°C = degrees Celsius, mmHg = millimeters of mercury

16.4 Laboratory Reference Values for Ghanaian Children

Laboratory reference ranges for Ghanaian children are provided in Table 8 (Dosoo et al. 2014; bicarbonate reference range Royal College of Pathologists of Australasia 2012).

Table 8: Laboratory Reference Ranges for Children

Parameter	Normal Reference Range (low to high)		
Age	**0.5 to < 5 years**	**5 to 12 years**	**> 12 to 18 years**
Enzymes			
Alanine aminotransferase (IU/L)	7 to 55	5 to 53	8 to 55
Aspartate aminotransferase (IU/L)	23 to 72	19 to 97	14 to 62
Amylase (IU/L)	12 to 136	33 to 133	31 to 120
Creatine kinase (IU/L)	35 to 291	59 to 515	94 to 562
Gamma-glutamyl transferase (IU/L)	3 to 34	7 to 31	6 to 45
Lactate dehydrogenase (IU/L)	360 to 995	277 to 823	252 to 737
Serum Proteins			
Total Proteins (g/dL)	56.0 to 87.0	54.0 to 87.9	46.4 to 86.5
Albumin (g/dL)	35.9 to 50.0	34.2 to 49.8	35.4 to 49.3
Metabolism			
Total Bilirubin (µmol/L)	1.8 to 21.0	1.7 to 18.9	3.3 to 21.6
Direct Bilirubin (µmol/L)	0.4 to 3.6	0.6 to 3.9	0.9 to 4.0
Cholesterol (µmol/L)	1.7 to 5.0	1.7 to 4.3	1.8 to 4.6
Glucose (µmol/L)	3.2 to 6.8	3.5 to 6.2	3.6 to 6.7
Iron (µmol/L)	4.2 to 20.1	3.88 to 19.00	4.6 to 23.3
Triglycerides (µmol/L)	0.5 to 2.7	0.5 to 1.91	0.40 to 1.70
Kidney Function			
Urea (mmol/L))	1.0 to 4.2	1.0 to 4.5	1.0 to 4.5
Creatinine (µmol/L)	17 to 52	33 to 74	39 to 79
Uric acid (µmol/L)	71 to 340	72 to 274	78 to 322
Chloride (mmol/L)	98 to 115	99 to 114	96 to 116
Phosphorus (mmol/L)	1.26 to 2.25	1.03 to 1.84	0.96 to 1.77
Potassium (mmol/L)	3.6 to 5.8	3.6 to 5.6	3.6 to 5.9
Sodium (mmol/L)	131 to 149	135 to 151	132 to 152
Bicarbonate (mmol/L)	17 to 30		20 to 32
2 years to < 10 years		17 to 30	
10 years to 18 years		20 to 32	
Hematology			
Hemoglobin (g/dL)	8.0 to 12.7	9.1 to 13.5	9.5 to 14.4
Hematocrit (%)	24.4 to 38.8	27.3 to 41.5	29.4 to 44.9
Red blood cell ($x10^{12}$/L)	3.22 to 5.55	3.45 to 5.29	3.53 to 5.57
Mean corpuscular volume (fL)	56 to 87	68 to 89	67 to 93
Mean corpuscular hemoglobin (pg)	16.9 to 29.7	21.4 to 30.3	21.2 to 32.0
Mean corpuscular hemoglobin concentration (g/dL)	30.0 to 36.9	30.9 to 36.0	30.5 to 36.6
Red blood cell distribution width (%)	12.5 to 21.6	11.5 to 17.9	11.6 to 16.1
Platelet ($x10^{12}$/L)	110 to 637	117 to 417	113 to 363
Platelet distribution width (%)	8.8 to 25.4	12.1 to 20.5	12.4 to 22.6
White blood cell, Total ($x10^{9}$/L)	5.1 to 17.6	4.1 to 11.9	3.7 to 9.4
Lymphocytes (%)	34.9 to 75.6	29.6 to 62.5	26.6 to 58.9
Lymphocytes ($x10^{9}$/L)	2.3 to 11.9	1.6 to 5.8	1.4 to 4.0
Monocytes (%)	4.9 to 13.6	5.0 to 13.3	4.9 to 14.4
Monocytes ($x10^{9}$/L)	0.2 to 1.0	0.2 to 1.1	0.2 to 0.9
Granulocytes (%)	18.5 to 59.7	28.3 to 62.4	31.0 to 64.0
Granulocytes ($x10^{9}$/L)	1.5 to 8.5	1.6 to 6.2	1.6 to 5.2

µmol/L = micromoles per liter, fL = femtoliter, g/dL = grams per deciliter, IU = international units, L = liter, mmol/L = millimoles per liter; pg = picogram

16.5 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ *3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18]**, High** (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

16.6 Model Adolescent (12 to 17 years) and Parent/Guardian Information Sheet and Assent and Consent Form

Title of Study:	An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in participants aged 4 to 17 years with (or at high risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years.
Principal Investigator:	Dr Nicholas Obuobisa Opoku
Organization:	University of Health and Allied Sciences (UHAS)
Sponsor	Medicines Development for Global Health
Protocol Number(s):	MDGH-MOX-1006 UHAS-REC A.7 [6] 18-19 GHS-ERC 015/06/19
Protocol / Information Document Version/Date:	Final v1.3 (incorporating Amendments 1, 2 and 3) / 27 Nov 2019

General Information About the Study

I am Dr....., a doctor working at the University of Health and Allied Sciences in Hohoe. We are testing a new medicine called moxidectin in children aged 4 to 17 years. Moxidectin is a new treatment for onchocerciasis (river blindness), which you call "*oncho*".

Testing new medicines is called doing "research" or "a study" and means we want to learn something about the new medicine.

Here, we explain to you and your parents or guardians what we already know about moxidectin, what will happen during the study and the risks and advantages of taking part in this study.

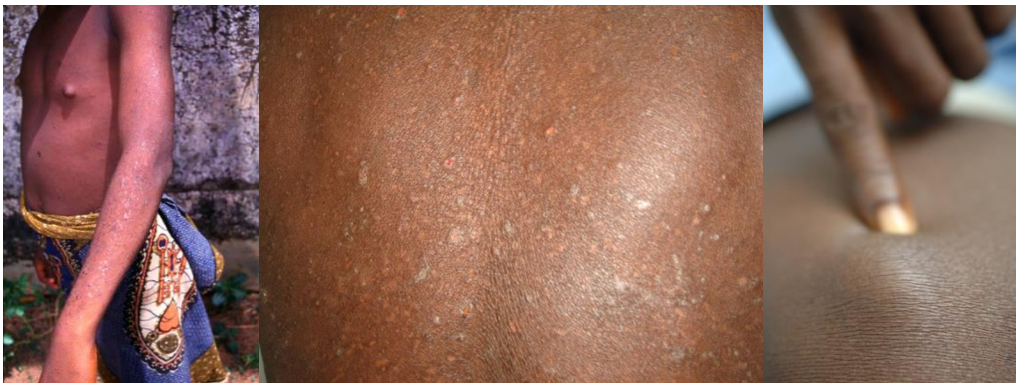
This will help you decide whether you want to take part in this study or not and it will help your parents or guardians decide whether they will allow you to take part or not.

If you do not want to take part or your parents or guardians don't want you to take part, please don't be afraid to tell us. Your care or the care of your parents or guardians at your local health care centers will not be affected by saying no to being in this study.

Please ask questions about anything that you don't understand or want to know more about. Before making a decision, you might also want to talk about it with others.

What is oncho and what is being done to help people with oncho now?

Oncho is caused by a worm that is passed from one person to another through the bites of the small black flies that you see at the riverside and in your community in the mornings and early evenings. Two types of these worms live in the human body. The young worms in the skin and eyes cause the disease, for example itching or a rash. The adult worms live for up to 14 years in swellings under the skin called nodules and produce millions of the young worms.



You and many of the adults and other children in your community may have oncho. Therefore, a medicine called ivermectin is now given to all people at least 5 years of age who are not pregnant or sick.

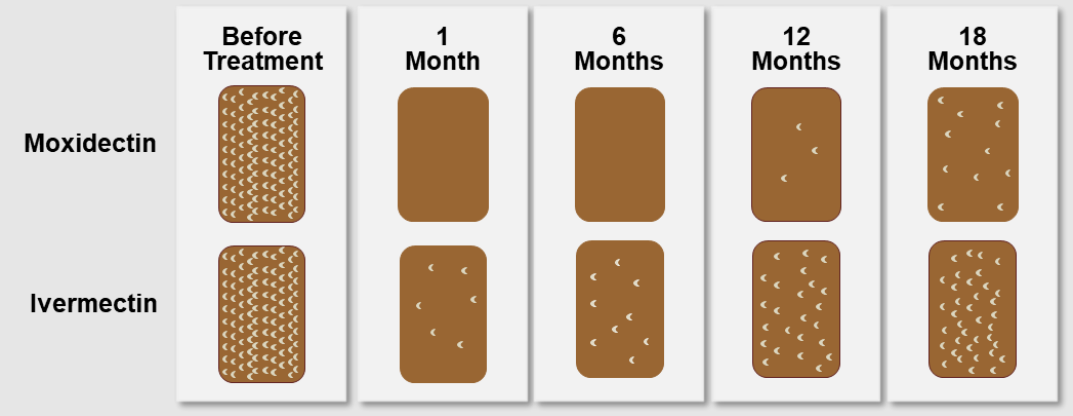
Ivermectin kills most of the young worms so that people who have oncho and take ivermectin have less or even none of the disease. However, the adult worms quickly start to make new worms and so ivermectin is given to you every six months.

What is the new medicine, moxidectin, and what does it do against the oncho worms?

You may have already heard about moxidectin because about 10 years ago, 219 people from Wii, Azua, Jagri Akua and Bitaaba who had oncho and were at least 12 years of age took part in a study to test moxidectin. In that study, some people were given moxidectin and some people were given ivermectin. If you know anybody who took part in that study, they can tell you about their experience in the study.

In the study, we found that moxidectin kills more young oncho worms in the skin than ivermectin and that moxidectin stops the adult worms from making new, young worms for a longer time than ivermectin. Here we are showing you pictures of the number of oncho worms in people before and after they took moxidectin or ivermectin.

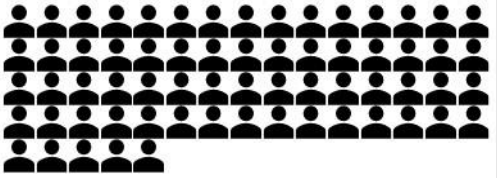
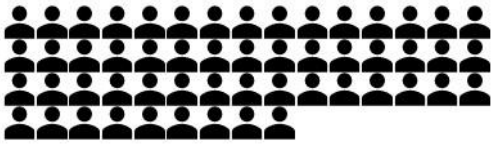
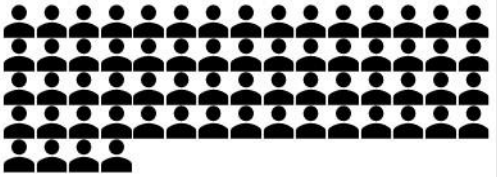
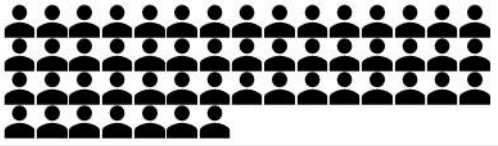
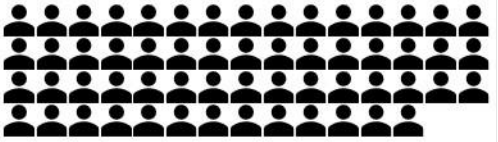
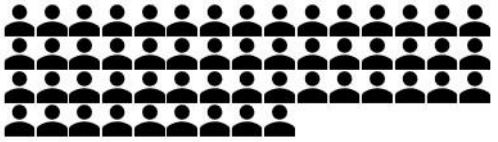
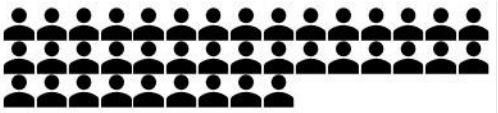
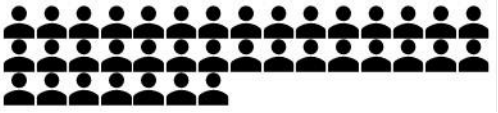
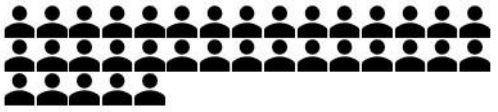
Number of Young Worms in the Skin Before and After Taking Moxidectin or Ivermectin



What do we know about unwanted effects of moxidectin?

In that study we also found that people who took moxidectin and people who took ivermectin had similar unwanted effects, but some unwanted effects occurred in more people who took moxidectin than in people who took ivermectin. Many of these unwanted effects are caused by the body getting rid of the young oncho worms after they have been killed by moxidectin or ivermectin. On the next page we show you how many out of 100 people had unwanted effects after taking moxidectin or ivermectin. Please ask me if you don't understand what these unwanted effects mean.

Number of People with Unwanted Effects in 100 People Who Took Moxidectin or ivermectin

Unwanted Effect	Moxidectin	Ivermectin
Itching	65 	54 
Muscle pain	64 	52 
Headache	58 	54 
Fast heartbeat	39 	30 
Rashes	37 	21 
Stomach pain	31 	35 
Feeling faint or dizzy when	30 	25 

Number of People with Unwanted Effects in 100 People Who Took Moxidectin or ivermectin

Unwanted Effect	Moxidectin	Ivermectin
standing up		
Fever /chills	27	18
Common cold	23	21
Cough	17	18
Upset belly (Stomach flu)	15	17
Lymph node pain	13	6
Dizziness	12	9
Swollen arm or leg	11	6

Why are we doing a study of moxidectin in 4 to 17 year olds and asking you to take part?

We have already given moxidectin to 1349 people with oncho. These included 53 adolescents aged 12 to 17 years with oncho who took 4 tablets of moxidectin (8 milligrams), the same number of tablets adults with oncho took. Thirty-one (31) of them lived in Wii, Azua, Jagri Akua or Bitaaba. From this study, we know that 4 tablets is the right number of tablets for people at least 12 years of age.

Because moxidectin works better against the oncho worms than ivermectin, it would be good if moxidectin could also be given to children aged 4 to 11 years. Therefore, we want to find the right number of moxidectin tablets for children aged 4 to 11 years.

How will we find out what number of moxidectin tablets is right for children aged 4 to 11 years?

When somebody takes moxidectin, it gets into their blood and from the blood, moxidectin can reach the young oncho worms in the body to kill them.

The right number of tablets for children aged 4 to 11 years is the number that leads to the same amount of moxidectin in their blood as in the blood of adults and adolescents 12 to 17 years of age who take 4 moxidectin tablets and does not cause severe unwanted effects.

To find out the right number of tablets for children aged 4 to 11 years, we need to first give moxidectin tablets to adolescents aged 12 to 17 years, take a bit of blood and measure the amount of moxidectin in their blood and find out what unwanted effects they have.

We think that we will have to give moxidectin to at least nine adolescents aged 12 to 17 years but not more than 18.

What will happen in the study, where will it happen and how long will it take?

First, we will do Screening. Screening means that we fill find out whether you have the oncho worm but are otherwise healthy and can take part in the study.

The first step of Screening will happen in your community:

- We will ask if you have a sister or brother who has already taken part in the study, because only one child from your family can take part.
- If you are a young woman, we will ask whether you are breast-feeding a child because then you cannot take part in the study.
- We will ask questions about health problems you have had in the past, medicines you have taken, look closely at your arms to see if it will be easy to take blood.

This will take 1 to 2 days.

If we find you cannot take part in the study, we will tell you and your parents or guardians why.

If we find that you can go on to **the second step of Screening**, we will drive you and one of your parents or guardians by car to our study center in Hohoe.

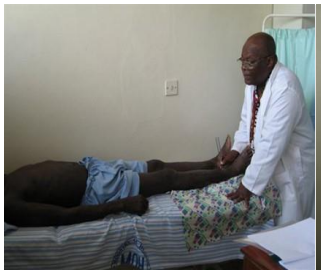
In Hohoe we have a special house for people taking part in our study and you will sleep there together with your parent or guardian and other children and their parents or guardians who take part in our study. We will give you free meals while you are in Hohoe.

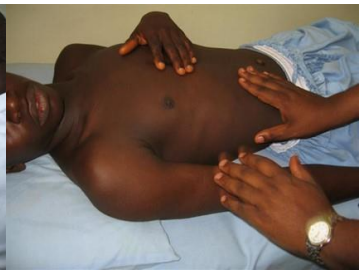


In Hohoe:

- We may ask you and your parent or guardian to tell us more about health problems you have had in the past and any medicines you have taken lately.
- We will measure your height and weight.
- We will examine how fast you breathe, how hard and fast your heart works and your body temperature (we call these measurements "vital signs").
- We will examine how well your heart works with a special machine called an electrocardiograph (an "ECG"). Here I am showing you the things we will put on your body for the ECG, like you see in this picture. This won't hurt.

- We will examine your body for signs of illness or pain. Some of this you can see in the pictures here.





- Doctors can learn a lot about whether you are sick by testing your blood. We will take a bit of your blood (12.5 milliliters or a little bit more than 2 teaspoons) like you can see in this photo. Before we take the blood, we will put a cream on your arm so you won't feel much pain.

  We will test the blood to find out how well some of the organs in your body work and for signs of HIV (AIDS infection) or the germs that cause liver disease (hepatitis B and C).

  If you have lived outside Ghana in an area where another worm called Loa loa occurs, we will test your blood to check whether you have the Loa loa worm. We will do this because people with lots of Loa loa worms can

have more unwanted effects when taking moxidectin and therefore they should not take part in our study.

- If you are a girl who has started her monthly bleeding, we will also test your blood to see whether you are pregnant. If you are pregnant, you cannot take part in the study.

All of this will take 1 to 2 days.

We will explain everything we learn about your health. We will let you and your parent or guardian know whether you can take part in the study.

What will happen after Screening if you cannot take part in the study?

We will explain to you and your parent or guardian why you cannot take part in the study. If you need to be taken care of by a nurse or doctor, we will arrange for you to visit a clinic or hospital.

On the day after Screening, we will drive you and your parent or guardian back to your community.

What will happen after Screening if you can take part in the study?

We will ask you to stay in Hohoe for 8 more days.

Girls can take part in this study only if they are not pregnant and if they avoid becoming pregnant until around 6 months after they have swallowed moxidectin. We will tell you more about this a bit later.

You will not be able to take ivermectin while you are on the study (for approximately 6 months).

On the day after Screening, we will:

- Repeat some of the examinations we did during Screening before we give you moxidectin.
- Ask you to swallow 4 moxidectin tablets 2 hours before you have breakfast.
- Repeat again some of the examinations we did during Screening.
- Take a bit of your blood (1.5 milliliters or 1/3 of a teaspoon) 4 times to measure the amount of moxidectin. We will use a special needle called a ‘cannula’ so that you only need to have one needle prick and we will use the special cream, so you won’t feel much pain.
- Ask you several times to tell us if you are feeling unwell or have any pain. If you have pain or are feeling unwell, we will examine you to find out what we can do to make you feel better. If necessary, we will give you medicine.
- We will also ask you and your parent or guardian to tell us immediately if you are not feeling well. Even during the night, there will always be a nurse to talk to.

During the next 7 days, we will:

- Repeat some of the examinations we did during Screening.
- Take a bit of your blood (1.5 milliliters or 1/3 of a teaspoon) on 2 days to measure the amount of moxidectin.
- Take a bit more of your blood (3.5 milliliters total, 2/3 teaspoon) on the last day to measure the amount of moxidectin and test how well some of the organs in your body work.

If you are feeling well, we will drive you and your parent or guardian back to your community on the 7th day after you have taken the moxidectin tablets. If not, we will ask you to stay longer until you feel well.

2 weeks, 1 month, 3 months and around 6 months after you have swallowed the moxidectin tablets, we will:

- Drive you and your parent or guardian to Hohoe again.
- Each time we will ask you to tell us about any health problems and any medicines taken since we last saw you.
- Each time we will repeat some of the examinations we did when you were last in Hohoe.
- We will take a bit of your blood (1.5 milliliters or 1/3 of a teaspoon) on 2 visits to measure the amount of moxidectin in it.
- We will take a bit more of your blood (3.5 milliliters or 2/3 teaspoon) on 1 visit to measure the amount of moxidectin in it and to find out how some of the organs in your body work.
- Each time you and your parent or guardian will spend one night with us and we will give you free meals.

What happens when you are in Hohoe during school time?

There will be a teacher in our study center in Hohoe. The teacher will help you keep going with some of your schoolwork, to help make up for the school time you miss.

What should you do if you are not feeling well when you are back in your community?

You should let your parents or guardians know and contact us, either through the community coordinator or directly or you should go to the closest health clinic. The ‘community coordinator’ is the person chosen by the adults in your community to contact us whenever you want. We have written down the name for you.

We will make sure that you are examined and receive medicine if you need it. If needed, we will drive you and your parent or guardian to the study center in Hohoe or a health clinic or hospital.

Are there any potential advantages of taking part in this study?

You may not have any advantages.

- You will have examinations of your health. These examinations are often used by doctors and nurses to find out whether people are sick.
- If you have young oncho worms in your skin or eyes, moxidectin will cause most or all of them to die and prevent new young worms in your skin for up to about 1 year.
- If you have health problems because of the young oncho worms in your skin or eyes, these will become better or even go away for up to about 1 year.

Are there any possible risks of taking part in this study?

Unwanted effects of taking moxidectin

Almost all medicines cause unwanted effects.

We have already told you about the unwanted effects we found in people with the oncho worm who took moxidectin or ivermectin. In most cases, these unwanted effects were mild, went away on their own and lasted less than a week. Please let me know if you would like us to look at the pictures again.

You may have none, some or all of these unwanted effects. They may be mild, moderate or severe. They may occur soon after you have taken moxidectin or many hours or days later.

Also, because moxidectin is a new medicine, there may be unwanted effects that we don't know about yet and we don't know whether they would be mild, moderate or severe or how long they may last. If we learn about new unwanted effects that may make you change your mind about taking part in this study, we will tell you and your parents or guardians immediately.

Unwanted effects of taking blood

Having blood taken may cause some pain, bruising, and a little bit of bleeding. Sometimes, it can also cause minor infection (where germs can get into the needle prick) or fainting. This has never happened in our studies because we get you to lie down and clean the skin to remove any germs before we take blood. If you have any unwanted effects, they can easily be treated.

Why should girls who are pregnant or breast-feeding not take moxidectin and why should girls ensure that they don't become pregnant during the study?

As you may know, when ivermectin is distributed in your community, women who are pregnant should not take ivermectin until at least a week after their baby is born.

We don't know the effects of moxidectin on an unborn child or newborn baby that is breastfed by a mother who has taken moxidectin. Because of this, girls who are pregnant or breast-feeding cannot take part in this study and girls should not become pregnant during the study.

If you already have monthly bleeding, we will test whether you are pregnant.

How can girls avoid becoming pregnant?

You must agree to avoid becoming pregnant for around 6 months (until your last visit to Hohoe).

A family planning nurse will discuss highly effective methods to avoid becoming pregnant with you and your parent or guardian. We call these methods "methods of contraception". One method of contraception is not having sex. If you choose another method of contraception, we will provide it to you.

What happens if a girl who takes part in the study becomes pregnant?

If you become pregnant between taking moxidectin and around 6 months later, you should let us know immediately. We will advise you to attend all ante-natal care visits the Ghana Health Service offers. A doctor specializing in treating babies and children will examine the baby after birth and at least once a year until 2 years of age.

What happens if a boy who takes part in the study makes someone pregnant?

If you make someone pregnant between taking moxidectin and around 6 months later, you should also inform us immediately. We will ask you to let us visit your partner. We will advise her to attend all ante-natal care visits the Ghana Health Service offers and ask her to agree that a doctor specializing in treating babies and children will examine the baby after birth and at least once a year until 2 years of age.

What happens to the blood samples?

We will send the blood for measuring the amount of moxidectin to people in another country (the United States of America) to make the measurements. We will do the other tests in our country.

We will not write your name on the blood samples, only a number. We call this number your 'participant number'. Only we know which number belongs to which adolescent or child who takes part in our study.

We will only use your blood for measuring the amount of moxidectin and for the tests we have told you about. Once these measurements and tests are done, any blood left over will be destroyed.

Who will know what we found out about your health during the study?

We will keep the information we collect about your health in what we call "records". We will keep these records private (confidential). This means that we will not share your name with anybody who does not belong to our study team without your permission, except when we must because it is the law.

We will keep all the records in a locked, secure area for at least 25 years and possibly longer. When we don't need them anymore, they will be destroyed.

The people who can see the records, including your name, are:

- The doctors, nurses and laboratory staff working in our study team.
- People coming to our study center in Hohoe to make sure that we do things right and follow the law. These are:
    - People from the Ghana Food and Drugs Authority and the United States Food and Drug Administration.
    - People from the 'Sponsor'. The Sponsor is Medicines Development for Global Health, who make moxidectin tablets. They are giving us the money and the moxidectin tablets for the study and helping us write reports about what we learn.
    - People from the "Ethics Committees". These are people that have been asked by the University of Health and Allied Sciences in Hohoe, the Ghana Health Service or the World Health Organization to make sure we do this study in the right way.

The people who can see the study records but NOT your name or the names of your parents or guardians are:

- People from the Sponsor and working with us and the Sponsor. The Sponsor will keep the study records without your name for at least 25 years.
- People from the Ghana Food and Drugs Authority, the United States Food and Drug Administration, or the authorities in other countries or at the World Health Organization who look at study results to decide whether moxidectin can be used in Ghana and other countries.
- Other people who want to learn about what happens when children 4 to 17 years of age take moxidectin.

If you change your mind about taking part in the study and don't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you want to stop being in the study. However, if you have an unwanted effect that has not stopped, we will ask you to let us visit you to find out whether you need any treatment for this effect. Also, if you are pregnant, we will ask you if the doctor working with us who specializes in treating babies and children can come and examine the baby after birth and at least yearly for 2 years. If you are male and your partner becomes pregnant, we will ask you if we can contact your partner to ask her if we can examine the baby. You do not have to agree to this.

Will you or your parents have to pay anything to take part in the study?

You or your parents or guardians will not pay anything.

- All examinations and medical care that are part of the study will not cost anything.
- When you and your parent or guardian stay overnight in Hohoe, you will not pay anything. We will give you free food and transportation by car to and from your home.

Will your parent/guardian be compensated for the time they spend with you at the study center?

The parent or guardian who goes with you to Hohoe will be compensated, that means get money to make up for loss of earnings. The amount will be based on the number of nights spent in Hohoe. The amount for each night's stay will be roughly the "by day" earnings of adults in your community, currently forty (40.00) Ghana Cedis per day.

What happens if you have a permanent injury or health problem because you take part in this study?

We do not think that anybody will have an injury from the study that will make them permanently sick or die. However, if this happens, the Sponsor's insurance will pay you or your parents or guardians compensation.

What happens after the study?

After the study, you should take ivermectin when it is distributed in your community.

We will tell you, your parents or guardians and your community about what we learnt. We will also tell you what we and the Sponsor plan to do so that the Ghana Health Service and the health services in other countries where people have oncho can decide whether they want to give out moxidectin in the way they are now giving out ivermectin.

Who can you talk to if you want more information before you agree to take part in the study or during the study?

If you want to talk to someone who is not in our study team about any worries about the study, your rights, an injury you may have suffered in the study, or any other questions, concerns or complaints about the study in the future, please contact:

- The **Administrator of the Research Ethics Committee, Institute of Health Research, University of Health and Allied Sciences** by email at **rec@uhas.edu.gh** or by telephone on **+233 362 196 193**.
- The **Secretary to the Research Ethics Committee, Institute of Health Research, University of Health and Allied Sciences, Mr. Fidelis Anumu**, by telephone on **+ 233 244 061 270**. If you or your child have any questions, concerns or complaints about the study in the future, you may also contact the Project Administrator later.

- The **Administrative Secretary of the Ghana Health Service Ethics Review Committee, Ms Nana Abena Apatu,** by telephone on **+233 503 539 896** or by writing to The Administrative Secretary, Ghana Health Service Ethics Review Committee, Research and Development Division, Ghana Health Service, P. O. Box M190 Accra Ghana.

If you have any questions about the study or need medical help during the study, please contact the following members of the study team or your community coordinator:

1. **Dr. Nicholas O. Opoku (On-site Principal Investigator)**
   University of Health and Allied Sciences
   School of Public Health Research Centre
   Municipal Hospital Hohoe,
   Telephone**: 03627 22042** or **0244 776668** (mobile)
2. **Dr. Felix Doe (Co-investigator)**
   Hohoe Municipal Health Directorate
   Telephone: **0208 437550** or **0245 118342** (mobile)
3. Your **Community Coordinator**

   Name: _____

   Telephone: _____

What if you or your parents/guardians do not want you to take part in the study or if you or your parents/guardians change your mind?

It is your and your parents' or guardians' decision to take part in this study.

You or your parents or guardians can tell us that you will stop taking part in the study at any time. You do not have to tell us why you want to stop.

Not taking part in the study or changing your mind will not change the health care you and your family will receive from the Ghana Health Service.

When you tell us that you will stop taking part in the study, we will ask you to let us do final examinations so that we know about your health and can tell you what you should look out for after leaving the study.

We may decide that you cannot continue in the study. We will do this if you are not ready to come to Hohoe or if you do not want us to do the examinations or take blood, or if we find that it is better for your health. If this happens, we will explain the reasons to you and your parents or guardians.

What do you and your parents/guardians need to do if you want to take part in the study?

You should discuss this with your parents and other people.

You can only take part if both you and your parents or guardians agree that you can take part.

After you have decided, please come and talk to us together with your parents or guardians and the person your community had chosen to be present when we provide you the information about the study. We will call this person "the witness".

We will ask you and your parents or guardians whether you have any questions. We will also ask you and your parents or guardians some questions to make sure you all know what will happen during the study. Then we will ask you and your parents or guardians to confirm that you want to take part in the study by putting your signature or thumbprint on a form. The witness will also sign the form.

Help for your discussion with your parents/guardians, friends, family and others you want to talk this over with

To help you in your discussions of the study with others, here is an overview of what will happen and where it will happen.

You and your parents or guardians discuss whether you can take part in the study and you all agree. → If you do not agree you don't need to do anything.

↓

If you agree, you let us know. We will check whether we need to tell you more about the study. We will ask you and your parents or guardians to sign or thumbprint a form.

↓

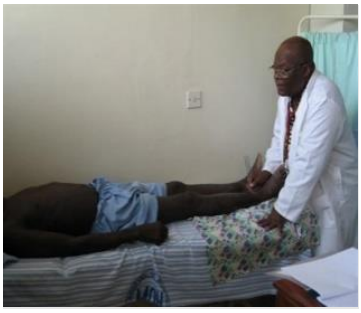
Step 1 Screening in your community to ask questions about your health (1-2 days). → If you cannot take part in Step 2 Screening, we will tell you why and tell you if you should see a nurse or doctor.

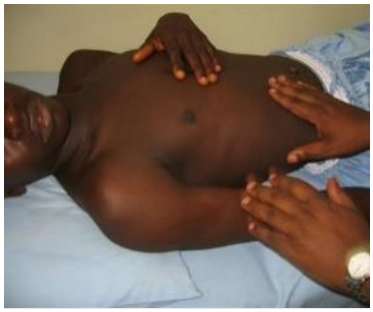
↓

If you can take part in **Step 2 Screening**, you and one of your parents/guardians will go to Hohoe.

You will stay in our special house with other children who will take part in the study and their parents or guardians.

We will ask more questions, do examinations and take bits of blood to learn more about your health and find out whether you can take part in the study (1-2 days).





If you can take part in the study and you still agree, you need to stay in Hohoe for 8 more days.

If you cannot take part in the study, we will tell you why and take you home. If you have a health problem, we will arrange a visit to a clinic or hospital near your community.

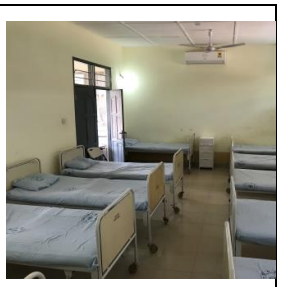
The next day, we will ask you to swallow the moxidectin tablets.

On that day and the next 7 days we will take more bits of your blood and repeat some of the examinations we did during Screening.

Then we will take you back to your community, unless you are not well, in which case you will stay until you are better.

2 weeks, 1 month, 3 months and around 6 months after you swallowed the moxidectin tablets, we will bring you and one parent or guardian back to Hohoe.





Each time we will repeat some of the examinations we did when you were in Hohoe last time and on 3 visits, we will take a bit of your blood.

Assessment of Informed Assent – Questions for Adolescents 12 to 17 Years	**Child Response**
Do you understand why you are being asked to participate in this study?	☐ Yes ☐ No
Have you been able to ask questions and discuss the study?	☐ Yes ☐ No
Questions:	
Do you understand that you can only take part if both you and your parents/guardians agree?	☐ Yes ☐ No
Do you understand that during Screening we might find that you cannot take part in the study?	☐ Yes ☐ No
Will we take blood during this study?	☐ Yes ☐ No
How long will you be in the study?	
Do you understand you can tell us at any time that you want to stop being in the study, without having to tell us why?	☐ Yes ☐ No
Is there any charge for being in the study?	☐ Yes ☐ No
Do you understand that this is a study and that we do not know all unwanted effects of moxidectin?	☐ Yes ☐ No
Do you know who to call if you have questions?	☐ Yes ☐ No
Do you know that we will share what we learn about your health with many different people but only those coming to Hohoe to check we do things right can learn your name?	☐ Yes ☐ No

Assessment of Informed Assent – Questions for Adolescents 12 to 17 Years	**Child Response**
Are you willing to come to Hohoe five times and have the examinations and blood taken that we told you about?	☐ Yes ☐ No
For girls who already have monthly bleeding: Do you understand that you must avoid becoming pregnant for around 6 months and that we will give you what you need if you chose a method other than not having sex?	☐ Yes ☐ No

Assessment of Informed Consent – Questions for Parents/ Guardians of Adolescents 12 to 17 Years	**Parent/Guardian Response**
Do you understand why your child/ward is being asked to participate in this study?	☐ Yes ☐ No
Have you been able to ask questions and discuss the study?	☐ Yes ☐ No
Questions:	
Do you understand that during Screening we might find that your child/ward cannot take part in the study?	☐ Yes ☐ No
Do you understand that it is your decision to allow your child/ward to take part in this study and that your child/ward must also agree (that means your child is a “volunteer”)?	☐ Yes ☐ No
Are you willing to allow your child/ward to have all the examinations?	☐ Yes ☐ No
Will we take blood from your child/ward during this study?	☐ Yes ☐ No
How long will your child/ward be in this study?	
Do you understand your child/ward can stop taking part in the study at any time, without having to tell us why?	☐ Yes ☐ No
Is there any charge for being in the study?	☐ Yes ☐ No
Do you understand that this is a study and that we do not know all unwanted effects of moxidectin?	☐ Yes ☐ No
Do you know who to call if you or your child/ward has questions?	☐ Yes ☐ No
Do you know that we will share what we learn about the health of your child/ward with many different people but only those coming to Hohoe to check we do things right can learn the child’s name?	☐ Yes ☐ No

Assessment of Informed Consent – Questions for Parents/ Guardians of Adolescents 12 to 17 Years	**Parent/Guardian Response**
Are you willing to come to Hohoe five times and so that your child/ward can have the examinations and blood taken that we told you about?	☐ Yes ☐ No
For parents/guardians of girls old enough to have a baby: Do you understand that your daughter/ward has to avoid becoming pregnant and that we will give her what she needs if you and she choose a method other than not having sex?	☐ Yes ☐ No

Agreement to Study Participation – Parents/Guardians and Adolescents 12 to 17 Years

CHILD PARTICIPATION AGREEMENT

I have read or have had someone read all of the above, asked questions, received answers regarding participation in this study, and I agree that my child/ward should participate in this study as a volunteer. I will not have waived any of my rights by signing this parental consent form. Upon signing this form, I will receive a copy for my personal records.

Name of Adolescent	Signature/ Thumbprint of Parent/ Guardian/ LAR		
Name of Parent/Guardian/LAR			Date
Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date

VOLUNTARY AGREEMENT (ADOLESCENTS 12 TO 17 YEARS)

By signing or thumbprinting below, it means that you:

- have understood what you will be doing for this study,
- have had all your questions answered,
- have talked to your parent(s)/legal guardian about this project, and
- agree to take part in this research

If you do not want to participate in this study, please **do not** sign or thumbprint this assent form. You and your parents/guardians will be given a copy of this form after you have signed/thumbprinted it.

Name of Adolescent	Signature/ Thumbprint of Adolescent		Date

IMPARTIAL WITNESS SIGNATURE

I was present while the benefits, risks and procedures were read to the volunteer and their parents/guardians. All questions were answered, and the child and their parents/guardians have agreed the child will take part in the study.

Name of Witness	Signature of Witness	Date

SIGNATURE OF PERSON WHO OBTAINED CONSENT

I certify that the reason the study is being done, what will happen in the study, and the potential advantages and possible risks associated with taking part in this research have been explained to the above-named adolescent and their parent(s)/guardian(s).

Name of Person who Obtained Consent	Signature of Person who Obtained Consent	Date

16.7 Model Information Sheet and Consent Form for Parents/Guardians of Children 4 to 11 Years, Including Assent Form for Children 7 to 11 Years

Title of Study:	An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in participants aged 4 to 17 years with (or at high risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years.
Principal Investigator:	Dr Nicholas Obuobisa Opoku
Organization:	University of Health and Allied Sciences (UHAS)
Sponsor:	Medicines Development for Global Health
Protocol Number(s):	MDGH-MOX-1006 UHAS-REC A.7 [6] 18-19 GHS-ERC 015/06/19
Protocol / Information Document Version/Date:	Final v1.3 (incorporating Amendments 1, 2 and 3) / 27 Nov 2019

General Information About the Study

I am Dr....., a doctor working at the University of Health and Allied Sciences in Hohoe. We are testing a new medicine called moxidectin in children 4 to 17 years of age. Moxidectin is a new treatment for onchocerciasis (River blindness), which you call "*oncho*".

Testing new medicines is called doing "research" or "a study" and means we want to learn something about the new medicine.

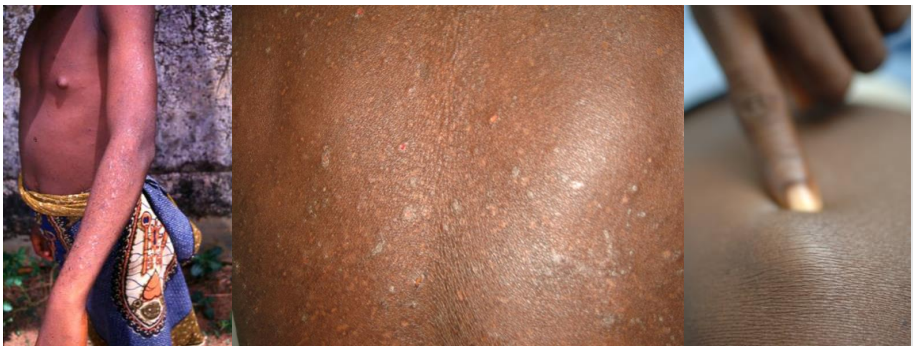
Here, we explain to parents of children aged 4 to 11 years what we already know about moxidectin, what will happen during the study and the risks and advantages of taking part in this study. This will help you decide whether you will allow your child or ward to take part in the study or not.

If you don't want your child or ward to take part, please don't be afraid to tell us. Your care or the care of your child or ward at your local health care centers will not be affected by saying no.

Please ask questions about anything that you don't understand or want to know more about. Before making a decision, you might also want to talk about it with others.

What is oncho and what is being done to help people with oncho now?

Oncho is caused by a worm that is passed from one person to another through the bites of the small black flies that you see at the riverside and in your community in the mornings and early evenings. Two types of these worms live in the human body. The young worms in the skin and eyes cause the disease, for example itching or a rash. The adult worms live for up to 14 years in swellings under the skin called nodules and produce millions of the young worms.



Many adults and children in your community may have oncho. Therefore, a medicine called ivermectin is now given to all people at least 5 years of age who are not pregnant or sick.

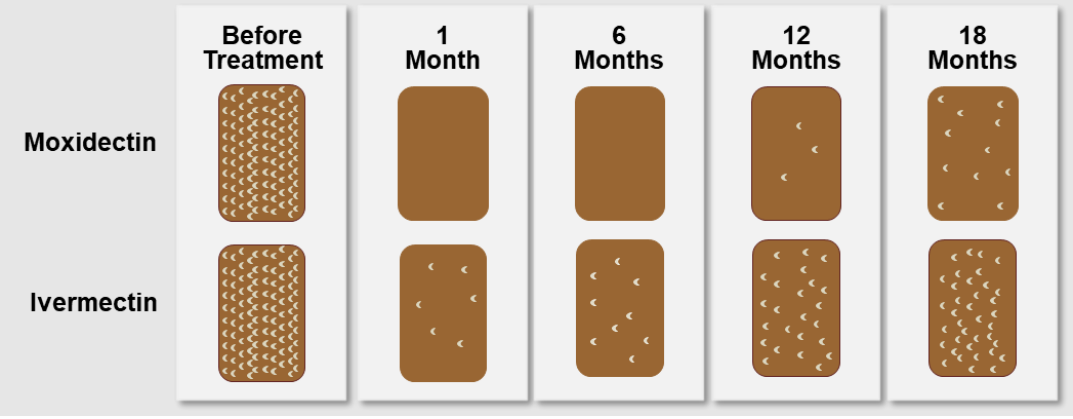
Ivermectin kills most of the young worms so that people who have oncho and take ivermectin have less or even none of the disease. However, the adult worms quickly start to make new worms and so ivermectin is given to you every six months.

What is the new medicine, moxidectin, and what does it do against the oncho worms?

You may have already heard about moxidectin because about 10 years ago, 219 people from Wii, Azua, Jagri Akua and Bitaaba who had oncho and were at least 12 years of age took part in a study to test moxidectin. In that study, some people were given moxidectin and some people were given ivermectin. If you know anybody who took part in that study, they can tell you about their experience in the study.

In the study, we found that moxidectin kills more young oncho worms in the skin than ivermectin and that moxidectin stops the adult worms from making new young worms for a longer time than ivermectin. We are showing you here pictures of the number of oncho worms in people before and after they took ivermectin or moxidectin.

Number of Young Worms in the Skin Before and After Taking Moxidectin or Ivermectin



What do we know about the unwanted effects of moxidectin?

In that study we also found that people who took moxidectin and people who took ivermectin had similar unwanted effects but some unwanted effects occurred in more people who took moxidectin than in people who took ivermectin. Many of these unwanted effects are caused by the body getting rid of the young oncho worms after they have been killed by moxidectin or ivermectin. On the next page we show you how many out of 100 people had unwanted effects after taking moxidectin or ivermectin. Please ask me if you don't understand what these unwanted effects mean.

Number of People with Unwanted Effects in 100 People Who Took Moxidectin or Ivermectin

Unwanted Effect	Moxidectin	Ivermectin
Itching	65	54
Muscle pain	64	52
Headache	58	54
Fast heartbeat	39	30
Rashes	37	21
Feeling faint or dizzy when standing up	30	25

Number of People with Unwanted Effects in 100 People Who Took Moxidectin or Ivermectin

Unwanted Effect	Moxidectin	Ivermectin
Stomach pain	31	35
Fever /chills	27	18
Common cold	23	21
Cough	17	18
Upset belly (Stomach flu)	15	17
Lymph node pain	13	6
Dizziness	12	9
Swollen arm or leg	11	6

Why are we doing a study of moxidectin in 4 to 17 year olds and asking your permission for your child/ward to take part?

We have already given moxidectin to 1349 people with oncho. These included 53 adolescents aged 12 to 17 years with oncho who took 4 tablets of moxidectin (8 milligrams), the same number of tablets adults with oncho took. Thirty-one (31) of them lived in Wii, Azua, Jagri Akua or Bitaaba. From this study, we know that 4 tablets is the right number of tablets for people at least 12 years of age.

Because moxidectin works better against the oncho worms than ivermectin, it would be good if moxidectin could also be given to children aged 4 to 11 years. Therefore, we want to find the right number of moxidectin tablets for children aged 4 to 11 years.

How will we find out what number of moxidectin tablets is right for children aged 4 to 11 years?

When somebody takes moxidectin, it gets into their blood and from the blood, moxidectin can reach the young oncho worms in the body to kill them.

The right number of tablets for children aged 4 to 11 years is the number that leads to the same amount of moxidectin in their blood as in the blood of adults and adolescents aged 12 to 17 years who take 4 moxidectin tablets. Of course, the children should also not have severe unwanted effects.

To find out the right number of tablets for children aged 4 to11 years, we need to give them moxidectin tablets, take a bit of blood and then measure the amount of moxidectin in their blood and find out what unwanted effects they have.

We will start by giving 4 moxidectin tablets to 9 adolescents aged 12-17 years and 9 children aged 8 and 11 years. We will measure the amount of moxidectin in their blood and examine them for unwanted effects. If the children aged 8 to 11 years have more moxidectin in their blood or more unwanted effects than we saw in adults or adolescents aged 12-17 years who took moxidectin, we will give a smaller number of moxidectin tablets to another group of 9 children 8 to 11 years of age and measure the amount of moxidectin in their blood and examine them for unwanted effects.

When we have learnt the right number of moxidectin tablets for children aged 8 to 11 years, we will ask 9 children aged 4 to 7 years children to take part in the study.

We will give them moxidectin tablets and measure the amount of moxidectin in their blood and examine them for unwanted effects. If they have less moxidectin in their blood than we saw in adults or adolescents aged 12 to 17 year or children 8 to 11 years of age, we will give more moxidectin tablets to a second group of 9 children aged 4 to 7 years. If the first group have too much moxidectin or too many unwanted effects, we will give fewer moxidectin tablets to a second group of children aged 4 to 7 years.

We think that we will have to give moxidectin to at least 9 children aged 8 to 11 and at least 9 children aged 4 to 7 years, but maybe up to 52 children aged 4 to 11 years.

What will happen in the study, where will it happen and how long will it take?

First, we will do Screening. Screening means that we fill find out whether your child or ward has the oncho worm but is otherwise healthy and can take part in the study.

The first step of Screening will happen in your community:

- We will ask if a sister or brother has already taken part in the study, because only one child or ward from your family can take part.

- We will ask questions about health problems in the past, medicines taken, look closely at the child's arm to see if it will be easy to take blood, and show an item that is the same size as the moxidectin tablets and ask the child and you if they could swallow a tablet of that size.

This will take 1 to 2 days.

If we find your child can not take part in the study, we will tell you and the child why.

If we find that your child can go on to **the second step of Screening**, we will drive the child and one of you by car to our study center in Hohoe.

In Hohoe we have a special house for people taking part in our study and you will sleep there together with the child and other children and their parents or guardians who take part in our study. We will give you free meals while you are in Hohoe.

In Hohoe:

- We may ask you and the child to tell us more about the child's health problems in the past and any medicines they have taken lately.
- We will measure the child's height and weight.
- We will examine how fast the child breathes, how hard and fast the heart works and the body temperature (we call these measurements "vital signs").
- We will examine how well the heart works with a special machine called an electrocardiograph (an "ECG"). Here I am showing you the things we will put on your body for the ECG, like you see in this picture. This won't hurt.
- We will examine the child's body for signs of illness or pain. Some of this you can see in the pictures here.

- Doctors can learn a lot about whether somebody is sick by testing the blood. We will take a bit of blood (no more than 8.5 milliliters or about 2 teaspoons) like you can see in this photo. Before we take the blood, we will put a cream on the child's arm so they won't feel much pain.

  We will test the blood to find out how well some of the organs in the child's body work and for signs of HIV (AIDS infection) or the germs that cause liver disease (hepatitis B and C).

  If the child has lived outside Ghana in an area where another worm called Loa loa occurs, we will test the blood to check whether the child has the Loa loa worm. We will do this because people with lots of Loa loa worms can have more unwanted effects when taking moxidectin and therefore they should not take part in our study.

All of this will take 1 to 2 days.

We will explain everything we learn about the child's health. We will let you and the child know whether the child can take part in the study.

What will happen after Screening if your child/ward cannot take part in the study?

We will explain to you and the child why they cannot take part in the study. If the child needs to be taken care of by a nurse or doctor, we will arrange for the child to visit a clinic or hospital.

On the day after Screening, we will drive you and the child back to your community.

What will happen after Screening if your child/ward can take part in the study?

We will ask you and the child to stay in Hohoe for 13 more days.

In each group of 9 children we will first give moxidectin to only 3 children. Once we know what unwanted effects these 3 children have during the first 3 days after they have swallowed the moxidectin tablets, we will give moxidectin tablets to the other children in that group.

Your child will not be able to take ivermectin while they are on the study (for approximately 6 months).

On the day after Screening (for the first 3 children) or 5 days later, we will:

- Repeat some of the examinations we did during Screening before we give moxidectin to the child.
- Ask the child to swallow moxidectin tablets 2 hours before the child has breakfast.
- Repeat again some of the examinations we did during Screening.
- Take a bit of their blood (1.5 milliliters or 1/3 of a teaspoon) 4 times to measure the amount of moxidectin. We will use a special needle called a 'cannula' so the child only needs to have one needle prick and we will use the special cream, so they won't feel much pain.
- Ask you and the child several times to tell us if the child is feeling unwell or has any pain. If the child has pain or is feeling unwell, we will examine them to find out what we can do to make them feel better. If necessary, we will give the child medicine.
- We will also ask you and the child to tell us immediately if the child is not feeling well. Even during the night, there will always be a nurse to talk to.

During the next 7 days, we will:

- Repeat some of the examinations we did during Screening.
- Take a bit of blood (1.5 milliliters or 1/3 of a teaspoon) on 2 days to measure the amount of moxidectin.
- Take a bit more blood (3.5 milliliters total or 2/3 teaspoon) on the last day to measure the amount of moxidectin and test how well some of the organs in the child's body work.

If the child is feeling well, we will drive you both back to your community on the 7th day after the child has taken the moxidectin tablets. If not, we will ask you and the child to stay longer until the child feels well.

2 weeks, 1 month, 3 months and around 6 months after the child has swallowed the moxidectin tablets, we will:

- Drive the child and one parent or guardian to Hohoe again.
- Each time we will ask you and the child to tell us about any health problems the child has had and any medicine they have taken since we last saw the child.
- Each time we will repeat some of the examinations we did the last time your child or ward was in Hohoe.
- We will take a bit of the child's blood (1.5 milliliters or 1/3 of a teaspoon) on 2 visits to measure the amount of moxidectin.
- We will take a bit more of your child's or ward's blood (3.5 milliliters or 2/3 teaspoon) on 1 visit to measure the amount of moxidectin in it and to find out how some of the organs in the child's body work.

- Each time, the accompanying parent or guardian and the child will spend one night with us and we will give you free meals.

What happens when your child/ward is in Hohoe during school time?

There will be a teacher in our study center in Hohoe. The teacher will help the children keep going with schoolwork, to help make up for the school time they miss.

What should you do if your child/ward is not feeling well when you are back in your community?

You should contact us, either through the community coordinator or directly, or you should take the child to the closest health clinic. The "community coordinator" is the person chosen by your community to contact us whenever you want. We have written down the name for you.

We will make sure that the child is examined and receives medicine if they need it. If needed, we will drive the child or ward and one parent or guardian to the study center in Hohoe or a health clinic or hospital.

Are there any potential advantages of taking part in this study?

The child may not have any advantages.

- The child will have examinations of their health. These examinations are often used by doctors and nurses to find out whether people are sick.
- If the child has the young oncho worms in their skin, moxidectin will cause most or all of the young worms to die and prevent new young worms in the skin for up to about one year.
- If child has health problems because of the young oncho worms in the skin or eyes, these will become better or even go away for up to about 1 year.

Are there any possible risks of taking part in this study?

Unwanted effects of taking moxidectin

Almost all medicines cause unwanted effects.

We have already told you about the unwanted effects we found in people with the oncho worm who took moxidectin or ivermectin. In most cases, these unwanted effects were mild, went away on their own and lasted less than a week. Please let me know if you would like us to look at the pictures again.

Your child may have none, some or all of these unwanted effects. They may be mild, moderate or severe. They may occur soon after the child has taken moxidectin or many hours or days later.

Also, because moxidectin is a new medicine, there may be unwanted effects that we don't know about yet and we don't know whether they would be mild, moderate or severe or how long they

may last. If we learn about new unwanted effects that may make you change your mind about your child or ward taking part in this study, we will tell you and the child immediately.

Unwanted effects of taking blood

Having blood taken may cause some pain, bruising, and a little bit of bleeding. Sometimes, it can also cause minor infection (where germs can get into the needle prick) or fainting. This has never happened in our studies because we get the children to lie down and clean the skin to remove any germs before we take blood. If your child or ward has any unwanted effects, they can easily be treated.

What happens to the blood we take?

We will send the blood for measuring the amount of moxidectin to people in another country (the United States of America) to make the measurements. We will do the other tests in our country.

We will not write the child's name on the blood samples only a number. We call this number the child's 'participant number'. Only we know which number belongs to which child who takes part in our study.

We will only use the blood for measuring the amount of moxidectin and for the tests we have told you about. Once these measurements and tests are done, any blood left over will be destroyed.

Who will know what we found out about the child's health during the study?

We will keep the information we collect about your child's or ward's health in what we call "records". We will keep these records private (confidential). This means that we will not share the child's name with anybody who does not belong to our study team without your permission, except when we must because it is the law.

We will keep all the records in a locked, secure area for at least 25 years and possibly longer. When we don't need them anymore, they will be destroyed.

The people who can see the records, including the child's name, are:

- The doctors, nurses and laboratory staff working in our study team.
- People coming to our study center in Hohoe to make sure that we do things right and follow the law. These are
    - People from the Ghana Food and Drugs Authority, and the United States Food and Drug Administration
    - People from the 'Sponsor'. The Sponsor is Medicines Development for Global Health, who make moxidectin tablets. They are giving us the money and the moxidectin tablets for the study and helping us write reports about what we learn.

- People from the "Ethics Committees". These are people that have been asked by University of Health and Allied Sciences in Hohoe, the Ghana Health Service or the World Health Organization to make sure we do this study in the right way.

The people who can see the records but NOT the child's name or the names of the child's parents or guardians are:

- People from the Sponsor and working with us and the Sponsor. The Sponsor will keep the records without the child's name for at least 25 years.
- People from the Ghana Food and Drugs Authority, the United States Food and Drug Administration, or the authorities in other countries or at the World Health Organization who look at study results to decide whether moxidectin can be used in Ghana and other countries.
- Other people who want to learn about what happens when children 4 to 17 years of age take moxidectin.

If you change your mind about allowing your child or ward to take part in the study or the child doesn't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you wanted your child or ward to stop taking part in the study (or your child or ward told us they want to stop taking part in the study). However, if your child/ward has an unwanted effect that has not stopped, we will ask you to let us visit you and your child/ward to find out whether they need any treatment for this effect. You and your child/ward do not have to agree to this.

Will you have to pay anything to take part in this study?

You will not pay anything.

- All examinations and medical care that are part of the study will not cost anything.
- When you and the child stay overnight in Hohoe, you will not pay anything. We will give you free food and transportation by car to and from your home.

Will the parent/guardian coming to Hohoe with the child be compensated for the time spent in Hohoe?

The parent or guardian who goes with the child to Hohoe will be compensated, that means get money to make up for loss of earnings. The amount will be based on the number of nights spent in Hohoe for the study. The amount for each night's stay will be roughly the "by day" earnings of adults in your community, currently forty (40.00) Ghana Cedis per day.

What happens if the child has a permanent injury or health problem because of taking part in this study?

We do not think that anybody will have an injury from the study that will make them permanently sick or die. However, should this happen, the Sponsor's insurance will pay you or the child compensation.

What Happens After the Study?

After the study, the child should take ivermectin when it is distributed in your community.

We will tell you, the child and your community about what we learnt. This will happen after the last children finish the study. We will also tell you what we and the Sponsor plan to do so that the Ghana Health Service and the health services in other countries where people have oncho can decide whether they want to give out moxidectin in the way they are now giving out ivermectin.

Who can you talk to if you want more information before you agree to let your child/ward take part in the study or during the study?

If you want to talk to someone who is not in our study team about any worries about the study, your rights, an injury the child may have suffered in the study, or any other questions, concerns or complaints about the study in the future, please contact:

- The **Administrator of the Research Ethics Committee, Institute of Health Research, University of Health and Allied Sciences** by email at **rec@uhas.edu.gh** or by telephone on **+233 362 196 193**.
- The **Secretary to the Research Ethics Committee, Institute of Health Research, University of Health and Allied Sciences, Mr. Fidelis Anumu**, by telephone on **+ 233 244 061 270**. If you or your child have any questions, concerns or complaints about the study in the future, you may also contact the Project Administrator later.
- The **Administrative Secretary of the Ghana Health Service Ethics Review Committee, Ms Nana Abena Apatu,** by telephone on **+233 503 539 896** or by writing to The Administrative Secretary, Ghana Health Service Ethics Review Committee, Research and Development Division, Ghana Health Service, P. O. Box M190 Accra Ghana.

If you have any questions about the study or need medical help during the study, please contact the following members of the study team or your community coordinator:

1. **Dr. Nicholas O. Opoku (On-site Principal Investigator)**
   University of Health and Allied Sciences
   School of Public Health Research Centre
   Municipal Hospital Hohoe,
   Telephone**: 03627 22042** or **0244 776668** (mobile)

2. **Dr. Felix Doe (Co-investigator)**
   Hohoe Municipal Health Directorate
   Telephone: **0208 437550** or **0245 118342** (mobile)

3. Your **Community Coordinator**

   Name: _____

   Telephone: _____

What if you do not want the child to take part in the study or the child does not want to take part in the study, or if you change your mind about taking part in the study?

It is your and your child's or ward's decision to take part in this study.

You or the child can tell us that the child will stop taking part in the study at any time. You do not have to tell us why you want to stop.

Not taking part in the study or changing your mind will not change the health care you and your family will receive from the Ghana Health Service.

When you tell us that you want the child to stop taking part in the study, or the child wants to stop, we will ask you to let us do final examinations so that we know about the child's health and can tell you what you should look out for after the child leaves the study.

If new information becomes available, we will tell you and your child or ward about it and discuss with you whether you and your child or ward want to continue in the study.

We may decide that the child cannot continue in the study. We will do this if we see that the child is not ready to come to Hohoe or if you or the child do not want us to do the examinations or take the blood samples we told you about, or if we find that it is better for the child's health. If this happens, we will explain the reasons to you and the child.

What do you need to do to let us know that you allow your child/ward to take part in the study and your child or ward also wants to take part?

You should discuss this with your child or ward and other people in your community.

For children 8 to 11 years of age, we have a special document describing the study which we will discuss with them while you and a witness your community has chosen are present. If you and the child agree, we will ask you some questions about the study so we can find out what we need to explain better. Then we will ask you, the witness and your child or ward to sign or thumbprint a form.

If your child or ward is 4 to 7 years of age, we will discuss the study with them using a simpler description of what will happen in the study. We will also do this if the child is older but you and we think they are not mature enough to understand the information in the document for the children aged 7 to 11 years. You and a witness your community has chosen will be present. We will look for signs that the child does not want to take part in the study. Because you know the child better than us, we will also ask you if you think the child is showing signs that they do not want to take part in the study. If your child or ward does not show such signs, we will ask you some questions about the study so we can find out what we need to explain better. Then we will ask you and the witness to sign or thumbprint a form.

Help for your discussion with your child/ward, friends, family and others you want to talk this over with

To help you in your discussions of the study with others, here is an overview of what will happen and where it will happen.

You and your child discuss whether the child wants to take part in the study and you all agree → If you do not agree you don't need to do anything

↓

If you agree, you let us know. We will check whether we need to tell you more about the study. We will ask you and your child (if they are old enough) to sign or thumbprint a form.

↓

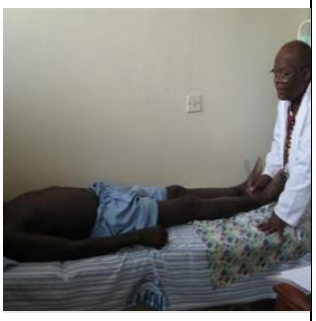
Step 1 Screening in your community to ask questions about the health of your child (1-2 days) → If your child cannot take part in Step 2 Screening, we will tell you why and tell you if your child should see a nurse or doctor

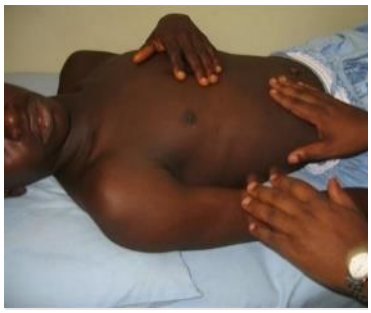
↓

If your child can take part in **Step 2 Screening**, your child and one of their parents/guardians will go to Hohoe

You will stay in our special house with other children who take part in the study and their parents or guardians

We will ask more questions, do examinations and take bits of blood to learn more about your child's health and find out whether your child can take part in the study (1-2 days)





If your child can take part in the study and you still agree, you need to stay in Hohoe for 13 more days.

If your child cannot take part in the study, we will tell you why and take you home. If your child has a health problem, we will arrange a visit to a clinic or hospital near your community.

The next day or 5 days later, we will ask your child to swallow the moxidectin tablets.

On that day and the next 7 days we will take more bits of blood and repeat some of the examinations we did during Screening.

Then we will take you back to your community, unless your child is not well and you stay until your child is well.

2 weeks, 1 month, 3 months and around 6 months after your child swallowed the moxidectin tablets we will bring your child and one parent or guardian back to Hohoe.

Each time we will repeat some of the examinations we did when your child was in Hohoe last time and on 3 visits we will take a bit of your child's blood.

Assessment of Informed Consent – Questions for Parents/ Guardians of Children 4 to 11 Years	**Parent/Guardian Response**
Do you understand why your child/ward is being asked to participate in this study?	☐ Yes ☐ No
Have you been able to ask questions and discuss the study?	☐ Yes ☐ No
Questions:	
Do you understand that during Screening we might find that your child/ward cannot take part in the study?	☐ Yes ☐ No
Do you understand that it is your decision to allow your child/ward to take part in this study and that your child/ward must also agree (7 to 11 years) or not show that they don't want to take part (4 to 6 years) (that means your child is a "volunteer")?	☐ Yes ☐ No
Are you willing to allow your child/ward to have all the examinations?	☐ Yes ☐ No
Will we take blood from your child/ward during this study?	☐ Yes ☐ No
How long will your child/ward be in this study?	
Do you understand your child/ward can stop taking part in the study at any time, without having to tell us why?	☐ Yes ☐ No
Is there any charge for being in the study?	☐ Yes ☐ No
Do you understand that this is a study and that we do not know all unwanted effects of moxidectin?	☐ Yes ☐ No
Do you know who to call if you or your child/ward has questions?	☐ Yes ☐ No

Assessment of Informed Consent – Questions for Parents/ Guardians of Children 4 to 11 Years	**Parent/Guardian Response**
Do you know that we will share what we learn about the health of your child/ward with many different people but only those coming to Hohoe to check we do things right can learn the child's name?	☐ Yes ☐ No
Are you willing to come to Hohoe five times and so that your child/ward can have the examinations and blood taken that we told you about?	☐ Yes ☐ No

Agreement to Study Participation – Parents/Guardians and Children 7 to 11 Years Mature Enough to Provide Assent (Check if Not Applicable ☐)

CHILD PARTICIPATION AGREEMENT

I have read or have had someone read all of the above, asked questions, received answers regarding participation in this study, and I agree that my child/ward should participate in this study as a volunteer. I will not have waived any of my rights by signing this parental consent form. Upon signing this form, I will receive a copy for my personal records.

Name of Child	Signature/ Thumbprint of Parent/ Guardian/ LAR		
Name of Parent/Guardian/LAR			Date
Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date

VOLUNTARY AGREEMENT (CHILDREN 7 to 11 YEARS PROVIDING ASSENT)

By signing or thumbprinting below, it means that you:

- have understood what you will be doing for this study,
- have had all your questions answered,
- have talked to your parent(s)/legal guardian about this project, and
- agree to take part in this research

If you do not want to participate in this study, please do not sign or thumbprint this assent form. You and your parents/guardians will be given a copy of this form after you have signed/thumbprinted it.

Name of Adolescent	Signature/ Thumbprint of Adolescent		Date

IMPARTIAL WITNESS SIGNATURE

I was present while the benefits, risks and procedures were read to the volunteer and their parents/guardians. All questions were answered, and the child and their parents/guardians have agreed the child will take part in the study.

Name of Witness	Signature of Witness	Date

SIGNATURE OF PERSON WHO OBTAINED CONSENT

I certify that the reason the study is being done, what will happen in the study, and the potential advantages and possible risks associated with taking part in this research have been explained to the above-named child and their parent(s)/guardian(s).

Name of Person who Obtained Consent	Signature of Person who Obtained Consent	Date

Agreement to Study Participation – Parents/Guardians and Children 4 to 6 Years or Too Immature for Assent (Check if Not Applicable ☐)

CHILD PARTICIPATION AGREEMENT

I have read or have had someone read all of the above, asked questions, received answers regarding participation in this study, and I agree that my child/ward should participate in this study as a volunteer. I will not have waived any of my rights by signing this parental consent form. Upon signing this form, I will receive a copy for my personal records.

Name of Child			
Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date
Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date

ASSESSMENT OF 'DELIBERATE OBJECTION'

In the judgement of the parents/guardians and person who obtained their consent, did the child express **'deliberate objection'**? **If yes, child cannot take part** in study.	☐ Yes ☐ No

Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date
Name of Parent/Guardian/LAR	Signature/ Thumbprint of Parent/ Guardian/ LAR		Date

IMPARTIAL WITNESS SIGNATURE

I was present while the benefits, risks and procedures were read to the volunteer and their parents/guardians. All questions were answered, and the child and their parents/guardians have agreed the child will take part in the study.

Name of Witness	Signature of Witness	Date

SIGNATURE OF PERSON WHO OBTAINED CONSENT

I certify that the reason the study is being done, what will happen in the study, and the potential advantages and possible risks associated with taking part in this research have been explained to the above-named child and their parent(s)/guardian(s).

Name of Person who Obtained Consent	Signature of Person who Obtained Consent	Date

16.8 Model Information Sheet for Children 7 to 11 Years

Title of Study:	An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in participants aged 4 to 17 years with (or at high risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years.
Principal Investigator:	Dr Nicholas Obuobisa Opoku
Organization:	University of Health and Allied Sciences (UHAS)
Sponsor:	Medicines Development for Global Health
Protocol Number(s):	MDGH-MOX-1006 UHAS-REC A.7 [6] 18-19 GHS-ERC 015/06/19
Protocol / Information Document Version/Date:	Final v1.3 (incorporating Amendments 1, 2 and 3) / 27 Nov 2019

Introduction

My name is ……..…. and I am a doctor working at the University of Health and Allied Sciences in Hohoe. I am testing a new medicine called moxidectin in children 4 to 17 years of age. Moxidectin is a new medicine for an illness that you call “oncho”.

Because of your age, I want to ask you whether you want to take part in this testing. Testing of a new medicine is called doing “research” or a “study” and means that we want to learn more about the new medicine.

Do you have to take part in the study?

Don’t worry, you and your parents or guardian will decide together whether or not you take part in this study. If you don’t want to take part, you don’t have to, even if your parents or guardian say that you can. You don’t have to tell us why you don’t want to take part. If you first decide to take part but then change your mind, you just have to tell us. You don’t have to tell us why you changed your mind. Nobody will get angry with you.

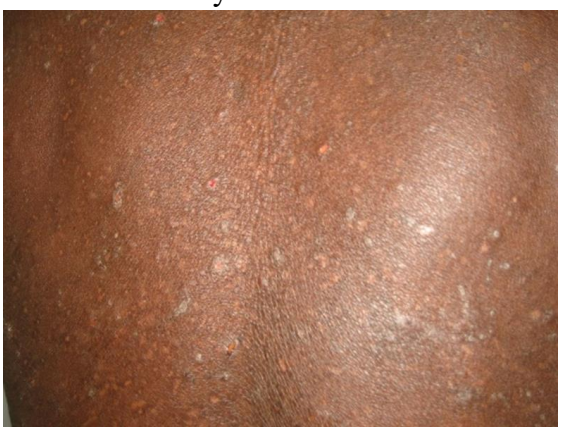
I will tell you and your parents or guardian now why we want to do this study and what will happen in the study. If I say anything that you don’t understand or you have a question, please interrupt me and ask me. You can ask me questions again and again until I have explained in a way that you understand.

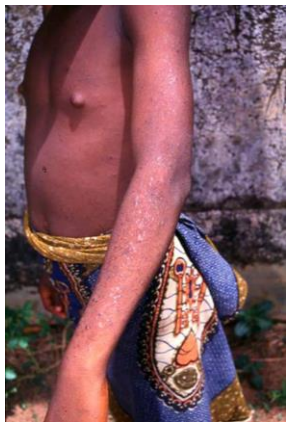
Afterwards, you and your parents or guardian and friends can talk about it. Then you and your parents or guardian can let me know whether you want to take part in the study or not.

What is oncho and what is being done now to help people with oncho?

Oncho is caused by a worm that is passed from one person to another through the bites of the small black flies that you see at the riverside and in your community in the mornings and early evenings. The very small young oncho worms in the skin and eyes can make people feel itchy, give them a rash or make them sick in other ways.

These photos show the skin of people who have a rash because of oncho worms.





Many adults and children in your community may have oncho. Therefore, a medicine called ivermectin is given two times a year to all people in your community who are at least 5 years of age. Ivermectin kills most of the young oncho worms.

What does moxidectin do?

We have already tested moxidectin in adults and children who were at least 12 years of age. Many of these adults and children were living in your community or in communities nearby. If you or your parents know some of these people, you can ask them about it.

We found out that when people at least 12 years of age take 4 tablets of moxidectin, the young oncho worms in the skin and eyes go away better and for longer than when people take ivermectin.

All medicines have what we call ‘unwanted effects’. For example, some people who take ivermectin may feel more itchy in the first few days after they have taken ivermectin than before they took ivermectin. But afterwards, their itching or itchy rash goes away. We found that when people at least 12 years of age took 4 tablets of moxidectin, some had unwanted effects just like some people have after taking ivermectin.

Why do we want to test moxidectin in children your age?

We want to do this testing to find out the right number of moxidectin tablets for children your age.

How will we find out the right number of moxidectin tablets for children your age?

When somebody takes moxidectin, the moxidectin gets into their blood and from the blood, it kills the young oncho worms in the body. To find the right number of moxidectin tablets for

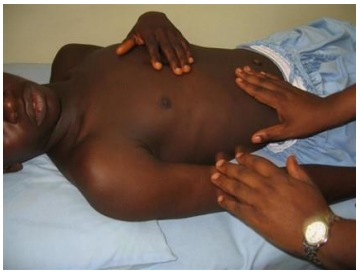
children your age, we need to find out how much moxidectin is in their blood after they swallow moxidectin tablets.

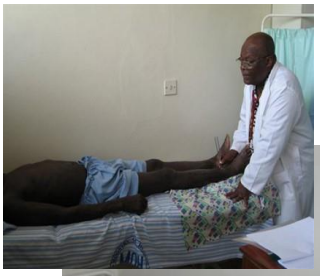
Also, by testing your blood, doctors can tell whether you are sick or getting sick.

To find out how much moxidectin is in your blood and whether you are sick or getting sick, we need to take blood from your arm with a needle. Before we put the needle in your arm, we will put a cream on your arm so that it goes numb and you won't feel much pain. Here I am showing you the needle and tube I will use and a picture of how I will use them.

[Note: The Investigator will show the syringe and needle]

To find out whether you have any unwanted effects after taking moxidectin, we will also need to do checks before and after you take moxidectin. None of these checks will hurt. Here are some pictures of these checks.





Where and when will this happen?

If you and your parents or guardian agree that you can take part, we will first need to learn about your health.

Here in your community, we will ask your parents or guardians about your health. If we learn something about your health that makes us think it is better for you not to take part, we will tell you that you cannot take part in the study.

If you are healthy and if you still want to take part, we will take you by car with one of your parents or guardians our place in Hohoe.

Your parent and you will sleep in a special house together with the other children and parents that have come. Here are some pictures.



We will take care of your food.

We will do examinations to learn about your health. Your parent or guardian will be with you. We will:

- Weigh you and measure how tall you are.
- Examine your body.
- Measure how hard and fast your heart works and examine how your heart works with a special machine called an “ECG” machine.
- Measure how fast you breathe.
- Find out whether you have a fever.
- Take bits of your blood from your arm with a needle, after we have put a special cream on your arm so you don’t feel the needle prick much.

If we find you have a health problem, you cannot take part in the study and we will drive you and your parent or guardian back home. We will tell you and your parent or guardian about the health problem so you can see a doctor or nurse close to your community if you need to do this to get better.

If you can take part in the study, you and your parent will need to stay in Hohoe for between 8 and 13 more days.

We will ask you to swallow up to 4 moxidectin tablets with water.

During the next days, we will take bits of your blood 7 times and we will do the health checks we did before you swallowed the moxidectin tablets. Every day, we will ask you how you are feeling. You and your parent or guardian should also tell us if you don’t feel well. We will always be there to talk to you whenever you want to, even at night.

After these 7 days, we will drive you and your parent or guardian home.

There will be 4 more trips from your community to Hohoe for you and your parent or guardian around 2 weeks, 1 month, 3 months and 6 months after you took the moxidectin tablets. Each time, we will do the examinations again and 3 times we will also take bits of your blood. You will stay at least one night each time before we take you home again.

Will you miss school?

You may miss school while you are in Hohoe. We have made sure that there will be a teacher to help you keep going with your schoolwork while you stay in Hohoe.

Will taking blood and swallowing moxidectin make you sick?

We don't think you will get sick during this study. You won't feel much pain when we take bits of your blood, but you might have some pain or get a bruise afterwards.

You might have unwanted effects, that means feel a bit unwell for a few days after you swallow the moxidectin tablets but if this happens, we are there to look after you.

Who will we tell that you took part in the study and what we found out about your health?

We will keep your name and everything we find out about your health private. This means that I will make sure that only the people working with me in Hohoe and people coming to Hohoe to check that we are doing the study the right way can know your name.

We will tell the people who make the moxidectin tablets what we found out about your health, but we will not tell them your name. We will do this so that they can help us find the right number of moxidectin tablets for children your age and then tell the people in our country, and people in other countries who want to learn about moxidectin, what we found in our study. None of these people will know you name.

What can you do if you want to know more before you and your parents/guardians decide whether you can take part in this study?

You can ask me more questions now. In case you want to talk to me or other people who know about this study later, your parents know how to talk to me and others.

How should you tell us that you and your parents/guardians have decided that you can take part in this study?

I will come back to ask you what you and your parents have decided.

If you don't want to take part in the study, you do not need to do anything.

If you have decided that you want to take part in this study and your parents agree, I will ask you to sign or thumbprint a form. Your parent or guardian and another person chosen by your community will be with you. Before you do this, I will ask you some questions to see whether I need to explain more to you.

Assessment of Informed Assent – Questions for Children 7-11 Years	**Child Response**
Do you understand why you are being asked to participate in this study?	☐ Yes ☐ No
Have you been able to ask questions and discuss the study?	☐ Yes ☐ No
Questions:	
Do you understand that during Screening we might find that you cannot take part in the study?	☐ Yes ☐ No
Do you understand that you can only take part if both you and your parents/guardians agree?	☐ Yes ☐ No
Will we take blood during this study?	☐ Yes ☐ No
How long will you be in the study?	
Do you understand you can tell us at any time that you want to stop being in the study, without having to tell us why?	☐ Yes ☐ No
Is there any charge for being in the study?	☐ Yes ☐ No
Do you understand that this is a study and that we do not know all unwanted effects of moxidectin?	☐ Yes ☐ No
Do you know that we will share what we learn about your health with many different people but only those coming to Hohoe to check we do things right can learn your name?	☐ Yes ☐ No
Are you willing to come to Hohoe five times and have the examinations and blood taken that we told you about?	☐ Yes ☐ No

16.9 Model Information Sheet for Children 4 to 6 Years and Older Children Considered Not Mature Enough to Provide Assent

Title of Study:	An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in participants aged 4 to 17 years with (or at high risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years.
Principal Investigator:	Dr Nicholas Obuobisa Opoku
Organization:	University of Health and Allied Sciences (UHAS)
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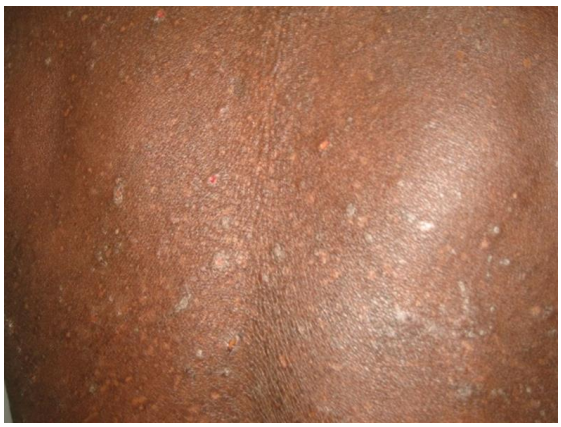
Protocol / Information Document Version/Date:	Final v1.3 (incorporating Amendments 1, 2 and 3) / 27 Nov 2019

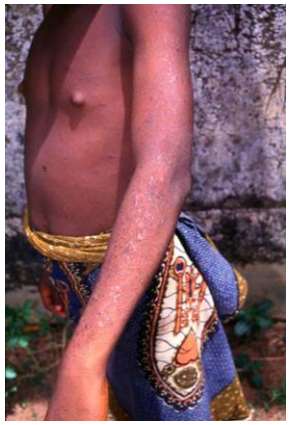
Introduction

My name is …….. and I am a doctor in Hohoe. I want to find out how many tablets of a new medicine for the illness that you call "*oncho*" children should take.

What is oncho?

Oncho is an illness caused by worms so small that you cannot see them with your eyes. The oncho worms can make people itchy, have a rash or make them feel sick. These photos show the skin of people who have a rash because of oncho worms.





To help people who have the oncho worm, a medicine called ivermectin is given to all children who are 5 years and older and all adults. Have you ever swallowed ivermectin?

What is the new medicine?

The new medicine is called moxidectin (we will call it "moxi" for short). When we gave moxi to children older than you and to adults, we found that it fights the oncho worms better than ivermectin.

I want to find out how many moxi tablets children the same age as you should take. To do this, I am asking you and other children your age to come with one of your parents to Hohoe.

How big are the tablets?

I am showing you here how big a moxi tablet is. The size is about the same as the size of ivermectin tablets. Do you think you can swallow a tablet like this?

[Note – The investigator will show a tablet of similar shape and size to moxidectin tablets. If the child or their parents/guardians do not think the child can swallow the tablet, the information session ends here with a thank you to the child and parents]

When people swallow moxi tablets, moxi gets into their blood and from the blood, moxi kills the oncho worms in the body. Do you know what blood is?

[Note – If not, the investigator will explain what blood is].

To know how many tablets children your age should take, I need to find out how much moxi is in your blood. I will get bits of your blood by putting a needle in your arm.

Please let me examine your arms to see whether it will be easy to take a bit of your blood. This won't hurt.

[Note – If the examination of the arms shows poor venous access, the information session ends here with a thank you to the child and parents]

I will put a special cream on your arm so that you don't feel much pain. I am showing you here the needle and the tube I will use to get bits of your blood and a picture of how I will use them.

[Note: The Investigator will show the syringe and needle]

Do you have to come to Hohoe?

Don't worry, you and your parents or guardians will together decide whether you do this. Nobody will get angry with you if you don't want to do this.

I will now tell you what will happen in Hohoe.

If I say anything that you don't understand or you have a question, please interrupt me and ask me. I will explain and if you don't understand what I say, ask me again and again until I have explained in a way that is right for you.

Afterwards, you and your parents or guardians can talk about it.

What if you first think you want to come to Hohoe but later you change your mind?

Don't worry, you just have to tell me or your parents or guardians. Nobody will get angry with you.

What will happen if you want to come to Hohoe?

We will ask your parents to tell us about your health.

If your parents tell us that you have health problems, you will not go to Hohoe since it will be better for you not to do that.

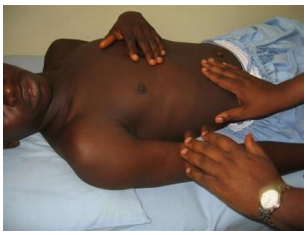
What will happen if you can go to Hohoe?

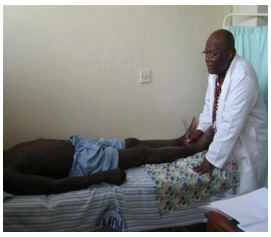
If you do not have health problems, you and one of your parents will ride in a car together with other children and one of their parents to Hohoe.

In Hohoe, you will all stay in our place. You and your parent will sleep in the same room together with the other children and parents who have come. We will give you food.



Before we give you tablets to swallow, we will do some checks to find out more about your health. Here are pictures of some of the checks and here are the things that I will put on your body, like in the picture. None of these checks will hurt.






If the checks find you are not healthy, it will be better for you not to swallow the tablets and we will drive you and your parent back to your community in the car.

If you are healthy, we will ask you to swallow the tablets with a lot of water.

After you have swallowed the tablets, you and your parent will stay with us in Hohoe for 7 more days. We will do checks and take bits of your blood like we did before you swallowed the tablets.

Afterwards we will bring you and your parent and the other children and their parents back to your community by car.

We will ask you and your parent to come back to us at Hohoe four more times so we can do more checks and take bits of your blood like we did before you swallowed the tablets.

Will you miss school?

You may miss school while you are in Hohoe. Therefore, we have made sure that there will be a teacher to help you keep going with your schoolwork while you are in Hohoe.

Will the checks and taking bits of your blood and swallowing the tablets make you sick?

We don't think you will get sick. You won't feel much pain when we take bits of your blood, but you might have some pain afterwards. You might feel a bit unwell for a few days after you swallow the tablets but if this happens, we are there to look after you.

16.10 Summary of Protocol Amendments

16.10.1 Rationale for Protocol Amendment No. 1

This is a single center study to be conducted at the Department of Public Health, University of Health and Allied Sciences (UHAS) Research Centre, Hohoe Municipal Hospital, Volta Region, Ghana. The UHAS Research Ethics Committee in its feedback on review of the study (dated 8 Mar 2019) requested site specific changes and clarifications to the protocol which have resulted in the requirement for this amendment.

The following sections of the protocol have been amended and details are provided in Table 9 and Table 10.

Table 9: Details of Administrative Protocol Amendments (Amendment 1)

Section	Original Text	Revised to Read	Rationale for Change
Throughout document	Not applicable	Correction of minor typographical errors, including addressing removal of the full term and either the acronym remains or, where necessary, the acronym is added to replace the term upon second or subsequent use in the document (Section headings and tables are the exception). Headings changed to title case.	Correction of grammar, spelling errors or abbreviation use to improve readability and consistency within the document
	Single line spacing	1.5 line spacing	Consistency with Ghana Health Service ethics committee format
Cover page and footers	Version 1.0 25 January 2019	Version 1.1 (incorporating Amendment 1) 01 April 2019	Version number updated to indicate protocol amendment
Footers	Page X of 66	Page X	Revised for publication to US FDA Investigational New Drug application
Footers	Page numbering restarted at Table of Contents	Pages numbered consecutively through document	Revised for publication to US FDA Investigational New Drug application
Page 15	Not applicable	List of Figures List of Tables	Added for consistency with Ghana Health Service ethics committee format
Section and sub-section headings	Not applicable	Some Section and subsection headings expanded	Addition of information to link original protocol headings with UHAS Research Ethics Committee defined protocol headings to assist locating information within protocol

Section	Original Text	Revised to Read	Rationale for Change
Abbreviations	Not applicable	LAR – legally authorized representative	Addition of a term used in the model consent form appended to the protocol as per UHAS Research Ethics Committee request
Abbreviations	IP – Investigational Product	Not applicable	Removal of abbreviation to ensure clarity in document
Abbreviations and Section 3.3.1.2.3	No Observed Adverse Event Level (NOAEL)	No Observed Adverse Effect Level (NOAEL)	Correction of term
Synopsis – Inclusion criteria	Live in a region designated by the World Health Organization (WHO) as endemic for *O. volvulus* infection.	Live in a region designated by the World Health Organization (WHO) as endemic for *O. volvulus* infection (World Health Organization, 2017).	Addition of the reference for WHO designation of endemicity
Appendix 16.5	Not applicable	Inclusion of Amendment 1	Provision of changes from version 1.0.

Table 10: Details of Non-Administrative Protocol Amendments (Amendment 1)

Section	Original Text	Revised to Read	Rationale for Change
Title: Pages 1, 2 and 4	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	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	As requested by the research ethics committee, the objective of the study was added to the title
Synopsis: Background Section 3.4.3 paragraph 5	….or has ever been exposed to *O. volvulus* infection.	…or has ever been exposed to *O. volvulus* infection, and to exclude those with no evidence of prior systemic exposure to that infection. This is to balance risks in study participation with potential individual benefit from treatment. Pharmacokinetic results are not anticipated to be affected by infection status. Potential adverse events (AEs) associated with effective treatment of onchocerciasis are expected to be manageable and transient.	To provide further explanation regarding the rationale for inclusion of participants with current or risk of infection (based on evidence of prior systemic exposure to the infection)

Section	Original Text	Revised to Read	Rationale for Change
Synopsis: Number of centers,	One	One – School of Public Health, University of Health and Allied Sciences (UHAS) Research Centre, formerly the Onchocerciasis Chemotherapy Research Centre (OCRC) research facility, Volta Region, Ghana	UHAS Research Ethics Committee requested addition of site details
Inclusion criteria (page 5 and Section 6.2)	Live in a region designated by the World Health Organization (WHO) as endemic for *O. volvulus* infection	Live in a region designated by the World Health Organization (WHO) as endemic for *O. volvulus* infection (World Health Organization 2017). Specifically, participants will be recruited from the Kpassa subdistrict of the Nkwanta North district. The specific communities will include Wii, Jagri-Do and Azua, where mass drug administration with ivermectin for onchocerciasis commenced in October 2017.	UHAS Research Ethics Committee requested inclusion of specific information about the region from which participants will be drawn
Exclusion criteria (page 6 and Section 6.3)	Not applicable	17. Is a sibling of another child already enrolled in this study	Addition of an exclusion criterion to ensure no more than one child from a family is enrolled in the study as per UHAS Research Ethics Committee request
Section 5.4 Study Sites	This will be a single center study.	This will be a single center study. The study will be conducted at the School of Public Health, University of Health and Allied Sciences (UHAS) Research Centre, formerly the Onchocerciasis Chemotherapy Research Centre (OCRC) research facility, Volta Region, Ghana	Additional details at the request of the Research Ethics Committee
Section 5.5, paragraph 2	It is anticipated that the total duration of the study will be up to 12 months, including 6 months for recruitment in the event that more than one cohort per age is required	It is anticipated that the total duration of the study will be up to 15 months, including 6 months for recruitment in the event that more than one cohort per age is required and for data analysis and reporting.	For consistency with Section 14.6 and clarification of what study 'duration' includes
Section 12.2 Criteria for Premature Withdrawal from Treatment or the Study	Subjects have the right to withdraw from the study at any time for any reason.	Participation in this study is voluntary. Please see Section 14.1.2 for further details on voluntary participation and informed consent. Subjects also have the right to withdraw from the study at any time for any reason.	UHAS Research Ethics Committee requested inclusion of information about voluntary participation as well as voluntary withdrawal in this section

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.1 Local regulations / Declaration of Helsinki, 2nd paragraph	…and those of applicable regulatory agencies.	…and those of applicable regulatory agencies, including the Ghana Food and Drugs Authority and the US FDA.	Specificity added at the request of the Research Ethics Committee
Section 14.1.2 Informed Consent, 1st paragraph	Information about the study and the written informed consent document must be presented in the language(s) of the potential subject population.	Information about the study and the written informed consent document should be presented in the language(s) of the potential subject population.	Removal of the word “must” as per UHAS Research Ethics Committee feedback
1st paragraph	Not applicable	The IECs responsible for review and approval of these documents include the Research Ethics Committee of the University of Health and Allied Sciences and the Ghana Health Service (GHS) Ethics Review Committee.	Addition of specific details of the three reviewing IECs Specificity added at the request of the
2nd paragraph	If the reviewing IRB or IEC(s) do not otherwise mandate, informed assent must be obtained from all children ≥ 12 years…	If the reviewing IRB or IEC(s) do not otherwise mandate, informed assent should be obtained from all children ≥ 12 years…	Removal of the word “must” as per UHAS Research Ethics Committee feedback
3rd paragraph	The Investigator must also explain that the subject is completely free to refuse to enter the study or to withdraw from it at any time for any reason.	The investigator should also explain that the subject is completely free to refuse to enter the study or to withdraw from it at any time for any reason.	Removal of the word “must” as per UHAS Research Ethics Committee feedback
Section 14.1.5 Institutional Review Boards or Ethics Committees, 1st paragraph	… will be submitted, by the Investigator, to at least one IRB or IEC.	…will be submitted, by the investigator, to the Research Ethics Committee of the University of Health and Allied Sciences, the Ghana Health Service (GHS) Ethics Review Committee and the WHO Ethics Review Committee.	Addition of specific IECs to which the protocol and other materials will be submitted (as requested by UHAS Research Ethics Committee)
Section 14.1.6 Conditions for Modifying the Protocol, 3rd paragraph	All protocol modifications must be submitted to the IRB or IECs in accordance with local requirements and to regulatory bodies as required.	All protocol modifications must be submitted to the IECs (UHAS, GHS and WHO) in accordance with local requirements and to regulatory bodies (Ghana Food and Drugs Authority and US FDA) as required.	Addition of named IEC and regulatory bodies.

Section	Original Text	Revised to Read	Rationale for Change
Model Parent Information Sheet and Consent Form			
General Information, Paragraph 2, Sentence 6	Their care will not be affected by saying no to this study.	Their care will not be affected by saying no to participation in this study.	Additional wording for clarification
General Information, Paragraph 4, dot point 4	Consent to the use of your child's personal and health information as described	Consent to the use of their personal and health information as described	Clarification
What is River Blindness (Oncho)? Paragraph 1, Sentence 2	Two types of worm live in the human body.	Two types of these worms live in the human body.	Correction to clarify meaning
How Do I Know if My Child Can Take Part? Paragraph 2	Not applicable	Not more than one child from your family may be enrolled in this study.	Additional sentence regarding limitation on enrolment per family
Confidentiality, Paragraph 4, sentence 3	This is roughly the "by day" amount paid to laborers in your community which is currently forty (40.00) Ghana Cedis per day.	The amount paid for each night's stay will be roughly the "by day" earnings of individuals in your community, currently forty (40.00) Ghana Cedis per day.	UHAS Research Ethics Committee requested clarification of the compensation to be paid to parents / carers of children in the study.
Consent form	Not applicable	Addition of signature and date panel for child 12 years and over	UHAS Research Ethics Committee requested children 12-17 years also sign the consent form
Model Child Information and Assent Form			
Possible Risks and Discomforts, sentence 2	If you have oncho, you might feel a bit unwell for a few days after you take the medicine.	You might feel a bit unwell for a few days after you take the medicine.	Removal of conditional phrase, as per UHAS Research Ethics Committee request

16.10.2 Rationale for Protocol Amendment No. 2

The GHS Research Ethics Committee in its feedback on review of the study (dated 18 Jul 2019) requested clarifications to the protocol which have resulted in the requirement for this amendment.

Details of sections of the protocol amended are provided in Table 11 and Table 12.

Table 11: Details of Administrative Protocol Amendments (Amendment 2)

Section	Original Text	Revised to Read	Rationale for Change
Throughout document	Not applicable	Correction of minor grammatical and typographical errors. Definition of abbreviations on first use and, where necessary, replacement of the term with the acronym upon second or subsequent use in the document (section headings and tables are the exception). Headings changed to title case.	To improve readability and consistency within the document.
Cover page and footers	Version 1.1 (incorporating Amendment 1) 01 April 2019	Version 1.2 (incorporating Amendments 1 and 2) 13 Aug 2019	Version number and date updated to indicate protocol amendment.
Abbreviations	Not applicable	Addition to the abbreviations table of definitions for abbreviated terms used within the document and removal of any abbreviated terms not used.	To ensure clarity of meaning of abbreviated terms and that all and only those terms used in the document have been included.
Section 3.1 Onchocerciasis	….the WHO and US Food and Drug Administration (FDA) as one of the neglected tropical diseases for which new treatments are sought (The Henry J. Kaiser Family Foundation, 2015).	… the WHO (African Programme for Onchocerciasis Control, 2015) and US FDA (The Henry J. Kaiser Family Foundation 2015) as one of the neglected tropical diseases for which new treatments are sought.	Addition of missing reference.
Section 3.4.3 Design Rationale Paragraph 3	…(identification of an optimal moxidectin dose for children 4 to 12 years of age)…	…(identification of an optimal moxidectin dose for children 4 to 11 years of age)…	Correction of typographical error to ensure consistency of specified age range.
Section 3.4.3 Design Rationale Paragraph 4	(World Health Organization).	(World Health Organization, 2017).	Addition of missing reference.

Section	Original Text	Revised to Read	Rationale for Change
Section 5.3 Cohorts and Dosing Regimens (Methodology)	Not applicable	Not applicable	Relocation of Figure 1 to follow in-text reference to the figure to improve readability.
Appendix 16.5 Model Parent Information and Consent Form Section on Contraception	Not applicable	Not applicable	Relocation of text next to the section on Pregnancy to keep associated topics together to assist understanding
Appendix 16.7.1 Rationale for Protocol Amendment No. 1	Nil New text	Not applicable Not applicable	To improve clarity of amendment details table.
	Not applicable	Table headings changed to captions and hyperlinked cross-references added in text.	To improve consistency and ease navigation within the document.
	Page X	Not applicable	Page references removed for consistency with Table 12.
Section 15 References	Not applicable	Addition to reference list of missing and new references	Revised to ensure completeness, following updates and additions to the text.

Table 12: Details of Non-Administrative Protocol Amendments (Amendment 2)

Section	Original Text	Revised to Read	Rationale for Change
Section 3.4.3 Design Rationale Paragraph 1	There is a large amount of data available in adults and children aged 12 to 17 years of age. Adverse effects associated with moxidectin use were non-serious and manageable (Section 3.3.2.2).	There is a considerable body of data available on the use of moxidectin in humans, including children aged 12 to 17 years of age. Moxidectin was well tolerated at all doses studied. In healthy volunteers, the safety profile was similar to placebo and no treatment-related laboratory or clinical toxicities were identified. In onchocerciasis patients, the nature, incidence and severity of adverse events associated with moxidectin efficacy was similar to ivermectin, and there were no serious adverse events due to efficacy and no treatment-related serious adverse events in any patient.	Text amended for clarity.

Section	Original Text	Revised to Read	Rationale for Change
Section 6.4.1 Contraception Paragraph 2	…a reliable method of birth control…	…a reliable method of birth control (failure rate of less than 1% when used consistently and correctly) in accordance with…	Definition of reliable method of birth control added for clarity.

Section 6.4.1 Contraception Paragraph 3	Not applicable	If no local guidelines exist, WHO guidelines will be used.
		Reliable methods of contraception include:
		• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
		  ○ oral
		  ○ intravaginal
		  ○ transdermal
		• progestogen-only hormonal contraception associated with inhibition of ovulation:
		  ○ oral
		  ○ injectable
		  ○ implantable
		• intrauterine device
		• sexual abstinence
		Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study. The reliability of sexual abstinence needs to be evaluated for each subject on an ongoing basis.
		Counselling and administration of contraceptives will be carried out by the staff of the Family Planning Unit of the Hohoe Municipal Hospital.
			Addition of information regarding reliable contraceptive methods and delivery of family planning services, including the family planning guidelines to be followed.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.3.3 Screening Paragraph 2	Subjects and their carers will be provided with housing at the clinical trial site from Screening for confirmation of eligibility through to Day 7.	As participants will be recruited from villages not proximal to the study center, they and their parents/guardians will be provided with accommodation for the duration of their stay in a newly renovated dormitory-style ward on the campus of the Hohoe Municipal Hospital. The dormitory will have separate rooms for males and females, with registered nurses on duty at all times. It will have comfortable beds with mattresses and sheets, a recreational area with large screen television, and an outdoor space. The participants and parents/guardians will be provided with three meals daily.	Addition of information on the facilities to be provided for participants and their parents/guardians during their stay at the study clinic.
Paragraph 5	Not applicable	If the subject is ineligible for the study, the investigator will discuss the reason for ineligibility with the subject and their parent(s)/guardian(s). If the subject is ineligible to participate in the study due to a clinically significant laboratory abnormality or medical condition, a referral to an appropriate Ghana Health Service (GHS) treatment facility for follow-up will be made. Transport for the subject and their parent(s)/guardian(s) to return to their village will be arranged for the day following Screening.	Addition of procedures to be followed in the event a subject is found to be ineligible for the study.
Section 7.3.5.2 Dosing Paragraph 1	Not applicable	If a subject vomits after taking the dose of moxidectin, the subject will be assessed as described in Section 12.4.	Addition of instruction referencing where to find information on what to do in the event a child vomits soon after taking a dose of study medication.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.4.1 Demographic Data, Medical History, Physical Examination, Vital Signs Paragraph 5	Not applicable	Vital signs will be assessed in association with other signs and symptoms detected upon physical examination for potential clinical significance and determination of study eligibility and AEs. Vital signs normal reference ranges as published in the American Heart Association Pediatric Advanced Life Support Guidelines 2015 and Canadian Paediatric Society Position Statement on Temperature Measurement in Paediatrics 2013 and as summarized in Appendix 16.3 may be used to assist a diagnosis.	Addition of information regarding assessment of vital signs, including provision of normal reference ranges.
Section 7.4.3.2 Safety Laboratory Tests Paragraph 2	Not applicable	Normal reference ranges for clinical chemistry and hematology for Ghanaian children (Dosoo, et al. 2014) will be used in this study. These reference ranges are included in Appendix 16.4 to the protocol and will be available in the SRM.	Addition of information regarding laboratory normal reference ranges to be used for the study.
Section 7.4.3.3 Pharmacokinetic Samples Paragraph 1	… will be sent to the accredited laboratory…	… will be sent to Frontage Laboratories (Exton, Philadelphia, United States of America) …in a fully validated liquid chromatography (LC) with mass spectrometry (MS) LC/MS/MS method used in previous studies.	Addition of details of the bioanalytical laboratory and method of analysis of moxidectin in plasma samples.
Section 8.5.1 Dosage and Administration of Moxidectin Tablets Paragraph 2	Each randomized subject…	Each enrolled subject….	Correction of an inconsistency in the text – study participants will not be randomized.
Section 8.5.2 Dispensing and Accountability Paragraph 3	…or, if approved in writing by the Sponsor, destroyed by the site in a manner pre-approved by the Sponsor in writing as arranged by the PI or their designee, provided such disposition can be performed safely.	….or, if pre-approved in writing by the Sponsor and Ghana Food and Drugs Authority, sent for safe destruction at an approved local facility.	Clarification of requirement for pre-approval by both the Sponsor and Ghana Food and Drugs Authority if study drug is sent for destruction at a local facility.

Section	Original Text	Revised to Read	Rationale for Change
Section 10.2.2Adverse Event Reporting Period Paragraphs 1 & 2	…must be reported… Not applicable	…must be reported to the Sponsor,,… All AEs, including SAEs and deaths, will be reported to the reviewing IECs/IRBs according to their specified timelines.	Clarification of AE reporting requirements.
Section 10.9 Risks for Women of Childbearing Potential or During Pregnancy	…as per local family planning guidelines.	(see Section 6.4.1).	For clarity, information that is covered in another section of the protocol removed and replaced with a cross-reference to the relevant section.
Section 10.10 Procedures to be Followed in the Event of Pregnancy Paragraph 2	Not applicable	…. and a pediatrician will conduct follow-up assessments of the health of the baby up to 2 years of age.	Inclusion of a 2-year follow-up period for a baby conceived during the 6 months of the study, as requested by the GHS Ethics Research Committee.
Section 12.4 Withdrawal of Subjects from the Study Paragraph 3	Not applicable	If a subject vomits up to 30 minutes after taking the dose of moxidectin, all Day 0 assessments should be completed and then the subject should be withdrawn from the study. Any AEs or SAEs still ongoing at the time of withdrawal will be followed in accordance with Section 10.	Addition of information regarding management of participants who may vomit immediately after administration of moxidectin.
Section 14.1.2 Informed Consent Paragraph 4	Not applicable	The anticipated potential risks of participation and the safety profile of moxidectin in adults and children at least 12 years of age with onchocerciasis are described in Sections 3.3.2.2, 3.4.3 and 10.9.	Inclusion of cross reference to additional safety information on moxidectin.
Section 14.1.2.1 Informing Communities about the Study Paragraph 4	3. ….and are presented in chronological order to facilitate comprehension;	3. These are presented in chronological order, and will be supplemented by a schematic diagram to facilitate comprehension and simplify the process for the parents/guardians and subjects;	Clarification and addition of information regarding obtaining informed consent from parents/guardians and subjects, including how study procedures will be explained and understanding confirmed.

Section	Original Text	Revised to Read	Rationale for Change
	Not applicable	4. Understanding of the study procedures will be assessed using a short test consisting of a series of open and closed questions in the local language for parents/guardians and subjects to answer. The questions to be asked are included at the end of the Parent Information Sheet and Consent Form, with space provided for recording responses (refer to Appendix 16.5);	
	Not applicable	7. At each subsequent study visit, the investigator will should verbally confirm the continued consent / assent of the subject and that they are free to withdraw from the study at any time for any reason.	

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.3, Compensation	Not applicable	All study-related costs, including study medication, laboratory tests, and medical care will be provided free of charge. In addition, transportation will be provided to and from the study center, and accommodation and food will be provided for participants and their family/carers while at the study center. If the child is at the study center during school time, a teacher will be employed to provide educational activities and/or oversee homework during their stay to compensate for school time missed. Family/carers who accompany children to the study site to participate will be compensated for loss of earnings according to the number of nights they are required to stay. The amount paid for each night's stay will approximate to "by day" earnings of individuals in the village communities, currently forty (40.00) Ghanaian Cedi per day. In addition, treatment-emergent adverse events occurring during the study will be treated in accordance with local treatment requirements and as clinically indicated without cost.	Addition of a Section describing compensation for study subjects and their family/carers
Section 14.1.5 Institutional Review Boards or Ethics Committees Paragraph 1	Approval from the committee….	Approval from all three ethics committees	Clarification that approval will be sought from three Research Ethics Committees and removal of text which is duplicated in the following section
Paragraph 2	Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the Investigator to the committee in accordance with institutional procedures and regulatory requirements.	Not applicable (text deleted)	

Section	Original Text	Revised to Read	Rationale for Change
Section 14.2.1 Investigator Files and Retention of Documents Paragraph 3	…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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.	… for at least 25 years after the end of the clinical trial.	Revision of requirement for essential document retention, per Ghana Food and Drug Authority requirements.
Appendix 16.3 Vital Signs Reference Values for Children	Not applicable	Addition of new appendix, Vital Signs Reference Values for Children	Inclusion of reference values for use for interpretation of vital signs.
Appendix 16.4 Laboratory Reference Values for Ghanaian Children	Not applicable	Addition of new appendix, Laboratory Reference Values for Ghanaian Children	Inclusion of reference values for use by the local safety laboratory.
Model Patient Information Sheet and Consent Form			
Throughout document	Not applicable	Not applicable	Simplification of words and phrases to assist in understanding of what will happen in the study
General Information About the Research Last paragraph	Not applicable	You will also be given information cards that will tell you when and where your child will be given treatment and have tests done.	Additional description of information cards explaining study visits and tests to be provided to parents.
Screening Paragraph 1	Not applicable	… (see information on contraception and pregnancy below) …	Additional text regarding location of information on contraception.
Paragraph 2	You and your child will be transported back to your village.	If treatment is needed, the study doctor will arrange for your child to visit a Ghana Health Service treatment facility for follow-up. You and your child will be transported back to your village the next day after screening.	Addition of information regarding provision of follow-up treatment, if needed, and timing of return to the village in the event a child is determined to be ineligible for the study.
Days 1, 2, 3, and 7	Not applicable.	In addition, if at any time your child is not feeling well or has a problem, you should tell the study doctor or nurse immediately.	Inclusion of advice to parents to tell study team members if a child is not feeling well.

Section	Original Text	Revised to Read	Rationale for Change
	Not applicable	The study team will try to time this long clinic stay during school holidays, but if it happens during school time, a teacher will be employed to provide educational activities for your child during their stay.	Inclusion of a description for parents about the steps taken to limit the effects of their child missing classes.
Side effects associated with moxidectin treatment	Catarrh	Catarrh (mucus in the nose and throat)	Addition of an explanation of the medical term.
Pregnancy Paragraph 1	A test will also be done 3 more times during the study (on Day 28, Week 12 and at Week 24)....the study doctor will follow the pregnancy until the birth of the baby to check if it is healthy.	She must use reliable contraception while she is on the study (see the section on contraception below). A pregnancy test will also be done 3 more times during the study (on Day 28, Week 12 and at Week 24)……The health of the baby will be checked at birth and until it is 2 years old. These checks will be carried out by a doctor who specializes in treating babies and children.	Expansion of the section on pregnancy to include reference to contraception and describe the follow up procedures for a child until 2 years in the event of a pregnancy occurring during the study.
Paragraph 2	Not applicable	If your child is male and fathers a child while participating in the research study, the study doctor should also be informed and they will ask for consent to follow up the baby.	Expansion to the section on pregnancy to request notification to the study team should a male participant father a child.
Contraception	If your daughter is able to become pregnant she will be asked to commit to using reliable contraception from Screening and for 6 months after taking the study medication. You and your daughter should discuss methods of reliable contraception with the study doctor. If she does become pregnant whilst participating in the research study, the study doctor should be informed immediately.	If your daughter is able to become pregnant she will be asked to commit to using reliable contraception (which may be that she does not have sex at all) from Screening and for 6 months after taking the study medication. The study family planning nurse will discuss methods of reliable contraception with you and your daughter and, if you agree, will give contraceptives to your daughter. If your daughter does become pregnant while she is in the research study, the study doctor should be informed immediately.	For clarity, text moved to follow section on pregnancy and information added regarding abstinence as a reliable method of contraception.

Section	Original Text	Revised to Read	Rationale for Change
	If your son fathers a child while participating in the research study, the study doctor should be informed. Consent to follow-up on the health of the baby at birth will be requested.	Not applicable (text deleted)	For clarity, text moved to section on pregnancy.
Medicines	Any other medicine or treatments they are prescribed or take, including vaccines, vitamins, herbal supplements or traditional remedies must be reported to the study team for inclusion in their study records	Any other medicine or treatments they are given, including vaccines, contraceptives, vitamins, herbal supplements or traditional remedies must be reported to the study team so that they can be recorded in their study records.	Simplification of text for clarity.
Privacy (Confidentiality) Paragraph 4	Not applicable	If reports are written or talks given about this research, they will only discuss group results. They will not use your child's name or any other personal information that could identify them.	Additional text included to explain how the subject's confidentiality will be protected.
Costs and Compensation Paragraph 1	There is no cost to you for your child to take part in this research study.	You will not pay any money for your child to take part in this research study… …In addition, if your child is at the study center during school time, there will be a teacher at the center who will help your child going with some of their school work during their stay, to help make up for the school time they miss.	Clarification and addition of text explaining compensation for missed work and school hours as a result of participation in the study.
Contacts for Additional Information	The Chairman Ghana Health Service Ethics Review Committee phone line at (+233 302 681 109) or write to The Chairman ….	The Administrative Secretary of the Ghana Health Service Ethics Review Committee by telephone +233 302 681 109 or write to The Administrative Secretary….	Amendment of contact details for GHS ERC Chair to GHS Administrator details.
Assessment of Informed Consent Questions	Not applicable	Reformatting of table to facilitate recording both Yes/No answers and free text. Addition of one question: 'Do you understand that this is a research study and not treatment?'	Proposed additional question at Principal Investigator's request and amended formatting to facilitate collection of response information.

Section	Original Text	Revised to Read	Rationale for Change
Model Child Information and Assent Form			
What Will Happen at the Study Visits? Paragraph 1	General Information … If you have, you will go by car with a parent or other adult from your village to the study clinic in Hohoe to stay for between 9 and 14 days.	What Will Happen at the Study Visits? …. If you have had the worms, and you still agree, you will go by car with a parent or other adult from your village to the study clinic in Hohoe. You will have to stay there for between 9 and 14 days. … This will include taking blood from your arm with a needle to test that you are well. We can use a special cream to numb your skin so you won't feel the needle prick. You will be weighed and measured and special equipment will be used to check how fast your heart is beating and if it is healthy, to measure your blood pressure and breathing are normal and that you don't have a fever.	Section heading revised and more specific description of study procedures in simple language added to assist understanding by children during the assent process.
Paragraph 2	You will be asked to swallow a dose of the medicine (up to 4 moxidectin tablets) with water. You will have some blood taken to measure how much medicine is in your body	After you have had dinner that night, you will not be able to eat any more food until after you have taken the study medicine. The next day, before you eat any breakfast, you will be asked to swallow up to 4 moxidectin tablets with water. You will have some more blood taken from your arm using a special needle that can stay in your arm for the whole day so that 4 more blood samples can be taken without needing another needle prick. This blood will be used to measure how much study medicine is in your body since taking the tablets. Two hours after you took the medicine, you will be given breakfast.	
Paragraph 3	Not applicable	You should also tell the doctors and nurses if you don't feel well or have had any problems. The day after you took the medicine and on day 3 and day 7 before you go home, you will also be asked to give samples of blood.	

Section	Original Text	Revised to Read	Rationale for Change
What Will Happen at the Study Visits? Paragraph 4	Not applicable	… and, except for the last visit, to take a sample of blood. These visits will happen at around week 2, 4, 12 and 24 after you took the dose of medicine.	Addition of text describing which of the 4 visits to the clinic after the initial stay will involve taking a sample of blood.
Possible Risks and Discomforts Paragraph 2	Not applicable	You may also miss some school while you are at the clinic. However, there will be a teacher to help you keep going with your schoolwork while you stay at the clinic.	Addition of text on what will happen to make up for school time lost when participating in the study.

16.10.3 Rationale for Protocol Amendment No. 3

The World Health Organization Responsible Officer, in her feedback on review of Version 1.2, requested:

1) clarifications to the protocol text, as well as minor modifications (updates relating to the implementation of ivermectin mass treatment programs in the recruitment area, references, grammar and customization of standard phrasing/terms to this study); and
2) simplification, addition of pictures, provision of context (ivermectin mass drug administration in the communities from which participants will be recruited, previous conduct of a moxidectin study with participants aged ≥12 years from these communities whom parents/guardians can contact about their experience) and improved targeting of the Model Information documents for different audiences (adolescents aged 12-17 years and their parents, parents of children aged 4 to 11 years, children aged 7 to 11 years and children aged 4 to 6 years or older children not considered mature enough to provide assent).

In response to these requests, the protocol has been amended. This amendment also afforded the opportunity to make administrative changes to improve document consistency and readability (e.g. corrections to formatting, grammar and use of abbreviations, and elimination of duplicated information and information not relevant for this study) and to update the information on the population pharmacokinetic modelling.

Details of sections of the protocol amended are provided in Table 13 and Table 14.

Table 13: Details of Administrative Protocol Amendments (Amendment 3)

Section	Original Text	Revised to Read	Rationale for Change
Throughout	Not applicable	Not applicable	Correction of grammatical and/or typographical errors. Definition of abbreviations on first use and replacement of the term with the acronym upon subsequent use in the document. Addition of cross references to facilitate document navigation. Removal of terms not used by applicable Ethics Committees (e.g. IRB, IEC). Adjustment of standard terminology to this study (e.g. reference to final or last dose) Addition, deletion or correction of literature references.

Section	Original Text	Revised to Read	Rationale for Change
Throughout	'Clinic' or 'study clinic' or 'in-clinic'/'inpatient'	Research center or center or in-center	Clearly differentiate between Ghana Health Service clinics and the research center.
	6 months	Approximately 6 months (Week 24)	Clarify that last follow up visit at Week 24 is only approximately 6 months after study drug.
	Informed consent Informed consent and assent Consent forms [or similar wording]	Informed consent and assent Informed consent and child assent / lack of 'deliberate objection' Consent/assent [or similar wording]	Clarify that informed consent by the parents/guardians and assent by the child is required for child participation in the study. Clarify that children too young or immature to provide assent will be informed about the study for evaluation of expression of 'deliberate objection' as per commentary to CIOMS Guideline 17. Note that for reasons of readability, 'assent' is used to refer to both obtaining assent and evaluation for expression of 'deliberate objection'.
Cover page, Study Acknowledgement and footers	Version 1.2 (incorporating Amendments 1 and 2) 13 Aug 2019	Version 2 (incorporating Amendments 1, 2 and 3) 27 Nov 2019	Version number and date updated to indicate protocol amendment.

Section	Original Text	Revised to Read	Rationale for Change
Cover page Confidentiality Statement	The information contained in this document, particularly unpublished data, is the property of, or under the control of Medicines Development for Global Health and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The information is only to be used by you in connection with authorized clinical studies of the investigational product described in the protocol. You will not disclose any of the information to others without written authorization from Medicines Development for Global Health, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.	Until publication of this protocol following approval by applicable Regulatory Authorities and Ethics Committees, any unpublished information contained in this document is the property of, or under the control of Medicines Development for Global Health and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and any applicable Regulatory Authority or Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational product described in the protocol. Prior to publication, you will not disclose any of the information to others without written authorization from Medicines Development for Global Health, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.	Adjusted for the fact that Medicines Development for Global Health is a not-for-profit organization and that the protocol will be published following all required ethics committee and regulatory approvals.
Synopsis, Inclusion Criteria Section 6.2, Inclusion Criteria	4. Provision of parental or guardian written informed consent and assent as appropriate 5. Females of childbearing potential must commit to using a reliable method of contraception as per local family planning guidelines from Screening until 6 months after treatment with study drug;	4. Provision of parental or guardian written informed consent and child assent / lack of expression of 'deliberate objection' (as appropriate for age) 5. Females of childbearing potential must commit to using a highly effective method of contraception as per local family planning guidelines from Baseline (pre-treatment on Day 0) until approximately 6 months (Week 24) after treatment with study drug;	Clarification of text relating to age appropriate assent, including in children too young to give assent. Clarification of timing of required contraceptive coverage.

Section	Original Text	Revised to Read	Rationale for Change
Synopsis, Exclusion Criteria Section 6.3 Exclusion Criteria	Synopsis: 3. Has received an investigational product within 28 days or 5 half-lives of Screening, whichever is longer; 4. Has received ivermectin or any other anti-helminthic treatments within 28 days of Screening; 5. Has received a vaccination within 7 days of Screening; 8. Unable to swallow tablets; Section 6.2: 4. Has received ivermectin or any other anti-helminthic treatments within 28 days of Screening; 5. Has received a vaccination within 7 days of Screening; 8. Unable to swallow tablets;	Both: 3. Has received an investigational product within 28 days or 5 half-lives of Baseline, whichever is longer; 4. Has received ivermectin or any other anti-helminthic treatments within 28 days of Baseline; 5. Has received a vaccination within 7 days of Baseline; 8. Unable to swallow tablets (flat oval, 8.0 millimeters (mm) x 4.5 mm x 3.0 mm);	Clarification of reference time point. Addition of tablet size to avoid misconception of the extent to which this exclusion criterion will impact study eligibility of small children.
Synopsis, Design Details and Dose Regimens	Cohort II: (8 to 11 years, n = 9) will receive moxidectin 8 mg (4 x 2 mg tablets) with adjustment as required based on pharmacokinetic outcomes For Cohorts II and III, if at least 3 of the subjects have moxidectin exposures below or above the target range, a revised dose will be determined in increments/decrements of 2 mg (maximum dose 8 mg) and the Cohort will be repeated with at least 9 new subjects enrolled at the new dose.	Cohort II: (8 to 11 years, n = 9) will receive moxidectin 8 mg (4 x 2 mg tablets). If for Cohorts II and III, the starting dose results in at least 3 of the subjects having moxidectin exposures above the target range, a revised dose will be determined in decrements of 2 mg and the Cohort will be repeated with at least 9 new subjects enrolled at the new dose. If for Cohort III, the starting dose results in at least 3 subjects having moxidectin exposures below the target range, a revised dose will be determined in increments of 2 mg to a maximum dose of 8 mg.	Clarification that this adjustment will apply to the first dose level. Clarification that for Cohort II there will be no dose increment, while for Cohort III there may be either a dose increment or decrement.
Synopsis, Study Procedures	Consent to participate will be conducted in the village setting and may be obtained up to 30 days prior to Screening. After obtaining written informed consent from the parent(s)/guardian(s) and assent from the child as appropriate (see Section 14.1.2 for details) the child will be tested for OV16 IgG4 antibody. Children with a positive test result and their parent, guardian or another trusted adult from the village assigned by the parent or guardian will be invited to attend the clinic for further Screening.	Consent and assent (lack of expression of 'deliberate objection', as appropriate for age) will be obtained in the village setting and may be obtained up to 30 days prior to Baseline. After obtaining written informed consent from the parent(s)/guardian(s) and assent (or determining lack of expression of 'deliberate objection') from the child (see Section 14.1.2 for details) the child will be tested for OV16 IgG4 antibody. Children with a positive test result and meeting other eligibility criteria evaluated in the village, together with one parent or guardian, will be invited to attend the research center in Hohoe for further Screening.	Clarification that assent will be sought from or a determination of lack of expression of 'deliberate objection' made for all children. Clarification that eligibility criteria other than OV16 IgG4 antibody can be evaluated in the village. Clarification that one parent or guardian will accompany all children to the research center in Hohoe.

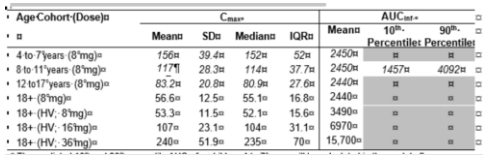
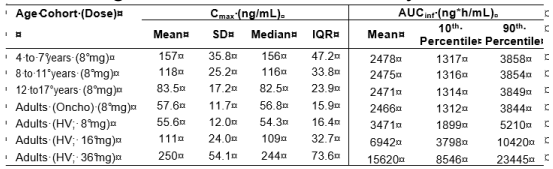
Section	Original Text	Revised to Read	Rationale for Change
Synopsis, Contraindications to Further Dosing	As all subjects will receive a single dose only, there are no contraindications to further dosing of individuals who receive treatment. Recruitment of additional subjects in the study will be guided by the DSMB.	Not applicable on an individual subject basis as all subjects will receive a single dose only. Dosing of additional subjects in the study will be guided by the DSMB.	Clarification of text.
Synopsis, Data and Safety Monitoring Board	A DSMB of independent experts will be established prior to recruitment start, with a charter that defines in detail its roles and responsibilities. The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II.	A DSMB of independent experts has been established, with a charter that defines in detail its roles and responsibilities. The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II and advise the sponsor on the dose with which Cohort III will be initiated.	Resolution of discrepancy between synopsis and body of protocol.
Synopsis, Special Protocol Requirements or Issues:	The study will be conducted in an area(s) endemic for *O. volvulus* and currently participating in or planned for implementation of ivermectin treatment. The study will be conducted in communities familiar with clinical research. This will facilitate understanding of the process and enable parents, as well as children, to provide appropriate informed consent for study participation. Villages in the Volta region of Ghana already involved in onchocerciasis research have been identified as suitable locations from which to enroll subjects	The study will be conducted in an area(s) endemic for *O. volvulus* and currently participating in implementation of ivermectin treatment The study will recruit subjects in communities in the Volta Region of Ghana familiar with clinical research and the research center in Hohoe where the in-center period of the study will be conducted, since participants in the Phase III study of moxidectin were recruited from these communities. This will facilitate understanding of the study and enable parents/guardians, as well as children, to provide appropriate informed consent and assent for study participation.	Update to current status of ivermectin treatment implementation in the study area. Clarification of reasons for community familiarity with clinical research.
Table 1, Table of Assessments	Not applicable	Addition of Baseline definition to Day 0 pre-dose heading and footnote. Addition of inclusion/exclusion criteria to Pre-screening assessments. Addition of footnotes to clarify that pregnancy testing is not required at unscheduled visits unless clinically indicated. Removal of redundant footnote regarding collection of pre-dose pharmacokinetic blood sample (table only specifies sample collection at Screening).	Clarification of requirements for and timing of study assessments.
Abbreviations	Not applicable	Addition of definitions for abbreviated terms used within the document and correction of one term.	To ensure clarity of meaning of abbreviated terms.

Section	Original Text	Revised to Read	Rationale for Change
Section 3.1 Onchocerciasis	Onchocerciasis is endemic in sub-Saharan Africa. Recent surveys indicate that the number of infected people in the African region is approximately 16 million (Zoure et al., 2014) and more than 200 million people are still considered to be at risk of infection (World Health Organization, 2018).	Onchocerciasis is endemic in sub-Saharan Africa (Zoure et al., 2014), More than 200 million people are considered to be at risk of infection (World Health Organization, 2018).	Correction of text attributable to the cited references. Data in Zoure *et al*. 2014 do not cover all of Africa and with onchocerciasis elimination now targeted, the number infected is not a critical measure of medical need.
	Onchocerciasis Control Program (a WHO/United Nations collaboration that ran from 1974 to 2002)	Onchocerciasis Control Program (a WHO-managed international collaboration that ran from 1974 to 2002)	Correction of information on Onchocerciasis Control Program.
	The larvae develop into mature adult worms (macrofilariae) and become encapsulated in skin nodules, from which they release millions of microfilariae that migrate through the skin and eyes, a critical step in the cycle of reinfection and disease perpetuation.	The larvae develop into mature adult worms (macrofilariae) and become encapsulated in nodules, from which they release millions of microfilariae that migrate through the skin and eyes, a critical step in the cycle of reinfection and disease perpetuation.	Clarification that nodules are not only palpable skin nodules but can be deep in the body
Section 3.2 Current Treatment and Unmet Need	In international programs, the most commonly used retreatment interval is 12 months. The aim of these international, community-directed ivermectin treatment programs is to achieve control in affected communities and, ultimately, to work towards elimination of onchocerciasis in areas currently assessed as meso- or hyper-endemic for O. volvulus infection (Uniting to Combat Neglected Tropical Diseases, 2012) 15 of 24 (62.5%) ivermectin treated subjects did not achieve zero skin microfilariae density at any time point (Month 1, Month 6, Month 12 and/or Month 18) compared with 1 of 53 (1.9%) moxidectin treated subjects.	In Africa, the most commonly used retreatment interval is during mass drug administration is 12 months. The aim of these community-directed ivermectin treatment programs is to achieve control of the disease as a public health problem in affected communities (Uniting to Combat Neglected Tropical Diseases 2012). Ultimately, the WHO and onchocerciasis endemic countries are working towards elimination of onchocerciasis where feasible Fifteen (15) of 24 (62.5%) ivermectin treated adolescents did not achieve zero skin microfilariae density at any time point (Month 1, Month 6, Month 12 and/or Month 18) compared with 1 of 53 (1.9%) moxidectin treated adolescents.	Clarification that information provided applies to Africa. Correction of text attributable to the cited reference. Clarification that numbers refer to adolescents.
Section 3.3.1.2.3 Juvenile Nonclinical Safety	There were no unscheduled deaths and clinical observations	There were no deaths and clinical observations	Clarification of text.

Section	Original Text	Revised to Read	Rationale for Change
Section 3.4.1 Study Rationale (Study Goals and Objectives)	Therefore, the purpose of this study is to determine an optimal pediatric dose of moxidectin for use in children with onchocerciasis aged 4 to 11 years. This will allow the use of moxidectin across the community affected by this disease.	Therefore, the purpose of this study is to determine an optimal pediatric dose of moxidectin for use in children with onchocerciasis aged 4 to 11 years to achieve exposure in the range observed in adults administered a dose of 8 mg. This will allow the use of moxidectin across the communities affected by this disease, including in mass drug administration programs for onchocerciasis control and elimination.	Clarification of study goals.
Section 3.4.3 Design Rationale	In the absence of skin snip assessments to confirm infection with O. volvulus, the study will recruit children from an area designated as endemic for O. volvulus infection and targeted for ivermectin treatment implementation.	In the absence of skin snip assessments to confirm infection with O. volvulus, the study will recruit children from an area designated as endemic for O. volvulus infection and undergoing ivermectin mass drug administration.	Update to current status of ivermectin mass drug administration.
	Specifically, subjects will be recruited from communities located in the Nkwanta district, northern Volta region, Ghana, an area assessed in 2017 as endemic for onchocerciasis by the Expanded Special Project for Elimination of Neglected Tropical Diseases and the WHO (World Health Organization 2017). In recognition of the risk of onchocerciasis in this region, community-directed treatment with ivermectin commenced in October 2017 with ongoing 6-monthly rounds of treatment planned.	Specifically, subjects will be recruited from communities located in the Nkwanta district, northern Volta region, Ghana, an area assessed as endemic for onchocerciasis by WHO (World Health Organization 2019). In recognition of the prevalence of onchocerciasis in this region, community-directed treatment with ivermectin commenced in October 2017 with ongoing 6-monthly rounds of treatment planned.	Correction of timing of endemicity assessment and date of reference. Elimination of reference to the Expanded Special Project for Elimination of Neglected Tropical Diseases since endemicity assessment pre-dates the creation of that project. Clarification that infection prevalence drives implementation of ivermectin community directed treatment.
	Potential AEs associated with effective treatment of onchocerciasis are expected to be manageable and transient	Potential AEs associated with effective treatment of onchocerciasis are expected to be manageable and transient based on the prior experience in the Phase II and Phase III study.	Clarification of basis for expectation that AEs will be manageable and transient.
	This assessment, and associated sample collection activities through the study, represent medical experiences commensurate with community experience in areas where onchocerciasis clinical investigations and/or surveillance programs have been implemented.	Since the Phase III study was recruited from the villages from which the participants for this study will be recruited, a number of members of these communities will be familiar with clinical studies and biological sample collection.	Clarification of source of familiarity with clinical investigations and sample collections

Section	Original Text	Revised to Read	Rationale for Change
Section 3.4.3 Design Rationale	Protocol MDGH-MOX-1006 is specifically designed to yield vital knowledge about onchocerciasis treatment in the 4- to 17-year-old age group, and the participating communities more generally. It is likely that at least some study participants will be actively infected with O. volvulus and, as such, moxidectin treatment would potentially be of benefit in these patients.	Protocol MDGH-MOX-1006 is specifically designed to determine the appropriate dose of moxidectin for onchocerciasis treatment in the 4- to 11-year-old age group. The inclusion of adolescents 12 to 17 years will provide additional pharmacokinetic data for inclusion in the population pharmacokinetic model used to predict drug exposures across all age groups and to support dose selection for children aged 4 to 11 years. All enrolled children will have confirmed exposure to O. volvulus. Some study participants may have skin microfilariae and moxidectin treatment will be of benefit to these individuals.	Clarification of design rationale.
	However, in recognition of the study involving a minor increase over minimal risk to children without known direct benefit to individual subjects (i.e. without confirmation of O. volvulus microfilarial burden pre-treatment), the Sponsor has engaged with investigators and communities and plans to consult with local, regional and independent (WHO) ethics committees prior to study conduct, and with consideration to the conduct of the study under IND 126876 and the requirements of the United States (US) Code of Federal Regulations, including Title 21 Sections 50.52, 50.53 and 50.55.	In recognition that the study involves a minor increase over minimal risk to children without known direct benefit to individual subjects (i.e. without confirmation of O. volvulus microfilarial burden pre-treatment), the Sponsor points to (1) engagement with the investigator, (2) confirmation that the study design is acceptable based on protocol review by local and regional independent experts on the DSMB, (3) protocol amendments based on the local (UHAS), country (Ghana Health Service (GHS)) and independent (WHO) ethics committee review and (4) protocol amendment following Ghana Food and Drugs Administration review prior to study conduct. The study is also being conducted under United States Food and Drug Administration IND 126876 and in accordance with the requirements of the United States (US) Code of Federal Regulations, including Title 21 Sections 50.52, 50.53 and 50.55.	Addition of information regarding protocol review by DSMB members and the Ghana Food and Drugs Administration.

Section	Original Text	Revised to Read	Rationale for Change
Section 3.4.4.1 Nonclinical Dose Rationale	In a neurofunctional and pulmonary study in male rats, the NOAEL was 5 mg/kg, with corresponding C_{max} of 1116 ng/mL, which was above the previously measured C_{max} in adults and predicted C_{max} to be reached in the pediatric study. Additionally, daily parental oral administration of dietary moxidectin to rats prior to mating, and through mating, gestation, and lactation was associated with decreased survival and body weights for first-generation offspring without maternal toxicity at moxidectin doses less than 2 times the recommended human dose based on body surface area comparison. However, daily dietary moxidectin did not produce maternal toxicity or adverse effects for first- and second-generation offspring at doses approximately equivalent to the recommended human dose based on body surface area comparison.	In a neurofunctional and pulmonary study in male rats, the NOAEL was 5 mg/kg, with corresponding C_{max} of 1116 ng/mL, which was above the previously measured C_{max} in adults and predicted C_{max} to be reached in the pediatric study if all age groups received a dose of 8 mg (Table 4). Daily parental oral administration of dietary moxidectin to rats for 70 days prior to mating, and through mating, gestation, and lactation was associated with decreased survival and body weights for first-generation offspring without maternal toxicity at moxidectin doses less than approximately 1.3 times the recommended human dose based on body surface area comparison (>1.1 mg/kg/day). However, daily dietary moxidectin did not produce maternal toxicity or adverse effects for first- and second-generation offspring at doses approximately equivalent to the recommended human dose based on body surface area comparison (0.82 mg/kg/day).	Clarification of text, including doses administered in maternal dosing studies.
	Specifically, the simulation model predicted that adolescents 12 to 17 years receiving 8 mg of moxidectin may achieve similar exposures (AUC) to adults receiving 8 mg, with a higher C_{max} (median 81 nanograms (ng) /mL vs. 55 ng/mL in adults). For children aged 8 to 11 years, exposures are also predicted to be similar to adults, while median C_{max} is predicted to be 114 ng/mL (maximum 228 ng/mL). This is well within the safety margins of moxidectin in humans; in adults, moxidectin has been studied up to a median C_{max} of 235 ng/mL and a maximum of 438 ng/mL. The full pharmacokinetic report has been provided for reference (see Appendix 16.2).	Specifically, the simulation model predicted that adolescents 12 to 17 years receiving 8 mg of moxidectin may achieve similar exposures (AUC) to adults receiving 8 mg, with a higher C_{max} (median 83.5 nanograms (ng) /mL vs. 56.6 ng/mL in adults). For children aged 8 to 11 years (as well as children 4 to 7 years), exposures are also predicted to be similar to adults, while median C_{max} is predicted to be 116 ng/mL (maximum 214 ng/mL). This is well within the safety margins of moxidectin in humans; in adults, moxidectin has been studied up to a median C_{max} of 244 ng/mL and a maximum of 473 ng/mL. The full pharmacokinetic report has been provided for reference (see Appendix 16.2).	Update of text to reflect modelling, including data from an additional PK study in adults.

Section	Original Text	Revised to Read	Rationale for Change
Table 4	Title: Summaries of Simulated Cmax (ng/mL) and AUC inf (ng*h/mL) for Children 4-11 years (8 mg), Adolescents 12 to 17 years (8 mg), Adults (8 mg) and Results for Healthy Volunteers (8 mg, 16 mg, 36 mg) in Clinical Studies  Footnote: * The predicted 10th and 90th percentile AUCinf for children 4 to 7 years will be calculated in the model after pharmacokinetic data for children 8 to 11 years and adolescents 12 to 17 years are updated in the model (see Section 13.5.3). Italicized values represent simulations. HV = healthy volunteers, IQR = interquartile range, AUCinf = AUC from time 0 extrapolated to infinity, SD = Standard Deviation.	Title: Summaries of C_{max} and AUC inf for Children 4 to 11 years (8 mg), Adolescents 12 to 17 years (8 mg), and Adult O. volvulus-infected Individuals and Healthy Volunteers (8 mg, 16 mg, 36 mg) Emerging from the Population Pharmacokinetic Model Used to Determine the Starting Dose for Children 8 to 11 years  Footnote: * The mean predicted and 10th and 90th percentile AUC_{inf} for children 4 to 7 years will be re-estimated after pharmacokinetic data for children 8 to 11 years and adolescents 12 to 17 years are available to update the model as a basis for determining the first dose for children 4 to 7 years to be proposed to the DSMB (see Section 13.5.3). Adults = 18+ years, Oncho = *O. volvulus* infected, HV = healthy volunteers, IQR = interquartile range, AUC_{inf} = AUC from time 0 extrapolated to infinity, SD = Standard Deviation	Modification of title of data table to aid interpretation. Update of data to take into consideration recent update of the model to include data from an additional PK study. Inclusion of 10th and 90th percentiles for all age/dose groups to facilitate comparison of exposure estimates for children 8 to 11 years of age receiving an 8 mg dose (first dose level planned) with exposure estimates based on measured PK data in adults. Adjustment of footnote to the updated table.
Section 5.3 Cohorts and Dosing Regimens (Methodology)	A sentinel group of three subjects will be enrolled in Cohort II. If safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled.	A sentinel group of three subjects will be enrolled in Cohort II. If the investigator considers, based on their experience with onchocerciasis treatments, that safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled. If safety concerns arise in the sentinel group, the DSMB will review the data and make a recommendation to continue dosing as planned, or to modify or stop dosing.	Clarification of process for assessment of safety in the sentinel group in Cohort II. Clarification of requirements for Cohort III dose level selection and initiation.
	If 3 or more of the 9 subjects in Cohort II have moxidectin exposures above the target range, defined as AUCs to Day 28 greater than the predicted 90th percentile mean AUC (see Table 4), a reduced dose of moxidectin will be selected for additional dosing of Cohort II subjects. The new dose will be in increments or decrements of 2 mg, reflecting the 2 mg moxidectin tablet format used in the study	If 3 or more of the 9 subjects in Cohort II have moxidectin exposures above the target range, defined as AUCs to Day 28 greater than the predicted 90th percentile mean AUC (see Table 4), a reduced dose of moxidectin will be selected for dosing of additional subjects in the Cohort II age range. The new dose will be in decrements of 2 mg, reflecting the 2 mg moxidectin tablet format used in the study.	Clarification that additional subjects in the Cohort II age range may be dosed and that dosing will be adjusted in decrements of 2 mg from the starting dose of 8 mg.

Section	Original Text	Revised to Read	Rationale for Change
Section 5.3 Cohorts and Dosing Regimens (Methodology)	Upon successful completion of Cohort II and selection of a dose based on pharmacokinetic modelling with inclusion of Cohort I and II data, and consideration of all predicted pharmacokinetic parameters, Cohort III will be enrolled. For Cohort III (n = 9, subjects aged 4 to 7 years, inclusive), a single oral dose of moxidectin will be at a dose to be determined by the population pharmacokinetics model but not exceeding 8 mg.	Upon successful completion of Cohort II and selection of a starting dose for Cohort III based on pharmacokinetic modelling with inclusion of Cohort I and II data and consideration of all predicted pharmacokinetic parameters, and DSMB recommendation (see Section 11), Cohort III will be enrolled. Cohort III (n = 9, subjects aged 4 to 7 years, inclusive) will receive a single oral dose of moxidectin at the recommended dose level.	Clarification that the DSMB will be involved in selection of the starting dose for Cohort III.
	Initially, a sentinel group of 3 subjects will be enrolled. If safety up to and including Day 3 in these subjects is acceptable, the additional 6 subjects will be enrolled.	Initially, a sentinel group of 3 subjects will be enrolled. If safety up to and including Day 3 in these subjects is considered acceptable, based on the investigator's experience with onchocerciasis treatments, the additional 6 subjects will be enrolled. If safety concerns arise in the sentinel group, the DSMB will review the data and make a recommendation to continue dosing as planned, or to modify or stop dosing.	Clarification of criteria for assessing safety in the sentinal group
	Once all Cohort III subjects complete Day 28, a safety and pharmacokinetic data review will be performed by the DSMB. If 3 or more of the 9 Cohort III subjects have moxidectin exposures to Day 28 below or above the target range, defined as AUCs less than the 10th percentile or greater than the 90th percentile mean AUC predicted by the population pharmacokinetic model, a revised dose of moxidectin will be determined in increments of 2 mg (maximum dose 8 mg) and Cohort III will be repeated with at least 9 new subjects enrolled at the new dose.	Once all Cohort III subjects complete Day 28, a safety and pharmacokinetic data review will be performed by the DSMB. If 3 or more of the 9 Cohort III subjects have moxidectin exposures to Day 28 below or above the target range, defined as AUCs less than the 10th percentile or greater than the 90th percentile mean AUC predicted by the population pharmacokinetic model, a revised dose of moxidectin will be determined in increments or decrements of 2 mg (maximum dose 8 mg) and Cohort III will be repeated with at least 9 new subjects enrolled at the new dose.	Clarification that if a second group of children in the Cohort III age range is enrolled, the dose may be an increment or a decrement.
	Subsequent to the enrolment of the initial group of 3 subjects in each of Cohort II and Cohort III, additional subjects will be enrolled in groups of at least 3. This is for operational and social reasons	Subsequent to the enrolment of the initial group of 3 subjects in each of Cohort II and Cohort III, additional subjects will be enrolled in groups of at least 3. This is for operational and social reasons (to ensure subjects have other children to spend their time with while in the research center so they don't feel lonely because).	Clarification of social reasons for enrolling additional subjects in groups.

Section	Original Text	Revised to Read	Rationale for Change
Section 5.4 Study Sites (Study Areas)	This will be a single center study. The study will be conducted at the School of Public Health, UHAS Research Centre, formerly the OCRC research facility, Volta Region, Ghana.	This will be a single center study. The study will be conducted at the School of Public Health, UHAS Research Centre, formerly the OCRC research facility, Volta Region, Ghana, which was the site for the Phase II and Phase III studies of moxidectin. The Investigator was a co-investigator on the Phase II study and the principal investigator on the Phase III study and thus has substantial experience with moxidectin.	Inclusion of rationale for site and investigator selection.
Section 5.5 Estimated Duration of the Study	The on-study period per subject is approximately 28 weeks total: up to 30 days for consent, including up to 7 days Screening (in-clinic) prior to Baseline, 7 days in clinic stay and 23 weeks outpatient follow -up post-treatment. It is anticipated that the total duration of the study will be up to 15 months, including 6 months for recruitment in the event that more than one cohort per age is required and for data analysis and reporting.	The on-study period per subject is approximately 28 weeks in total: up to 30 days for Pre-screening (including consent/assent) and Screening (including up to 7 days in the research center for Screening) prior to Baseline (pre-treatment on Day 0) and 7 days stay in the research center and 23 weeks outpatient follow-up post-treatment. It is anticipated that the total duration of the study will be up to 15 months, including 6 months for recruitment in the event that more than one cohort per age group is required and for data analysis and reporting.	Clarification of study phases and timelines. Clarification that cohorts are defined by age group, not age.

Section	Original Text	Revised to Read	Rationale for Change
Section 6.1 Selection of Subjects	The nature of the study and the possible risks will be explained to all potential subjects and their families/guardians and communities. Written informed consent will be obtained from each child's parents/guardian and, where possible, assent will be obtained from each child prior to performing any study related procedures. The consent process is described in Section 14.1.2.	Study recruitment will occur in villages in the Kpassa sub-district of the Nkwanta North district, including Wii, Azua and Jagri-Do (for ethically relevant considerations relating to the choice of these villages see Section 14.1.2). The nature of the study and the possible risks will be explained to all potential subjects and their parent(s)/guardian(s) (legally acceptable representative, LAR) and communities. Written informed consent will be obtained from each child's parent(s)/guardian(s) and assent will be obtained from each child (as and if appropriate for age) prior to performing any study -related procedures. For children too young or immature to give assent, the investigator will search for indication of 'deliberate objection' as per commentary to the Council for International Organizations of Medical Sciences (CIOMS) Guideline 17 (Council for International Organizations of Medical Sciences (CIOMS), 2016) (this is subsequently considered to be implied in the use of the term 'assent'). The consent/assent process is described in Section 14.1.2.	Clarification of subject selection process, specifically: • relating to the selection of the villages from which participants will be recruited; and • reference to the fact that parental consent as well as participant assent will be obtained and that children too young or immature to provide assent will be assessed for signs of 'deliberate objection'.
	After providing written informed consent and testing for OV16 IgG4, children will be admitted at the study site and enrolled for Screening assessments	After obtaining written informed consent/assent and testing for OV16 IgG4, children who are positive for OV16 IgG4 will, where possible, be assessed in the village setting against other eligibility criteria not requiring medical or other laboratory examinations, as described in Section 6.2 and Section 6.3. This is intended to minimize the number of potentially ineligible children who travel to the study site to determine eligibility. Those who continue to be eligible for the study will receive transportation to the study site together with a parent or guardian for the remaining Screening assessments	Clarification of subject selection process, specifically that screening in the communities can include evaluation of eligibility criteria other than Ov16 IgG4 antibodies and the rationale for this.

Section	Original Text	Revised to Read	Rationale for Change
Section 6.4.1 Contraception	Female subjects of child-bearing potential (post-commencement of menarche and physically able to bear children) must have a negative pregnancy test (with a sensitivity of at least 50 International Units (IU)/mL) performed at Screening (serum) and Day 0 (urine) and at Day 28, Week 12 and Week 24 (urine or serum) as indicated in Table 1.	Female subjects of child-bearing potential (post-commencement of menarche and physically able to bear children) must have a negative pregnancy test (with a sensitivity of at least 50 International Units (IU)/mL) performed at Screening (serum) and at Day 28, Week 12 and Week 24 (urine) as indicated in Table 1.	Clarification of pregnancy testing requirements.
	The reliability of sexual abstinence needs to be evaluated for each subject on an ongoing basis.	Compliance with the commitment to sexual abstinence will be evaluated at the Day 14, Day 28, Week 12 and Week 24 visits by asking subjects whether they have been abstinent. In addition, a pregnancy test will be carried out for all girls of child-bearing capacity as described above, regardless of the chosen method of contraception.	Clarification of method for assessing compliance with commitment to sexual abstinence.
	Counselling and provision of contraceptives will be carried out by the staff of the Family Planning Unit of the Hohoe Municipal Hospital.	Counselling and administration of contraceptives (if needed) will be carried out by the staff of the Family Planning Unit of the Hohoe Municipal Hospital.	Clarification that administration of contraceptives will be by appropriately experienced staff.
Section 7.2 Visit Windows	Consent may be obtained up to 30 days prior to Screening. Screening must be conducted post-consent and in the window of Day -7 to Day 0.	Consent/assent may be obtained up to 30 days prior to the day of planned study drug administration (Day 0) and before any study-specific procedures are conducted. Screening (with the exception of OV16 IgG4 testing and initial assessment of eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1) must be conducted in the window of Day -7 to Day -1.	Clarification relating to: • assent being obtained; • reference time point for consent/assent; and • screening conducted in the communities prior to transport of participants and a parent/guardian to the research center.
Section 7.3 Study Procedures / Assessment Periods	Not applicable	Study procedures will be conducted in the presence and with the help of the parent/guardian who accompanies the subject to the research center, as per the wishes of the accompanying parent/guardian and child.	Clarification that the child's parent/guardian will be present during all study procedures as per the wishes of parent/guardian and child.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.3.1 Consent and Assent	Written informed consent may be obtained up to 30 days prior to Baseline. Informed consent must be obtained prior to any study related procedure. The process for obtaining informed consent and assent is described in Section 14.1.2. Further details may be described in an institutional Standard Operating Procedure (SOP).	The process for obtaining informed consent and assent is described in Section 14.1.2.	Removal of repetitious text.
Section 7.3.2 Pre-screening (Screening Conducted in the Community)	Testing will be conducted between Day -30 and Day -1. This test may be performed in the subject's home village or at the clinic prior to Screening. An OV16 IgG4 rapid format card test will be used (see Section 7.4.3.1).	Subjects for whom informed consent and assent has been obtained (as described in Section 14.1.2) are to be tested for exposure to O. volvulus infection using an OV16 IgG4 rapid format card test (see Section 7.4.3.1). Those testing positive for OV16 IgG4 may also be evaluated for other study eligibility criteria as described in Section 6.1. These evaluations will be conducted between Day -30 and Day -1 and may also be performed in the research center during Screening.	Clarification of 'Pre-screening' assessments, including that eligibility criteria other than OV16 IgG4 may be evaluated in the community.
Section 7.3.3 Screening	Subjects and their parent, guardian or a trusted adult member of the community assigned by the subject's parent/guardian will be invited to attend the clinic for Screening.	Subjects who pass pre-screening and their parent or guardian will be invited to attend the research center for Screening	Clarification that accompanying adult must be a parent or guardian.
	The dormitory will have separate rooms for males and females	The dormitory ward has four separate rooms and each group of parents/guardians with their children can choose how to occupy these. A registered nurse will be on duty at all times.	Clarification that dormitory has four rooms and that study participants and their accompanying parents/guardians will decide how these are allocated.
	Following confirmation of informed consent, the following will be performed and documented: • Medical history (see Section 7.4.1) • A complete physical examination including assessment of all appropriate body systems to determine study eligibility (see Section 7.4.1)	Unless already conducted at Pre-screening, the following assessments / study requirements will be performed and documented: • Medical history, including medication history and evaluation of ability to swallow tablets (see Section 7.4.1) • A complete physical examination including assessment of all appropriate body systems and evaluation of venous access to determine study eligibility (see Section 7.4.1)	Revised to allow for the fact that some eligibility criteria may have already been evaluated during Screening in the communities (referred to as Pre-screening) and that consent/assent/evaluation for deliberate objection has been obtained in the villages before OV16IgG4 evaluation.
	o Ov16 IgG4 (see Section 7.4.3.1)	Deleted	Since OV16IgG4 testing will have been conducted in the villages.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.3.3 Screening	Not applicable	The ability of children to swallow tablets will be assessed by the investigator based on discussion with the child and their parent(s)/guardian(s) of the child's previous experience with taking tablets of a similar size (see Section 3.4.4.3). Parent(s)/guardian(s) and the child will be shown a tablet of a similar size to moxidectin as an example.	Clarification of how ability to swallow tablets will be assessed.
	Not applicable	Eligible girls of child-bearing potential and their accompanying parent/guardian will have a discussion with a family planning nurse about the need for contraception and the different options available, and will be provided with a contraceptive as needed, as described in Section	Clarification that counselling relating to birth control will be conducted after eligibility has been assessed.
	Transport for the subject and their parent(s)/guardian(s) to return to their village will be arranged for the day following Screening.	Transport for the subject and their parent/guardian to return to their village will be arranged for the day following Screening.	Clarification that each child will be accompanied by only one parent or guardian.
Section 7.3.4 Day -1	Subjects will be required to fast overnight (from midnight) prior to dosing (See Section 8.5.1).	Subjects will be required to fast overnight (from after dinner, which will be served at approximately 19:00) prior to dosing (see Section 8.5.1).	Adjustment remove discrepancy between protocol body and information documents (since as per investigator the idea of having a meal after dinner and thus information of fasting after midnight would be alien to the study participants and their parents/guardians).
Section 7.3.5.1 Pre-dose	• A targeted physical examination (see Section 7.4.1) • 12-lead safety ECG (see Section 7.4.2) • Vital signs measurement (see Section 7.4.1) • Final confirmation of eligibility. Only subjects continuing to meet all of the inclusion criteria and none of the exclusion criteria will be dosed with moxidectin	The following will be performed and documented pre-dose: • A targeted physical examination (see Section 7.4.1) • Vital signs measurement (see Section 7.4.1) • Final confirmation of eligibility. Only subjects continuing to meet all of the inclusion criteria and none of the exclusion criteria will be dosed with moxidectin	Grammatical adjustment and deletion of 12 lead ECG, which is not required on Day 0 Pre-dose, per the schedule of assessments.
Section 7.3.5.2 Dosing	If a subject vomits after taking the dose of moxidectin, the subject will be assessed as described in Section 12.4.	If a subject vomits within 30 minutes of taking the dose of moxidectin, the subject will be assessed as described in Section 12.2.	Clarification of timing of vomiting and update of section with further details.
Section 7.3.5.3 Sections 7.3.6 – 7.3.14	Not applicable	Addition of procedures to be conducted if clinically indicated.	To ensure consistency with the schedule of assessments.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.4.1 Demographic Data, Medical History, Physical Examination, Vital Signs	Demographic data will include sex, date of birth, height (in centimeters [cm]) and upper arm circumference (in cm) and weight (in kg). The medical history will include any significant diagnosed medical conditions or surgical history. A complete physical examination (including head, eyes, ears, nose, throat, lungs, lymph nodes, heart, abdomen and skin) will be conducted at Screening to determine study eligibility. A targeted physical examination based on prior findings and reported AEs will be performed on Day 0 pre-dose, Hour 1 and Hour 8 and at all subsequent visits. Weight will be repeated at the Week 24/Early Withdrawal visit.	Demographic data will include sex, date of birth, height (in centimeters [cm]), upper arm circumference (in cm) and weight (in kg), as well as history of living in a Loa loa endemic area. The medical history will include any significant diagnosed medical conditions or surgical history and medication history. A complete physical examination (including head, eyes, ears, nose, throat, lungs, lymph nodes, heart, abdomen and skin) and body weight and height measurements will be conducted at Screening to determine study eligibility. A targeted physical examination based on prior findings and reported AEs will be performed on Day 0 pre-dose and at all subsequent visits. Targeted physical examinations may also be performed at Hours 1, 2, 4 and 8 on Day 0 and at unscheduled visits as clinically indicated. Body weight measurement will be repeated at the Day 28 and Week 24/Early Withdrawal visits and may be performed at unscheduled visits if clinically indicated.	Provision of additional details to ensure consistency other sections and the schedule of assessments.
Section 7.4.3 Blood and Urine Samples	• a 0.5 mL sample of blood for hematology assessments and 1.5 mL for biochemistry assessments at each of Screening, Days 7 and 28, and Week 12 (total 8 mL across all visits) (see Section 7.4.3.2) • up to 4 mL for serum pregnancy testing (see Section 7.4.3.5)	• a 0.5 mL sample of blood for hematology assessments and 1.5 mL for biochemistry assessments at each of Screening, Days 7 and 28, and Week 12 (total 8 mL across all visits) and at other visits if clinically indicated (see Section 7.4.3.2) • up to 4 mL for serum pregnancy testing at Screening (see Section 7.4.3.5)	Clarification of blood volume that might be required in case of clinically indicated hematology or biochemistry assessments

Section	Original Text	Revised to Read	Rationale for Change
Section 7.4.3 Blood and Urine Samples	Planned blood sample collection will be no more than 33.5 mL for females requiring pregnancy testing and 29.5 mL for all other subjects. The maximum blood sample collection in any 4-week period for any subject is 30 mL (when pregnancy testing is required). For a child of 4 to 7 years weighing an allowable minimum 12 kg, the blood volume required in any 4 week period is less than the recommended maximum 3% of blood volume of 28 mL (2001/20/EC, 2008, Zisowsky et al., 2010)	Planned blood sample collection will be no more than 33.5 mL for females requiring pregnancy testing (≥ 12 years and ≥ 30 kg) and 29.5 mL for all other subjects. The maximum blood sample collection in any 4-week period for any subject is 30 mL (when pregnancy testing is required). For a child of 4 to 7 years weighing an allowable minimum 12 kg, the blood volume required in any 4 week period (26 mL) is less than the recommended maximum 3% of blood volume of 28 mL and the maximum amount drawn within a single day (8.5 mL) is less than the recommended maximum 1% of blood volume of 9.6 mL (2001/20/EC, 2008, Zisowsky et al., 2010)	Addition of minimum reference weight for females requiring serum pregnancy test. Addition of assessment of maximum single blood draw relative to guidance.
	A single mid-stream urine sample will be collected from female participants of childbearing potential for pregnancy testing (See Section 7.4.3.5).	A single mid-stream urine sample will be collected from female participants of childbearing potential for pregnancy testing at Day 28, Week 12 and Week 24 / Early Withdrawal visits and, if clinically required, at unscheduled visits as (See Section 7.4.3.5).	Addition of timing of urine samples for consistency with the schedule of assessments and information provided for blood samples.
Section 7.4.3.1 *O. volvulus* Exposure Test	A Standard Diagnostics Bioline Onchocerciasis IgG4 Rapid Test will be performed at Screening to determine prior exposure to O. volvulus. Instructions on sample collection and testing will be provided in the SRM.	A Standard Diagnostics Bioline Onchocerciasis IgG4 Rapid Test will be performed at Pre-screening to determine prior exposure to O. volvulus, as per the manufacturer's instructions.	Clarification that test will be conducted as per manufacturer's instructions.
Section 7.4.3.2 Safety Laboratory Test	Blood will be collected at scheduled time points for safety laboratory testing. Approximately 2 mL per visit will be collected, at Screening, Days 7 and 28 and Week 12 (8 mL total).	Blood will be collected at scheduled time points and, if clinically indicated, at unscheduled visits, for safety laboratory testing. A maximum of 2 mL per visit will be collected at the scheduled time points at Screening, Days 7 and 28 and Week 12 (8 mL total; see Section 7.4.3 for evaluation of blood volumes collected relative to guidance on blood collection in children).	Clarification of blood volume drawn Addition of cross reference to information on evaluation of volumes of planned blood sample collection relative to guidance to facilitate ethics committee review.
Section 7.4.3.3 Pharmacokinetic samples	Plasma will be prepared from 1.5 mL blood collected (with samples for safety testing as appropriate) at Screening and post-dose at Hours 1, 2, 4, 8, 24 and 72, Days 7, 14 and 28 and Week 12 (16.5 mL in total).	Plasma will be prepared from 1.5 mL blood collected (with samples for safety testing as appropriate) at Screening and post-dose at Hours 1, 2, 4, 8, 24 and 72, Days 7, 14 and 28 and Week 12 (16.5 mL in total; see Section 7.4.3 for evaluation of blood volumes collected relative to guidance on blood collection in children).	Addition of cross reference to information on evaluation of volumes of planned blood sample collection relative to guidance to facilitate ethics committee review.

Section	Original Text	Revised to Read	Rationale for Change
Section 7.4.3.4 Laboratory Testing for Other Infections	Testing for the presence of infection with HIV, chronic hepatitis B and C will be conducted at Screening. Not applicable	Testing for the presence of infection with HIV, chronic hepatitis B and C will be conducted at Screening using commercially available rapid test kits as per the manufacturer's instructions. Testing for other infections (e.g. malaria) will be conducted as per investigator judgement in case of clinical suspicion.	Clarification that commercial rapid diagnostic tests will be used according to the manufacturer's instructions. Clarification on how exclusion criterion 12 will be evaluated.
Section 7.4.3.5 Pregnancy test	At Day 28 and Week 12, a urine pregnancy test will be performed.	At Day 28, Week 12 and Week 24 / Early Withdrawal, a urine pregnancy test will be performed. Commercially available rapid test kits will be used as per the manufacturer's instructions.	Clarification that urine pregnancy test will also be conducted at Week 24 or early withdrawal. Clarification of method to be used.
Section 8.3 Treatment Allocation	A Screening identification (ID) number will be allocated to each subject for whom informed consent is provided.	A Screening identification (ID) number will be allocated to each subject for whom parental/guardian informed consent and child assent (as appropriate for the age group, see Section 14.1.2) is provided	Clarification that child assent (as age appropriate, i.e. including evaluation for deliberate objection as specified in section 14.1.2) will also be required before a Screening ID is attributed.
Section 8.5 Storage and Handling	Only subjects enrolled in the study may receive moxidectin 2 mg tablets	Only subjects enrolled in the study (i.e. those for whom eligibility has been confirmed on Day 0, see Section 13.3)	Clarification of when participants are considered enrolled.
Section 10.2.1 Assessment of Adverse Events	AEs should be recorded, and severity graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017. This is provided in the SRM and available at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.	AEs should be recorded, and severity graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017. This is provided in Appendix 16.5 and is available at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.	An additional appendix has been provided to facilitate availability of the AE grading scale.
Section 10.3.2.1 All Serious Adverse events	• send to the Safety Desk within 24 hours of the investigator's knowledge of the event. Safety Desk contact details are in the SRM	• send to the Safety Desk within 24 hours of the investigator's knowledge of the event by emailing to: sae@medicinesdevelopment.com	Provision of SAE reporting address.
Section 10.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs	Any laboratory test result that meets the criteria for a SAE (refer to Section 10.3) should be recorded as an AE, the AE page of the CRF completed and a SAE form also completed in order for the Sponsor to collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken and resolution.	Any laboratory test result that meets the criteria for a SAE (refer to Section 10.3) should be recorded as an AE, the AE page of the CRF completed and a SAE form also completed in order to provide the Sponsor with additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken and resolution.	Clarification text.

Section	Original Text	Revised to Read	Rationale for Change
Section 10.7 Guidance for Dose Modification or Discontinuation of Treatment	There will be no dose modification.	There will be no dose modification for individual subjects, since this is a single dose study.	Clarification of sentence in the context of this study (e.g. a second group within the Cohort II age group may be treated with a dose different from the initial dose depending on the outcome of Cohort II treated with 8 mg).
Section 10.9 Risks for Women of Childbearing Potential or During Pregnancy	The risks of treatment with moxidectin during pregnancy have not been evaluated.	The risks of treatment with moxidectin during pregnancy have not been evaluated in humans. For information on the risk assessed in animal studies, see Section 3.3.1.2.2 and the Investigator's Brochure for moxidectin.	Clarification that the original statement only refers to humans (animal reproductive toxicology data are available).
Section 10.10 Procedures to be Followed in the Event of Pregnancy	The subject must be instructed to inform the investigator IMMEDIATELY if she or, if male, their partner, becomes pregnant during the study period. The investigator should report all pregnancies to the Sponsor or designee within 48 hours of becoming aware of the pregnancy.	The subject and their parent(s)/guardian(s) must be instructed to inform the investigator IMMEDIATELY if the subject or, if male, their partner becomes pregnant during the study period. Contact information is provided on the study information sheet and the participant identification card each subject will receive. Subjects can also choose to ask the community coordinator (see Section 14.1.2.1) to contact the study team.	Clarification that parents and guardians will also be requested to inform the investigator if the child becomes pregnant. Clarification that subjects and parents/guardians will be provided with contact information for the investigator and can also chose to inform investigator with the community-selected coordinator.

Section	Original Text	Revised to Read	Rationale for Change
Section 10.10 Procedures to be Followed in the Event of Pregnancy	Monitoring of the subject should continue until conclusion of the pregnancy. The outcome of the pregnancy should be reported to the Sponsor and a pediatrician will conduct follow-up assessments of the health of the baby up to 2 years of age.	In the event of pregnancy in a subject, the investigator will advise the subject to attend all ante-natal visits and refer them to the appropriate GHS ante-natal service. Monitoring of the subject should continue until conclusion of the pregnancy (i.e. the investigator will ask the pregnant woman to contact him in case the GHS ante-natal service staff informs her about any abnormal findings). The outcome of the pregnancy should be reported to the Sponsor. Post-natal follow-up assessments of the health of the baby will be conducted by a pediatrician at least annually up to 2 years of age. In the event of a pregnancy in the partner of a subject, the investigator should seek informed consent from the partner to monitor and report the outcome of the pregnancy to the Sponsor and to conduct post-natal follow-up assessments of the baby at least annually for 2 years in the same way as for pregnant study participants). All abnormal GHS ante-natal service staff findings and results of follow-up assessments of babies will be reported to the Sponsor.	Clarification of requirements for monitoring of a pregnancy in a study subject and that consent will also be sought for monitoring of pregnancies and follow-up of babies fathered by male study participants.
Section 11 Data and Safety Monitoring Board (DSMB)	The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II.	The DSMB will review the safety and pharmacokinetic data following completion of enrolment and pharmacokinetic data analysis for both Cohorts I and II and recommend a starting dose for Cohort III.	Clarification of the purpose of DSMB data review relating to the starting dose for Cohort III.
Section 12.2 Criteria for Premature Withdrawal from Treatment or the Study	Subjects also have the right to withdraw from the study at any time for any reason. The PI must make every reasonable effort to retain each subject in the study. Not applicable	Subjects (or their parent(s)/guardian(s)) also have the right to withdraw themselves (or their child/ward) from the study at any time for any reason. The PI must make every reasonable effort to understand the reason and, if possible, retain them in the study if their specific concerns can be addressed. If a subject vomits in the 30 minutes after taking the dose of moxidectin, all Day 0 assessments should be completed, and the subject should be withdrawn from the study. Any AEs or SAEs still ongoing at the time of withdrawal will be followed in accordance with Section 10.	To clarify that parents/guardians also have the right to withdraw their child/ward. To clarify that the investigator will make every effort to retain a subject in the study whilst still respecting the right of subjects and parents/guardians to withdraw themselves or their child. Text moved here from section 12.4, which deals with procedures to be followed in case of withdrawal, but not criteria for withdrawal.

Section	Original Text	Revised to Read	Rationale for Change
Section 12.2 Criteria for Premature Withdrawal from Treatment or the Study	The PI also has the right to withdraw subjects from the study in the event of concurrent illness, AEs, pregnancy, protocol violations, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals from the study can render the study difficult to interpret. In particular, missing data could significantly impact on the interpretation of the results; therefore, unnecessary withdrawal of subjects from the study should be avoided The reasons for withdrawal of the subject must be recorded on the CRF.	The PI also has the right to withdraw subjects from the study for safety reasons (e.g. in the event of concurrent illness, AEs, or pregnancy), protocol non-compliance, or administrative or other reasons (see Section 12.6). An excessive rate of withdrawals from the study can render the study difficult to interpret. In particular, missing data could significantly impact on the interpretation of the results; therefore, unnecessary withdrawal of subjects from the study (e.g. based on misconceptions) should be avoided. The reasons for withdrawal of the subject must be recorded on the CRF (if given; if a reason is not given, this will be recorded).	Clarification that the PI has the right to withdraw the subject from the study for any reason related to subject safety, not only those listed. Addition of reference for administrative or other reasons. Clarification to avoid misconception that this paragraph is intended to motivate the investigator to minimize withdrawal even when this is in the interests of the subject's safety and consistent with their and their parents/guardians rights to withdraw themselves or their child.
Section 12.4 Withdrawal of Subjects from the Study	Should a subject decide to withdraw from the study, … A complete final evaluation at the time of the subject withdrawal should be made with an explanation as to why the subject is withdrawing from the study. If a subject vomits up to 30 minutes after taking the dose of moxidectin, all Day 0 assessments should be completed and then the subject should be withdrawn from the study. Any AEs or SAEs still ongoing at the time of withdrawal will be followed in accordance with Section 10.	Should a subject, and/or their parent(s)/guardian(s)) and/or the investigator decide on the withdraw of a subject from the study, A complete final evaluation should be made at the time of the subject withdrawal, with an explanation for the withdrawal from the study. Not applicable.	Clarification that parents/guardians have the right to withdraw their child from the study. Clarification that this applies to subject withdrawing and investigator withdrawal of a subject. Moved to section 12.2, since this is a criterion for withdrawal.
Section 12.5 Replacement of withdrawn subjects	Any subjects who discontinue a clinical study of their own volition or by the PI are defined as "withdrawals".	Any subjects who discontinue a clinical study of their own and/or parent(s)/guardian(s) volition or are withdrawn by the PI are defined as "withdrawals". Replacement subjects (up to a total study maximum of 63 participants treated)	Clarification that parents/guardians can also withdraw their child/ward and of the number of replacement subjects that may be enrolled in the study.
Section 12.6 Premature Termination of the Study	In the event that data obtained for Cohorts I or II does not enable determination of an optimal dose for Cohort III	In the event that data obtained for Cohorts I or II does not enable determination of a starting dose for Cohort III or Cohorts I to III data does not enable determination of an optimal dose	Clarification of requirements for study termination.

Section	Original Text	Revised to Read	Rationale for Change
Section 13.3 Enrolment and Randomization	Subject disposition will be described according to the numbers of subjects screened (not enrolled), enrolled (not treated) and treated. Screen failure data will not be databased.	Subject disposition will be described according to the numbers of subjects screened (not enrolled), enrolled (not treated) and treated. Screen failure data will be included in the database only as necessary to determine the number of subjects screened but not enrolled and the reason(s) for ineligibility.	Clarification of the extent of data to be entered into the database screen failures.
Section 13.4 Analysis Populations	As such, it is strongly recommended to adhere to the full pharmacokinetic sampling schedule as best as possible. Subjects in this population will be analyzed according to the dose received (actual drug amount).	As such, it is strongly recommended to adhere to the full pharmacokinetic sampling schedule as best as possible, unless non-adherence is required to safeguard subject safety. Subjects in this population will be analyzed according to the dose received (actual amount of investigational product swallowed).	Clarification that subject safety is the prime consideration. Clarification of how 'actual drug amount' will be determined.
Section 13.5.4 Analysis of Safety	AEs, concomitant medications and laboratory data will be listed and summarized by Cohort	AEs, concomitant medications and laboratory data will be listed and summarized by Cohort, and/or by dose if more than one dose level is evaluated in an age group.	Clarification of summarization in case more than one dose level is evaluated in Cohorts II and III.
Section 13.6 Pharmacokinetic Assessments for Dose Determinations	The dose for children aged 4 to 7 years (Cohort III) will be selected following additional population pharmacokinetic modelling with allometric scaling including data obtained from Cohorts I and II.	The first dose level to be proposed to the DSMB for administration in children aged 4 to 7 years (Cohort III) (and subsequent dose levels, if applicable, see Section 5.3) will be selected following additional population pharmacokinetic modelling with allometric scaling including data obtained from Cohorts I and II.	Clarification of DSMB role in dose selection for Cohort III.
Section 14.1.3 Compensation	In addition, transportation will be provided to and from the study center, and accommodation and food will be provided for participants and their family/carers while at the study center. If the child is at the study center during school time, a teacher will be employed to provide educational activities and/or oversee homework during their stay to compensate for school time missed.	In addition, transportation will be provided to and from the study center, and accommodation and food will be provided for each (potential) subject and their accompanying parent/guardian while at the study center	Clarification that this applies to subjects and the accompanying parent/guardian. The Information on provision of teachers was extracted into a separate section since it is not a compensation.
Section 14.1.4 Provision for Study Visits During School Time	Not applicable	If the child is at the study center during school time, a teacher will be employed to provide educational activities and/or oversee homework during their stay to compensate for school time missed.	Information on provision of teachers extracted from Section 14.1.3.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.5 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 by the investigator as described in Section 14.1.1 and to the Research Ethics Committee of the UHAS, the GHS Ethics Review Committee and the WHO Ethics Review Committee. Approval from all three ethics committees will be obtained before starting the study and must 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.	This protocol and any accompanying material provided to the potential subject and their parents/guardian (such as information sheets with descriptions of the study used to obtain informed consent/assent) will be submitted by the investigator to the Research Ethics Committee of the UHAS and the GHS Ethics Review Committee. Furthermore, the protocol will be submitted to the WHO Ethics Review Committee. Approval from all three ethics committees will be obtained before starting the study and must be documented in a letter to the investigator (or the WHO Responsible Officer submitting the protocol to the WHO Ethics Review Committee) specifying the protocol number and version and the date on which the committee met and the date it granted the approval.	Section heading updated to accord with local terminology relating to ethics committees. Clarification that information documents are provided to potential study subjects and that this applies for both consent and assent. Modified to account for the fact that as per WHO ERC procedures, an investigator cannot submit a protocol or receive the WHO ERC response, and this will be done through the WHO Responsible Officer.
Section 14.1.6 Conditions for Modifying the Protocol	The PI will then notify the ECs of such administrative changes.	The PI (or WHO Responsible Officer) will then notify the ethics committees of such administrative changes.	Clarification relating to WHO ERC procedures as outlined above.
Section 14.1.8 Blood Volumes Sampled relative to the Maximum Recommended Volumes	Not applicable	Please refer to Section 7.4.3.	Introduced to facilitate locating this ethically relevant information for reviewers.
Section 14.4 Confidentiality of Trial Documents and Subject Records	All information concerning the study treatment and the Sponsor and its operation, such as patent applications, formulae, manufacturing processes, basic scientific data and material not previously published are considered confidential and shall remain the sole property of the Sponsor	All information concerning the study treatment shall remain the sole property of the Sponsor	Elimination of language not applicable for the Sponsor as a not-for-profit organization.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.5 Publication of Data (Dissemination of Results)	The results of this study may be published or presented at scientific meetings. If this is envisaged, the PI agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the PI. 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 PI and the appropriate the Sponsor personnel. Authorship will be determined by mutual agreement prior to the completion of the study.	The results of this study may be published or presented at scientific meetings. Sponsor-initiated publications and/or presentations will be agreed upon between the PI and Sponsor. PI-initiated publications and/or presentations will be provided for review by the Sponsor at least 30 days prior to submission to allow the Sponsor to provide comments based on information from other studies that may not yet be available to the PI. 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 PI and the appropriate Sponsor personnel. Authorship will be determined by mutual agreement in accordance with International Committee of Medical Journal Editors recommendations. Additional authors will be agreed prior to journal submission	Update of Section Heading given that the Sponsor is a not-for-profit organization Clarification for preparation of publications and criteria for determining authorship.
Section 16.5 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017	Not applicable	Not applicable	New appendix to facilitate access for protocol users and reviewers.

Table 14: Details of Non-Administrative Protocol Amendments (Amendment 3)

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2 Informed Consent	Not applicable	Not applicable	Section restructured to group together general principles relating to investigator responsibility and informing potential study participants and their parents/guardians in the presence of an independent witness. Information relating to informing potential participants and their parents/guardians previously provided in subsection 14.1.2.1 has been given its own subject heading for clarity.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2 Informed Consent	Not applicable	Children who do not provide assent, including those aged 4-6 years and those 7-11 year old who may not be mature enough to give assent (as assessed by their parent(s)/guardian(s) and the person informing them about the study) will be assessed for expressions of 'deliberate objection' (i.e. expressions of disapproval or refusal), as per CIOMS guidelines (Council for International Organizations of Medical Sciences (CIOMS), 2016). Refusal to provide assent or an expression of 'deliberate objection' by a child/adolescent must be respected even if the parent(s)/guardian(s) have given consent for their participation in the study. The investigator will consider the child ineligible and record this on the informed consent provided by the parent(s)/guardian(s).	Clarification that children who are not considered able to provide assent will be evaluated for expression of 'deliberate objection' as per CIOMS 2016.
Section 14.1.2.1 Informing Communities about the Study	The council of elders will appoint a coordinator whom they think will best serve the community. Finally, the community will propose an impartial witness or witnesses for the informed consent procedure.	During the community meeting, a 'community coordinator' will be selected. This will be a community member that the community thinks will best serve as a link between the subjects and the study team. Finally, the community will propose an impartial witness or witnesses for the informed consent/assent procedure	Correction of the process for selection of the 'community coordinator' and clarification that the witness(es) selected will also be witnessing the obtaining of assent.
Section 14.1.2.2 Informing Potential Subjects and their Parents/Guardians	In order to address these factors, the following informed consent procedure is planned:	In order to address these factors, recruitment will occur in communities from which participants in the Phase III study of moxidectin and another study conducted by the PI were recruited. Thus potential subjects and their parents/guardians themselves, or people they can talk to, are likely to have first-hand experience in research study participation and procedures, the research center and moxidectin treatment, and therefore will be able to better understand the information provided about the study during the informed consent process.	Clarification of factors inherent in selection of the villages for recruitment which will provide potential participants and their parents/guardians with additional sources of information about participation in clinical studies of moxidectin at the research center in Hohoe.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2.2 Informing Potential Subjects and their Parents/Guardians	1. The process will take place in the community in order to remove any pressures imposed by its occurrence in the alien hospital environment;	1. The process will take place in the community in order to remove any pressures imposed by its occurrence in the possibly unfamiliar research center environment.	Clarification that the study will not be conducted at a hospital but at a research center.
	Not applicable	2. Initial information will be provided at a community meeting, which will allow meeting participants to benefit from the questions asked by other meeting participants. This will be followed by discussions with individual parent(s)/guardian(s) and their child/ward.	Clarification of the benefit of initial presentation of the study at a community meeting.
	2. Information will be conveyed in the local language. This means that the English version of the informed consent form (ICF) will be translated and authenticated by a reputable individual or agency and available for use as appropriate;	3. Study information will be conveyed in the local language. The English version of the informed consent/assent information and forms will be translated and authenticated by a reputable individual or agency. Four different information documents have been generated.	Introduction of four different consent/assent and/or information documents and characterization of the target audience for each.
	Not applicable	i. the adolescent (12 to 17 years) and parent/guardian information sheet and assent and consent form is written in language that is understandable to a 12-year-old (see Appendix 16.6);	
	Not applicable	ii. a separate parent/guardian information sheet and consent/assent form for parents of children aged 4 to 11 (see Appendix 16.7), also written in language understandable to children aged 12 years and including two consent/assent forms: 1. one for parents and children <12 years who are providing assent (includes written parent/guardian consent confirmation and child assent); 2. one for parents/guardians of children considered too immature to provide assent (includes written parent/guardian consent and documentation of assessment of expression of “deliberate objection”);	

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2.2 Informing Potential Subjects and their Parents/Guardians	Not applicable	iii. a simpler study information sheet for children aged 7 to 11 years considered mature enough to provide assent (see Appendix 16.8);	
	Not applicable	iv. an even simpler information sheet for children 4 to 6 years or older children considered too immature to provide (see Appendix 16.9).	
	3. Every effort will be made to ensure that all aspects of the study and all the elements regarded as essential to validate the informed consent process are specified in the ICF. These are presented in chronological order, and will be supplemented by a schematic diagram to facilitate comprehension and simplify the process for the parents/guardians and subjects;	4. Every effort has been made to ensure that all aspects of the study and all elements regarded as essential for the informed consent/assent are specified in the information documents for consent/assent. These are presented in chronological order and supplemented by images and schematic diagrams to facilitate comprehension.	To clarify that the focus is on obtaining informed consent/assent, not just validating the process. Addition of information that images have now been included in the information documents to aid comprehension and retention of information.
	4. Understanding of the study procedures will be assessed using a short test consisting of a series of open and closed questions in the local language for parents/guardians and subjects to answer. The questions to be asked are included at the end of Parent Information Sheet and Consent Form, with space provided for recording responses (refer to Appendix 16.5);	5. Understanding of the information provided about the study will be assessed using a short questionnaire consisting of a series of open and closed questions in the local language for parents/guardians and adolescents and children considered mature enough to give assent to answer. The questions to be asked are included at the end of the informed consent/assent documents, with space provided for recording responses and any questions asked by the adolescent/child or parent(s)/guardian(s) (refer to Appendix 16.6, Appendix 16.7, Appendix 16.8).	Provision of information that age appropriate questionnaires have been added to the information sheets to examine the comprehension of adolescents 12 to 17 years and children 7 to 11 years and considered mature enough to provide assent.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2.2 Informing Potential Subjects and their Parents/Guardians	5. An impartial, literate local resident agreed to by the subject (impartial witness) must countersign the document to attest to the fact that the information has been given to and understood by the parent/guardian;	6. An impartial, literate local resident agreed to by the potential subject and their parent(s)/guardian(s) (impartial witness) must be present when study information is provided and discussed, and must countersign the consent/assent form to attest to the fact that the information has been given to and understood by the parent(s)/guardian(s) and child.	Clarification of the role of the witness relating to adolescents/children providing assent.
	6. The ICF must be signed in 2 originals, one of which must be given to the parent(s)/guardian(s) in front of the impartial literate witness on the same day that the informed consent procedure takes place	7. The informed consent/assent forms must be signed / thumbprinted in 2 originals, one of which must be given to the parent(s)/guardian(s) in front of the impartial literate witness on the same day that the informed consent/assent is given.	Clarification that this process also applies for assent.
	7. At each subsequent study visit, the investigator should verbally confirm the continued consent / assent of the subject and that they are free to withdraw from the study at any time for any reason	8. At each subsequent study visit, the investigator should verbally confirm the continued consent / assent / lack of deliberate objection of the subject and that they are free to withdraw from the study at any time for any reason.	Clarification that continued lack of deliberate objection should also be evaluated.

Section	Original Text	Revised to Read	Rationale for Change
Section 14.1.2.3 Informing Children Too Young/Immature to Give Assent	Not applicable	Information about the study, primarily based on pictures (Appendix 16.9) will be presented to children 4-6 years old as well as older children considered not mature enough to provide assent in the joint judgement of the parent(s)/guardian(s) and the investigator. Early on in the presentation and discussion, a tablet similar in size and shape to moxidectin tablets will be shown and the child and their parent(s)/guardian(s) will be asked whether they think the child can swallow such tablets. If a child or their parent(s)/guardian(s) states that they cannot swallow a tablet of that size and shape, there will be no further discussion. Subsequently children will be told about the need to take blood and venous access will be assessed. If a child has poor venous access, there will be no further discussion. It is acknowledged that this constitutes evaluation of exclusion criteria 7 and 8 before the child has been presented with all information about the study and had the opportunity to express 'deliberate objection' to all other elements of the study. This sequence was chosen since it does not include an invasive procedure or confidential health information and obtaining all other information about the study has no value for a child who will be excluded on the basis that they cannot swallow the tablets or have poor venous access.	Addition of a new section to provide the rationale for the order in which information about the study will be provided to children 4 to 6 years and older children considered too immature to provide assent to be evaluated for 'deliberate objection'.

Section	Original Text	Revised to Read	Rationale for Change
Section 16.6 Model Adolescent (12 to 17 years) and Parent/Guardian Information Sheet and Assent and Consent Form	Not applicable	The document has been rewritten to: • address the adolescent (with clarification that this is also the information for their parent(s)/guardian(s)); • include relevant context (ivermectin mass drug administration in the villages, conduct of the Moxidectin Phase III study with participants from these villages); • provide more details on unwanted effects occurring after taking moxidectin and compare them with those occurring after taking ivermectin; • eliminate information applicable only to younger children and not relevant for adolescents and their parents; • add pictures of critical study elements; • simplify language; • add a short overview of all steps of the study primarily based on pictures; • provide separate questionnaires to assess comprehension of adolescents and of their parents/guardians; and • rearrange the consent and assent forms so that all required signatures/thumbprints (parents/guardians, subject, witness, person obtaining consent/assent) are on a single page.	Provide information that is easier to understand and relevant for this age group and their parents/guardians Provide a basis for assessing comprehension of adolescents.
Section 16.7. Model Information Sheet and Consent Form for Parents/Guardians of Children 4 to 11 Years, Including Assent Form for Children 7 to 11 Years	Not applicable	This document has been newly generated since information relevant for the parents/guardians of children 4 to 11 years of age differs slightly from that which is relevant for parents/guardians of children aged 12 to 17 years. The principles followed in this document are identical to those listed above for the document for adolescents 12 to 17 years and their parents/guardians.	Provide information targeted to the parents of children aged 4 t0 11 years.

Section	Original Text	Revised to Read	Rationale for Change
Section 16.8 Model Information Sheet for Children 7 to 11 Years Mature Enough to Provide Assent	Not applicable	This document has been rewritten following the principles outlined above for the document for adolescents and their parents/guardians, including generation of an age-adapted questionnaire to assess potential subject comprehension.	Provide information in a way that is that is understandable to children 7 to 11 years who are giving assent. Provide a basis for assessing comprehension of children 7 to 11 years.
Section 16.9 Model Information Sheet for Children 4 to 6 Years and Older Children Considered Not Mature Enough to Provide Assent	Not applicable	This document has been newly generated	Provide information about the study in a way that is understandable to children 4 to 6 years. Provide a basis for assessing these children for expressions of 'deliberate objection'.

16.10.4 Rationale for Protocol Amendment No. 4

This amendment was made in response to comments received from the World Health Organization Research Ethics Review Committee following its review of the protocol at the meeting held on 12 December 2019.

The amendments are all considered to be administrative in nature, since they do not change the conduct of the study or result in any increase in risk to subjects. Details of sections of the protocol amended are provided in Table 15.

Table 15: Details of Administrative Protocol Amendments (Amendment 4)

Section	Original Text	Revised to Read	Rationale for Change
Throughout document	Not applicable	Correction of minor grammatical and typographical errors.	To improve readability and consistency within the document.
Cover page, Investigator Statement page (page 2) and page footers	Version 1.3 (incorporating Amendment 1, 2, and 3) 27 Nov 2019	Version 1.4 (incorporating Amendments 1, 2, 3 and 4) 21 Jan 2020	Version number and date updated to indicate protocol amendment.
Section 14.1.9 Informing Study Subjects and Community about the Study Results, page 86	Not applicable – new text	**14.1.9 Informing Study Subjects and Communities about the Study Results** **Once the final data from the study are available and a decision on further evaluation of moxidectin has been made, each community will be visited. The study subjects and their parents, as well as other interested community members, will be informed about the study results and any future activities to be undertaken to enable the use of moxidectin for control and elimination of onchocerciasis in endemic countries. Age appropriate information documents to be used for this purpose will be submitted for review and approval by the responsible ethics committees.**	Addition of a new section (14.1.9) to the protocol, corresponding to the section in the participant information sheet describing the plan for sharing the results of the study with study subjects and their families and communities.
14.1.3 Compensation, page 84	All study-related costs, including study medication and provision, and medical care will be provided free of charge.	All study-related costs, including study medication, laboratory tests, **contraceptives counselling and provision,** and medical care will be provided free of charge.	Clarification that costs of counselling and provision of contraceptives, if required, will be borne by the study.

Section	Original Text	Revised to Read	Rationale for Change
Model Adolescent (12 to 17 years) and Parent/Guardian Information Sheet and Assent and Consent Form, page 168	If you change your mind about taking part in the study and don't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you want to stop being in the study.	If you change your mind about taking part in the study and don't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you want to stop being in the study. **However, if you have an unwanted effect that has not stopped, we will ask you to let us visit you to find out whether you need any treatment for this effect. Also, if you are pregnant, we will ask you if the doctor working with us who specializes in treating babies and children can come and examine the baby after birth and at least yearly for 2 years. If you are male and your partner becomes pregnant, we will ask you if we can contact your partner to ask her if we can examine the baby. You or your partner do not have to agree to this.**	Clarification that information will no longer be collected from subjects when they leave the study, unless they (or their partner, as appropriate) agree to follow-up of the baby in the event of a pregnancy (in the subject or their partner) or to follow-up of an ongoing adverse event.
16.7 Model Information Sheet and Consent Form for Parents/Guardians of Children 4 to 11 Years, Including Assent Form for Children 7 to 11 Years, page 186	If you change your mind about allowing your child or ward to take part in the study or the child doesn't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you wanted your child or ward to stop taking part in the study (or your child or ward told us they want to stop taking part in the study).	If you change your mind about allowing your child or ward to take part in the study or the child doesn't want to take part anymore, we will stop collecting information. We and the Sponsor will still use the information that we collected before you told us you wanted your child or ward to stop taking part in the study (or your child or ward told us they want to stop taking part in the study). **However, if your child/ward has an unwanted effect that has not stopped, we will ask you to let us visit you and your child/ward to find out whether they need any treatment for this effect. You and your child/ward do not have to agree to this.**	Clarification that information will no longer be collected from subjects when they leave the study, unless the subject and their parents/guardians agree to follow-up for an ongoing adverse event.

16.10.5 Rationale for Protocol Amendment No. 5

The Ghana Food and Drugs Authority in its feedback on review of the study (dated 18 May 2020) requested clarifications to the protocol which have resulted in the requirement for this amendment.

In addition, the GHS Ethics Review Committee released guidelines for researchers during the COVID-19 pandemic, effective 7 May 2020, that require research protocols to take the current COVID-19 pandemic and public health measures into consideration by ensuring that the proposed research and methods for data collected can be conducted in a safe environment that also adheres to national directives on social distancing. As a result, the potential risks of conducting the study under the current circumstances have been assessed and risk mitigation strategies addressed in this amendment.

Furthermore, the requirement for Ov16 IgG4 testing at Screening has been removed in this amendment based on recently-published results of a WHO external advisory committee review of large-scale evaluation of Ov16 IgG4 assays in various settings which has identified significant discrepancies between the results obtained with different assays and concerns about both false positive and false negative results. These concerns, together with the fact that the Ov16 IgG4 antibody test selected is designed to be a surveillance tool for onchocerciasis elimination programs in the late and post-control stages and not an individual diagnostic, suggested that it will not be possible to reliably identify individual children who have been exposed to *O. volvulus*. In addition, the Ov16 IgG4 antibody test is not registered in Ghana and is consequently an investigational diagnostic. The study presents a minor increase over minimal risk to the participating children but remains justified on the basis that it is not possible to gather the necessary data in adults and the study is being conducted in a region designated as endemic for *O. volvulus*, where children are at risk of *O. volvulus* infection. Consequently, the participants represent the population which will benefit from the identification of a paediatric dose that will allow children younger than 12 years to be included in moxidectin-based elimination strategies.

The following sections of the protocol have been amended and details are provided in Table 16 and Table 17.

Table 16: Details of Administrative Protocol Amendments (Amendment 5)

Section	Original Text	Revised to Read	Rationale for Change
Throughout document	Not applicable	Correction of minor grammatical and typographical errors.	To improve readability and consistency within the document.
Cover page and footers	Version 1.4 (incorporating Amendments 1, 2, 3 and 4) 21 Jan 2020	Version 1.5 (incorporating Amendments 1, 2, 3, 4 and 5) 03 Jul 2020	Version number updated to indicate protocol amendment.
Abbreviations	Not applicable	Addition of definitions for abbreviated terms used within the document.	To ensure clarity of meaning of abbreviated terms.

Section	Original Text	Revised to Read	Rationale for Change
Section 15: References	Not applicable	Removal and addition of references.	Revised to ensure completeness following updates and additions to the text.
Section 16.10.5: Rationale for Protocol Amendment No. 5	Not applicable	Inclusion of Amendment 5 Summary of Protocol Amendment	Provision of details of changes from version 1.4.

Table 17: Details of Non-Administrative Protocol Amendments (Amendment 5)

Section	Original Text	Revised to Read	Rationale for Change
Synopsis: Background	However, to determine eligibility to the study, *O. volvulus* immunoglobulin G4 (Ov16 IgG4) testing will be performed to determine if the child is currently infected or has ever been exposed to *O. volvulus* infection and to exclude those with no evidence of prior systemic exposure to that infection. This is to balance risks in study participation with potential individual benefit from treatment,	To balance risks in study participation with potential individual benefit from treatment, participants will be recruited from an area where onchocerciasis is endemic.	Ov16 IgG4 testing for *O. volvulus* infection removed from protocol based on a recently published WHO report identifying significant discrepancies between different assays and concerns about both false positive and false negative results. See changes described for Section 3.4.3, below.
Synopsis: Inclusion Criteria Section 6.2: Inclusion Criteria	6. Test positive for Ov16 IgG4 antibody by rapid format antibody card test.	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Synopsis: Study Procedures	After obtaining written informed consent from the parent(s)/guardian(s) and assent (or determining lack of expression of 'deliberate objection') from the child (see Section 14.1.2 for details) the child will be tested for OV16 IgG4 antibody. Children with a positive test result and meeting other eligibility criteria evaluated in the village, together with one parent or guardian, will be invited to attend the research center for further Screening.	After obtaining written informed consent from the parent(s)/guardian(s) and assent (or determining lack of expression of 'deliberate objection') from the child (see Section 14.1.2 for details), children meeting eligibility criteria that are able to be evaluated in the village will be invited to attend the research center for further Screening, together with one parent or guardian.	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Synopsis: Safety Parameters Table 1: Table of Assessments Section 7.3.3: Screening	Tympanic temperature	Temperature	Removal of requirement for contact temperature measurement as part of measures taken to minimize risks associated with conduct of the study during the COVID-19 pandemic.

Section	Original Text	Revised to Read	Rationale for Change
Synopsis: Specialized Tests and Analyses	Prior exposure of each subject to O. volvulus infection will be determined by OV16 IgG4 rapid format antibody card test prior to undertaking further screening assessments.	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Synopsis: Special Protocol Requirements or Issues	Exposure to O. volvulus will be confirmed by OV16 IgG4 rapid format antibody card test.	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Table 1: Table of Assessments	OV16 IgG4 test Footnote Abbreviations: OV16 IgG4 = *O. volvulus* 16 antigen immunoglobulin G4	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Table 1: Table of Assessments	Footnote b: Blood pressure, and pulse, tympanic temperature and respiratory rate will be measured lying semi-supine for 5 mins.	Footnote b: Blood pressure, pulse, temperature and respiratory rate will be measured lying semi-supine for 5 mins.	Clarification to ensure consistency with Section 7.4, Details of Scheduled Assessments.
Table 1: Table of Assessments Section 7.3.3: Screening	Not applicable	Adverse events and concurrent medications assessments added to Consent and Pre-screening and Screening visits.	Clarification to ensure consistency between Table of Assessments, Section 7.4, Details of Scheduled Assessments and Section 10.2, Adverse Events.
Section 3.3.2.2.2: Overview of Safety and Efficacy in Patients with Onchocerciasis	Table 2: Adverse Reactions Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III) Adverse Reaction	Table 2: Treatment-emergent Adverse Events Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III) Adverse Event	Correction of table caption and column heading to align with the updated Investigator's Brochure v6 dated 12 Jun 2020.
Section 3.4.3: Design Rationale	Additionally, O. volvulus infection risk on an individual participant basis will be determined by OV16 IgG4 testing to confirm if the child is currently infected or has ever been exposed to O. volvulus infection and to exclude those with no evidence of prior systemic exposure to that infection. This is to balance risks in study participation with potential individual benefit from treatment.	Ov16 IgG4 antibody positivity determined using the Ov16 IgG4 antibody rapid format card test was originally included as an eligibility criterion in order to provide a benefit to study participants, since it was assumed that a positive test would indicate that the participant had been exposed to O. volvulus. However, this criterion has now been eliminated for the following reasons: • Recently-published results of a WHO external advisory committee review of large-scale evaluation of different assays for detecting Ov16 IgG4 antibodies in different settings and countries has	Addition of rationale for removal of Ov16 IgG4 testing for *O. volvulus* infection from the protocol.

Section	Original Text	Revised to Read	Rationale for Change
		identified significant discrepancies between the results obtained with different assays and concerns about both false positive and false negative results (WHO 2020). • The concerns about false positive and false negative results, together with the fact that Ov16 IgG4 antibody testing is designed to be a surveillance tool for onchocerciasis elimination programs in the late and post-control stages and not an individual diagnostic (Abbott 2020), indicate that it will not be possible to reliably identify individual children who have been exposed to O. volvulus using the Ov16 IgG4 antibody test. In addition, the Ov16 IgG4 antibody test is not registered in Ghana and is consequently an investigational diagnostic. • While the study presents a minor increase over minimal risk to the participating children, it can be justified on the basis that it is not possible to gather the necessary data in adults and the study is being conducted in a region designated as endemic for *O. volvulus*, where children are at risk of *O. volvulus* infection. Consequently, the participants represent the population which will benefit from the identification of a paediatric dose that will allow children younger than 12 years to be included in moxidectin-based elimination strategies.	
Section 3.4.3: Design Rationale	All enrolled children will have confirmed exposure to O. volvulus.	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Section 6.1: Selection of Subjects	After obtaining written informed consent/assent, and testing for OV16 IgG4, children who are positive for OV16 IgG4 will, where possible, be assessed in the village	After obtaining written informed consent/assent, children will, where possible, be assessed in the village setting against eligibility criteria not requiring medical or	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

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	setting against other eligibility criteria not requiring medical or other laboratory examinations, as described in Section 6.2 and Section 6.3.	laboratory examinations, as described in Section 6.2 and Section 6.3,	
Section 6.2: Inclusion Criteria	6. Tests positive for OV16 IgG4 antibody by rapid format antibody card test.	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Section 7.2: Visit Windows	Screening (with the exception of OV16 IgG4 testing and initial assessment of eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1) must be conducted in the window of Day -7 to Day -1.	Screening (with the exception of initial assessment of eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1) must be conducted in the window of Day -7 to Day -1.	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Section 7.3.2: Pre-Screening (Screening Conducted in the Community)	Subjects for whom informed consent/assent has been obtained as described in Section 14.1.2 are to be tested for exposure to O. volvulus infection using an OV16 IgG4 rapid format card test (see Section 7.4.3.1). Those testing positive for OVG16 IgG4 may also be evaluated for other eligibility criteria as described in Section 6.1.	Subjects for whom informed consent/assent has been obtained as described in Section 14.1.2 will be evaluated for eligibility criteria not requiring medical or laboratory examinations, as described in Section 6.1.	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Section 7.3.3: Screening	If the subject is ineligible to participate in the study due to a clinically significant laboratory abnormality or medical condition, a referral will be made to an appropriate GHS treatment facility for follow-up.	If the subject is ineligible to participate in the study due to a clinically significant laboratory abnormality or medical condition, including a positive test for HIV, hepatitis B or hepatitis C, a referral will be made to an appropriate GHS treatment facility for follow-up.	Clarification that potential subjects testing positive for HIV, hepatitis B or hepatitis C at Screening will be referred for appropriate follow-up.
Section 7.4.2: Electrocardiograms	Not applicable	The following parameters will be reported: QRS, QT, QTcB (Bazett's correction formula), QTcF (Fridericia's correction formula), RR and PR intervals.	Based on feedback from Ghana Food and Drugs Authority, both Bazett's and Fridericia's formulae will be used to calculate the corrected QT in order to make comparisons between the two calculations.
Section 7.4.3: Blood and Urine Samples	• 10 microliters (µL) for OV16 IgG4 testing (see Section 7.4.3.1)	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.
Section 7.4.3.1: *O. volvulus* Exposure Test	A Standard Diagnostics Bioline Onchocerciasis IgG4 Rapid Test will be performed at Pre-screening to determine	Not applicable	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

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	prior exposure to O. volvulus, as per the manufacturer's instructions.		
Section 8.5: Storage and Handling	Unless otherwise labelled, the full contents of the container should be used within 24 hours or unused contents discarded.	Unless otherwise labelled, the full contents of the container should be used within 7 days or unused contents discarded.	Correction of the in-use period of the investigational product to align with the MDGH-MOX-1006 Investigational Product Dossier.
Section 10.3.2.2: Investigator Reporting Requirements for SAEs	An SAE may qualify for reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the investigational product and is unexpected (Suspected Unexpected Serious Adverse Reaction [SUSAR]) based upon the current Investigator's Brochure. In this case, investigators will receive a formal notification describing the SAE. Where required by local regulations, and in accordance with the local institutional policy, the investigator should notify the EC of SAEs within the required timelines.	Per Ghana Food and Drugs Authority guidelines, the investigator should report all SAEs to the Authority within 48 hours. Where required by local regulations, and in accordance with the local institutional policy, the investigator should also notify the EC of SAEs within the required timelines.	Based on feedback from Ghana Food and Drugs Authority, investigator SAE reporting requirements revised to reflect regulatory guidelines.
Section 13.5: Statistical and Analytical Plan	Not applicable	The SAP will be submitted to regulatory authorities prior to database lock, as required.	Clarification that SAP will be submitted to regulatory authorities prior to database lock, as required.
Section 14.1.10: Implementation of the Study in the Context of the COVID-19 Pandemic	Not applicable	Addition of new section (Section 14.1.10) describing the review of protocol procedures and measures that will be taken to adhere to national public health directives in relation to COVID-19 to ensure the safety of participants, their communities and the study team during the pandemic.	Per GHS Ethics Review Committee Guidelines for Researchers During the COVID-19 Pandemic (effective 7 May 2020), inclusion of information on procedures that will be put in place during the conduct of the study to minimize the risk of COVID-19 infection.
Section 14.5: Publication of Data (Dissemination of Results)	Not applicable	Per local regulatory guidelines, publication will only proceed 30 days after the Sponsor receives Ghana Food and Drug Authority's acknowledgement of receipt of the final study report.	As requested by the Ghana Food and Drugs Authority, section updated in accordance with regulatory guidelines.
Section 16.6: Model Adolescent (12 to 17 years) and Parent/Guardian	**What will happen in the study, where will it happen and how long will it take?**	**What will happen in the study, where will it happen and how long will it take?**	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

Section	Original Text	Revised to Read	Rationale for Change
Information Sheet and Assent and Consent Form	• We will take some drops of blood from a finger to see if you have ever had the oncho worms. If the test shows “no”, then you cannot take part in the study.  • If the test shows “yes”, then we will ask questions about health problems you have had in the past, medicines you have taken, look closely at your arms to see if it will be easy to take blood. **Help for your discussion with your parents/guardians, friends, family and others you want to talk this over with** • Step 1 Screening in your community to see whether you have oncho and ask questions about your health (1-2 days). 	• We will ask questions about health problems you have had in the past, medicines you have taken, look closely at your arms to see if it will be easy to take blood. **Help for your discussion with your parents/guardians, friends, family and others you want to talk this over with** • Step 1 Screening in your community to ask questions about your health (1-2 days).	
Section 16.7: Model Information Sheet and Consent Form for Parents/Guardians of Children 4 to 11 Years, Including Assent Form for Children 7 to 11 Years	**What will happen in the study, where will it happen and how long will it take?** • We will take some drops of blood from a finger to see if the child has the oncho worms. If the test shows “no”, then the child cannot take part in the study.	**What will happen in the study, where will it happen and how long will it take?** • We will ask questions about health problems you have had in the past, medicines taken, look closely at the child’s arm to see if it will be easy to take blood, and show an item that is the same size as the moxidectin tablets and ask the child	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

Section	Original Text	Revised to Read	Rationale for Change
	 • If the test shows “yes”, then we will ask questions about health problems you have had in the past, medicines taken, look closely at the child’s arm to see if it will be easy to take blood, and show an item that is the same size as the moxidectin tablets and ask the child and you if they could swallow a tablet of that size. **Help for your discussion with your parents/guardians, friends, family and others you want to talk this over with** • Step 1 Screening in your community to see whether you have oncho and ask questions about your health (1-2 days). 	and you if they could swallow a tablet of that size. **Help for your discussion with your parents/guardians, friends, family and others you want to talk this over with** • Step 1 Screening in your community to ask questions about the health of your child (1-2 days).	
Section 16.8: Model Information Sheet for Children 7 to 11 Years	**Where and when will this happen?** Here in your community, we will take a few drops of blood from your finger to test whether you have the oncho worm.	**Where and when will this happen?** Here in your community, we will ask your parents or guardians about your health. If we learn something about your health that makes us think it is better for you not to take part, we will tell you that you cannot take part in the study. If you are healthy and if you still want to take part, we will take you by car with one of your parents or guardians our place in Hohoe.	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

Section	Original Text	Revised to Read	Rationale for Change
	 We will also ask your parents or guardians about your health. If you do not have the oncho worm or we learn something about your health that makes us think it is better for you not to take part, we will tell you that you cannot take part in the study. If you have the oncho worm and if you still want to take part, we will take you by car with one of your parents or guardians our place in Hohoe.		
Section 16.9: Model Information Sheet for Children 4 to 6 Years and Older Children Considered Not Mature Enough to Provide Assent	**What will happen if you want to come to Hohoe?** First, we will ask your parents to tell us about your health and take a bit of blood from one of your fingers to find our whether you have the oncho worms.  If you don't have the oncho worm, you will not go to Hohoe. Also, if your parents tell us that you have health problems you will not go to Hohoe since it will be better for you not to do that. **What will happen if you can go to Hohoe?** If you do have the oncho worm, you and one of your parents will ride in a car together with	**What will happen if you want to come to Hohoe?** We will ask your parents to tell us about your health. If your parents tell us that you have health problems you will not go to Hohoe since it will be better for you not to do that. **What will happen if you can go to Hohoe?** If you do not have health problems, you and one of your parents will ride in a car together with other children and one of their parents to Hohoe.	Removal of Ov16 IgG4 testing for *O. volvulus* from protocol.

Section	Original Text	Revised to Read	Rationale for Change
	other children and one of their parents to Hohoe.		