Medicines Development for Global Health

CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double blind, parallel trial in the Democratic Republic of Congo (DRC) comparing the safety and efficacy of annual or biannual doses of moxidectin or ivermectin for treatment of onchocerciasis			
Sponsor:	Medicines Development for Global Health Level 1, 18 Kavanagh Street Southbank, Victoria 3006, Australia			
Investigational New Drug (IND) Number (if applicable):	IND 126876			
Protocol Number:	MDGH-MOX-3001			
Medical Monitor:	Dr Jolanta Airey Consultant Clinical Development Physician SJA Consulting Services, Australia Telephone: +61 409 020 209			
Protocol Version/Date:	**Current:**	Final v 03 (including Amendments 1 and 2)	**Date:**	30 Jun 2020
	Prior version:	Final v 02 (including Amendment 1)	**Date:**	16 Mar 2020

CONFIDENTIALITY STATEMENT

This study is being performed in compliance with Guidelines for Good Clinical Practice (GCP) as described in this protocol and all essential documents are being archived.

Until publication of this protocol following approval by the Ministère de la Santé Publique de la République Démocratique du Congo (MdSP) and the Ethics Committee (EC) assigned by the MdSP, any unpublished information contained in this document is the property of, or under the control of the Sponsor, and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and the MdSP and the EC. 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 the Sponsor, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

STUDY ACKNOWLEDGEMENT

A randomized, double blind, parallel trial in the Democratic Republic of Congo (DRC) comparing the safety and efficacy of annual or biannual doses of moxidectin or ivermectin for treatment of onchocerciasis

Protocol Number: MDGH-MOX-3001

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

MARK SULLIVAN	
Name (Printed)	Signature
	23 Jul 2020
	Date (dd mmm yyyy)

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details to conduct this study as described. I will conduct this study as outlined herein and in accordance with the principles outlined in the Declaration of Helsinki (2013), the International Ethical Guidelines for Health-related Research Involving Humans (2016), the ICH Good Clinical Practice guidelines (ICH E6(R2), 2016) and all applicable regulations and any updates to these if issued during the course of this study. I will make a reasonable effort to complete the study within the time designated.

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

TONY UKETY	
Principal Investigator's Name (Printed)	Signature
	06 AUG 2020
	Date (dd mmm yyyy)

STUDY SYNOPSIS

Protocol No.:	MDGH-MOX-3001
Study Title:	A randomized, double blind, parallel trial in the Democratic Republic of Congo (DRC) comparing the safety and efficacy of annual or biannual doses of moxidectin or ivermectin for treatment of onchocerciasis.
Investigational Products:	moxidectin, ivermectin, placebo
Indication:	Onchocerciasis.
Development Phase:	3b
Treatment arms:	1. Annual moxidectin treatment with 8 milligram (mg) per oral at Day 0, Months 12 and 24. 2. Annual ivermectin treatment with approximately 150 microgram/kilogram (µg/kg) per oral at Day 0, Months 12 and 24. 3. Biannual moxidectin treatment with 8 mg per oral at Day 0, Months 6, 12, 18 and 24. 4. Biannual ivermectin treatment with approximately 150 µg/kg per oral at Day 0, Months 6, 12, 18 and 24. To maintain the study blind, participants randomized to annual moxidectin or ivermectin will receive placebo at Months 6 and 18. The randomization algorithm will yield the following allocation ratios among the 4 treatment arms: 1:1 allocation ratio for the moxidectin biannual vs moxidectin annual treatment arms, 1:1 allocation ratio for the ivermectin biannual vs ivermectin annual treatment arms, 3:1 allocation ratio for moxidectin vs ivermectin for both the biannual and annual treatment arms.
Primary objectives:	To evaluate and compare: • The efficacy of moxidectin 8 mg at Month 12 after administration of one dose (at Day 0) and after administration of two doses (at Day 0 and Month 6) in individuals with *O. volvulus* infection; and • The safety of repeat dosing of moxidectin 8 mg and ivermectin (approximately) 150 µg/kg administered annually for three doses or biannually for five doses, up to 12 months after the last dose (Month 36).
Secondary objectives:	To evaluate and compare the efficacy of moxidectin 8 mg and ivermectin (approximately) 150 µg/kg administered annually or biannually to individuals with *O. volvulus* infection, in terms of microfilariae densities in the skin and the anterior chamber of the eyes up to Month 36.
Exploratory objectives:	To evaluate the impact of the four treatment regimens on: • Clinical signs and symptoms of onchocerciasis; and • *O. volvulus* macrofilariae.

Primary endpoints:	• Proportion of Full Analysis Set (FAS) participants in the moxidectin annual and biannual treatment arms with zero *O. volvulus* skin microfilariae at both Months 6 and 12 (sustained microfilariae response, SMR12); Microfilaridermia is determined by the count of four skin snips for each participant at each assessment; • Safety across all dose groups will be evaluated by the incidence and severity of adverse events (AEs) and measurement of vital signs up to and including Month 36 and liver function tests up to and including Month 12.
Secondary endpoints:	The following will be determined for each treatment arm: • SMR, defined as zero *O. volvulus* skin microfilariae sustained at all post-Baseline assessments up to and including each of Months 12, 18, 24, 30 and 36, respectively; • Sustained ocular microfilariae response, defined as zero live *O. volvulus* microfilariae in the anterior chambers of the eyes at all post-Baseline assessments up to and including each of Months 12, 18, 24, 30 and 36, respectively, in those with live microfilariae in the anterior chambers of the eyes before the first treatment; • Mean and median percent reduction (from pre-treatment) of skin microfilariae density (microfilariae per milligram, mf/mg) and live microfilariae in the anterior chambers of the eyes at Months 6, 12, 18, 24, 30 and 36; • The proportion of participants in each treatment group with zero skin microfilariae and zero live microfilariae in the anterior chambers of the eyes at each post-Screening assessment; • Mean skin microfilariae density at each post-Screening assessment and the mean and mean change from baseline; and the same endpoints for the number of live microfilariae in the anterior chambers of the eyes at each post-Screening assessment in those with live microfilariae in the anterior chambers of the eyes before the first treatment.
Exploratory endpoints:	The following will be determined across all dose groups: • The proportion of participants with, and nature and severity of, signs and symptoms of onchocerciasis at Months 6, 12, 18, 24, 30 and 36 in those with onchocerciasis signs and symptoms at Screening; and • The viability and fertility of male and female macrofilariae as determined by histopathology after nodulectomy 12 months after the last treatment.
Study design:	This is a randomized, double-blind, active controlled, single center, parallel clinical trial.
Number of participants:	Approximately 1000.
Study duration/participant:	Approximately 3 years.
Number of centers:	One coordinating center.

Inclusion criteria:	1. Provision of written informed consent, or assent with parental or guardian written consent. 2. Mean ≥ 10 *O. volvulus* mf/mg skin, determined by four skin snips. 3. Living in a village selected for the study. 4. Age ≥ 12 years. 5. All female participants of childbearing potential must commit to the use of a reliable method of birth control for the duration of treatment and until 3 months after completion of dosing with investigational product.
Exclusion criteria:	1. Pregnant or breast-feeding. 2. Any concurrent condition that, in the opinion of the Investigator, would preclude evaluation of response to treatment or would pose undue risk to the participant's health. 3. Has received ivermectin, oral diethylcarbamazine (DEC) or doxycycline (for > 2 weeks) within 6 months of Baseline. 4. Has received treatment with an investigational agent within the last 30 days (or 5 half-lives, whichever is longer) prior to Baseline. 5. Known or suspected allergy to ivermectin or moxidectin or their excipients. 6. Self-reported planned or ongoing activities within the study period that would make it unlikely that a participant will be available for all planned treatment rounds and follow-up examinations. 7. Weight > 88 kilograms. 8. Infection with *Loa loa*.
Duration of treatment per participant:	24 months.
Study procedures:	Individuals who provide voluntary written informed consent (or for minors, assent with parental/guardian consent) will be screened for eligibility. Those meeting all of the inclusion and none of the exclusion criteria will be eligible to participate. Participants will be randomized to one of the four treatment arms and treatment will be observed. Participants will be assessed for AEs (type, incidence, severity, temporal association with treatment and relatedness), vital signs, liver function (until 5 days after Month 12 study drug administration), skin microfilariae density, and, if present at Screening, selected onchocerciasis signs and symptoms and live microfilariae in the anterior chambers of the eyes. Nodulectomies for assessment of potential investigational product effect on macrofilariae will be conducted 12 months after the last treatment in those providing separate written consent. Refer to the Schedule of Assessments (Table 1).
Safety parameters:	See parameters detailed in Table 1.

Specialized analyses:	Assessment of skin microfilariae densities will be based on four skin snips from each participant (one from each iliac crest and each calf) at each assessment (i.e. Screening and every 6 months throughout the study). The samples will be weighed, immersed in normal saline for at least 8 hours and the emerging microfilariae counted by trained laboratory staff using an inverted microscope. Live microfilariae in the anterior chamber of the eye will be determined with a portable slit lamp. Viability and fertility of macrofilariae in the excised nodules will be determined via histopathology.
Sample size:	The sample size and randomization ratio will provide safety data for up to a total of 3000 exposures to moxidectin and 1000 exposures to ivermectin, providing a probability of around 0.95 and 0.63 to detect at least 1 or more AEs with a true background rate of 0.001, respectively, assuming exposures are independent. This is considered to provide sufficient data for assessment of safety of repeat doses of moxidectin compared with ivermectin. This sample size provides greater than 95% statistical power at a two-tailed alpha level of 0.05 for the comparison of the primary outcome, SMR at Month 12 (SMR12) in the biannual versus annual moxidectin treatment arms.
Statistical analyses:	The primary efficacy hypothesis is a test of the average treatment effect with respect to achieving a sustained microfilariae response at Month 12 (SMR12) when comparing FAS participants in the moxidectin biannual versus annual treatment arms. The average treatment effect will be estimated by the standardized risk difference (RD) using the methodology outlined by Steingrimsson and colleagues (Steingrimsson et al. 2017).
Further analyses:	The data from this study will be combined with the data from other studies to model the time to *O. volvulus* elimination with annual or biannual mass drug administration with moxidectin or ivermectin and the cost-effectiveness of each strategy.
Data Safety Monitoring Board Review:	A data safety monitoring board (DSMB) will undertake a review of serious adverse events (SAEs) reported during the first month after each round of treatment to advise the Sponsor on initiation of the next treatment round.

Table 1: Schedule of Assessments

	Screening	Baseline		Follow Up											Early Exit [i]
	D-30 to -1	D-1 to D0	D0	D1 to 5	M6 (+/-1M)	M6 +D1 to 5	M12 (+/-1M)	M12 +D1 to 5	M18 (+/-1M)	M18 +D1 to 5	M24 (+/-1M)	M24 +D1 to 5	M30 (+/-1M)	M36 (+/-2M)	
Written informed consent [a]	X	X												X	
Demography	X														
Medical History and Concurrent Conditions	X														
Prior and Concurrent Medications	X	X[f]		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [b]	X	X[f]		X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X														
Nodule count	X													X	
Onchocerciasis signs and symptoms	X				X		X		X		X		X	X	X
Height	X														
Weight	X				X		X		X		X				
Urine pregnancy test [c]	X	X[f]			X		X		X		X		X		
Ocular microfilariae count [d]	X				X		X		X		X		X	X	
Ocular examination [d]	X						X				X			X	
***Loa* assessment [e]**	X														
Skin snips	X				X		X		X		X		X	X	X
Determination of eligibility	X	X													
Targeted physical examination		X[f]		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Liver function tests [g]		X		X	X	X	X	X							X[h]
Randomization	X														
Investigational product administration			X		X		X		X		X				
Blood pressure and pulse rate				X		X		X		X		X			
Nodulectomy														X	

Abbreviations: D: day; M: month.

[a] Written informed consent (or assent with parental/guardian written consent) will be obtained separately for Screening, study participation and nodulectomy.

[b] Body temperature, respiratory rate, pulse rate and blood pressure assessed semi-supine at Screening and before each treatment; Pulse rate and blood pressure on Day 1 to 5 after each investigational product administration.

[c] For women and girls of childbearing potential who will also undergo counselling on contraception.

[d] Follow up examinations for participants as indicated by findings at Screening.

[e] If participant has lived or worked or is currently temporarily working in an area endemic for loaisis or reports symptoms compatible with *Loa* infection such as a history of eye worm.

[f] Targeted physical examination, concurrent medication, and vital signs if > 3 days, and pregnancy test only if > 1 day have elapsed since Screening.

[g] Pre-treatment and at Day 5 after dosing (D0, Month 6 and Month 12 only).

[h] If early exit is before Day 5 after dosing at Day 0, Month 6 or Month 12

[i] Not required in case of withdrawal at or after the Month 30 visit.

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Table 2: Abbreviations and Acronyms

Abbreviation	Term
%	percent
<	less than
>	greater than
±	plus or minus
≤	less than or equal to
≥	greater than or equal to
°C	degrees Celsius
β-HCG	beta-human chorionic gonadotrophin
µg	microgram
µL	microliter
µM	micromolar
µmol	micromole
AE	adverse event
AP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
APOC	African Programme for Onchocerciasis Control (1995-2015)
AST	aspartate aminotransferase
CECA/20	20ème Communauté Evangélique au Centre de l'Afrique
CI	confidence interval
CIOMS	Council of International Organizations of Medical Sciences
cm	centimeters
CNS	central nervous system
CRMT	Centre de Recherche en Maladies Tropicales
CYP	cytochrome
DEC	diethylcarbamazine
DPS	Division Provinciale de la Santé
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDCTP	European & Developing Countries Clinical Trials Partnership
eSource	Electronic Source, defined as data captured directly into a permanent electronic record
FAS	full analysis set
GABA	gamma aminobutyric acid
GCP	good clinical practice
GGT	gamma-glutamyl transferase
Ha	alternative hypothesis
H_0	null hypothesis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
kg	kilogram
LDH	lactate dehydrogenase
LD_{50}	50% lethal dose
MDGH	Medicines Development for Global Health
MdSP	Ministère de la Santé publique (Ministry of Health)
mf	microfilariae
mg	milligram
mmHg	millimeter of mercury
mL	milliliter
N	number
NDA	new drug application

Abbreviation	Term
NTD	neglected tropical diseases (MTN Maladies Tropicales Négligées)
O. volvulus	*Onchocerca volvulus*
OR	odds ratio
P-gp	P-glycoprotein
PICF	participant information document and informed consent and assent forms
PK	pharmacokinetics
QT	cardiac Q-wave to T-wave
RA	Regulatory authority, the unit in the MdSP responsible for authorizing and overseeing use of investigational products
REMO	Rapid Epidemiological Mapping of Onchocerciasis
RD	risk difference
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SFP	study focal point (village member(s) selected by the villagers to serve as focal point(s) within a village)
SMR	sustained microfilariae response
SMR12	zero *O. volvulus* skin microfilariae counts at both Months 6 and 12
SMR18	zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, and 18
SMR24	zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18 and 24
SMR30	zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18, 24, and 30
SMR36	zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18, 24, 30, and 36
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half life
TEAE	treatment emergent adverse event defined as AEs which start after the first administration of investigational product
t_{max}	median time of maximum observed concentration
US FDA	Food and Drug Administration of the United States of America
WHO	World Health Organization
WHO/TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
ZSR	Zone de Santé Rurale (Rural Health Zone), administrative health care unit in rural areas of DRC. A ZSR includes several Aire de Santé.

2 INTRODUCTION

2.1 Onchocerciasis

Onchocerciasis (river blindness) is a serious, debilitating, and stigmatizing parasitic disease caused by the helminth *Onchocerca volvulus* (*O. volvulus*). It is recognized as an important public health issue by health authorities worldwide and is listed by the World Health Organization (WHO) (African Programme for Onchocerciasis Control 2015) and United States (US) Food and Drug Administration (FDA) (The Henry J. Kaiser Family Foundation 2015) as one of the Neglected Tropical Diseases (NTDs) for which new treatments are sought.

Onchocerciasis is endemic in sub-Saharan Africa. More than 200 million people are currently 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 area of the Onchocerciasis Control Program in West Africa (a WHO managed international collaboration that ran between 1974 to 2002) (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 into the eyes. Macrofilariae 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 skin microfilariae are the reservoir of transmission of the parasite by the vector (Remme et al. 2017)

The Global Burden of Disease 2013 study estimated that onchocerciasis is the sixth highest cause of NTD-related years lived with disability, predominantly due to onchocercal skin disease (Herricks et al. 2017). In the Global Burden of Disease study 2017, it was identified as the leading cause of years lived with disability for the Democratic Republic of the Congo (DRC) (Vos et al. 2017). The disease reduces income-generating capacity, incurs substantial health expenditures, and exerts a devastating socioeconomic effect on already challenged communities.

2.2 Current Treatment and Unmet Need

Ivermectin is an endectocide approved in 1996 for the treatment of onchocerciasis in the US and is available through the Mectizan Donation Program to all onchocerciasis endemic countries, including 29 countries in sub-Saharan Africa, for treatment of onchocerciasis. It is the current standard of care for onchocerciasis. The recommended regimen for the treatment of onchocerciasis is a single oral dose of ivermectin 150 µg/kg.

In sub-Saharan Africa, including the DRC, ivermectin mass drug administration is now the standard strategy of onchocerciasis control programs. It is implemented as community directed treatment with ivermectin, with height, rather than weight-based dosing, and most commonly with a retreatment interval of 12 months. More than 200 million people are currently considered to require community directed treatment with ivermectin. In the DRC, 39.8 million people received ivermectin in 2018 among an estimated 50.4 million requiring mass drug administration (World Health Organization 2018).

Epidemiological evaluations via microscopic examination of skin snips and health impact assessments conducted by the African Programme for Onchocerciasis Control (APOC, 1995 to 2015) in collaboration with country control programs (including in the DRC) have shown that long term community directed treatment with ivermectin significantly reduces *O. volvulus* infection prevalence and morbidity (Coffeng et al. 2014, Tekle et al. 2016).

Despite the positive impact of ivermectin treatment, onchocerciasis is still a cause of significant morbidity. Incomplete clearance of dermal or ocular microfilariae and/or rapid repopulation have been observed in a substantial subset of both ivermectin-naïve and ivermectin-experienced *O. volvulus*-infected individuals (African Programme for Onchocerciasis Control , Awadzi et al. 2004, Awadzi et al. 2004, 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). This also occurred in ivermectin-treated participants in the moxidectin Phase III study, which included 472 participants from Ituri and 487 from Nord-Kivu of the DRC (Opoku et al. 2018). Using a responder definition of < 20% of pre-treatment skin microfilariae density at 6 months and ≤ 40% of pre-treatment skin microfilariae density at 12 months, there were no suboptimal responders at Month 6 in the moxidectin group and 10/941 (1.1%) at Month 12. By contrast, 59/492 (12.0%) and 88/481 (18.3%) ivermectin recipients were suboptimal responders at Months 6 and 12, respectively.

The primary goal of onchocerciasis control in Africa has recently shifted from control as a public health problem (reduction of morbidity and transmission in meso- and hyperendemic areas: i.e. areas with villages with around 35 to 60% and > 60% infection prevalence, respectively (Prost 1987)) to elimination of infection and transmission across all endemic areas. The time of elimination using ivermectin alone is predicted to be after 2040 in some territories (Kim et al. 2015). As summarized by APOC, which supported onchocerciasis control until 2015, the global health community recognizes that onchocerciasis will not be eliminated without new tools and strategies (African Programme for Onchocerciasis Control 2015).

In the Phase II and III studies conducted in Ghana, Liberia and the DRC (Ituri, Nord Kivu), a single dose of moxidectin was superior to a single dose of ivermectin in reducing microfilaridermia and in maintaining low microfilariae densities for 18 months after dosing (Awadzi et al. 2014, Opoku et al. 2018). Consequently, moxidectin has the potential to accelerate progress towards elimination of onchocerciasis (Turner et al. 2015).

2.3 Moxidectin

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

Evaluation of moxidectin for its utility for onchocerciasis control was initiated by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) executed by WHO. The pharmaceutical company with which WHO/TDR was working for potential regulatory registration of moxidectin discontinued the collaboration. WHO licensed all data to Medicines Development for Global Health (MDGH), the Sponsor of this study. MDGH raised the funds, initiated discussions for registration with the US FDA, completed development and assembly of the New Drug Application (NDA) and submitted the NDA to the US FDA in 2017 (Sullivan and Kuesel 2018).

Moxidectin 8 mg was approved in June 2018 by the US FDA for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older (information available at www.accessdata.fda.gov/scripts/cder/daf). This study corresponds to one of the commitments MDGH made to the US FDA. It is, along with a pediatric study to determine

the moxidectin dose for 4 to 11 year olds (MDGH-MOX-1006, Study 1006, https://clinicaltrials.gov/ct2/show/NCT03962062), being conducted under a US FDA Investigational New Drug (IND) Application. For further information see Sections 15.24 and 18). In addition, MDGH will concurrently conduct a large single-dose safety study (Protocol number MDGH-MOX-3002, Study 3002) in Ituri (and potentially other locations) based on discussions with the WHO Neglected Tropical Disease Department.

Prior to submission of this protocol to the Regulatory Authority (RA) within the Ministère de la Santé publique de la République Démocratique du Congo (MdSP) and the ethics committee (EC) in DRC, it underwent scientific and regulatory review by the US FDA and requested changes were implemented.

This section presents a brief summary of the known preclinical and clinical data of moxidectin that formed the basis for the June 2018 US FDA approval. 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).

2.3.1 Nonclinical Data

2.3.1.1 Pharmacology

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 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 *O. ochengi* model in cattle (Trees et al. 2000).

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

2.3.1.2 Nonclinical Safety

2.3.1.2.1 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 IC_{50} value for a 50% decrease 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 electrocardiogram (ECG), including the cardiac Q-wave to T-wave (QT) interval.

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

2.3.1.2.2 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 of moxidectin 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 (50% lethal dose (LD_{50}) was 0.46 and 2.3 micromole (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.

2.3.1.3 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/ABCG2 (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 2.3.2.1).

In rats, 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.

2.3.2 Clinical Data

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

In the six Phase I studies, 243 healthy volunteers received moxidectin at doses of 3 to 36 mg and 16 healthy volunteers received placebo:

- A single-ascending dose, placebo-controlled, double-masked, safety, tolerability, and pharmacokinetic study of orally administered moxidectin in normal volunteers (Study 100, protocol 3110A1-100-EU) (Cotreau et al. 2003);
- A study of the relative bioavailability of a tablet and a liquid formulation of moxidectin in healthy participants (Study 101, protocol 3110A1-101-EU) (Korth-Bradley et al. 2012);
- An open-label, single-dose study to evaluate the excretion of moxidectin into the breast milk of lactating, non-breastfeeding women (Study 1002, protocol 3110A1-1002-EU) (Korth-Bradley et al. 2011);
- An open-label, single-dose, four-period, sequential study to determine the effect of moxidectin on CYP3A4 activity in healthy participants using midazolam as a probe substrate (Study 1004, protocol 3110A1-1004-EU) (Korth-Bradley et al. 2014);
- 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 participants (Study 1005, protocol 3110A1-1005-EU) (Korth-Bradley et al. 2012); and
- A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the potential effect of a single oral dose of moxidectin on the cardiac Q-wave to T-wave (QT interval) of healthy volunteers (Study 1008, protocol MDGH-MOX-1008) (Kinrade et al. 2018).

In one Phase II and one Phase III study enrolling participants with onchocerciasis, 1105 participants received moxidectin at doses of between 2 and 8 mg while 539 received ivermectin at the standard-of-care dose of 150 µg/kg and as used in ivermectin-based control programs:

- A randomized, single-ascending-dose, ivermectin-controlled, double-blind, safety, tolerability, pharmacokinetic, and efficacy study of orally administered moxidectin in participants with *Onchocerca volvulus* infection (Phase II, protocol 3110A1-200-GH) (Awadzi et al. 2014); and
- A single dose, ivermectin-controlled, double blind, efficacy, safety, and tolerability study of orally administered moxidectin in participants infected with *Onchocerca volvulus* (Phase III, protocol ONCBL60801) (Opoku et al. 2018).

2.3.2.1 Clinical Pharmacology

Moxidectin displays linear, dose-proportional pharmacokinetics. Following a single oral moxidectin dose administered to fasting healthy volunteers, the non-compartmentally-derived apparent moxidectin plasma clearance ranged from 2760 to 3506 mL/hour in healthy volunteers and was 3500 mL/hour in *O. volvulus* infected individuals. The mean $t_{½}$ ranged from 485 to 1139 hours (approximately 20 to 47 days) in healthy volunteers and was 559 hours in *O. volvulus* infected individuals. Moxidectin was rapidly absorbed; the median time of maximum observed plasma concentration (t_{max}) in a fasted state was 3 to 4 hours post-dose. Moxidectin has a large apparent volume of distribution, and rapid decline of moxidectin concentrations occurred within 48 hours of dose administration in all studies, and, thereafter, plasma concentrations declined slowly in accordance with the long $t_{½}$.

Population pharmacokinetic analyses showed that the long t½ was governed by tissue distribution rate-limited elimination.

There were no clinically relevant effects of age, sex, 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.

2.3.2.2 Clinical Safety

2.3.2.2.1 Overview of Safety in Healthy Volunteers

Safety data are available from 6 studies in healthy adult volunteers. Moxidectin was well tolerated when given as a single dose of between 3 and 36 mg to healthy volunteers. There was no treatment or dose 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 electrocardiograms (ECGs)/cardiac function. In placebo-controlled studies, moxidectin had a safety profile similar to placebo. No participant 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.

2.3.2.2.2 Overview of Safety in Individuals with Onchocerciasis

In individuals infected with *O. volvulus* who received treatment that led to the death of microfilariae, the common AEs observed are the signs and symptoms associated with microfilariae death, i.e. drug efficacy associated AEs, referred to as the "Mazzotti reaction". These reactions are caused by an immune reaction to the dead and dying 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.

The safety of moxidectin has been evaluated in comparison to the safety of ivermectin in two studies in *O. volvulus* infected individuals (3110A1-200-GH and ONCBL60801) (Awadzi et al. 2014, Opoku et al. 2018). In both studies, the profile of AEs reported for individuals having received moxidectin was similar to the profile in ivermectin recipients.

In these studies, the most commonly occurring events were signs and symptoms attributable to the body's response to dying microfilariae: pruritus, edema, headache, hypotension and compensatory tachycardia, rash and urticaria, myalgia, arthralgia, pyrexia and chills, lymphadenopathy, paresthesia and asthenia. 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 participants 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 treatment guidance to patients and physicians in the US FDA prescribing information for moxidectin are otherwise unchanged compared to ivermectin.

Treatment Emergent Adverse Events (TEAEs) occurring in > 10% of moxidectin-treated participants in the Phase III study compared with ivermectin-treated participants are summarized in Table 3.

For further information refer to the Investigator's Brochure.

Table 3: Treatment Emergent Adverse Events Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III)

Treatment Emergent Adverse Events	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

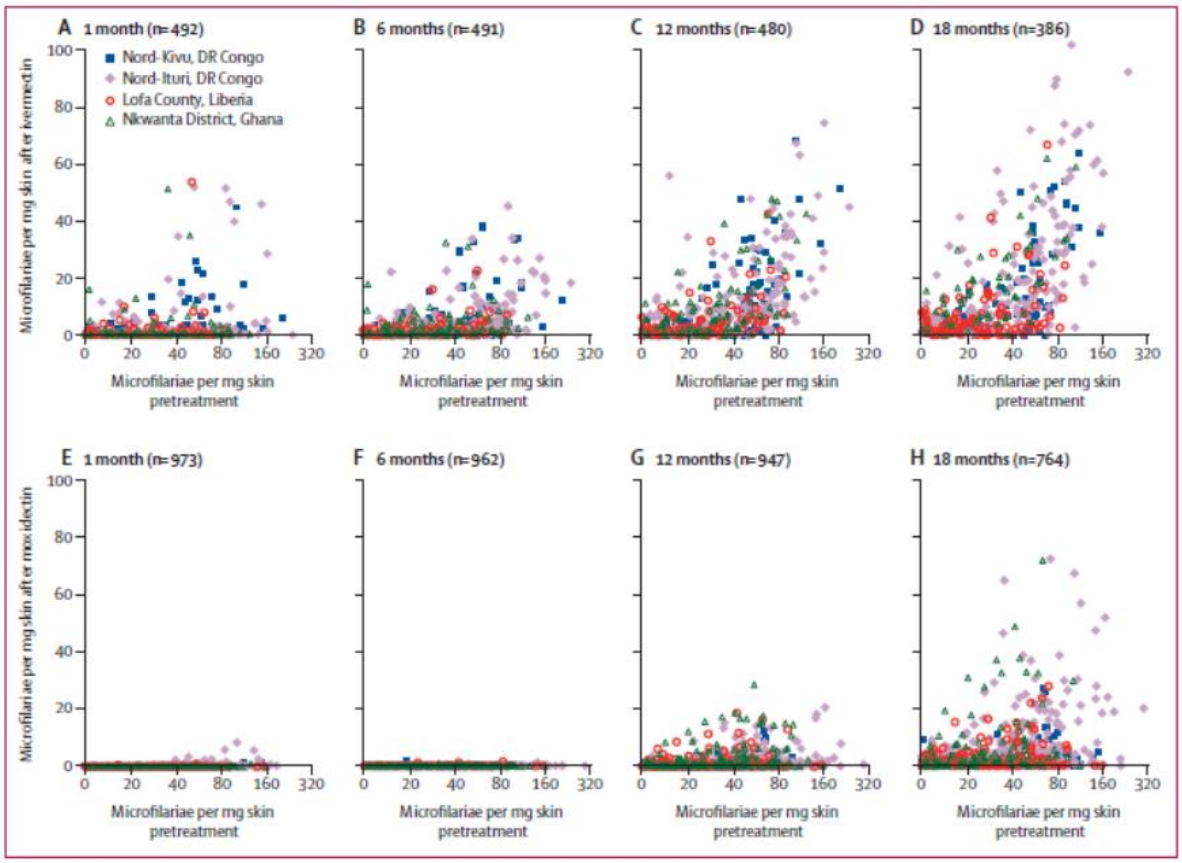
There was no pattern indicating a temporal association with treatment or with body system of SAEs occurring in either the 3110A1-200-GH or the ONCBL60801 studies. In both studies, there were no SAEs regarded by the investigator (or Sponsor) as being treatment-related. Treatment-emergent SAEs (occurring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

2.3.2.3 Clinical Efficacy

In the two studies conducted in *O. volvulus* infected individuals (3110A1-200-GH and ONCBL60801), a single dose of moxidectin was superior to a single dose of ivermectin in reducing skin microfilariae density and maintaining low skin microfilariae density (Awadzi et al. 2014, Opoku et al. 2018).

In the Phase III study (ONCBL60801), the mean skin microfilariae density at 12 months after treatment was significantly lower in the moxidectin group (1.79 mf/mg) than in the ivermectin group (9.83 mf/mg) (95% Confidence Interval (CI) for the difference -9.11, -6.98, $p < 0.0001$) (moxidectin Prescribing Information, available at www.fda.gov/drugsatfda). Skin microfilariae densities were also significantly lower in the moxidectin than the ivermectin treatment group at all other post-treatment time points evaluated in this study (Figure 1).

Figure 1: Skin Microfilariae Densities 1, 6, 12 And 18 Months after a Single Dose of Ivermectin (A-D) and after a Single Dose of Moxidectin (E-H) in the Phase III Study By Study Area and Pre-Treatment Skin Microfilariae Density



X-axis shows pre-treatment skin microfilariae density on a logarithmic scale; y-axis shows post-treatment skin microfilariae density on an arithmetic scale. From Opoku, Bakajika et al. 2018 (Opoku et al. 2018).

Both ivermectin and moxidectin reduced the number of live microfilariae in the anterior chambers of the eyes.

2.4 Study Overview

Onchocerciasis affects all members of a community, with risk of infection increasing with transmission exposure over time. A single dose of moxidectin 8 mg was shown to be superior to ivermectin 150 µg/kg in suppressing skin and ocular microfilariae in the moxidectin Phase II and III studies, in more patients, to a greater extent and for longer.

Based on the Phase II and III data, it is anticipated that biannual moxidectin administration may be better than annual re-treatment to achieve complete clearance of microfilariae between treatments, thus minimizing onchocerciasis symptoms in infected individuals and the reservoir for parasite transmission.

This study is designed to provide comparative data on the safety and efficacy of moxidectin given at annual and biannual re-treatment frequencies for two years to assess whether biannual dosing with moxidectin results in even greater treatment benefit than annual dosing. Furthermore, this study will provide comparative data on the safety and efficacy of moxidectin and ivermectin.

Study 3001 is open to participants meeting all the inclusion and none of the exclusion criteria, including adolescents aged 12 to 17 years. This age group was also enrolled in the Phase III study and the adolescent data was submitted in 2017 to the US FDA in support of moxidectin's marketing application and is reflected in the US FDA moxidectin Prescribing Information.

An appropriate dose for children under 12 years is yet to be established. A study in children 4 to 11 years (Study 1006) will be conducted to establish an appropriate dose for this age group. (https://clinicaltrials.gov/ct2/show/NCT03962062)

The data from study 3001 will complement already available data as well as those obtained from the pediatric study (Study 1006) and the large single dose safety study (Study 3002) to inform potential inclusion of moxidectin in onchocerciasis control and elimination guidelines and policies.

2.4.1 Design Rationale

A randomized, double-blind study design was selected to minimize bias in treatment allocation, participant assessment and recording and management of the study data. Annual and biannual treatment was chosen because this reflects the most common ivermectin dosing frequencies used by African onchocerciasis control and elimination programs.

The two year treatment duration with three annual or five biannual treatments was chosen because it is expected to be sufficient to inform onchocerciasis elimination programs about the relative benefits and risks of the four treatment regimens. To further increase the information available for decision making by the programs, the data generated in this study will complement those available from previous studies to model time-to onchocerciasis elimination with annual or biannual mass administration of moxidectin or ivermectin and the cost-effectiveness of these four strategies (Section 15.20.1).

Randomization in a ratio 3:1 to moxidectin:ivermectin treatment for both the annual and biannual treatment arms was chosen to maximize the amount of safety data available for moxidectin treatment while ensuring sufficient concurrently obtained data on the safety of ivermectin treatment.

Randomization will be stratified by Aire de Santé of residence to minimize the potential impact of confounding effects of the incidence of new infections (which depends on local vector density and prior history of ivermectin treatment in the area where study participants live and work). Furthermore, randomization will be stratified by screening skin microfilariae density (< 20 mf/mg skin vs. ≥ 20 mf/mg skin) because the frequency and severity of some Mazzotti reactions as well as the post-treatment increase in skin microfilariae density are impacted by pre-treatment skin microfilariae density (Opoku et al. 2018).

2.4.2 Study Population and Location

The study population is designed to be similar to the population recruited into the Phase III study: people ≥ 12 years with at least 10 mf/mg skin from areas where community directed treatment with ivermectin has not yet or only relatively recently been implemented.

The study will be conducted in Ituri Province (Figure 2), principally in the Zone de Santé Rurale (ZSR) of Logo, with possible extension of the recruitment area into the ZSR of Nyarambe (primary recruitment area) (Figure 3).

In view of civil unrest in these areas or the Ebola outbreak possibly preventing implementation or completion of the study in that area, the ZSR of Aru is planned as the backup recruitment area (Figure 4).

Figure 2: Map of the Democratic Republic of Congo with its 26 Provinces

Figure 3: Map of the Zone de Santé Rurale (ZSR) Logo with adjacent ZSR Nyarambe in Ituri Province (primary recruitment area)

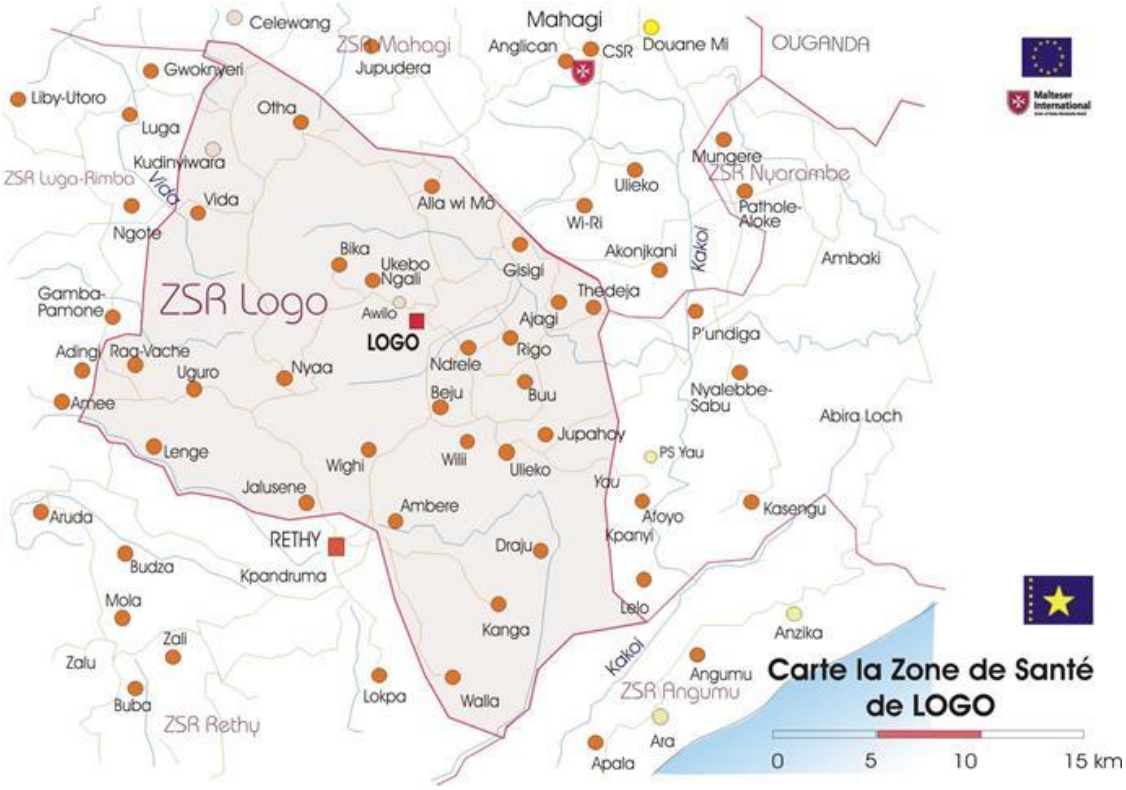
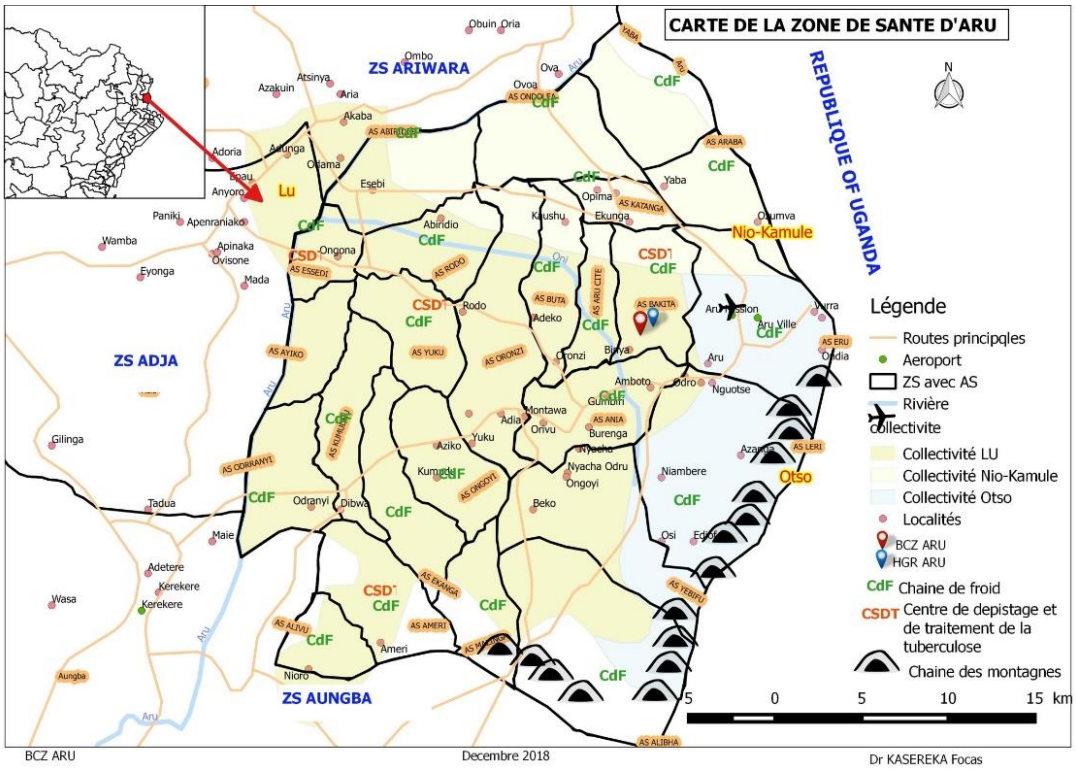


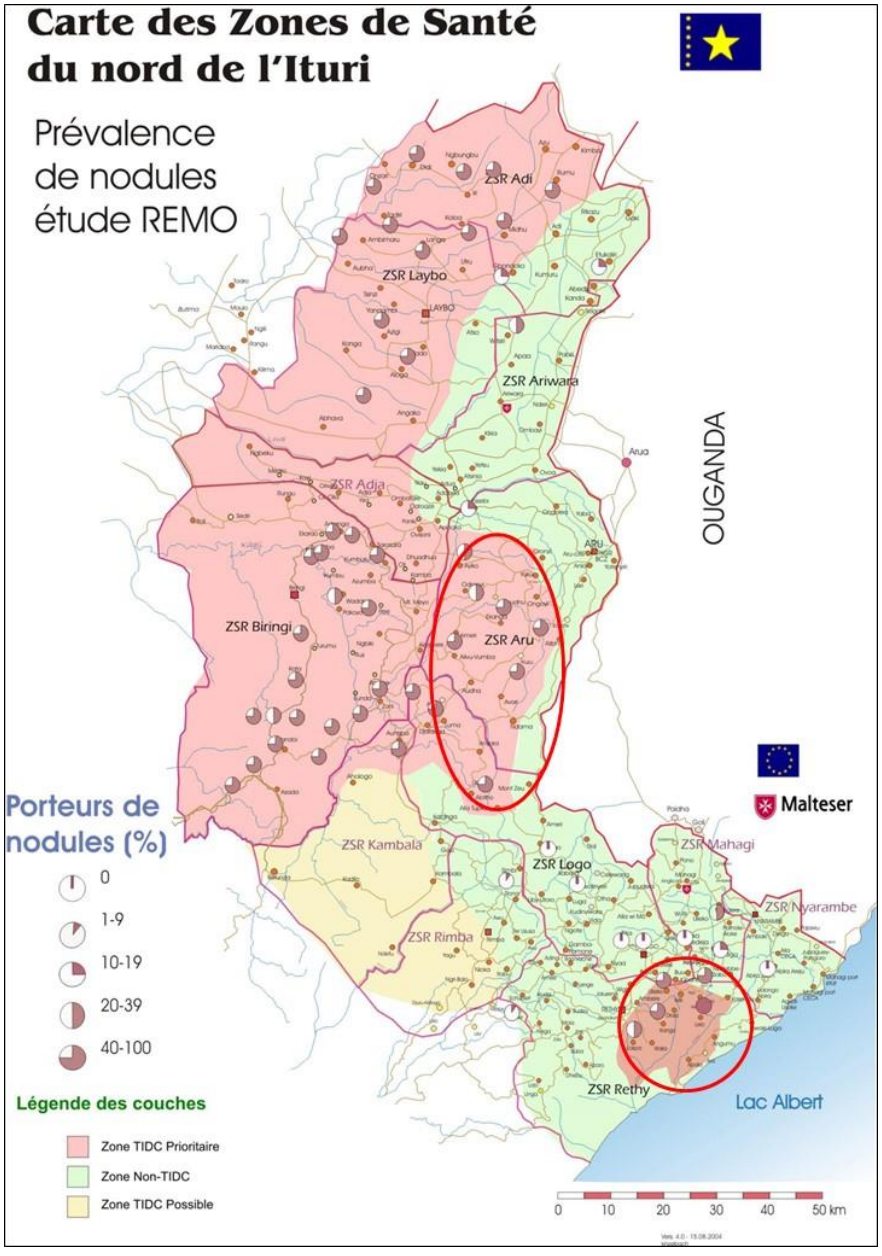
Figure 4: Map of the Zone de Santé Rurale (ZSR) Aru in Ituri Province (backup recruitment area)



The primary as well as the backup recruitment areas were selected for the following reasons:

- Epidemiological surveys conducted by the national onchocerciasis control program in 2002 indicate that many villages are onchocerciasis meso- or hyper-endemic (Figure 5);
- Data obtained during screening in the ZSR Logo for the Phase III moxidectin study found 66.7% were infected with *O. volvulus* (by skin snip);
- The areas are not endemic for *Loa loa* infection; and
- Ivermectin treatment has not yet been implemented (ZSR Logo and Aru) or only relatively recently (since 2016 in the ZSR Nyarambe for lymphatic filariasis control).

Figure 5: Results of Rapid Epidemiological Mapping (REMO) of onchocerciasis conducted by the national onchocerciasis control program Ituri Nord in 2002 with the primary and backup recruitment areas encircled in red



Considerations for identifying the villages from which individuals will be recruited will include the following:

- Acceptability of the research to the village community;
- Prior information on onchocerciasis endemicity including, but not limited to, available endemicity data and/or proximity to known vector breeding sites;
- The number and timing of prior ivermectin treatment rounds;
- Accessibility of the village; and
- Proximity of the village to local health facilities.

2.4.3 Rationale for Efficacy Assessments

Efficacy will be determined by microscopic measurement of *O. volvulus* skin microfilariae density in skin snips, the method used in previous ivermectin and moxidectin studies and the most accepted, robust and reproducible quantitative measure of efficacy for microfilaricidal drugs. Skin microfilariae are the primary cause of non-ocular morbidity and the reservoir for transmission.

Effects on ocular microfilariae will be assessed by the standard and field-suitable method for counting live microfilariae in the anterior chambers of the eyes using a portable slit lamp. Ocular microfilariae are the primary cause of ocular morbidity.

The effect on macrofilariae viability and reproductive activity will be explored via histopathology, the standard method used in clinical studies examining this effect. The macrofilariae are the source of dermal and ocular microfilariae.

The effect on onchocerciasis clinical signs and symptoms will be explored for those signs and symptoms that are reversible and can be attributed with reasonable certainty to *O. volvulus* infection (reactive skin lesions and pruritus).

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

The primary objectives of this study are to evaluate and compare:

- The efficacy of moxidectin 8 mg at Month 12 after administration of one dose (at Day 0) and after administration of two doses (at Day 0 and Month 6) in individuals with *O. volvulus* infection; and
- The safety of repeat dosing of moxidectin 8 mg and ivermectin (approximately) 150 µg/kg administered annually for three doses or biannually for five doses, up to 12 months after the last dose (Month 36).

3.1.2 Secondary Objective

The secondary objective of this study is to evaluate and compare the efficacy of moxidectin 8 mg and ivermectin (approximately) 150 µg/kg administered annually or biannually to individuals with *O. volvulus* infection, in terms of microfilariae densities in the skin and the anterior chamber of the eyes up to Month 36.

3.1.3 Exploratory Objectives

The exploratory objectives of this study are to evaluate the impact of the four treatment regimens on:

- Clinical signs and symptoms of onchocerciasis; and
- *O. volvulus* macrofilariae.

3.2 Endpoints

3.2.1 Primary Endpoints

The primary endpoints for this study are:

- Proportion of FAS participants in the moxidectin annual and biannual treatment arms with zero *O. volvulus* skin microfilariae at both Months 6 and 12 (sustained microfilariae response, SMR12);
  Microfilaridermia is determined by the count of four skin snips for each participant at each assessment;
- Safety across all dose groups will be evaluated by the incidence and severity of adverse events (AEs) and measurement of vital signs, up to and including Month 36 and liver function tests up to and including Month 12.

3.2.2 Secondary Endpoints

The secondary endpoints for this study will be determined for each treatment arm and are:

- SMR, defined as zero *O. volvulus* skin microfilariae sustained at all post-Baseline assessments up to and including each of Months 12, 18, 24, 30 and 36, respectively;
- Sustained ocular microfilariae response, defined as zero live *O. volvulus* microfilariae in the anterior chambers of the eyes at all post-Baseline assessments up to and including each of Months 12, 18, 24, 30 and 36, respectively, in those with live microfilariae in the anterior chambers of the eyes before the first treatment;
- Mean and median percent reduction (from pre-treatment) of skin microfilariae density (mf/mg) and live microfilariae in the anterior chambers of the eyes at Months 6, 12, 18, 24, 30 and 36;
- The proportion of participants in each treatment group with zero skin microfilariae and zero live microfilariae in the anterior chambers of the eyes at each post-Screening assessment;
- Mean skin microfilariae density at each post-Screening assessment, and the mean and mean change from Baseline, and the same endpoints for the number of live microfilariae in the anterior chambers of the eyes at each post-Screening assessment in those with live microfilariae in the anterior chambers of the eyes before the first treatment.

3.2.3 Exploratory Endpoints

The exploratory endpoints for this study will be determined across all dose groups and are:

- The proportion of participants with, and nature and severity of, signs and symptoms of onchocerciasis at Months 6, 12, 18, 24, 30 and 36 in those with onchocerciasis signs and symptoms at Screening;
- The viability and fertility of male and female macrofilariae as determined by histopathology after nodulectomy 12 months after the last treatment.

4 STUDY DESIGN

4.1 Study Design

This is a randomized, double blind, active controlled, single center, parallel clinical trial. For further details and the rationale, see Section 2.4.1.

4.2 Dosing Regimens

Participants will be randomized to one of the following four treatment regimens:

1. Annual moxidectin: 8 mg per oral given on Day 0, Months 12 and 24.

2. Annual ivermectin: approximately 150 µg/kg per oral on Day 0, Months 12 and 24.
3. Biannual moxidectin: 8 mg per oral on Day 0, Months 6, 12, 18 and 24.
4. Biannual ivermectin: approximately 150 µg/kg per oral on Day 0, Months 6, 12, 18 and 24.

To maintain the study blind, participants randomized to annual moxidectin or ivermectin will receive placebo at Months 6 and 18.

4.3 Number of Participants and Randomization

Approximately 1000 eligible participants will be randomized in a ratio of 3:1:3:1 to annual moxidectin, annual ivermectin, biannual moxidectin or biannual ivermectin treatment, respectively.

4.4 Study Site

This will be a community-based study conducted in the north-east of the DRC coordinated by the Centre de Recherche en Maladies Tropicales (CRMT) de l'Ituri. The CRMT was established for the moxidectin Phase III study. The infrastructure provided for the Phase III study will be utilized and expanded upon for this study. Some of the personnel involved in the Phase III study will also work on this study.

Details on the areas in which participants will be recruited are provided in Section 2.4.2 .

4.5 Study Duration for Each Participant

The study duration for each participant is approximately 3 years including approximately 1 month for screening and 36 months for treatment and follow up.

4.6 Estimated Duration of the Study

It is anticipated that the total duration of the study from initiation to completion will be approximately 50 months, comprised of approximately 5 months for recruitment, 36 months treatment and post-treatment follow up, and 9 months for data analysis and reporting.

4.7 Concurrent Safety Study

People ineligible for this study (e.g. because their mean skin microfilariae density is < 10 mf/mg) and/or people who don't want to commit to participation in the 3 year Study 3001 which includes multiple efficacy assessments, will be offered participation in a concurrent study.

In the concurrent study (Study 3002), participants with any skin microfilariae density and without detectable skin microfilariae will be randomized to receive a single dose of moxidectin 8 mg or ivermectin approximately 150 µg/kg and followed up for adverse events for 3 months.

Study 3002 will be conducted under a separate protocol (numbered MDGH-MOX-3002) in response to information obtained from the WHO Neglected Tropical Disease Department regarding safety data required to inform WHO Guidelines on the use of moxidectin for onchocerciasis control and elimination. Please refer to that study protocol for more information.

5 PRE-STUDY ENGAGEMENT

5.1 Community Mobilization

All relevant communities will be provided with general information about onchocerciasis and its control, clinical research, and the two studies planned to be conducted in the area (this protocol and Study 3002).

For the purpose of this study, "Community" includes the following groups:

- Government authorities, including the Governor of the Ituri Province, Ministry of Health of the Ituri Province and local security forces;
- Members of the provincial and national parliament representing the area from which participants will be recruited;
- Civil society (e.g. associations of different professional, religious groups, non-governmental organizations);
- Health care authorities including the Director of the Division Provinciale de la Santé de l'Ituri (DPS), Health District Officers, coordinators of onchocerciasis and lymphatic filariasis control within the Program for Neglected Tropical Diseases Control using Preventive Chemotherapy of Ituri Sud at Bunia and/or Ituri Nord at Aru as applicable;
- The National Program of Reproductive Health within the DPS Ituri (supporting birth control initiatives and contraceptive use as well as antenatal and postnatal care);
- Staff of the local health care facilities;
- Local staff of non-governmental organizations including Malteser International which supports health care and Sightsavers which supports the local NTD control and elimination programs in the implementation of onchocerciasis and lymphatic filariasis control activities in Ituri;
- Staff of local news, radio stations and social media (local media);
- Village/community leaders and elders, religious leaders; and
- Inhabitants of the villages from which study participants are planned to be recruited (Section 2.4.2 and Section 6.1).

5.2 Coordination and Collaborations with the Local Health System

5.2.1 National Program for Neglected Tropical Diseases Control using Preventive Chemotherapy

Conduct of this study will be in consultation with the National Program for Neglected Tropical Diseases Control using Preventive Chemotherapy, including both the coordinators of the program in Ituri and the non-governmental organizations which support this program.

5.2.2 National Program of Reproductive Health

This study will be conducted in consultation with the National Program of Reproductive Health within the DPS Ituri so that the contraceptives offered to study participants are consistent with those offered by this program in the ZSR of Logo and/or Aru, as applicable. This will also ensure that messaging on contraception will be consistent with messaging of that program.

5.2.3 Local Health Facilities

A collaborative relationship will be established with all local healthcare facilities that study participants might approach for AEs (whether treatment-related or not). This is to ensure that the study team will be informed about and can report the relevant data in the electronic Case Report Form (eCRF) for the following:

(1) AEs reported by study participants along with any medication/procedures provided by the local healthcare staff;

(2) The findings during ante-natal care visits and any medication/procedures provided by the local health care staff should a study participant become pregnant between the first, and 3 months after the last investigational product administration (or the partner

of a study participant becoming pregnant during the equivalent time period, provided she agrees to the study team accessing these data);

(3) The findings of post-natal care visits during the first year of life of any babies born to study participants becoming pregnant between the first, and 3 months after the last investigational product administration (or the partner of a study participant becoming pregnant during the equivalent time period, provided she agrees to the study team accessing these data).

Study participants will be informed about the need for collection of these data from the local health facilities and consent (or assent with parental/guardian consent) to this (see Section 6.2.2). All data collected from local health facility records during the study are subject to the same confidentiality provisions as data collected directly by the study team (see Section 15.17 and Section 17).

Staff of these facilities will receive training on this study, with particular emphasis on AEs expected after treatment with ivermectin or moxidectin (see Section 10.5), assessment of AEs and current Good Clinical Practice (GCP) compliant documentation.

5.2.4 Relais Communautaires (Community Liaisons)

Collaboration will be established with the Relais Communautaires (Community Liaisons). Relais Communautaires are selected by their communities to support the implementation of public health programs (e.g. they serve as drug distributors for community-directed treatment with ivermectin).

Collaboration with them will be sought when they are selected by the village communities as points of contact (Study Focal Point, SFP) with the study team within their villages. The SFP will also be part of the system established for facilitating participants contacting the study team or local health facilities when they experience AEs outside the scheduled study team visits and for reminding participants of upcoming follow up visits by the study team. They will furthermore be the conduit for any complaints the study participants have regarding the study conduct for those participants who prefer not to convey these complaints directly or via another person of their choice (such as the village chief).

It is anticipated that depending on the size of a village and the geographic terrain it covers the number of Relais Communautaires in the villages (and/or those willing and selected by the village community to be an SFP) may be below the number of SFP necessary. Depending on the outcome of discussions with the village leaders and elders and during community meetings, villagers will be asked to select additional community members as SFP for this study during the initial meetings and consultation (Section 5.5).

The SFP will receive the training they require to fulfill their role in this study, be provided with the material they need (for example a mobile phone with phone units) and compensated for the time they spend on study related activities.

5.3 Information to Local Media

Information to staff of local media (local online news, radio and/or social media) will be provided to ensure that they have correct information about clinical research in general, and the two moxidectin studies (Study 3001 and Study 3002) planned in the area specifically.

This information will not be provided with the objective of this information being published or for the purpose of participant recruitment but only for the benefit of education of the local media staff. Informing the local media (including new staff coming on board during study conduct) was proven helpful in the moxidectin Phase III study to reduce the possibility of incorrect information (rumors) being distributed in the study area.

5.4 Consultations with Religious, Village/Community Leaders, and Elders

As per local customs and the procedures of the DPS Ituri for introduction of any new activities in the area, informing village/community leaders and elders, religious leaders and leaders of subgroups (e.g. youth groups) about the study will precede any contact with the villagers. Their guidance will be sought on:

- How to organize the study conduct and who should be involved in discussions on study conduct organization (including set up of areas where individuals can be examined in privacy);
- How to inform community members about onchocerciasis and the two studies planned in the area; and
- Suggestions from them for any other topic related to study conduct.

The agreement and support for village community meetings (or meetings with subgroups) will be obtained from the village/community leaders and elders before community meetings are held.

5.5 Consultation with Village Communities

5.5.1 Cultural and Socio-economic Characteristics of the Population from which Participants will be Recruited

5.5.1.1 Primary Recruitment Area

In the rural areas of the ZSR of Logo and in the villages in the ZSR Nyarambe, 98% of the population are from the Alur ethnic group. In the Aire de Santé targeted for recruitment, 100% of the population speak the Alur language (Dhu-Alur). The other languages spoken are Lingala (20% of the population) and French (60% of the literate population) and Kiswahili (5%).

Consequently, the information documents and the discussion about the studies will be in Dhu-Alur. The Principal Investigator is Alur.

The most practiced religion across the primary recruitment area is Catholicism (80%). There is a growing presence of traditional religions such as “Mungu lonycon” or “Karwo” who believe that God is all powerful and able to solve all problems in response to prayers and whose leaders are preaching against all modern health care. Special advocacy work with these leaders is required to encourage participation in health programs, as well as to obtain their permission to approach the communities regarding research studies.

The belief in the effectiveness of traditional healers is also high.

The majority of the population is poor and lives off agricultural activities, including subsistence farming. The area is known for production of coffee, mostly sold in Uganda, which constitutes the main source of income and employment in this region.

The area is characterized by high fertility rates, poor nutrition and low educational attainment with high rates of illiteracy. Fewer than 20% of the girls complete secondary school.

Children have a very high degree of respect for their parents and the elderly. Children and adolescents usually live with their parents until they get married. Orphans live with other family members. The head of the household is their ‘guardian’ and makes all decisions for these minors without there necessarily being an ‘official document’ attesting this. Minors may also be sent by their parents to live with other relatives.

The average daily earning is around 5 US Dollars. The currency most frequently used is the Ugandan Shilling.

5.5.1.2 Backup Recruitment Area

The majority of the population in the ZSR Aru are from the Lugbara ethnic group (around 90%) and speak Lugbara-tii (75%) and Lingala (25%). However, Lingala speakers live in the urban areas, not the rural areas where recruitment would take place.

Consequently, to prepare for conduct of the study exclusively or partly in this area, the information documents have been translated into Lugbara-tii and the discussion about the studies will be in Lugbara-tii.

The most practiced religions are Catholicism (40%) and Protestantism (35%) with other religions practiced by around 25% of the population. Aru territory is, like Logo, characterized by high levels of fetishism practice and belief in traditional healers.

The other cultural and socioeconomic characteristics are similar to the ones described for the primary recruitment area.

The average daily earning is around 5 US Dollars. The currency most frequently used is the Ugandan Shilling.

5.5.2 Community Meetings

After RA and EC approval of the protocols and Participant Information Documents and Informed Consent/Assent Forms (PICF) for this Study 3001 and for Study 3002 (Section 4.7, Section 15.2, Section 15.3) and in consultation with village leaders and elders (Section 5.4), two community meetings will be held in the villages from which participants are planned to be recruited. Villagers ≥ 12 years will be invited to these meetings.

The objective of the first meeting will be to inform the villagers about onchocerciasis, current DRC onchocerciasis control strategies, information about moxidectin already available, the plan and rationale for conducting this study and the single dose safety study and the requirements for study conduct. Details provided on the studies will be limited to those required to obtain community input into the implementation plans including:

- Identification of location(s) where study procedures can be conducted in privacy;
- Selection of Relais Communautaires and possibly other community members willing to be SFP (Section 5.2.4), i.e. to serve as conduit for questions, suggestions or complaints study participants may prefer not to address directly to the study team, remind villagers of upcoming follow up visits, support villagers in contacting the study team or local health facilities in case of AEs, and any other roles the villagers consider useful;
- Selection of literate witnesses for informed consent and assent with parental consent (Section 15.9);
- Planning for the next community meeting to inform the villagers about details of the study and discuss these with them; and
- Any other study related topics the villagers want to discuss.

If villagers indicate that they would like their village to be included among the villages from which study participants are to be recruited, a second community meeting will be arranged to which villagers ≥ 12 years will again be invited. The objectives of this second community meeting will be to:

- Inform the participants about and discuss with them all details of the studies they need to have to decide whether or not they want to give written informed consent or assent with parental/guardian consent to study participation; and

- Arrange meetings between community members interested in participation in one or the other study and study team members for further discussion of the details of the studies.

The information to be provided in both meetings is included in the PICF submitted to the ECs. During each meeting the relevant section of the PICF will be read and discussed paragraph by paragraph in the local language.

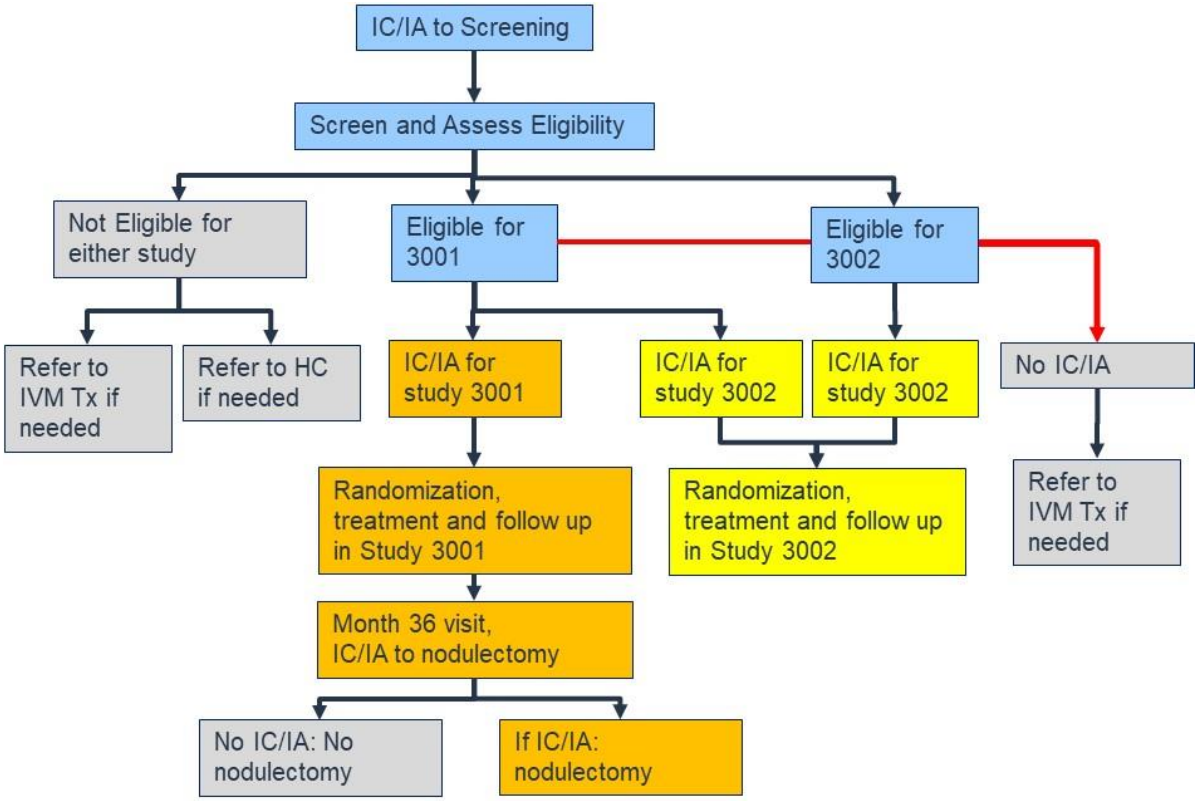
6 STUDY PARTICIPANT POPULATION

6.1 Participant Recruitment and Retention

Section 2.4.2 and Section 5 provide details on the selected study area and activities that will precede participant recruitment and the characteristics of the population from which participants will be recruited.

The process for identifying individuals willing to participate in Screening and, if eligible, willing to participate in the study is described below. As described in Section 4.7, a comparative single dose safety study (Study 3002) will be run concurrently. Concurrent conduct and recruitment into both this study and/or Study 3002 (Figure 6) was decided upon to avoid having to tell people not eligible for study 3001 or not wanting to commit to this study, but interested in participating in a study to come back later when individuals with their characteristics and interests 'are wanted'. Such an approach is considered disrespectful of their interests and their time, since they would have to be screened again and may, at that time, not be eligible for Study 3002.

Figure 6: Overview of Recruitment with Stepwise Informed Consent/Assent



IC/IA = Informed Consent/Assent, Tx = Treatment, HC = Health Center/Facility, IVM = ivermectin

The main retention strategy will consist of implementation of lessons learnt from public health programs, the Phase III study and other research studies:

- Ensuring that the communities from which participants will be recruited are engaged in study preparation and implementation;
- Treating participants with the respect they deserve as 'partners', not 'subjects' in this research (which includes e.g. concurrent recruitment into this study and study 3002 and provisions such as the SFP that allow the study team to quickly learn about and respond to questions and concerns); and
- Maintaining communication with participants via the trained site staff and SFPs, including about the importance of attending the follow-up visits organized in their villages.

6.2 Informed Consent and Assent with Parental/Guardian Consent

The principles guiding obtaining informed consent and assent from minors with parental/guardian informed consent (subsequently referred to as consent/assent) are described in Section 15.9.

Informed consent/assent in this study is divided into informed consent/assent for Screening for eligibility (Section 6.2.1), and informed consent/assent for study participation (Section 6.2.2). In addition, at Month 36, participants with palpable onchocercal nodules will be asked whether they will consent/assent to nodulectomy (Section 6.2.3).

The amount of information potential participants need to understand before deciding on study participation for themselves and/or their children/ward is substantial. Therefore, the information document is written in language considered suitable for 12 year old adolescents, allowing adults and adolescents to be informed simultaneously.

6.2.1 Informed Consent and Assent with Parental/Guardian Consent for Screening

Following approval of the study by the RA, the MdSP-assigned EC and the WHO Ethics Review Committee, the study team will initiate the community meetings described in Section 5.5.2.

The 2nd meeting to which villagers at least 12 years old will be invited and which will be attended by the witnesses the community chose during the first meeting, is the first step in recruitment:

- The section of the approved participant information document designed for this 2nd community meeting will be read and discussed in the local language paragraph by paragraph. This will allow all to benefit from answers to questions others are asking;
- Meeting participants will then be asked to approach study team members for further information and discussion in the presence of the selected witness if they are interested in participation in this study or the single dose safety study being conducted concurrently (Study 3002, Section 4.7);
- Those who continue to be interested in participating after having had adequate time to consider the study information and telling the study team members they want to participate, will be asked specific questions included in the EC approved PICF to confirm their understanding of key screening elements in the presence of the selected witness (Section 15.9.2). These questions are not meant as a 'pass-fail test' but to allow the team to identify key elements of consent/assent that require further discussion with the participant and/or parent(s)/guardian before they can provide informed consent/assent; and

- Subsequently, the potential participant and, if applicable, his/her parents(s)/guardian will provide written informed consent/assent with parental/guardian consent to Screening which will be confirmed by the witness.

Individuals who have signed (or finger printed/marked) and dated the written informed consent/assent will be assigned a participant code and invited to attend screening.

See Section 15.9 for further information on the informed consent process, including for illiterate participants and minors.

6.2.2 Informed Consent and Assent with Parental/Guardian Consent for Study Participation

The results of Screening will be presented to each individual (and parents/guardian, if applicable).

Their options for participation in this study, or the single dose safety study (Study 3002) being conducted concurrently (or the need to exclude them from either study with or without referral to the local health care system, if applicable (see Section 6.5), will be discussed and considered further by each person (or each person and their parent(s)/guardian).

Eligible individuals having decided that they want to participate in a study (and their parents/guardian, if applicable) will be asked specific questions included in the EC approved PICF to confirm their understanding of key elements of the study they are eligible for and/or have chosen in the presence of the selected witness. As for the consent for screening, these questions are not meant as a 'pass-fail test' but to allow the team to identify key elements of consent/assent for which additional clarification needs to be provided to the potential participant and/or his/her parents(s)/guardian.

Subsequently, eligible participants (with their parent(s)/guardian, if applicable) will provide written informed consent/assent to participation in the study they are eligible for and/or in which they have chosen to participate which will be confirmed by the witness.

See Section 15.9 for further information on the informed consent process, including for illiterate participants and minors.

6.2.3 Informed Consent and Assent with Parental/Guardian Consent to Nodulectomies

Information about nodulectomies will be provided when potential participants are informed about the study for their decision to participate in screening and the study. However, considering that the time between informed consent to study participation and the nodulectomies is 36 months, detailed information on the nodulectomy procedure, its risks and benefits, and that it is voluntary, will be provided to those with palpable onchocercal nodules and written consent/assent sought at the Month 36 visit. Confirmation of the understanding of key elements will be done as described above for consent/assent to screening and study participation. Only those who have given written consent/assent parental/guardian at this time will have nodulectomies performed.

See Section 15.9 for further information on the informed consent process, including for illiterate participants and minors.

6.3 Eligibility Criteria

Study participants must satisfy all eligibility criteria to participate. There will be no exemptions. Inclusion and exclusion criteria are to be determined at Screening unless otherwise indicated.

6.3.1 Inclusion Criteria

The criteria for entry into the study are:

1. Provision of written informed consent, or assent with parental or guardian written consent.
2. Mean ≥ 10 *O. volvulus* microfilariae/mg skin, determined by four skin snips.
3. Living in a village selected for the study.
4. Age ≥ 12 years.
5. All female participants of childbearing potential must commit to the use of a reliable method of birth control for the duration of treatment and until 3 months after completion of dosing with investigational product.

6.3.2 Exclusion Criteria

The criteria for exclusion from the study are:

1. Pregnant or breast-feeding.
2. Any concurrent condition that, in the opinion of the Investigator, would preclude evaluation of response to treatment or would pose undue risk to the participant's health.
3. Has received ivermectin, oral diethylcarbamazine (DEC) or doxycycline (for > 2 weeks) within 6 months of Baseline.
4. Has received treatment with an investigational agent within the last 30 days (or 5 half-lives, whichever is longer) prior to Baseline.
5. Known or suspected allergy to ivermectin or moxidectin or their excipients.
6. Self-reported planned or ongoing activities within the study period that would make it unlikely that a participant will be available for all treatment rounds and follow-up examinations.
7. Weight > 88 kilograms.
8. Infection with *Loa loa.*

6.4 Other Eligibility Considerations

In order to assess any potential impact of a concurrent condition identified during Screening on participant eligibility and/or the safety of potential study participants, the Investigator must refer to the information on adverse reactions, precautions and warnings outlined in Section 10.5 and the documents referenced in that section (and reviewed at the Initiation visit, see Section 15.8).

6.4.1 Pregnant and Breast-feeding Women

As no adequate and well-controlled studies of moxidectin or ivermectin in pregnant women have been conducted, the safety of moxidectin or ivermectin in pregnancy has not been established (information available at

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm ;
https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ;
http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Consequently, girls and women of childbearing potential must undergo a pregnancy test (Section 7.4.7) and must commit to using a reliable method of birth control until Month 27 of the study. Women of childbearing potential who withdraw from the study within 3 months of investigational product administration should be advised to avoid becoming pregnant until 3 months after their last treatment.

All girls and women of childbearing potential will be counselled on reliable methods of birth control (including abstinence) and available contraceptive measures recommended by the

National Program of Reproductive Health. The chosen contraceptives will be made available to these study participants by the Sponsor free of charge.

For participants not choosing abstinence, reliable methods (failure rate of less than 1% when used consistently and correctly) of contraception offered by the National Program of Reproductive Health include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation,
- progestogen-only hormonal contraception associated with inhibition of ovulation,
- intrauterine devices.

A pregnancy test will be conducted at Month 6, 12, 18, 24 and 30.

Study staff counselling women on contraception will have the relevant experience.

Women who are not of childbearing potential (before menarche or those who have been postmenopausal for at least 12 consecutive months without alternative medical cause or have undergone hysterectomy, bilateral oophorectomy or tubal ligation) are not required to undergo pregnancy testing or to commit to contraception.

A study in lactating, non-breastfeeding women (Study 1002) showed that after a single dose of 8 mg moxidectin, moxidectin was present in the breast milk at a relative infant dose of less than 10% of the maternal dose (Korth-Bradley et al. 2011). There is currently insufficient data on the potential risk of moxidectin exposure for the breast-feeding infant.

For ivermectin, the US FDA approved prescribing information advises that ivermectin is excreted in human milk in low concentrations and that ivermectin treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn

(https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Consequently, women who are breast-feeding are not eligible for the study.

6.4.2 *Loa loa* Infection

Individuals heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma.

Moxidectin has not been tested in patients co-infected with *Loa loa*.

Consequently, neither the primary nor the back-up recruitment area selected for this study are *Loa loa* co-endemic. Individuals will be asked about their exposure to *Loa loa* endemic areas. Those reporting a history of living or working or still temporarily working in *Loa loa* endemic areas or symptoms suggestive of *Loa loa* infection (e.g. ‘eye worm’) will undergo screening for loiasis (Sections 7.3.1 and 7.4.11).

6.5 Referral of Individuals Not Eligible for Study Participation

Individuals identified as *O. volvulus* infected but not qualifying for or willing to participate in this study (or Study 3002) will be given referral information for the local health system/ Program for Neglected Tropical Diseases Control using Preventive Chemotherapy for ivermectin treatment if community-directed treatment with ivermectin is not implemented in

their village or else be advised to participate in each round of community-directed treatment with ivermectin .

Individuals not eligible for participation in either study because of a health condition requiring medical attention will be given referral information for the local health system.

Individuals not eligible for participation because of *Loa loa* infection will be provided with a written note to that effect for presentation at future community directed treatment with ivermectin campaigns so that national program mandated precautions for the treatment of these individuals can be taken as per national guidelines.

6.6 Rescreening

Individuals may be rescreened once under a new participant code if, in the opinion of the Investigator, the eligibility criteria are likely to be met upon rescreening.

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

The assessments on the first five days after each investigational product administration must occur on the specified days.

For other assessments, the visit windows are:

- plus or minus one month for each of the Month 6, 12, 18, 24 and 30 visits; and
- plus or minus two months for the Month 36 visit.

7.3 Study Procedures

The study procedures to be conducted for each individual participating in the study are listed below. The results will be documented in the source records and, as required, entered or uploaded into the eCRF (Section 16.1 and Section 16.2).

No study procedures will be conducted prior to the provision of written informed consent/assent for the relevant procedures. Unless otherwise indicated, all procedures will be conducted in the villages in a private place set up as agreed with village communities (see Section 5.4 and Section 5.5.2).

Additional detail on study procedures is provided in Section 7.4.

Any deviation from study procedures will be noted in the source records and eCRF, as required, and the Sponsor will be notified.

After each visit, participants will be informed about the results obtained.

7.3.1 Screening (Day -30 to Day -1)

Following the provision of written informed consent/assent to Screening, the following procedures will be undertaken to determine eligibility:

- Demography (date of birth and sex, history of living or working or still temporarily working in loiasis endemic areas) (Section 7.4.1);
- Medical history (medical conditions or surgical history, and potential history of *Loa loa* infection/eye worm) (Section 7.4.2);
- Prior and concurrent medication (Section 6.3.2 and Section 9);
- Vital signs assessment (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
- A complete physical examination (Section 7.4.3) including:
  - Body weight and height (Section 7.4.6);
  - Assessment of all body systems to determine study eligibility (Section 7.4.3);
  - Onchocerciasis signs and symptoms (Section 7.4.4); and
  - Palpation for subcutaneous nodules (Section 7.4.3);
- A urine pregnancy test for women and girls of childbearing potential (Section 7.4.7);
- Ocular examinations including visual acuity, fundoscopy and slit lamp examination to assess ocular lesions and count live microfilariae in the anterior chambers of the eyes (Section 7.4.9);
- Calibrated blood smear for determination of *Loa loa* infection in individuals who have lived or worked in loiasis endemic areas and/or who report symptoms suggestive of *Loa loa* infection. (Section 7.4.11);
- Collection of four skin snips (one from each iliac crest and each calf) for assessment of skin microfilariae density (Section 7.4.8);
- AE assessment (Section 10).

7.3.2 Randomization and Investigational Product Preparation

For all participants who meet all the inclusion criteria and none of the exclusion criteria, and have given informed consent/assent to study participation, randomization and investigational product preparation will occur as described in Section 8.1 and Section 8.6.

7.3.3 Baseline and Confirmation of Eligibility (Day – 1 to 0)

To confirm eligibility and/or obtain up to date baseline data, the following assessments will be performed, if required:

- If more than 1 day has passed between the Screening pregnancy test and planned study drug administration:
  - Urine pregnancy test for women and girls of childbearing potential (Section 7.4.7); and
- If more than 3 days have passed between Screening and planned study drug administration, or if clinically indicated:
  - A targeted physical examination (based on previous findings and current symptoms or health issues that have occurred since Screening) (Section 7.4.3);
  - Vital signs assessment (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
  - Concurrent medication review (Section 9).

If participants continue to be eligible, the following Baseline assessments will be performed:

- 3.0 mL of blood will be collected for liver function tests (Section 7.4.10);
- AE assessment (Section 10).

7.3.4 Investigational Product Administration (Day 0)

Participants continuing to meet all the inclusion criteria and none of the exclusion criteria will be administered investigational product while being observed by study staff (Section 8.6).

Any investigational product dispensed but not administered will be returned to the Pharmacy and accounted for as described in Section 8.7.

7.3.5 Daily Assessments on the First Five Days after Each Investigational Product Administration

For the first five days after each investigational product administration, the following assessments will be conducted:

- AE assessment (Section 10);
- Concurrent medication assessment (Section 9);
- A targeted physical examination (based on symptoms) (Section 7.4.3);
- Blood pressure (semi-supine) and pulse measurement (Section 7.4.5).

Should the participant experience signs and symptoms of the Mazzotti reaction or other adverse events, treatment should be provided if requested by the participant or considered clinically indicated (see Section 10.5). Any medication provided by the study team or in a local health facility (see Section 9) must be documented and reported in the source records and eCRF together with the indication for which it was provided.

Additional follow-up visits will be scheduled should they be indicated for appropriate follow-up of AEs and recorded in the source records and eCRF as unscheduled visits.

7.3.6 Assessment on the Fifth Day after Investigational Product Administration at Day 0, Month 6 and Month 12

Five (5) days after investigational product is administered at Day 0, Month 6 and Month 12 (Day 5), 3.0 mL of blood will be collected for liver function tests (Section 7.4.10).

7.3.7 On-Treatment Visits (Months 6, 12, 18, and 24)

Each participant will be assessed at Months 6, 12, 18, and 24 (± 1 month).

The following assessments will be performed prior to investigational product administration:

All participants at all on-treatment visits:

- AE assessment (Section 10);
- Concurrent medication (Section 9);
- Vital signs (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
- Body weight (Section 7.4.6);
- A targeted physical examination (based on symptoms) (Section 7.4.3);
- Collection of four skin snips (one from each iliac crest and each calf) for assessment of skin microfilariae density (Section 7.4.8);

Selected participants at all on-treatment visits:

- Evaluation for selected onchocerciasis signs and symptoms in those with these signs and symptoms at Screening (Section 7.4.4);
- Pregnancy test for girls and women of childbearing potential (Section 7.4.7);
- Slit lamp examination for counting of live microfilariae in the anterior chambers of the eyes in those with live microfilariae in the anterior chambers of the eyes at Screening (Section 7.4.9);
- Girls who were pre-menarche before the first treatment or the applicable previous On-Treatment Visit will be asked whether they have had menarche.

All participants only at Month 6 and 12:

- At Month 6 and 12, 3.0 mL of blood for determination of liver function tests (Section 7.3.6 and Section 7.4.10);

Selected participants at Month 12 and Month 24:

- Fundoscopy or slit lamp examination for those with onchocerciasis related ocular lesion(s) at Screening, as indicated by the lesion(s) (Section 7.4.9).

Once assessments are completed, investigational product should be administered as described in Section 8.6.

Participants will receive post-treatment follow up daily for five days as described in Section 7.3.5 and have blood drawn for liver function tests 5 days after Month 6 and Month 12 investigational product administration as described in Section 7.3.6.

7.3.8 Post-Treatment Visit (Month 30)

Each participant will be assessed at Month 30 (± 1 month).

The following assessments will be performed:

All participants:

- AE assessment (Section 10);

- Concurrent medication (Section 9);
- Vital signs (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
- A targeted physical examination (based on symptoms) (Section 7.4.3);
- Collection of four skin snips (one from each iliac crest and each calf) for assessment of skin microfilariae density (Section 7.4.8);

Selected participants:

- Evaluation for selected onchocerciasis signs and symptoms for those with these signs and symptoms at Screening (Section 7.4.4);
- Pregnancy test for women and girls of childbearing potential (Section 7.4.7);
- Slit lamp examination for counting of live microfilariae in the anterior chambers of the eyes in those with live microfilariae in the anterior chambers of the eyes at Screening (Section 7.4.9).

7.3.9 End of Study Visit (Month 36)

Each participant will be assessed at Month 36 (± 2 months).

The following assessments will be performed:

All participants:

- AE assessment (Section 10);
- Concurrent medication (Section 9);
- A targeted physical examination (based on symptoms) (Section 7.4.3);
- Palpation for subcutaneous nodules (Section 7.4.3);
- Vital signs (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
- Collection of four skin snips (one from each iliac crest and each calf) for assessment of skin microfilariae density (Section 7.4.8);

Selected participants:

- Evaluation for selected onchocerciasis signs and symptoms for those with these signs and symptoms at Screening (Section 7.4.4);
- Slit lamp examination for counting of live microfilariae in the anterior chambers of the eyes in those with live microfilariae in the anterior chambers of the eyes at Screening (Section 7.4.9);
- Fundoscopy or slit lamp examination for those with onchocerciasis related ocular lesion(s) at Screening, as indicated by the lesion(s) (Section 7.4.9).

Discussion will be held with participants with palpable nodules considered onchocercal about the procedure, risks and potential benefits of voluntary nodulectomies. Written informed consent (or assent with parental or guardian written consent) will be obtained from all individuals deciding to have a nodulectomy (Section 6.2.3);

Individuals who have given written informed consent/assent to nodulectomies will be scheduled for the nodulectomy and followed up to assess wound healing as described in Section 7.4.12.1.

7.3.10 Exit Examination at Early Withdrawal or Early Study Termination

Participants have the right to withdraw from the study or withdraw from treatment at any time for any reason and without giving any reason for the decision to do so or may be withdrawn by the investigator (for criteria for withdrawal from treatment or the study and follow up, see Sections 13.2).

Study team members will attempt to visit each participant who withdraws or is withdrawn. The reason for withdrawal should be recorded, including, if applicable, that the participant prefers not to provide a reason or could not be reached.

If permitted by the participant, an exit examination should be conducted 3 months after the last treatment or another time of the participants choosing to allow evaluation for investigational product related adverse events (for further information on the rationale for this examination, see Section 13.2.3). No Exit examination is required if a participant withdraws on or after the 30 Month visit.

The Exit Examination will include the following:

All participants:

- AE assessment (Section 10), including need for further follow-up;
- Concurrent medication assessment (Section 9);
- A targeted physical examination (based on symptoms) (Section 7.4.3);
- Vital signs (blood pressure, temperature, heart rate and respiratory rate) (Section 7.4.5);
- Four skin snips (one from each iliac crest and each calf) will be collected for assessment of skin microfilariae density (Section 7.4.8).
- Liver function test if participants' Exit Examination occurs at or before the Day 5 assessment following Month 12 (Section 7.4.10);

Selected participants:

- Evaluation for selected onchocerciasis signs and symptoms in participants who had these signs and symptoms at Screening (Section 7.4.4).

This exit examination will also be performed in case of early termination of the study for all study participants who have not yet had a Month 36 evaluation (Section 13.5).

7.4 Details of Scheduled Assessments

The results of all assessments will be recorded in the source records. On the source records, participants will be identified via their participant code as well as their initials and/or names.

As required, data from the source records will be entered or uploaded to the eCRF (Section 16.1 and Section 16.2). In the eCRF, study participants will be identified only by their participant code: their name or initials are not collected, to ensure participant confidentiality.

Confidential Screening logs will be completed with details of both participant codes and participant names (Section 16.3).

The following provides details of the assessments to be undertaken. Scheduling of assessments is described in Section 7.3 and

Table 1.

7.4.1 Demography

Demographic data includes sex, date of birth, and history of living or working or still temporarily working in an area(s) where *Loa loa* is endemic.

7.4.2 Medical History, Concurrent Conditions and Prior and Concurrent Medications

This will include any past or current medical conditions or surgical history, prior and concurrent medication, and questioning about a potential history of *Loa loa* infection (eye worm).

7.4.3 Physical Examination

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

At the Screening visit and at Month 36, the number and location of all palpable nodules will be determined during the physical examination including, if identifiable, likely sources other than onchocerciasis.

At all other visits, a targeted physical examination will be performed as clinically indicated, guided by symptoms.

Any new abnormalities or worsening of screening conditions detected during physical examinations must be recorded as AEs (see Section 10 for details).

7.4.4 Onchocerciasis Signs and Symptoms

At Screening, each participant will be examined for signs of reactive skin lesions associated with onchocerciasis (acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis), atrophy (if participant is under 50 years old) and depigmentation, and questioned about the presence of pruritus (itching of skin).

Participants with acute papular onchodermatitis, chronic papular onchodermatitis and/or lichenified onchodermatitis, and/or pruritus considered by the Investigator as at least possibly related to *O. volvulus* infection at Screening will be re-examined for these skin signs and questioned about pruritus (and other symptoms) at Months 6, 12, 18, 24, 30 and 36 and at the Exit Examination in case of early withdrawal or study termination, if permitted by the participant.

Each area of skin lesion and pruritus will be graded for severity with a scale informed by that described by Murdoch and colleagues (Murdoch et al. 1993).

Signs and symptoms of onchocerciasis that worsen or emerge after commencement of treatment must also be reported as AEs (see Section 10 for details).

7.4.5 Vital Signs

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

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

If abnormally high or low blood pressure is observed, two further measurements, taken 5 minutes apart should be performed and recorded.

Blood pressure and pulse rate will also be measured daily during the first five days after each treatment.

Vital signs should also be measured at other times if deemed clinically appropriate.

7.4.6 Weight and Height

Height will be measured in centimeters (cm) without shoes.

Weight will be measured in kilograms (kg) wearing light clothing without shoes.

7.4.7 Pregnancy Test

A β-HCG urine pregnancy test will be performed for women and girls of childbearing potential before each investigational product administration. They will be instructed by the study staff in how to collect a urine sample for testing.

Upon completion of the pregnancy test, study staff will review the result to confirm that the woman is not pregnant prior to proceeding to administration of investigational product.

Pregnancy will require immediate withdrawal of the woman from further treatment.

Pregnancy does not, however, require withdrawal from the study unless the participant elects to withdraw, or the Investigator decides that the participant should be withdrawn in the interest of her health and pregnancy. Sections 10.6 and 13.2 provide details on follow up of pregnancies and in case of withdrawals for any reason.

Urine remaining from these samples will be stored frozen for potential future use (Sections 15.19 and 15.20.3), provided the participant has given informed consent/assent to this.

7.4.8 Quantification of Skin Microfilariae Density

Four skin snips will be taken (one from each of the left and right iliac crest, and left and right calf) using a 2 mm Holth-type corneoscleral punch after cleansing the snip sites with 70% alcohol.

Punches will be steam-sterilized before use on the next individual.

Briefly, each snip will be weighed and incubated for at least 8 hours in isotonic saline. The microfilariae that have emerged from the skin snip will be counted using an inverted microscope. At Screening, the mean mf/mg across the four skin snips will be calculated to assess study eligibility and, if applicable, determine the participant randomization stratum (< 20 mf/mg skin vs. ≥ 20 mf/mg skin, Section 8.1).

Microfilariae will be preserved in alcohol after counting for future use (Sections 15.19 and 15.20.2).

If microfilariae of *Mansonella streptocerca* are present in the skin specimen (identified visually on microscopy), their number will be noted on the source records but not collected in the participant's eCRF.

7.4.9 Ophthalmological Assessments

Ophthalmological assessment will comprise visual acuity measurement in daylight with tumbling E chart and examination of the anterior segment of the eyes by portable hand-held slit lamp. The number of live microfilariae in the anterior chambers of the eyes will be counted after the participant has been in a head-down position for at least 5 minutes.

The disc and retina will be assessed by non-mydriatic fundus camera. Photos will be retained as source records.

Participants with live microfilariae in the anterior chambers of the eyes at Screening will be followed up for live microfilariae in the anterior chambers at Months 6, 12, 18, 24, 30 and 36.

Ophthalmologic abnormalities at Screening will be recorded and classified as possibly onchocerciasis-related or unrelated. Participants with ocular lesion(s) at Screening classified as onchocerciasis-related will have repeat fundoscopy and/or slit lamp examination at Months 12, 24, and 36, as indicated by the lesions identified at Screening.

Any new abnormalities or worsening of conditions present at Screening must be recorded as AEs (see Section 10.2 for details).

Individuals with ophthalmological diagnoses amenable to treatment (e.g. glaucoma) will be provided with this treatment or referred to the appropriate intervention.

7.4.10 Liver Function Tests

A 3.0 mL blood sample will be collected for liver function tests that will examine aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), and conjugated and unconjugated bilirubin.

Follow up of abnormal values will be determined by the Investigator based on clinical judgement. Grade 3 or 4 abnormalities (see Section 10.2.2) should be retested as soon as possible and both values with the date of sampling and testing will be collected in the eCRF.

Serum remaining from these samples will be stored frozen for potential future use (Sections 15.19 and 15.20.3), provided the participant has given informed consent/assent to this.

7.4.11 Diagnosis of *Loa loa* Infection

Individuals with a history of living or working or still temporarily working in an area where *Loa loa* is endemic or with a history of eye worm or other symptoms suggestive of *Loa loa* infection will undergo a test for *Loa loa* infection. For these participants, diagnosis of *Loa loa* infection will be performed via calibrated blood smear. Briefly, blood will be collected (between approximately 1100 and 1400 hours) by finger prick with a 60 µL non-heparinized capillary tube, after careful cleaning of the finger. The blood will be spread on a labeled slide, dried and Giemsa stained and dried at ambient temperature. All *Loa loa* microfilariae on the slide will be counted at a magnification of 100x.

If *Loa loa* microfilariae are present, the number of parasites will be recorded in the source records and the individual will be excluded from the study.

7.4.12 Evaluation of the Effect on Macrofilariae

7.4.12.1 Nodulectomy

Palpable nodules clinically judged to be onchocercal will be surgically excised by physicians experienced in minor surgery in the surgical theater of the local health facility close to where the participant lives in the ZSR Logo, or Nyarambe (or Aru in case the study is conducted completely or partly in the back-up recruitment area, see Sections 5.5.1.1 and 5.5.1.2).

When consenting/assenting to nodulectomy, participants can designate nodules they do not wish to have removed.

The procedure will be conducted under local anesthesia (1% xylocaine) using sterile technique to minimize pain and the risk of infection at the incision site.

Wound management by the study team will include daily examination for bleeding, hematoma formation and dehiscence. Approximately two days after the procedure, participants will be returned to their villages where a study nurse will continue daily wound management. Participants will be advised to stay off work for the first week after surgery to assist in wound healing. They will be compensated for each day they do not work (Section 15.12). The first change of dressing is done on the first day after nodulectomy. Subsequent dressing changes will occur on alternate days until the wound is completely healed. Participants will be provided with medication to reduce pain once the local anesthesia has worn off both in the hospital and during follow up in their village.

Approximately 7 days post-nodulectomy, sutures will be removed by a study nurse.

7.4.12.2 Histopathological Examination of Excised Nodules

The excised nodules will be processed for histopathology and slices stained with hematoxylin-eosin or specific stains available at that time. Slides will be read by one and if feasible a second experienced reader to determine viability and reproductive capacity of the macrofilariae contained within the nodule. Details of macrofilarial morphology including number of live, moribund, dead, or dead and calcified worms by sex, absence or presence of embryos overall and by developmental stage (oocytes, stretched, pretzel etc.) and absence or presence of spermatogenetic stages will be recorded. This will be performed by researchers specializing in histopathological examination of excised nodules. Given that this will occur only at the end of the study, these researchers will be selected close to the time of the first nodulectomies. The ECs will be informed about the selection and the transfer of the nodules will be under a Material Transfer Agreement as described in Section 15.19 for left-over biospecimen. Some of the material in the nodules will be preserved in alcohol for research for new tools for onchocerciasis elimination programmes (Section 15.20.2).

7.4.13 Collection and Processing of Biological Specimens

Skin, blood and urine specimens collected during the trial may contain harmful pathogens. All personnel involved in collecting and handling biological specimens will be trained on Prevention and Control of Infection in order to be able to implement appropriate precautionary procedures for handling biohazardous materials as currently recommended by the WHO Emerging and Communicable Diseases, Surveillance and Control Guidelines (World Health Organization 1997) or relevant updates or country guidance. The processing of all biological specimens will be in accordance with relevant SOPs and as required for the objectives of their collection, as described above.

For storage, ownership and future use of left over serum, urine and *O. volvulus* parasites, see Sections 15.19, 15.20.2 and 15.20.3.

8 INVESTIGATIONAL MEDICINAL PRODUCT

In this study investigational medicinal product is moxidectin, ivermectin and/or placebo.

8.1 Randomization and Treatment Allocation

The randomization code will be generated using computer-generated random treatment allocations with randomly permuted blocks, which may include random block sizes. Each block of sequential numbers will include in random order moxidectin annual, ivermectin annual, moxidectin biannual and ivermectin biannual treatment allocations, reflective of the 3:1:3:1 treatment allocation planned for this study (Section 4.3).

The randomization will be stratified by Screening skin microfilariae density (< 20 mf/mg skin or ≥ 20 mf/mg skin) and by Aire de Santé.

Individuals found to be eligible for study participation will be allocated the next available number in sequential order, from lowest to highest, on the randomization list for their Aire de Santé and Screening skin microfilariae density stratum. The staff randomizing participants will not be involved in participant follow up.

The randomization algorithm will be generated by an independent statistician not otherwise participating in the study. A separate document outlining the specifics of the randomization algorithm will be prepared and available upon study completion.

8.2 Blinding

The study will be conducted as a double-blind study. To maintain the blind, each participant will receive four matching capsules prepared by unblinded staff authorized by DRC law to dispense drugs and who will not be involved in participant assessment. Neither the participants nor staff involved in their follow up or examination of participant samples will know which treatment is being administered, nor whether it is being given annually or biannually.

Participants randomized to annual treatment will receive four placebo capsules at Months 6 and 18.

8.3 Unblinding

The Investigator has the right to break the blind or authorize a study team member to break the blind when knowledge of the study treatment is considered important for optimal medical management of a participant. For this purpose, sealed envelopes (or equivalent) with the treatment assigned to each randomization number will be held at the site by the Investigator (or delegate). Duplicate envelopes (or equivalent) will be held by the Sponsor/Medical Monitor.

Wherever possible without jeopardizing participant safety, the Investigator should discuss the intention to break the blind with the Medical Monitor before breaking the blind. The final decision rests with the Investigator.

If the code is broken, the envelope must be signed and dated on both seals by the code breaker. The name and signature of the code breaker, and date and time of the code break needs to be recorded on the outside of the envelope. Information must be entered into the participant's source records and the relevant eCRF page, explaining the reason and date that the sealed envelope was opened. This must be countersigned by the Investigator.

The Investigator must notify the Sponsor/Medical Monitor by e-mail at sae@medicinesdevelopment.com. or if that is not feasible, via telephone (+61 409 020 209) within 24 hours after having broken the blind including the participant code, randomization number and the circumstances leading to the decision to unblind. Furthermore, the

Investigator must provide a written report of the event to the Sponsor within five working days.

8.4 Formulation

The investigational products to be administered in this clinical trial are encapsulated moxidectin tablets, 2 mg (manufactured by MDGH) and ivermectin tablets, 3 mg (manufactured by Edenbridge LLC).

Moxidectin tablets contain 2 mg of moxidectin supplied as 100 mg white to pale yellow, uncoated, oval-shaped tablets. Moxidectin tablet components are provided in Table 4.

Table 4: Moxidectin Tablet Components

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

Ivermectin will be a 3 mg tablet (US Authorized product National Drug Code NDC 42799-806-01) containing the ingredients as per Table 5.

Table 5: Ivermectin Tablet Components

Component	Function
Ivermectin 3 mg	Active ingredient
Microcrystalline cellulose	Inactive
Pregelatinized starch	Inactive
Magnesium stearate	Inactive
Colloidal silicon dioxide	Inactive
Croscarmellose sodium	Inactive

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

Matching placebo capsules will be filled with the same inert excipient powder.

8.5 Supply, Packaging and Labelling, Storage and Handling

Investigational product will be supplied by the Sponsor as moxidectin 2 mg in capsules, ivermectin 3 mg in capsules or placebo capsules. The investigational product will be supplied in white high density polyethylene bottles with a polypropylene closure and induction seal, a pharmaceutical coil (filler) and silica gel desiccant sachet.

Investigational product will be shipped to the site after receipt of required documentation of study approval and in accordance with applicable regulatory requirements.

The Investigator or authorized designee will ensure that the investigational product is stored below 25°C and protected from light and moisture in a secure area with access limited to authorized staff, and according to relevant regulations. The capsules must not be frozen or stored at temperatures above 30°C. Temperature excursions are permitted up to 30°C for up to 12 months.

Labelling of the bottles with moxidectin in capsules, with ivermectin in capsules or with placebo-to-match capsules will be in accordance with local regulations and as approved by the regulatory authority and include at a minimum:

- Sponsor name;
- Protocol number;
- Product name;
- Product strength;
- Route of administration;
- Lot number;
- Expiry date or retest date; and
- 'For Clinical Trial Use Only'.

8.6 Dosage and Administration

After randomization and determination of the regimen to which the participant is allocated, a dose of investigational product will be dispensed.

Dispensed investigational product will be administered only to participants confirmed to be eligible on Day -1 to Day 0.

Participants will swallow the investigational product with water under the direct observation of study staff.

8.6.1 Moxidectin

The dosing of moxidectin does not depend on participant weight or height.

Participants randomized to annual moxidectin will receive four moxidectin capsules at each of Months 0, 12 and 24 and four placebo capsules at each of Months 6 and 18.

Participants randomized to biannual moxidectin will receive four moxidectin capsules at each of Months 0, 6, 12, 18 and 24.

8.6.2 Ivermectin

Ivermectin is provided as 3 mg tablets and dosing is weight-based (150 µg/kg).

The Prescribing Information for ivermectin (available at https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf) translates this into the number of ivermectin 3 mg tablets for individuals up to 84 kg/weight, resulting in actual dose/kg of between 136 µg/kg and 231 µg/kg. For weights ≥ 85 kg, the prescribing information specifies only that dosing should be 150 µg/kg. Administration of four 3 mg ivermectin tablets to individuals weighing 85 to 88 kg results in an actual dose/kg of between 136 µg/kg and 141 µg/kg. Above that weight, five 3 mg tablets are required to achieve the dose range equivalent to that of lower weight groups described in the prescribing information. Given that this is a blinded study and to eliminate the need for all participants to take additional placebo capsules, individuals with a weight of > 88 kg will be excluded. Based on the target recruitment population, it is not anticipated that this will result in exclusion of many individuals.

The number of ivermectin capsules to be administered is determined according to the weight of the participant at each timepoint, as per ivermectin label and described in Table 6.

Table 6: Ivermectin Weight Based Dosing Schedule

Bodyweight[#] (kg)	Number of Ivermectin 3 mg Capsules	Number of Placebo Capsules	Range of Actual Ivermectin dose (µg/kg)
26 to 44	2	2	231 - 136
45 to 64	3	1	200 - 141
65 to 88	4	0	185 - 136

[#] Rounded to the nearest whole kg

Participants randomized to annual ivermectin treatment will receive the number of ivermectin and placebo capsules corresponding to their weight at Months 0, 12 and 24 and four placebo capsules at Months 6 and 18.

Participants randomized to biannual ivermectin treatment will receive the number of ivermectin and placebo capsules corresponding to their weight at Months 0, 6, 12, 18 and 24.

8.7 Dispensing and Accountability

The Investigator is responsible for ensuring that the investigational product is dispensed in accordance with the protocol. Only individuals legally authorized by the DRC to dispense drugs and by the Investigator will dispense investigational product.

For each participant, the investigational product corresponding to their randomized treatment allocation will be prepared.

The date of investigational product preparation, participant code, randomization code and the number and types of capsules dispensed must be recorded in the Drug Dispensing and Accountability log provided for the study.

Any investigational product dispensed but not administered to a participant must be recorded in the log and the unused capsules stored in a separate container, appropriately labelled, for accountability review by the unblinded Study Monitor.

The Investigator will be responsible for ensuring accurate records are maintained for all investigational products received, dispensed, dispensed and not administered, returned or destroyed. The inventory and dispensing logs must be available to the unblinded Study Monitor. Investigational product supplies, including partially used or empty bottles, and dispensed and not administered investigational product must be accounted for by the unblinded Study Monitor and returned to the Sponsor for destruction at the end of the study. Copies of the records of investigational product returned to the Sponsor must be retained by the Investigator.

As required by national law and in consultation with the Sponsor, unused investigational product supplies may be destroyed locally consistent with the local regulations. Copies of records on the destroyed investigational product shall be retained by the Investigator. These records must show the identification and quantity of each investigational product capsule disposed of, the method of destruction, and the person who disposed of the investigational product. Copies of such records shall be submitted to the Sponsor.

8.8 Shipment of Investigational Medicinal Product

Investigational product will be shipped to the site only after export is permitted from the US, an import permit into DRC has been received by the Sponsor and the Sponsor has confirmed that all relevant DRC required authorizations and Sponsor documentation requirements for the study have been met. Shipment of investigational product may occur before the Site Initiation Visit with secure storage at the site under quarantine until the study has been initiated.

9 CONCURRENT MEDICATIONS

At each study visit or contact, the Investigator should ask the participant about any concurrent medications or medications taken since the previous visit or contact.

All concurrent medications, including any traditional medicines, herbal remedies as well as traditional spiritual interventions, must be recorded in the appropriate section of the eCRF, including start and stop date, dose and dosing indication.

9.1 Special Dietary Requirements

There are no special dietary requirements during the study.

9.2 Prohibited Concurrent Medications

Throughout the study, participants should not receive any of the following medications without a physician having determined that this medication is necessary for the health of the participant:

- Anti-onchocercal treatments including ivermectin, oral DEC;
- Doxycycline for a duration of more than 2 weeks; and
- Other investigational products for non-life threatening conditions.

In case of non-compliance, the prohibited concurrent medication taken should be documented in the source records and the information requested on the concomitant medication page of the eCRF should be completed.

9.3 Permitted Investigational Products

In the interest of the health of study participants, as well as potentially public health, investigational products for life threatening conditions for which no or insufficient effective and safe treatments or vaccines are available are permitted. This includes, but is not necessarily limited to, Ebola Virus Disease Vaccination.

The Ebola Virus vaccine rVSVΔGP-ZEBOV-GP (ERVEBO, Merck&Co, Inc.) has been prequalified by WHO (World Health Organization. 2020) and received conditional marketing authorization by the European Medicines Agency in November 2019 (European Medicines Agency. 2020).

Ring vaccination with rVSVΔGP-ZEBOV-GP is deployed at large scale by the MdSP for control of the outbreak in Nord Kivu and Ituri. Thus, its use is authorized by the MdSP outside clinical trials. Consequently, and in the interest of the health of study participants, their communities and public health, rVSVΔGP-ZEBOV-GP is not considered an investigational product in this protocol and consequently rVSVΔGP-ZEBOV-GP vaccination is permitted.

Applications for European Medicines Agency approval have been submitted for each of the two components of another Ebola Virus vaccine consisting of a dose of Ad26.ZEBOV followed by a dose of MVA-BN-Filo and are undergoing Accelerated Assessment. The RA has authorized use of this vaccine within a Phase III study in North Kivu (https://clinicaltrials.gov/ct2/show/NCT04152486). Should this or subsequent studies, or MdSP authorized deployment of this vaccine, be implemented in the area where Study 3001 is being conducted, participants may receive this vaccine.

The study team will coordinate assessment activities for this study and the vaccine study with the staff involved in the evaluation of the vaccine.

Vaccination will be documented in the source records and eCRF as required for all concomitant medication.

10 ADVERSE EVENTS AND MANAGEMENT

10.1 Safety Assessments

Safety assessments will include physical examinations, ocular examinations, AEs, concomitant treatments (pharmacological or non-pharmacological), vital sign measurements and liver function tests.

10.2 Adverse Events

10.2.1 Adverse Event Definition

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an AE is any untoward medical occurrence in a clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

Pre-existing signs, symptoms, or diseases, which increase in frequency or severity or change in nature following administration of the investigational product, are also considered an AE.

Post-treatment complications that occur as a result of protocol-mandated procedures (e.g. as a result of skin snips or nodulectomies) are also AEs.

AEs as per ICH definition are referred to as 'Treatment Emergent Adverse Events' (TEAE).

In addition to the events defined as AE by the ICH, any new event, exacerbation of a pre-existing condition or complication from a protocol mandated procedure with onset after written informed consent/assent up to the first investigational product administration will also be recorded in the source records and reported as an AE on the appropriate eCRF page(s).

The following are **not** AEs:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); in contrast, the condition that leads to the procedure is an AE if it started or worsened informed consent/assent but not if it was present before informed consent/assent;
- Pre-existing diseases or conditions (i.e. present prior to informed consent/assent) that do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, or overnight stays in a health care facility or the research center for social and/or convenience reasons e.g. because of road conditions it is not considered safe to transport the participant back to the home village at night); and
- Overdose of either investigational product or concomitant medication without any signs or symptoms unless the participant is hospitalized for observation.

10.2.2 Grading of Severity of Adverse Events and Evaluation of Relationship to Investigational Product

All AEs will be assessed by the Investigator and recorded in the source records and on the appropriate eCRF page, including the date of onset and resolution, severity, relationship to investigational product, outcome and action taken including regarding further treatment with investigational product.

Each AE will be graded for severity using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (Appendix 1: Adverse Events Toxicity Grading Scale). For AEs not specifically described in the DAIDS grading table, the grades presented in Table 7 should be applied.

Table 7: Adverse Event Severity Assessments for Events not Included in the DAIDS Table

Grade	Severity	For CLINICAL events not otherwise described in the DAIDS AE grading table, the following descriptions of severity apply
1	Mild	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.
2	Moderate	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention.
3	Severe	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
4	Potentially life-threatening	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The relationship to investigational product should be assessed using the following definitions (Table 8).

Table 8: Investigational Product Causality Assessments

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 investigational product is such that investigational product is not likely to have any reasonable association with the AE.
Possible	The AE could have been produced by the participant's clinical state or investigational product.
Probable	The AE follows a reasonable temporal sequence from the time of investigational product administration, and cannot be reasonably explained by the known characteristics of the participant's clinical state.
Definite	The AE follows a reasonable temporal sequence from the time of investigational product administration, and/or reappears when investigational product is re-introduced.

10.2.3 Adverse Event Reporting

All AEs, regardless of severity, causality or seriousness (Section 10.3), and whether initially recorded at a local health facility a participant may choose to go to (Section 5.2.3), or by a study team member during the protocol-scheduled follow up visits, or ad-hoc visits at the request of a participant, must be reported from the date of written informed consent/assent up to the last day on the study or for 3 months after the last dose of investigational product, whichever is later.

This is required to obtain as comprehensive an AE data set as possible to support further characterization of the safety profile of moxidectin and ivermectin: a priori it is not possible to know which AEs may have a relationship to the study drugs and thus exclude some from collection/reporting. Participants will be informed about collection of data related to health problems they report to local health facilities during the discussions preceding Informed Consent/Assent. All AEs, whether initially recorded at a local health facility or by a study team member are subject to the same confidentiality provisions (see Section 15.17 and Section 17).

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 in the eCRF and, if applicable, reported as a SAE, and not the individual signs/symptoms recorded in the source documents.

10.3 Serious Adverse Events

10.3.1 Definition

A **serious adverse event** is defined as any AE that results in any of the following outcomes:

- Death;
- Life-threatening situation (participant is at immediate risk of death);
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity; and/or
- Congenital anomaly/birth defect in the offspring of a participant who received investigational product.

Furthermore, the following are considered a SAE:

- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, if, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
  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.

10.3.2 Clarification of Serious Adverse Events Definition and Terminology

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.

“Life-threatening” means that the participant 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, that AE is a SAE.

“In-patient hospitalization” means the participant has been formally admitted to a hospital (or another type of health facility) for medical reasons, not for a protocol specified procedure (nodulectomy), for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department or an overnight stay at a hospital for 'social/convenience reasons' (i.e. the participant cannot be safely brought home at night).

10.3.3 Serious Adverse Event Reporting Requirements

10.3.3.1 SAE Reporting to the Sponsor

The Sponsor must be notified immediately about any SAE that occurs after the informed consent/assent has been obtained.

The study site was provided with internet access to ensure that SAE report forms can be sent expeditiously. If that is not feasible, notification will be via phone to the medical monitor until the SAE report forms can be sent electronically.

The procedures for reporting all SAEs occurring until the last study visit, regardless of causal relationship and outcome, are as follows:

- Complete the "Serious Adverse Event Report"; and
- Send the completed "Serious Adverse Event Report" by e-mail to the MDGH safety desk (sae@medicinesdevelopment.com), or as otherwise advised in writing by the Sponsor within 24 hours of the Investigator's knowledge of the event.
    - For fatal or life-threatening events, also send copies of hospital case reports, autopsy reports, and other documents when requested by the Safety Desk and available. Participant name and other participant identifying information on these documents must be obscured and the participant code added.
- Medical Monitor phone number for notification until reporting to the e-mail address is feasible: +61 409 020 209

Regardless of the cause, all deaths occurring up to the last study visit or 3 months after the last treatment, whichever is later, must be reported to the Sponsor within 24 hours of the Investigator's knowledge of the death to the e-mail address or phone number provided for SAE reporting.

The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports to the regulatory authorities. All additional information requested has to be sent anonymized and with the participant code added.

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 source records and the concurrent medication section of the participant's eCRF.

A SAE may qualify for expedited 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)). An unexpected adverse reaction is defined by the ICH as 'An adverse reaction, the nature or severity of which is not consistent with the applicable product information'. The applicable product information for this study are the Investigator's Brochure for moxidectin and the Ivermectin Prescribing Information (available at www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

10.3.3.2 SAE Reporting to Regulatory Authority and Ethics Committee

The Investigator will notify the RA and the EC of SAEs as per the reporting requirements specified in the regulatory authority and ethics committee approval letters.

If the letters do not include specific requirements for expedited reporting of SAEs or SUSARs, all SAEs will be included in the Investigator's annual update to the EC and RA.

10.4 Follow Up of Serious and Non-Serious Adverse Events

Follow-up of serious and non-serious AEs will continue through to the last day on study. For participants completing the study, this will be the Month 36 visit. The Month 36 visit includes completion of the post-nodulectomy follow up period for participants having nodulectomies.

If a participant withdraws early from the study, AEs will continue to be collected until 3 months after last dose of investigational product, if permitted by the participant.

The Sponsor may request that certain AEs be followed until resolution or until the Investigator and/or the Sponsor determine that the participant's condition is stable. For participants who have withdrawn from the study, their agreement is required.

Based on prior experience of treatment related AEs in the Phase II and Phase III clinical trials of moxidectin and ivermectin, it is anticipated that the majority of AEs will occur and

resolve within the first five to six days after administration of investigational product without treatment (i.e. day of administration (Day 0) to 5 days later). In these previous studies, when treatment was provided, it was primarily administered for alleviation of symptoms such as itch or minor pain. To capture such AEs in this study, an appropriately trained member of the study team will visit each participant daily during the five days following each investigational product administration (see Section 7.3.5). The need for treatment will be assessed and treatment provided as clinically indicated and the treatment and the reason documented in the source records and eCRF.

For illnesses that are common in the study population and that occur while on study, for example malaria, respiratory infections, diarrhea or conjunctivitis, the study team will in general provide appropriate treatment.

Else, and for other conditions not related to the investigational products or study procedures that occur on study and require hospital treatment or ongoing management (e.g. appendicitis, broken bones, snake bite, epileptic attacks), study participants will be referred to a local health clinic or hospital. Costs of treatment for conditions not possibly, probably or definitely related to investigational product or study conduct will not be covered by the study.

Study participants may prefer to visit local health care staff/clinics rather than to contact a study team member (directly or via the SFP in their village) in case of an AE they experience after Day 5 after each treatment. As outlined in Section 5.2.3, collaborations with the local health care system will be set up to ensure that the study team is informed and can collect all AE and treatment data, as well as compensate the health system for treatment of all AEs possibly, probably, or definitely related to treatment with investigational product, or due to a study procedure. This is included in the PICF.

10.5 Precautions for Treatment with Moxidectin or Ivermectin

For more information regarding precautions and AEs with ivermectin, the Investigator is referred to the Prescribing Information (available at https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

For more information regarding precautions and AEs with moxidectin, the Investigator is referred to the Prescribing Information (available at Drugs@FDA; www.fda.gov/drugsatfda) and the Investigator's Brochure.

Warnings and precautions associated with treatment of individuals with onchocerciasis with moxidectin or ivermectin are summarized below.

10.5.1 Adverse Reactions Associated with Moxidectin or Ivermectin

Treatment of *O. volvulus* infected individuals with moxidectin or ivermectin may cause cutaneous, ophthalmological, and/or systemic reactions of varying severity (Mazzotti reactions).

These adverse reactions are due to allergic and inflammatory host responses to the death of microfilariae following treatment. Just as with the signs and symptoms of onchocerciasis, there is both significant variability in the frequency and severity of these reactions between individuals and a trend toward an increased incidence and severity of some of these reactions in individuals with higher microfilarial burden.

Treatment of severe Mazzotti reactions has not been evaluated in controlled clinical trials. Symptomatic treatments such as oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat orthostatic hypotension.

Antihistamines and/or analgesics have been used for most mild to moderate Mazzotti reaction cases.

10.5.1.1 Clinical, Ophthalmological and/or Systemic Adverse Reactions

The clinical manifestations of Mazzotti reactions include pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia.

An increased number of participants in the Phase III study who received moxidectin developed symptomatic orthostatic hypotension, with inability to stand without support, after lying down for at least 5 minutes in an orthostatic hypotension provocation test: 47/978 (5%) compared with 8/494 (2%) who received ivermectin. The decreases in blood pressure were transient, managed by resumption of recumbency and most commonly occurred on Days 1 and 2 post-treatment with moxidectin and slightly later post-treatment with ivermectin. Study participants should be advised that if they feel dizzy or light-headed after taking investigational product, they should lie down until the symptoms resolve.

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 without intervention.

Laboratory changes include eosinophilia, eosinopenia, lymphocytopenia, neutropenia, and increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) Proteinuria has also been reported. These changes generally resolve without intervention.

10.5.1.2 Edema and Worsening of Onchodermatitis in Individuals with Hyperreactive Onchodermatitis (Sowda)

Moxidectin has not been evaluated in patients with hyper-reactive onchodermatitis (sowda), but based on the experience with other microfilaricidal drugs, such patients may be more likely than others to experience severe edema and worsening of onchodermatitis following the use of moxidectin tablets.

The same information is provided in the ivermectin Prescribing Information (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Symptomatic treatment has been used to manage patients who have experienced edema and worsening of onchodermatitis.

10.5.1.3 Encephalopathy in *Loa loa* Co-infected Individuals

Individuals heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma.

This syndrome has been seen very rarely following the use of ivermectin (ivermectin Prescribing Information, https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Moxidectin has not been studied in individuals infected with *Loa loa*. Therefore, it is recommended that individuals who have had exposure to *Loa loa*-endemic areas undergo diagnostic screening for loiasis prior to treatment.

Consequently, both the primary and the back-up study area selected for this study are not *Loa loa* co-endemic. Individuals with a history of living or working or still temporarily working in *Loa loa* endemic areas or symptoms suggestive of *Loa loa* infection such as eye worm will undergo screening for loiasis and, if found to be *Loa loa* infected, will be excluded from this study (Sections 7.3.1 and 7.4.11).

10.5.1.4 Comparative Data on Adverse Events after Moxidectin and Ivermectin Treatment

For comparative data on the incidence of AEs reported in the moxidectin and ivermectin treatment arms of the Phase II and Phase III studies, the Investigator is referred to the moxidectin Prescribing Information (available at Drugs@FDA; www.fda.gov/drugsatfda) or the Investigator's Brochure.

10.5.2 Risks during Pregnancy

The risks of treatment with moxidectin during pregnancy have not been evaluated.

There are no adequate and well-controlled studies of ivermectin in pregnant women and the US FDA approved prescribing information advises 'Ivermectin should not be used during pregnancy since safety in pregnancy has not been established' (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Therefore, pregnant women are excluded from the study and women of childbearing potential must commit to using a reliable method of birth control for the duration of treatment and until 3 months after completion of dosing. See Sections 6.4.1 and 7.4.7 for further details on pregnancy testing and contraceptive requirements.

10.6 Reporting of Pregnancies and Follow up of Pregnancies

The participants must be instructed to inform the Investigator immediately (women) if she becomes pregnant or (men) if his partner becomes pregnant during the study period.

The Investigator should report all pregnancies to the Sponsor Safety Desk (Section 10.3.3.1) within 24 hours of becoming aware of the pregnancy. Pregnancies, pregnancy outcomes and the findings should be reported using the appropriate form(s) for reporting the occurrence and outcome of pregnancies in participants having received at least one dose of investigational product in the study, or their partner.

Any participants (or their partner, if she agrees) who become pregnant up to 3 months after administration of the last dose of investigational product (Month 27 or earlier in case of early withdrawal) should be monitored until the end of the pregnancy. In addition, the outcome of the pregnancy should be followed for the first year of life and reported to the Sponsor.

The required information will be obtained from the local health clinics (see Section 5.2.3). The study team will advise women becoming pregnant up to 3 months after administration of the last dose of investigational product to attend all ante-natal care visits, deliver at a health care facility and attend all post-natal care visits for the first year after birth provided by the local health care system. If necessary, the study team will facilitate attendance at these visits and delivery at the health care facility. The study team will collect the findings of the local health care staff for reporting in the eCRF. The same applies for the partner of a male participant who becomes pregnant within 3 months of the male participant having received the last administration of investigational product, provided she agrees to her

identity being provided to the study team and, if applicable, collection of the information from the health care clinics. In case of any abnormalities during the pregnancy or in the development of the baby during its first year of life for which a role of investigational product cannot be excluded, the team will arrange and pay for a specialist to evaluate the mother and/or the baby, as applicable.

10.7 Risks of Study Procedures Not Routinely Used in Health Care

10.7.1 Skin Snips

Skin snipping is the gold standard for quantifying infection with *O. volvulus*. Skin snipping with microscopic determination of microfilariae in the snips was the standard method used by the Onchocerciasis Control Program in West Africa and APOC in collaboration with the National Onchocerciasis Control and Elimination Programs for assessing patent *O. volvulus* infection. This included assessing progress towards onchocerciasis elimination in DRC (Bas-Congo, Sankuru and Uélé), Congo (Bouenza, Pool), Burundi, Cameroon, Central African Republic, Chad, Ethiopia, Liberia, Malawi, Nigeria, Tanzania, and Uganda (Tekle et al. 2016).

Skin snip sites heal within four to eight days without intervention. Therefore, it is expected that most skin snip sites will be healed by the end of the five daily visits by a study team member after each investigational product administration (Section 7.3.5). Should this not be the case, and for follow up after the skin snips at Month 30 and Month 36, additional visits to the participant will be conducted as indicated.

Participants will be advised not to self-medicate but to contact a study team member or a local health facility should they need medical attention (Section 5.2.3 and 15.12).

10.7.2 Nodulectomies

Excision of palpable nodules (subcutaneous nodules containing macrofilariae) involves minor surgery. Large scale implementation of nodulectomies in Guatemala, Mexico and Ecuador (WHO Expert Committee on Onchocerciasis 1987, Guderian 1988) have been used as part of onchocerciasis control efforts. The effect of nodulectomy as a means of reducing parasite transmission has been evaluated in Africa (Liberia, Burkina Faso) (WHO Expert Committee on Onchocerciasis 1987). Today, nodulectomies remain a standard procedure in the majority of studies of new anti-onchocercal treatments but are no longer used for onchocerciasis control.

Nodulectomies will be conducted under local anesthesia and using sterile technique to minimize pain and the risk of infection at the incision site and participants followed up by a study team member to complete healing (Section 7.4.12.1).

11 POTENTIAL BENEFITS TO STUDY PARTICIPANTS

Participation in the study is anticipated to provide a direct benefit as all participants will receive repeat doses of an anti-onchocercal therapy. Based on data from the Phase III study, direct benefits anticipated include reduction in skin microfilariae density and, if applicable, in live microfilariae in the anterior chambers of the eyes. Reduction in microfilariae is a meaningful measure of treatment efficacy as clinical symptoms of onchocerciasis are caused by the hosts' inflammatory reactions to microfilariae in the skin and eyes.

Participants excluded from the study because of a condition identified at Screening that requires medical attention will benefit from the Screening examination and receipt of referral information to a health facility.

Participants with a history of living or working or still temporarily working in areas where they might have become infected with *Loa loa* or signs and symptoms potentially caused by *Loa loa* infection, will benefit from having their *Loa loa* infection status evaluated. Those found to be *Loa loa*-infected will be given a note recording their infection status for presentation to the local onchocerciasis control/elimination (or lymphatic filariasis control/elimination) program and during ivermectin mass distribution so that the program can act accordingly (Section 6.4.2).

12 DATA SAFETY MONITORING BOARD REVIEW

A Data Safety Monitoring Board (DSMB) has been established by the Sponsor that is independent of the Sponsor, Investigator and site study team. DSMB members were selected to include expertise in research methodology and statistics, pharmacology, clinical management and treatment of onchocerciasis, and pediatric and adult infectious diseases.

Meeting objectives and schedule are specified in a DSMB charter and span the requirements of this study, the large single dose safety study (Study 3002) conducted concurrently in the same study area(s) in DRC, and the pediatric dose-finding study (Study 1006, conducted in Ghana). The DSMB may request additional review meetings.

Attendance at meetings will include DSMB members and non-voting members as required. Review of unblinded data may only occur in the presence of DSMB voting members and an unblinded biostatistician. Sponsor representatives may only attend that part of the meeting where data to be discussed remains blinded.

The first DSMB data review for this study will be convened after completion of a one month period after the first round of investigational product administration.

The DSMB will review all SAEs reported during the first month after each round of investigational product administration and provide a recommendation to the Sponsor on study continuation as planned, protocol amendment, or study discontinuation, following which the Sponsor will determine study continuation, protocol amendment, or study discontinuation.

The outcome of the deliberations and recommendations of the DSMB to the Sponsor will be documented. The recommendations will be provided to the Investigator and the ECs.

13 PARTICIPANT COMPLETION OR WITHDRAWAL AND FOLLOW UP

13.1 Participant Completion

A participant will be deemed to have completed the study once all trial procedures have been conducted.

Any AEs or SAEs still ongoing at the End of Study Visit (Month 36, Section 7.3.9), at the Exit Examination for individuals withdrawing/withdrawn early (Section 7.3.10) or at the Exit Examination in case of Early Study Termination (Section 7.3.10), will be followed in accordance with Section 10.4.

13.2 Premature Withdrawal from Treatment or the Study

13.2.1 Criteria for Premature Withdrawal from Treatment or the Study

Participants have the right to withdraw from treatment or the study at any time for any reason and without providing a reason. This will be discussed in the village meetings and with individuals (and their parent(s)/guardian for minors) as per the information in the EC approved participant information document (Section 5.1 and Section 15.9).

The Investigator has the obligation to withdraw study participants from further treatment in case of pregnancy.

The Investigator may also withdraw participants from further treatment or from the study in the event of concurrent illness or an AE if it is considered to be in the best interest of the participant.

The Investigator also has the right to withdraw participants from further treatment or the study in the case of protocol violations (e.g. continued failure or inability of the participant to be available for follow up visits; treatment with doxycycline for more than 2 weeks). The Sponsor and Investigator will discuss and agree whether withdrawal from the study may also be necessary.

13.2.2 Follow up of Participants Withdrawing or Withdrawn from Further Treatment

If a participant permanently discontinues dosing with investigational product, for example as a result of an AE or pregnancy, the investigator should discuss continued participation in the study with the participant so that, if the participant agrees, the study-required follow-up and procedures can be performed to Month 30.

The reason for withdrawal from further treatment should be noted in the source records and on the eCRF (including if there is no reason given). If a participant is withdrawn from further treatment because of a treatment-limiting AE, thorough efforts must be made by the investigator to obtain agreement from the participant for follow up of this AE so that the investigator can clearly document the outcome of the AE in the source records and on the eCRF.

Women who are withdrawn from further treatment because of a pregnancy should be asked to allow evaluation of the outcome of the pregnancy and newborn to the end of its 1st year of life. (Section 10.6).

13.2.3 Follow up of Participants Withdrawing or Withdrawn from the Study

Should a participant decide to withdraw from the study, all efforts should be made to contact them, determine the reason for the withdrawal (and resolve any misconceptions that might motivate participant withdrawal) if the participant is willing to provide it. Furthermore, the investigator should ask the participant for his/her agreement for an Early Exit Examination

(Section 7.3.10). Unless an earlier time is chosen by the former participant, the Exit Examination should be conducted at least 3 months after the last treatment to monitor the participant for possible investigational product related AEs.

The request to participants withdrawing from the study to agree to an Early Exit Examination (Section 7.3.10) is motivated by the following considerations:

- The Early Exit Examination is designed to characterize the health at the time of withdrawal. This is important independent of whether the participant withdraws because of an AE or for other reasons (including reasons they choose not to disclose). Participants withdrawing for AE-unrelated reasons may nevertheless have AEs that the investigator should identify for two reasons: (a) to offer the participant follow up of ongoing AEs, and (b) to obtain as complete as possible characterization of the safety profile of the study drug.
- Determine the number of skin microfilariae at the time of withdrawal. This will serve two purposes: (a) motivate those likely to benefit most from further treatment i.e. those with detectable skin microfilariae levels, to take ivermectin when distributed in their community, and (b) it will allow inclusion of actual skin microfilariae counts at that time in the analysis, thus increasing the accuracy of efficacy evaluation.

Advice regarding participation in ivermectin distribution in the area will be provided. Furthermore, if permitted by the participant, follow up of AEs ongoing at the Exit Examination to resolution should be conducted.

As applicable, inability to reach the participant, reason for withdrawal (including unknown or unwillingness of the participant to provide it), refusal of the participant of the Exit Examination, or, if applicable, follow up of ongoing AEs or of a pregnancy should be recorded in the source records and on the eCRF.

If the Investigator withdraws a participant from the study, the principal reason will be recorded in the source records and on the eCRF and the relevant activities specified above for the case of a participant withdrawing implemented (provided the former participant agrees).

13.3 Replacement of Withdrawn Participants

Participants who decide to withdraw from treatment or this study or are withdrawn by the Investigator will not be replaced.

13.4 Temporary Suspension of Study Conduct

Continuation of the study, in particular further treatment, may be temporarily suspended by the Sponsor, or on the recommendation of the Investigator or the DSMB based on identification of AEs that require further examination before resumption of treatment or continuation of the study. Study conduct will continue once the concerns that resulted in suspension have been addressed. The RA and ECs will be informed about the suspension, its rationale and resolution of the concerns.

Continuation of the study may also be put on hold if requested by the RA or the responsible ECs, or the Sponsor in response to information it generates/receives from sources outside of the study, including communications from the US FDA. Study conduct will continue once authorized by the RA, the responsible ECs, or the Sponsor, respectively.

13.5 Premature Termination of the Study

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

- New information regarding safety that indicates a change in the risk/benefit profile for moxidectin, such that this may no longer be acceptable to study participants, as per recommendation of the DSMB, the Sponsor (including in response to information it generates/receives from sources outside of the study, including communications from the US FDA), the Investigator, the RA and/or the responsible EC; and/or
- Significant violation of GCP that compromises the rights and safety of the study participants or the ability to achieve the primary study objective.

Conduct of the study may also be terminated if the Investigator or site staff are found in significant violation of contractual agreements, or are unable to ensure adequate performance of the study.

The Investigator has the right to request termination of the study if it is considered in the best interest of current and potential future study participants' safety or the investigator finds it impossible to complete the study as required by the protocol and GCP.

Sponsor and Investigator need to consult with each other before the decision to terminate the study prematurely and agree on a termination procedure to ensure that, for example, participant safety is protected (follow up of ongoing AEs), investigational product is disposed in a manner consistent with the regulatory requirements and all study documentation stored in a manner that safeguards participant confidentiality.

14 STATISTICAL ANALYSIS

This trial is a randomized, double blind, parallel group, active control study design comparing the safety and efficacy of annual or biannual doses of moxidectin (8 mg) or ivermectin (approximately 150 µg/kg) for the treatment of onchocerciasis. Participants meeting all inclusion and no exclusion criteria will be randomized to one of four treatment groups (as described in Section 4.2), stratified by their baseline microfilariae skin density (<20 mf/mg versus ≥ 20 mf/mg) and Aire de Santé of residence (Section 4.2 and Section 8.1).

Following Baseline assessments and randomization, participants will be followed for 36 months.

For the purpose of the analysis, the term Baseline will refer to the last assessment taken prior to administration of the first dose of investigational product and therefore includes assessments taken during Screening per the schedule in

Table 1 or if scheduled Day -1 to 0 (pre-dose) assessments are missing.

14.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants in the Full Analysis Set (FAS) (Section 14.8.1) who achieve a sustained skin microfilariae response (SMR) at Month 12 (SMR12) defined as an undetectable (zero) *O. volvulus* skin microfilariae count for each skin snip at both Months 6 and 12.

For each FAS participant, the calculation of zero *O. volvulus* skin microfilariae at a given time point will use all available, non-missing, skin snips. Participants with a zero count for each non-missing skin snip at both Months 6 and 12 will be categorized as a SMR12 responder. Participants with a non-zero count at either Month 6 or 12 will be categorized as a SMR12 non-responder. Participants with no available skin snip data at either Month 6 or 12 will be imputed as a non-responder for their SMR12 status. See Section 14.11.6 for further information on handling of missing data for this endpoint.

14.2 Secondary Efficacy Endpoints

14.2.1 Sustained Skin Microfilariae Response (SMR)

SMR is defined as zero *O. volvulus* skin microfilariae detected in all skin snips at all relevant post-Baseline assessments:

- **SMR12** is defined as above but for pairwise comparisons other than annual or biannual moxidectin treatment (Section 14.11.2.1)
- **SMR18** is defined as zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, and 18;
- **SMR24** is defined as zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18 and 24;
- **SMR30** is defined as zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18, 24, and 30; and
- **SMR36** is defined as zero *O. volvulus* skin microfilariae counts at all of Months 6, 12, 18, 24, 30, and 36.

The calculation of these SMR endpoints will follow the same algorithm defined above for the SMR12 primary endpoint as relevant.

14.2.2 Mean Skin Microfilariae Density

The mean skin microfilariae density (mf/mg skin) at a given time point will be the arithmetic average of the skin microfilariae densities across FAS participants.

For an individual participant the skin microfilariae density value is defined as the average skin microfilariae density among the non-missing skin snips at each time point. For some analyses the skin microfilariae density for a given participant may be transformed using a log transformation (log(x + 1)).

See Section 14.11.6 for further details of how missing data will be handled for this endpoint.

14.2.3 Mean and Median Percent Change (Reduction) from Screening (Baseline) in Skin Microfilariae Density

The mean percent change from Screening (Baseline) in skin microfilariae density (as defined above) at a given time point is defined as the arithmetic mean of the individual percentage change from Screening per participant. The median percent change from Screening (Baseline) in skin microfilariae density at a given time point is defined as the median of the individual percentage change from Screening per participant.

See Section 14.11.6 for further details of how missing data will be handled for this endpoint.

14.2.4 Proportion of Participants with Zero Skin Microfilariae at Each 6 Monthly Assessment

This endpoint will provide the cross-sectional proportion of FAS participants with zero skin microfilariae detected in each skin snip at each distinct 6 month assessment. The proportion at each 6 month assessment will be cross-sectional without regard to the participant's skin count status at other time points. There will be no imputation for missing data.

14.2.5 Endpoints for Live Microfilariae in the Anterior Chambers

For live microfilariae in the anterior chambers of the eyes, the endpoints will be calculated as follows:

- Sustained ocular microfilariae response defined as zero live *O. volvulus* microfilariae in the anterior chambers of the eyes at all post-Baseline assessments up to and including each of Months 12, 18, 24, 30, and 36, respectively.
- Mean, and mean change from baseline, with respect to the number of live microfilariae in the anterior chambers of the eyes at each post-Screening assessment.
- Mean and median percent reduction (from pre-treatment) of live microfilariae defined as the arithmetic mean and median of the individual percentage change from Screening per participant with respect to the number of live microfilariae in the anterior chambers of the eyes at each post-Screening assessment.
- Proportion of participants with zero live microfilariae in the anterior chambers of the eyes at each post-Screening assessment.

For these endpoints, only FAS participants with at least one live microfilariae in the anterior chambers across both eyes at Screening (Baseline) will be eligible for these analyses. If sufficient participants have a Screening count of ≥ 10 live microfilariae in the anterior chambers of the eyes, this group will be analyzed separately.

Since the mean and median endpoints are calculated using the total live microfilariae count per participant only participants with non-missing data from both eyes will be eligible for those endpoints. To maintain comparability across the ocular endpoints, the requirement for non-missing data in both eyes will be used for all the ocular endpoints. Data for these

endpoints will not be imputed. See Section 14.11.6 for further details of how missing data will be handled for this endpoint.

14.3 Exploratory Endpoints

14.3.1 Signs and Symptoms of Onchocerciasis

Presence and severity of reactive skin lesions and pruritus will be analyzed descriptively for each 6 monthly visit. Only participants in the safety analysis set with these signs and symptoms at Screening (Baseline) will be included in follow-up and eligible for these analyses.

14.3.2 Viability and Fertility of Male and Female Macrofilariae

Viability endpoints will be descriptive only and include the proportion of live, moribund, dead or dead and calcified male and female macrofilariae, per participant averaged across all participants by treatment and overall.

Fertility endpoints will be descriptive only and include:

- The proportion of female worms by absence or presence of oocytes or embryos overall and by developmental stage (oocytes, morula, coiled, stretched, pretzel) per participant averaged across all participants by treatment and overall, and
- The proportion of male worms by absence or presence of spermatogenic stages and type of spermatogenic stages per participant averaged across all participants by treatment and overall.

Depending on the histopathological stains available at the time of histopathology, additional endpoints may be defined.

14.4 Safety Endpoints

Safety endpoints will be AEs, vital signs, concomitant medications and liver function tests and use the safety analysis set.

If applicable, the outcomes of pregnancies and health-related findings on the neonates to 1 year of age will be included.

14.5 Primary Efficacy Hypothesis

The primary efficacy hypothesis is a test of the average treatment effect with respect to achieving SMR at Month 12 (SMR12) when comparing the biannual versus the annual moxidectin treatment arms. The average treatment effect will be estimated by the standardized risk difference (RD) using the methodology outlined by Steingrimsson and colleagues (Steingrimsson et al. 2017), see Section 14.11.1. The null (H_o) and alternative (H_a) hypotheses for a two-tailed test are depicted below:

$$H_o: \pi_{biann\_moxi} - \pi_{ann\_moxi} = 0$$

$$H_a: \pi_{biann\_moxi} - \pi_{ann\_moxi} \neq 0$$

Where:

π_{biann_moxi} = the proportion in the target population achieving a SMR12 when assigned treatment with biannual moxidectin, and
π_{ann_moxi} = the proportion in the target population achieving a SMR12 when assigned treatment with annual moxidectin.

A statistically significant result, $p < 0.05$ two-tailed, with a RD favoring biannual moxidectin treatment, will confirm the superior efficacy of two 6-monthly moxidectin treatments over a single moxidectin treatment with respect to the proportion of the target population achieving a sustained microfilariae response at Month 12 (SMR12). The primary analysis will use the full analysis set (FAS, Section 14.8.1).

14.6 Sample Size

The sample sizes per randomized treatment group are shown in Table 9 and reflect the allocation ratios for each of the four treatment groups.

Table 9: Sample Size by Randomized Treatment Group

Dosing Schedule	Randomized Treatment Group (N = number)	
	Moxidectin	Ivermectin
Annual	N = 375	N = 125
Biannual	N = 375	N = 125

The sample sizes between the moxidectin and ivermectin groups reflecting a 3:1 randomization ratio (Section 14.7) will provide safety data for up to a total of 3000 exposures to moxidectin and 1000 exposures to ivermectin, providing a probability of around 0.95 and 0.63 to detect at least 1 AE with a true background rate of 0.001, respectively, assuming exposures are independent.

The estimated treatment effects were calculated from the large single dose Phase III trial with similar inclusion/exclusion criteria (Section 2.3.2.3). In that trial, an 'annual moxidectin group' (N = 977; as-randomized set) was included in the study design; however, there was no 'biannual moxidectin group' included in that trial or elsewhere. Hence, hypothetical SMR12 rates for a biannual moxidectin group using the previous Phase III data were calculated assuming that participants with zero microfilariae at Month 6 would continue to have zero microfilariae at Month 12 with biannual treatment. The hypothetical SMR12 rate for the annual moxidectin group was estimated from the Phase III data for all moxidectin participants with zero microfilariae at Months 6 and 12. For both estimates, calculations were derived imputing non-response for participants with missing skin snip data. Given these assumptions, the hypothetical SMR12 rates for the biannual and annual moxidectin groups were estimated to be 90% and 43%, respectively.

Given these hypothetical SMR12 rates and assuming 375 participants meeting the FAS criteria (all randomized participants exposed to at least one dose of investigational product) within each of the two moxidectin groups, the power of the primary efficacy hypothesis, comparison of the biannual versus the annual moxidectin arm with respect to SMR12, was estimated to be greater than 95% via a z-test for two independent proportions at a two-tailed alpha level of 0.05. A sensitivity analysis using the lower limit of the 95% CI for the biannual SMR12 estimate and the upper limit of the 95% CI for the annual SMR12 estimate also yielded a power greater than 95%. Although these power calculations do not account for adjustment of covariates which will be incorporated into the primary analysis of the SMR12 endpoint, they should provide reasonable power estimates.

14.7 Randomization and Randomization Ratio

Participants will be randomized using an algorithm stratified by Baseline microfilariae density (< 20 mf/mg versus ≥ 20 mf/mg) and Aire de Santé.

The randomization algorithm will yield the following allocation ratios among the 4 treatment groups: 1:1 allocation ratio for the moxidectin biannual vs moxidectin annual treatment arms, 1:1 allocation ratio for the ivermectin biannual vs ivermectin annual treatment arms, 3:1 allocation ratio for moxidectin vs ivermectin for both the biannual and annual treatment arms.

The 3:1 randomization ratio for the moxidectin and ivermectin treatment arms was chosen to maximize the safety data base after exposure to moxidectin while preserving the ability to compare the type, frequency and severity of AEs after moxidectin with those after ivermectin in the same population within the same time period.

The randomization lists will be generated by an independent statistician not otherwise participating in the study. The randomization algorithm implemented will be documented, remain secured by the independent statistician, and provided in the clinical study report.

14.8 Analysis Populations

14.8.1 Full Analysis Set

The FAS is defined as all randomized participants exposed to at least one dose of investigational product. Participants in the FAS will be analyzed as randomized regardless of the actual treatment received.

14.8.2 Safety Analysis Set

The safety analysis set is defined as all participants exposed to investigational product. For the safety analysis set, participants will be analyzed according to the actual investigational product received regardless of their randomized treatment group.

14.8.3 Per Protocol Analysis Set

The per protocol analysis will be used for selected sensitivity analyses. The per protocol analysis set will include participants with no major protocol violations which will be specified *a priori* before database lock and analysis.

14.9 Group Comparability

Since the study is randomized and stratified by Baseline microfilariae density and Aire de Santé it is expected that the treatment arms will, on average, be balanced with respect to known and unknown prognostic factors.

Statistical tests to assess group comparability with respect to baseline characteristics will not be conducted.

Exploratory subgroup analyses and/or statistical models adjusting for baseline covariates suspected as being prognostic factors, other than those pre-specified, may be conducted for descriptive and supportive purposes.

14.10 Data Analysis Methods

The FAS and safety analysis sets will be used for the analysis of efficacy and safety, respectively, unless otherwise stated.

Aggregate data summaries will be provided by treatment arm and overall. If relevant, data summaries will also be provided by study time point. Line listings of study data will also be included. Unless otherwise stated, all p-values will be two-tailed. Adjustment for multiple comparisons for secondary and exploratory endpoints will not be conducted.

Further analysis details will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to unblinding and the undertaking of any analysis. Any changes to the

finalized SAP during the study will be documented. Deviations from the planned statistical analyses outlined in the SAP will be identified and described in the clinical study report.

14.11 Statistical and Analytical Plan

14.11.1 Statistical Analysis of the Primary Efficacy Hypothesis

Following the methodology of Steingrimsson and colleagues (Steingrimsson et al. 2017), a logistic regression model with SMR12 as the dependent variable and main effects for Baseline microfilariae density (< 20 mf/mg density vs. ≥ 20 mf/mg density), the continuous metric for Baseline microfilariae density, village, and randomized treatment groups (moxidectin biannual versus moxidectin annual) will be fitted using the FAS. The predicted probabilities from the resulting logistic regression model will be calculated for each participant for each of these two treatments, regardless of the participant's actual randomized treatment group. In essence, for each FAS participant two predicted probabilities will be calculated: one reflecting the probability of a SMR12 if the participant were assigned to biannual moxidectin treatment, and a second reflecting the probability of a SMR12 if the participant were assigned to annual treatment. The average of the predicted probabilities for each treatment across all FAS participants are the estimates corresponding to the target population proportions denoted in the null and alternative hypotheses above. Their difference is the standardized RD of Steingrimsson and colleagues (Steingrimsson et al. 2017) and an estimate of the average treatment effect. The standard error (SE) of the standardized RD is obtained via a bootstrap from 1000 samples. The statistical test of the null hypothesis above is a Wald test obtained by dividing the standardized RD by its bootstrapped SE and comparing the result to the inverse of the standard normal cumulative distribution function appropriate for a two-sided test at alpha = 0.05. The 95% CIs will also be calculated using the bootstrapped SE.

Participants in the FAS with no available data at any post-Baseline time point included in the calculation of the SMR12 will be categorized as a SMR12 non-responder. Participants missing Baseline microfilariae density will have their Baseline value imputed using the mean of their Aire de Santé. For the standardized RD, the point estimate, SE, the 95% CI, Wald statistic, and p-value will be provided along with the estimated treatment proportions. Standardized odds ratios (ORs) and relative risk will also be calculated using the same methodology.

Should the logit model fail to converge with the inclusion of both the continuous and dichotomous covariates for Baseline microfilariae density, the dichotomous Baseline microfilariae density will be removed from the model.

Sensitivity analyses supportive of the primary efficacy analyses will include comparison of the SMR12 in the biannual and annual moxidectin groups for each stratum used in the randomization and re-running the primary analysis using the per-protocol and safety analysis set. Additionally, sensitivity analyses for the primary efficacy endpoint will explore various imputation algorithms for participants with missing data. Further details will be outlined in the SAP.

14.11.2 Statistical Analysis of Secondary and Exploratory Efficacy Endpoints

14.11.2.1 SMR12 Additional Pairwise Group Comparisons

The SMR12 endpoint for additional pairwise group comparisons will be analyzed similar to that described above for the primary efficacy analysis using the FAS. These pairwise comparisons include:

- Annual moxidectin versus annual ivermectin;
- Biannual moxidectin versus biannual ivermectin; and/or

- Annual moxidectin versus biannual ivermectin.

As the secondary analyses will be supportive to the primary analysis, no adjustment for multiple comparisons will be made.

14.11.2.2 SMR18, SMR24, SMR30, and SMR36

The analysis of the SMR endpoints at Months 18, 24, 30 and 36 and the pairwise comparisons will be conducted in a manner similar to that described for the SMR12 endpoint.

14.11.2.3 Mean Skin Microfilariae Density

The mean skin microfilariae density will be analyzed using an Analysis of Covariance (ANCOVA) model separately for each time-point and pairwise comparison noted in Section 14.11.2.1 and the annual vs biannual moxidectin comparison. Randomized treatment group, Baseline mean skin microfilariae density (continuous), and the two randomized stratification factors will be included as main effect covariates in the ANCOVA model. The analysis will include robust (sandwich) standard error estimates for statistical assessment of the regression coefficients and CIs. Prior to analysis, for each participant, the skin microfilariae density will be log transformed (natural log) with a 1 added, (log(x + 1)). Summary statistics will be transformed back for presentation. Should the ANCOVA model fail to converge with the inclusion of both the continuous and dichotomous covariates for Baseline microfilariae density, the dichotomous Baseline microfilariae density will be removed from the model.

Additional sensitivity analyses may include nonparametric tests via permutation methods.

In addition to the adjusted means, summary descriptive statistics including the mean and median for the raw and raw change from baseline values will also be provided by timepoint and randomized treatment arm.

See Section 14.11.6 for further details of how missing data will be handled for this endpoint.

14.11.2.4 Mean and Median Percent Change (Reduction) from Baseline in Skin Microfilariae Density

The percent change from Baseline in skin microfilariae density will be analyzed descriptively using the raw skin microfilariae density data. Both the mean and median percent change will be provided. Analyses will be provided by treatment group, time point, and overall. FAS

See Section 14.11.6 for further details of how missing data will be handled for this endpoint.

14.11.2.5 Proportion of FAS Participants with 0 Skin Microfilariae at Each 6 Monthly Assessment

This analysis will consist of descriptive summary statistics providing the cross-sectional results. The proportion will be calculated on the number of FAS participants with non-missing data at each time point. As such, no imputation for missing data will be done. For each time point the number of participants with non-missing data and the 95% CI will be provided. The summary tables will be categorized by randomized treatment group and overall as well as by time point and skin microfilariae density stratum at randomization.

As a sensitivity analysis, these data may also be analyzed imputing a non-response (i.e. assuming detectable skin microfilariae levels) for participants with missing data at each relevant time point.

14.11.2.6 Live microfilariae in the Anterior Chambers of the Eye

Analysis of live microfilariae in the anterior chambers of the eyes in FAS participants with live microfilariae in the anterior chambers of the eyes at Baseline will be descriptive, as the number of participants in this subgroup is likely to be small. For each time point, descriptive summary statistics will be calculated for each endpoint. For continuous endpoints, summaries will include the mean, median, standard deviation (SD), min, max, and the number of FAS participants contributing to the statistics. For sustained ocular microfilariae response endpoints, the SMR proportion, the number of responders, the 95% CI, and the number of FAS participants contributing to the statistics will be calculated.

Missing data will not be imputed for the descriptive analyses described above and only participants with non-missing data for both eyes will be included. If the sample size is not unreasonably small, a sensitivity analysis imputing a non-zero outcome for participants with missing data may be conducted for the sustained ocular response endpoint.

If sufficient participants have a Screening count of ≥ 10 live microfilariae in the anterior chambers of the eyes, this group may be analyzed separately.

14.11.2.7 Signs and Symptoms of Onchocerciasis

Descriptive summary statistics will be provided for these endpoints. Only participants in the safety analysis set with these signs and symptoms at Screening (Baseline) will be included in follow-up and eligible for these analyses. Missing data will not be imputed.

14.11.2.8 Viability and Fertility of Male and Female Macrofilariae as Determined by Histopathology of Nodules Excised at Month 36

Descriptive summary statistics will be calculated for these endpoints including only participants with histological evaluation data. Missing data will not be imputed.

14.11.3 Description of Subgroups to Be Analyzed

The SMR endpoints and the mean skin microfilariae density endpoints for the FAS will be descriptively summarized and analyzed by treatment group for the following subgroups:

- Baseline skin microfilariae density (< 20 mf/mg versus ≥ 20 mf/mg skin);
- Age categories (specified in the SAP);
- Sex; and
- Aire de Santé.

14.11.4 Analysis of Participant Disposition, Demographics, and Baseline Characteristics

Descriptive summary tables will be provided summarizing participant disposition by randomized treatment arm for each analysis set, including all participants randomized regardless of exposure to investigational product along with reasons for early withdrawal from investigational product and early withdrawal from the study. Demographic and medical history summary statistics will also be provided by randomized treatment group and overall.

14.11.5 Analysis of Safety

Safety will be assessed using the safety analysis set and will include TEAEs, vital signs, liver function, concomitant medications and pregnancy outcomes.

Imputation of partial AE and concomitant medication dates will be done in order to categorize an event or medication as treatment emergent or as having started or been taken after the first treatment and subsequent treatments, respectively. Details of the date imputation algorithm will be provided in the SAP.

14.11.5.1 Adverse Events

TEAE participant incidence will be summarized by body system and preferred term. Data will be tabulated by severity, investigator assessment of relationship to investigational product, serious TEAEs and TEAEs leading to death or study withdrawal. They will be summarized as follows:

- Overall
- TEAEs will be summarized overall and by 6 month time period after each investigational product administration.

An additional analysis of TEAEs starting, or worsening, after the nodulectomies will be conducted separately for those participants in the safety analysis set which underwent nodulectomies.

Key TEAEs of interest may be further analyzed by skin microfilariae density before each investigational product administration and, using Kaplan-Meier methods, assessed for time-to-first events and/or time-to-resolution. Additionally, for key TEAEs exposure adjusted rates may be provided along with the timing of TEAEs relative to each dose of investigational product.

TEAEs may also be summarized by age and sex and by pre-treatment skin microfilariae density.

Line listings of all TEAEs will be provided.

For participants in the safety analysis set, events occurring after signing of informed consent/assent but prior to the first exposure to investigational product will be provided in separate line listings.

14.11.5.2 Vital Signs

Aggregate summary data for vital signs will be provided at Screening and post-Screening time points along with changes from Baseline and the subsequent applicable pre-treatment time points. Means, medians, standard deviations, minimums and maximum values will be provided.

14.11.5.3 Liver Function Tests

Aggregate summary data for liver function test results will be provided for pre- and five day post-dose assessments associated with Day 0, Month 6 and Month 12 investigational product administration. Means, medians, standard deviations, minimums and maximum values will be provided. Change from Baseline, and from the pre- Month 6 and Month 12 investigational product administration values, as relevant, may also be provided.

14.11.5.4 Concomitant medications

Concomitant medications for TEAEs will be summarized overall and by 6 month time period after each investigational product administration specified in Section 14.11.5.1.

14.11.5.5 Pregnancy Outcomes

Narratives will be provided for each pregnancy and baby born for the first year of its life.

14.11.6 Handling of Missing Data

For the SMR endpoints FAS participants with missing data at a given time point for a SMR endpoint will be imputed with a non-response value at that timepoint. Participants who died on-study will be imputed as a non-responder for all time points subsequent to their death. Additionally, participants who took a medication prohibited because of the potential impact on *O. volvulus* identified by the clinical team prior to any unblinding and data analysis will

be categorized as a non-responder for any subsequent time points post prohibited-medication exposure.

For the ANCOVA analyses of the mean skin microfilariae densities participants with missing data at a given time point will have their Baseline value imputed, including missing data for participants who died on study. For exposure to prohibited medication as defined above, the timepoints subsequent to exposure will also be imputed with the participants baseline value. Participants missing Baseline microfilariae density will have their Baseline value imputed using the mean of their Aire de Santé.

The descriptive analyses for the mean and median percent reduction endpoints will impute missing data in a similar manner.

The same principles apply for the analysis of the relevant ocular endpoints if inferential analyses are conducted for those endpoints.

Partial start/end dates for TEAEs and concomitant medications will be imputed as outlined in Section 14.11.5.1.

Further details including sensitivity analyses conducted to assess the impact of missing data will be described in the SAP.

14.11.7 Interim Analysis

A DSMB will review safety data for the duration of the study (Section 12).

With respect to efficacy, no interim analyses are expected to be conducted.

However, after the last participant has completed their Month 12 assessment, the Month 12 data entered into the database will be cleaned and locked (frozen) to support a final analysis of the Month 12 data prior to the study's completion. The rationale for conducting early analysis of the primary endpoint is to provide timely information to the WHO, policymakers, regulators and the onchocerciasis research and control community necessary for planning efforts toward future inclusion of moxidectin in national control programs.

The Investigator and study staff, participants, and Sponsor will remain blinded to individual treatment assignments. An independent statistical group will conduct the analysis, thus maintaining the blind to individual data for personnel responsible for final analysis of the study upon completion of the study. The primary efficacy endpoint (proportion of participants achieving SMR12 for moxidectin biannual compared with moxidectin annual treatment arms), mean skin microfilariae density, and aggregate safety data through Month 12 will be reported. Individual participant and minimum or maximum for aggregate mean microfilariae density data will not be reported at this time.

The results included in any report provided to the Sponsor will be submitted to regulatory authorities (RA, US FDA) and ECs.

The unblinded treatment allocations will be applied to secured analysis data model (ADaM) files and not entered into the trials database. Operating details will be provided in the SAP or an additional document provided prior to undertaking an analysis.

14.11.8 Supplemental Analyses for Informing Guidelines and Policies

The types of analyses required by regulatory agencies do not always meet the requirements for decisions on inclusion of an intervention in guidelines and policies. A separate SAP will be written for supplemental analyses addressing these requirements. The analyses will not be executed until the Study's conclusion.

14.11.9 Update of Statistical Analysis Plans in View of Potential Impact of COVID-19 Pandemic on Study Conduct and Data

Before unblinding, the data will be reviewed to assess which protocol deviations such as treatments, efficacy assessments or safety assessments that were missed or conducted outside the protocol prescribed window are attributable to the COVID-19 pandemic. The Statistical Analysis Plans will then be updated to reflect complementary or appropriately modified approaches to the analyses.

15 ETHICAL ASPECTS

15.1 Declaration of Helsinki and Applicable Regulations

The Investigator will ensure that this study is conducted in full conformance with the protocol, the latest version of the "Declaration of Helsinki", the International Ethical Guidelines for Health-related Research Involving Humans of the Council of International Organizations of Medical Sciences (CIOMS), the ICH-GCP Guideline and all applicable regulations.

15.2 Approval of Study Conduct by the Regulatory Authority

This protocol, material used to inform potential study participants about the study (participant information document and informed consent and assent forms, PICF), the Investigator's Brochure and a dossier in the investigational medicinal products will be submitted by the Sponsor through the Investigator to the RA. Approval of study conduct by the RA is required before the study can be started.

Protocol amendments as well as memoranda summarizing administrative changes of the protocol (Section 15.5) will be submitted to the RA as specified in the letter of approval of study conduct.

15.3 Ethics Committee Approval

This protocol, PICFs and the Investigator's Brochure, will be submitted by the Investigator to the EC assigned to the study by the MdSP. Furthermore, they will be submitted to the WHO Ethics Review Committee.

Approval from the ECs must be obtained before starting the study and should specify the protocol number and/or title and protocol version, PICF version number and/or date and the date on which the EC met and the date the EC granted the approval and/or the date of signature on the approval.

Any protocol amendments (Section 15.5) after receipt of the original EC approval must also be submitted to the ECs and approved by the ECs before the amendment can be implemented (except where required to ensure participant safety). The ECs will be notified of changes to the protocol that are purely administrative (Section 15.5).

Documents to be used for informing participants of any early termination of the study (Section 13.5), new data that might impact their decision on continued study participation (Section 15.10) and the results of the study (Section 15.22) will also be submitted for EC approval prior to use.

15.4 Reports to RA and ECs

Reports to the RA and the ECs will be submitted as requested by the RA and ECs in their decision/approval letters. In the absence of specific requests, a progress report summarizing the number of individuals screened and treated in the past year and the number and type of SAEs reported since the last report will be submitted to the ECs annually.

15.5 Protocol Amendments

Administrative changes of the protocol are defined as corrections and/or clarifications that have no effect on the safety of the participant, scope, design, assessments or scientific validity of the study. These administrative changes will be agreed upon by the Sponsor and the Investigator, and will be documented in a memorandum. The Investigator will then notify the EC and the RA of these administrative changes.

Other modifications of the protocol (protocol amendments) must be prepared in consultation between the Sponsor and the Investigator and must be reviewed and approved by the Sponsor-designated Medical Monitor and the Statistician before sign off by the Sponsor and the Investigator. Investigator and Sponsor-approved protocol amendments will be submitted to the ECs, to the RA as well as to the US FDA IND 126876 (Section 18). They must be approved by the RA (if indicated in the RA study approval letter) and/or ECs prior to the amendment being implemented.

In the event of an emergency, the Investigator may institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor Clinical Development Manager for this study and the Medical Monitor, and the ECs.

15.6 Study Site Capacity

CRMT was one of the research centers established for the moxidectin Phase III study (protocol ONCBL60801). It is located at Referral Hospital (Hôpital de Réference) at Rethy, Ituri Province, and managed by the 20th Communauté Evangélique au Centre de l'Afrique (CECA/20), Bunia, member of the Église du Christ au Congo, in the DRC.

Establishment of the CRMT in preparation for the Phase III study included renovation of buildings not used by the Hôpital de Réference to provide rooms and facilities required for that study. These facilities, including laboratories, locked storage facilities for study documentation, locked and temperature controlled room for the storage and preparation of investigational product, a meeting room and staff offices will be used for this study.

Clinical, ophthalmological and laboratory equipment and material and other infrastructure elements such as cars, motorcycles, back-up generators, fuel reservoirs and communications means (satellite dish for internet connectivity) were also provided for the Phase III study and will be utilized for this study as needed. Additional and/or replacement equipment and material needed for this study will be purchased by CECA/20 from the grant obtained from the European and Developing Countries Clinical Trials Partnership (EDCTP) by the Sponsor, the Investigator (Dr. T. Ukety, CECA/20) and Co-Investigator (Dr. M. Mandro, DPS Ituri) and other researchers.

15.7 Study Team

The study will be led by Dr. T. Ukety, who is an ophthalmologist from Ituri, has conducted onchocerciasis-related studies in Ituri prior to joining WHO and was involved in the Phase III study as a technical advisor.

The co-investigator, Dr. M. Mandro, is also from Ituri and has conducted onchocerciasis-related studies in Ituri and was a clinical monitor of the moxidectin Phase III study, in particular the site in Ituri. He has been seconded to this study from the DPS Ituri.

Some staff who conducted the Phase III study in Ituri will be involved in this study as well.

These staff, as well as additional staff hired for this study, will undergo (re)training on the ethical requirements for study conduct, the requirements for study conduct as outlined in the ICH-GCP, the protocol, protocol required procedures and protocol required documentation.

The Standard Operating Procedures (SOPs) established for the Phase III study will be adapted or complemented for the study procedures required in this study.

15.8 Study Initiation

The study can only be started after approval by the RA and the assigned ECs and after the Sponsor has approved study start following the study initiation visit.

The objective of the initiation visit is to verify that the Investigator and study team have the means and knowledge to conduct the study. During the initiation visit, the Sponsor representative(s) will review with the Investigator and study team all Declaration of Helsinki, CIOMS and ICH-GCP requirements, the profile of AEs occurring after ivermectin and moxidectin treatment, all protocol requirements, study required equipment, material and consumables, study implementation plans including plans for study participant recruitment, SOPs, study documentation requirements including source records and eCRFs (Section 16), SAE reporting requirements and forms (Section 10.3.3), pregnancy reporting and follow requirements and forms (Section 10.6), study team training records and the study Authorization and Delegation Log. This verification will include the review of study team member CVs and copies of qualification or licensure documents to confirm that study team members have the qualifications DRC law requires for the activities delegated to them on the study Authorization and Delegation Log, as well as records of training on study procedures delegated to them and which are not part of routine health care (e.g. skin snipping, counting of microfilariae, procedures for liver function tests).

Furthermore, team members will be trained on the use of the eCRF and data management processes (Section 16.2). The Sponsor will ensure that its representatives are fluent in both English and French.

Any deficiencies found will be discussed with the Investigator and need to be addressed before the Sponsor will approve study start.

15.9 Informed Consent and Assent with Parental/Guardian Consent

It is the responsibility of the Investigator to obtain written informed consent (or informed assent from minors with parental/guardian informed consent) from each individual participating in this study after explanation of the aims, methods, objectives and anticipated benefits and risks of the study in the local language(s) (Section 5.5.1) and wording they can understand. The Investigator must also explain to the potential study participants that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The Investigator must utilize the EC-approved PICFs for informing potential study participants and for documenting written informed consent/assent.

Information about the study will be provided and written informed consent or assent with parental/guardian consent obtained by a physician. Should the physician not speak the local language, another member of the study team who speaks the local language must be present to act as interpreter. The study team members authorized to inform study participants of the study and obtain written informed consent/assent with parental/guardian consent will be documented on the Authorization and Delegation Log.

The appropriate consent or assent with parental/guardian consent must be obtained before any Screening or other study procedures are initiated (Section 6.1).

The information and consent/assent forms in French and the local language(s) (see Sections 5.5.1.1 and 5.5.1.2) will be included separately in the RA and EC submissions. A final approved version of these documents will be retained in the study files and must be used in the informed consent/assent discussions with potential study participants.

15.9.1 Considerations during the Development of the Participant Information Documents

The Participant Information documents were written and the wording chosen to fit:

- The planned step-wise process (Section 5.5.2) for informing communities and interested individuals about all aspects of the study required for the community to advise on study implementation and for individuals to decide upon their own or their child/ward's participation;
- The full age range for study eligibility so that adolescents and their parents/guardian can be informed simultaneously;
- The step-wise consent/assent (to screening, to study participation, to nodulectomies, Section 6.2);
- The decision to run the single dose safety study concurrently, so that individuals not eligible for this study (or not wanting to commit to a 3 three year study with repeated skin snips and 27 months requirement for contraception) can be immediately offered participation in a study with less stringent eligibility criteria, fewer evaluations and lasting only 3 months (Section 4.7);
- The notions in the population in the recruitment areas to ensure that they are familiar with specific concepts (e.g. currency exchange rates) or that unfamiliar concepts are explained (e.g. blinding) or presented in terms meaningful to the potential participants (e.g. randomization as 'decided by chance', insurance as 'Sponsor having put money aside', password-protected as 'in a locked and secure area').

15.9.2 Provisions for Informed Consent and Assent with Parental/Guardian Consent by Illiterate Individuals

A high percentage of the population in the recruitment areas is illiterate (Section 5.5.1). Furthermore, the 'literacy' criteria from the Informed Consent/Assent perspective are much higher than the criteria used locally. To avoid these different literacy criteria and different provisions for informed consent/assent from illiterate and literate individuals being perceived as insulting or lacking respect, it was decided that a literate witness will be required for all participants.

Consequently, all adults and minors will confirm their consent or assent with parental/guardian consent via signature, mark or finger print (as per their preference) on the consent form in the presence of a literate witness they have chosen. The literate witness will confirm through their dated signature that they were present when the information was provided and that they witnessed that any questions asked were answered to the satisfaction of the potential participant and their parent/guardian, if applicable, and that voluntary informed consent or assent with parental/guardian consent was given.

15.9.3 Provisions for Informed Assent for Minors with Parental/Guardian Informed Consent

Informed assent with written parental/guardian consent will be obtained for minors aged 12 to 17 years old.

Refusal of the parent(s)/guardian or minor constitutes dissent and precludes the minor's participation in the research. Every effort should be made to obtain, if possible, the consent of both parent(s).

In order to respect local culture and unless otherwise advised by the RA or the EC, for orphans living with relatives, the head of the household (guardian) will be providing informed consent to complement the minors informed assent as the guardian.

Minors living with family members other than their parents, will require parental consent.

If an adolescent turns 18 years during their participation in screening or the study, he or she will be asked to provide written informed consent as soon as practically reasonable on the same form the minor signed for assent.

15.10 Information to Study Participants in Case of New Data Emerging during the Course of Their Study Participation

Should new data emerge during the course of this study that may affect the willingness of study participants to continue in the study, the data will be submitted to the ECs together with a PICF for informing the study participants about these data as a basis for their decision to continue study participation.

Upon approval of the PICF by the EC, study participants will be contacted to provide and discuss with them this information and ask them about their decision or not to reconsent (or re-assent with parental/guardian re-consent). The Investigator will seek guidance from the chiefs and elders of the villages where the participants live on how to provide the information (e.g. participant meeting, visit to each individual participant).

At the time these data emerge, the PICFs for use during continued recruitment of new participants will be updated accordingly and submitted to the EC for approval.

15.11 Information to Study Participants about 'Incidental Findings'

Health problems identified during Screening or a study that are not related to the health problem being studied (in this case onchocerciasis and the response to the administration of moxidectin or ivermectin) are these days sometimes referred to as 'incidental findings'. Plans for informing participants need to distinguish 'anticipatable' findings (i.e. health problems known to be diagnosed with the examinations and tests used) and 'unanticipatable' findings (i.e. health problems that cannot be expected to be identified based on current state of scientific knowledge).

All examinations and tests used in this study are long established and not undergoing further scientific/methodological development (in contrast to, for example, imaging methods). Consequently, all health problems identified at each visit are 'anticipatable'. All of them will be discussed with the participant and treatment will either be provided by the study team or the participant will be referred to the health system for appropriate care.

'Unanticipatable' findings could only emerge from the use of the *O. volvulus* microfilariae or macrofilariae or left-over serum or left-over urine during research for improved tools and strategies for control and elimination of onchocerciasis and other Neglected Tropical Diseases (Sections 15.19, 15.20, 15.20.2, 15.20.3). The Sponsor has developed a process that provides for the scientists who conduct the research on the left over *O. volvulus* parasites and left-over serum and left-over urine to report to the Sponsor any findings that they consider of possible interest for the health of a participant. The Sponsor will convene a meeting of members of the DSMB, clinicians specializing in the discipline(s) indicated by the nature of the unanticipated finding and the Investigator (or delegate) to discuss the possible clinical significance of the unanticipated finding. This process also ensures that the participant anonymity will be preserved. Unanticipated findings will be provided to the participant only if approved by the ECs based on a dossier submitted that details the unanticipatable finding, the process and outcome for validating its health significance and the actions that can be taken for the benefit of the participant. In the Participant Information document, potential participants are told that it is unlikely that the research on their *O. volvulus* parasites or on their left-over serum (referred to as 'left-over blood') or left-over urine will reveal any information relevant for their health, but that if this is the case, they will be informed.

15.12 Risks due to Study Procedures

Information on risks associated with study procedures which are not used during routine health care is provided in Section 10.7.

15.13 Risks associated with Investigational Products

Information on risks associated with moxidectin and ivermectin are provided in Section 10.5.

15.14 Compensation of Study Participants for Time Spent on the Study and Costs Incurred for Treatment of an AE in a Local Health Facility

As study participants will be recruited among villagers who are continuing to pursue their usual daily activities, the time participants spend on study activities will be time they are unable to pursue gainful work. To compensate study participants for the resulting loss of earnings, participants will be compensated for time spent undergoing assessments with the average daily earning of the population from which the study participants are being recruited, estimated by the Investigator at 5 US Dollars (US$). This is the equivalent of approximately 8500 Congolese francs (CDF) and approximately 20 000 Uganda Shillings (USH), the currency commonly used in both the primary and back-up recruitment area. The exchanges rates vary over time and the local population is very familiar with the impact of these variations. To minimize participants suffering financially from exchange rates becoming unfavorable to them, the compensation is set based on the US$ and will be provided at the up-to-date exchange rate and in the currency the individual participant choses.

The time spent prior to Screening (i.e. for informing the potential participants and obtaining informed consent to Screening) will not be compensated for.

On Day 1 to Day 5 after investigational product administration, when the reactions to the microfilaricidal effect of moxidectin or ivermectin typically start and resolve (Section 10.5), an appropriately trained study team member will visit each participant daily (Section 7.3.5). If after that period study participants chose to visit a local health facility rather than contact the study team (directly or via the SFP (Section 5.2.4)) because of an AE, study participants will be compensated for any costs incurred for visiting the local health facility and for the treatment of an AE in the facility if that AE could possibly, probably or definitely be related to treatment with ivermectin or moxidectin.

Study participants will not be compensated for costs incurred for treatment at health facilities of AEs unambiguously not related to investigational product or study conduct (e.g. malaria, appendicitis, snake bites, respiratory infections, intestinal infections and parasitosis, epilepsy, trauma) or related to treatments they obtained from traditional healers.

15.15 Safety of Study Participants Withdrawing Prematurely from Further Treatment or the Study

For provisions to ensure follow up of study participants withdrawing or withdrawn from further treatment or the study, see Section 13.2.

15.16 Volume of Blood Sampled

Blood will be drawn for liver function tests (3.0 mL/draw) and for infection with *Loa loa* (0.06 ml), if applicable. Liver function tests conducted before and five days after investigational product administration on Day 0, Month 6 and Month 12 will require a total of 18.0 mL and a maximum of 6.0 mL within a 4 week period. These volumes are below the acceptable maximum volumes for single blood draws and blood draws over a four week period in paediatric studies of 1% and 3% of the total blood volume, respectively (2001/20/EC 2008, Zisowsky et al. 2010). These would be 24 ml and 72 ml, respectively, assuming a weight of 30 kg and 80 ml of blood/kg, consistent with weights in the range to be expected for 12 year old girls in the population from which participants will be recruited.

15.17 Confidentiality of Trial Documents and Participant Records

The Investigator must ensure that the participants' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, participants will not be identified by their names, but by the participant's code assigned to each participant (Section 7.4).

The Investigator will keep a participant screening log showing the names and addresses as well as participant codes. This log, as well as other documents not for submission to the Sponsor (e.g. participant's signed informed consent/assent forms), will be maintained by the Investigator in strict confidence.

All documents with results of the examinations conducted during this study, including, but not limited to the documents identifying study participants by name, will be stored in a locked cabinet or room with access restricted to authorized study team members and electronic records will be password protected (Sections 16.1 and 16.2).

15.18 Clinical Trial Insurance

Clinical trial insurance equivalent to at least US$10,000,000 has been secured by the Sponsor to provide appropriate compensation to the participants should they suffer harm as a result of their participation in this study. This will also provide financial protection for those responsible for review and approval of the study protocol and for its conduct.

The insurance policy will be provided to the RA and the MdSP designated EC at the time of protocol submission.

15.19 Ownership and Future Use of Biological Specimen Remaining After Completion of the Protocol Required Examinations

Biological specimens left over and not destroyed after all tests have been completed (serum left over from liver function tests, urine left over from pregnancy tests, *O. volvulus* microfilariae and macrofilariae) will be owned jointly by CECA/20 and the Sponsor who agree to make these available for other research, in the interest of developing new tools and strategies primarily for onchocerciasis and secondarily for other NTDs prevalent in Africa.

This intended use and the duration of the sample storage (20 years) is included in the PICF for potential participants.

Should specimens be requested by for-profit organizations, CECA20 and the Sponsor will negotiate with the potential specimen users provisions for access to resulting products for the public health systems in the African countries at cost with no more than a minimum profit margin. A dossier summarizing the intended use and commitments of potential for-profit users will be submitted to an EC and the RA for approval before specimens are provided.

In all cases, specimen-accompanying information collected during this study needed for the research will be anonymized and the transfer covered by a Material Transfer Agreement. The Material Transfer Agreement will also specify that the researchers have to inform the Sponsor should they identify 'unanticipatable findings' (Section 15.11).

For further information on identified recipients of the parasites, left over serum and urine, see Sections 15.20.2 and 15.20.3, respectively.

15.20 Maximization of Study Outputs for Improved Tools and Strategies for Control/Elimination of Onchocerciasis and other Neglected Tropical Diseases

This research requires a significant investment of time (by the study participants, study team members, Sponsor and review committee members) and financial investment (EDCTP,

Sponsor). Consequently, consideration has been given to how this investment can contribute to advance research for other improved tools and strategies for control and elimination of onchocerciasis and other NTDs without unacceptable increase in risk for study participants.

15.20.1 Modelling of Time to Onchocerciasis Elimination and Cost-Effectiveness of Ivermectin vs Moxidectin-Based Elimination Policies

For countries to decide whether to include moxidectin in their onchocerciasis elimination policies, they need not only efficacy and safety data, but also estimates of (a) epidemiological impact/time to onchocerciasis elimination and (b) cost-effectiveness of annual and biannual treatment with moxidectin relative to annual and biannual treatment with ivermectin. The skin microfilariae data and the data from the histopathological examinations of excised nodules from this study will be combined with the data from other studies of moxidectin and of ivermectin and used to model both (a) and (b).

15.20.2 Use of Skin Microfilariae and Macrofilariae

The challenges African onchocerciasis endemic countries face for elimination of onchocerciasis transmission include that onchocerciasis is endemic across large contiguous areas which cross administrative boundaries within countries and borders between countries. Furthermore, different areas and countries initiated mass drug administration at different times and implementation has encountered different challenges. This is particularly so for countries suffering from past or current conflict, such as DRC. It results in different areas reaching the criteria for stopping treatment at different times. The recent WHO 'Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis' provide criteria for when transmission can be considered interrupted within a transmission zone so that mass drug administration can be stopped, but does not provide criteria for delineating transmission zones (World Health Organization 2016).

To ensure that treatment is stopped in one area only when stopping criteria are met across the total geographic area of a 'transmission zone', and to minimize the risk that new infections are introduced from neighboring areas where transmission is still ongoing into areas where mass drug administration was stopped, countries need tools to delineate transmission zones.

Furthermore, in several areas in Africa with long-term ivermectin mass drug administration, individuals with ‘suboptimal’ response to ivermectin have been identified. Serial skin snipping or nodulectomies and histological examination of macrofilariae are currently the only methods available for monitoring the prevalence of suboptimal response to ivermectin. This makes it impossible for control and elimination programs to monitor *O. volvulus* susceptibility to ivermectin. Countries need tools suitable for large scale monitoring.

Research for such tools is currently ongoing through WHO/TDR (Hedtke et al. 2020). The research also targets a tool to allow control/elimination programs to quantify the number of reproductively active male and female *O. volvulus* that contributed to a sample of parasites obtained from skin snips or infected/infective vectors and to monitor the prevalence of suboptimal response to ivermectin. One of the WHO/TDR funded investigators (Dr. W. Grant) at La Trobe University, Melbourne, Australia, has received a grant from United States of America National Institute of Health which allows significantly accelerated progress towards the WHO/TDR targeted tools and includes funding for the preservation and shipment of parasites for this research. Following completion of skin microfilariae counts, the microfilariae will be preserved in alcohol and shipped to that investigator (Sections 7.4.8 and 7.4.12.2). Furthermore, following excision of onchocercal nodules, some nodule material will be preserved in alcohol and shipped to Dr. Grant. Samples will be shipped anonymized and under a Material Transfer Agreement which specifies 20 year maximum

storage time and that all parasite genetic sequences obtained during this research will be deposited in a publicly available repository (Sections 15.19).

Parasites not needed for this research will be shipped anonymized under a Material Transfer Agreement to the 'Molecular Resources Division' of the NIH-NIAID Filariasis Research Reagent Resource Center (FRRRC, or FR3, http://www.filariasiscenter.org/, http://www.filariasiscenter.org/resources/molecular-resources) to ensure that they can be used world-wide for research in support of control and elimination of NTDs.

FR3 was established in 1969 and has a long history of partnership with (and at times funding from) WHO and supporting WHO funded researchers (including WHO/TDR funded research which led to development of moxidectin for onchocerciasis) (Michalski et al. 2011). FR3 not only provides material to researchers world-wide but also offers free protocols and technical support to researchers. Over the past 7 years, FR3 has made 741 shipments to recipients in 61 countries, including 33 countries in Africa (Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Democratic Republic of the Congo, Ethiopia, Gabon, Gambia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Namibia, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, South Africa, South Sudan, Sri Lanka, Swaziland, Tanzania, Togo, Uganda) (personal communication to Annette C. Kuesel, WHO/TDR, by Dr. Steven A. Williams, Director of Molecular Resources FRRRC (FR3), Director of the River Blindness Genome Project (1997-2005), Coordinator of the World Health Organization Filarial Genome Project (1994-2005), http://www.filariasiscenter.org/resources/molecular-resources). Prerequisite for receipt of material by researchers is signature of a Material Transfer Agreement.

15.20.3 Use of Left-over Serum and Urine

Left-over serum (see Section 7.4.10) and urine (see Section 7.4.7) will be frozen and preserved for biomarker, drug and vaccine research conducted by academic researchers or developers of diagnostics, drugs and vaccines for control and elimination of onchocerciasis or other NTDs (Section 15.19).

For this purpose, the samples will be shipped to the 'Molecular Resources Division' of FR3 (for further information on FR3, see Section 15.20.2).

After minors who have agreed to participate in the study become adults, they will be asked whether they continue to agree to study participation (see Section 15.9.3) and, if applicable, to the use of the left-over serum and urine for future research. In case they change their mind, the Material Transfer Agreement between the Sponsor and CECA/20 and FR3 includes the following provisions:

- Samples identified as coming from minors will be put 'in quarantine' at FR3, i.e. will not be shipped to any requesters. They will be moved out of quarantine only after confirmation from the Sponsor or CECA/20 that the minor has confirmed agreement to future use of the left-over samples upon becoming an adult.
- Upon receipt of information from the Sponsor or CECA/20 that the minor has not maintained agreement to future use of left-over samples when becoming an adult or that further follow up of the minor for consent to future use of the left over serum is not possible, FR3 will retrieve and destroy the samples.

Retrieval of samples for 'moving them out of quarantine' or for destruction is made possible through the bar code system based sample management in place at FR3 and the fact that FR3 will provide bar-code labelled vials to CECA/20 for shipment of the samples.

For provisions for specimen anonymity and Material Transfer Agreement see Section 15.19.

15.21 Complaints Process

During the consultation with village communities during study preparation (Section 5.1), paths for study participants to convey complaints or suggestions to the study team will be discussed. Independent of whether they choose to provide these via intermediates (e.g. village chief, SFP) or directly to a study team member, feedback will be provided by a study team member. The study team member providing the feedback will be selected by the Investigator depending on the type of feedback/complaint.

15.22 Ownership of Study Data

The data generated during the study will be owned by MDGH as per the agreement for the EDCTP grant concluded by MDGH and CECA/20. MDGH has committed to providing anonymized study data to the US FDA in support of a request to expand the moxidectin US Prescribing Information.

In addition, MDGH will provide the anonymized data and reports to the WHO and country policy makers at their request.

15.23 Post-Study Activities

15.23.1 Post-Study Reports to RA and EC

Following completion of the data analysis, a summary report will be provided to the RA and the ECs.

15.23.2 Post-Study Information about the Study to Study Participants

The summary report to the ECs will be accompanied by an Information Document containing the information to be conveyed to study participants about the results of the study and planned future activities. This EC-approved Information Document will be the basis for informing the study participants (and interested other inhabitants of their villages) about the study.

At that time participants will also be informed about the treatment regimen they were randomized to.

15.23.3 Post-Study Reports to Other Stakeholders

Summary reports will be provided to and discussed with other relevant stakeholders, including those involved in the preparation of this study (Section 5.1) and presented to the Comité d'Experts Independants pour l'Elimination de l'Onchocercose de la RDC, the WHO/AFRO Expanded Special Project for Elimination of Neglected Tropical Diseases and relevant departments in WHO Headquarters.

15.24 Post-Study Access to Moxidectin

Moxidectin has been approved in the US for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older, but is not yet registered in DRC. Consequently, moxidectin cannot be provided post-study to the population in the study area or anywhere else in DRC without approval by the RA via registration of moxidectin in DRC, another type of authorization, or in a RA and EC approved clinical trial.

At the request of the RA, the Sponsor will submit the dossier that formed the basis of the US FDA registration to the RA.

Given that the dossier is in English and includes >400 000 pages, the Sponsor is exploring the possibility for registration via the 'Collaborative Procedure for Accelerated Registration' of drugs approved by stringent regulatory authorities such as the US FDA currently being piloted by WHO in a number of countries, including DRC

(https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras (World Health Organization 2018).

Until moxidectin has been integrated into WHO guidelines and/or DRC onchocerciasis control/elimination policies, the Sponsor will ensure access to treatment with moxidectin to clinical trial participants and their communities, provided the Sponsor receives the appropriate request with authorization and implementation and pharmacovigilance plans from the RA.

15.25 Provisions for the implementation of the Study during the COVID-19 Pandemic

All activities required for successful implementation of the study, ranging from community mobilization and information (Section 5), over obtaining informed consent/assent (Section 15.19) to screening, treatment and follow up (Sections 7.3 and 7.4) were reviewed in conjunction with the relevant national and local guidance on management of the COVID-19 pandemic.

The objective of this review was to determine whether the study can be conducted during the pandemic in a way that minimizes risk of transmission of SARS-CoV-2 and could have an overall positive benefit-risk ratio through re-enforcement of the education of the population in the villages in the recruitment area on COVID-19 measures and contribution to screening for COVID-19 cases.

Specifically, the review of the activities determined:

- the extent to which they can be conducted with physical distancing and the operational measures to be taken,
- the extent to which those involved will have already undergone education on COVID-19 and required pre-cautions to minimize SARS-CoV-2 transmission,
- the need for the study team to provide the initial education on COVID-19 (based on Information, Education and Communication material provided by the local COVID-19 task force) vs. re-enforcing previous education about COVID-19 provided by the local COVID-19 task force,
- how screening for suspected COVID-19 cases through temperature measurement, questioning for symptoms defining individuals as suspected COVID-19 cases, advice to such cases to self-isolate and information to the responsible public health system units can be incorporated and take place at the beginning of all other protocol planned activities,
- additional measures that need to be taken to minimize the risk of SARS-CoV-2 transmission during all activities where physical distancing is not possible.

The details of the measures to be taken during the different activities are provided in Appendix 21.2. As national or local health system directives evolve during the course of the pandemic, the measures described in the Appendix will be adapted accordingly.

Furthermore, in view of possible outbreaks of potentially life threatening diseases (such as Ebola or COVID-19), treatment with investigational drugs or vaccines for such diseases have been included among permitted investigational products in Section 9.3.

All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the national/local COVID-19 response team which will also ensure that the study will adapt its measures as required by changing government/health system guidance. All communication and community engagement about COVID-19 will be done in coordination and collaboration with the national/local COVID-19 response team and based on their communication material.

16 STUDY DOCUMENTATION, eCRFs AND RECORD KEEPING

16.1 Source records

Data collection is the responsibility of the clinical trial site staff, under the supervision of the site Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility and veracity of the reported data.

The data will be documented either on paper (written records, print outs of analytical devices, retinal/disc photographs) or onto a tablet equipped with the CliniOps App Suite developed by CliniOps (a Mobile, Cloud-based, Digital Solutions company based in Freemont, CA, USA) that allows storage and backup of all data entered as well as uploading of selected data into the eCRF. Data documented with this Direct Data Capture system are referred to as electronic source data (eSource).

All paper source records should be typed or filled out using a black or blue pen, and must be legible. Errors should be crossed out with a single strike line and not obliterated (e.g. via use of correction fluid), the correction inserted, and the change initialed and dated by the Investigator or his/her authorized delegate. Printouts and photos that might fade overtime should be copied and/or digitized to ensure long-term availability.

The data to be captured manually or as eSource will be agreed between the study team and the Sponsor and documented prior to initiation of the study.

16.2 Electronic Case Report Forms and Data Management

For each participant screened, an eCRF must be completed and signed electronically by the Investigator or delegated co-Investigator. For requirements for eCRFs for participants who withdraw from treatment or from the study or are withdrawn from treatment or the study by the Investigator, see Section 13.

In view of the possible impact of the COVID-19 pandemic on study conduct, the eCRF will include fields allowing to capture which protocol deviations are attributable to the COVID-19 pandemic (including, but not limited to, study participants cannot be treated or assessed within the protocol specified time frame because they are self-isolating, or they or their family are under quarantine, or study team members are under quarantine).

The eCRF software developed by CliniOps is compliant with the US Code of Federal Regulations for Electronic Records and Electronic Signatures (21 CFR Part 11) and the US Health Insurance Portability and Accountability Act (HIPAA) and is validated to meet data security, data quality and data monitoring requirements in accordance with ICH GCP guidelines. The data system includes password protection and internal quality controls, such as automatic range checks, to identify data that appears inconsistent, incomplete or inaccurate.

Participants will be identified in the eCRF only via their participant code, not by name or any other information that might allow identification of the participant (see Section 15.17).

Data management will be conducted by Sponsor-trained study team members at the site and by CliniOps, contracted by the Sponsor. The data manager at CliniOps will implement integrated testing and verification controls to ensure data completeness and internal consistency. Each operation performed is tracked by an audit trail. Each person at CliniOps is subject to professional secrecy.

16.3 Investigator's Files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These

documents should be classified into two separate categories: (i) Investigator's Study File, and (ii) participant source records (Section 16.1).

The Investigator's Study File will contain essential documents such as the protocol/amendments, EC and RA approvals with correspondence, approved PICF and signed consent/assent forms, screening logs, randomization lists, investigational product records, staff curricula vitae and authorization forms and other documents and correspondence. The eCRFs with data queries and audit trails will also be retained in an archive acceptable format.

Participant source records may include physician's and nurse's notes, original laboratory reports, and any other records generated during and for this study.

The storage system used during the trial and for archiving (irrespective of the type of media used) will allow for document identification, version history, search, and retrieval. The Sponsor will ensure that the Investigator has control of and continuous access to the data reported to the Sponsor. The Investigator will have control of all essential documents and records generated by the investigator and the study team before, during, and after the trial.

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 Investigator must notify the Sponsor prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party (due to retirement or leaving the site organization) or to move them to another location, the Sponsor must be notified in advance.

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

17 MONITORING, AUDITING AND INSPECTION OF THE STUDY

17.1 Access to Source Records

The Investigator shall supply the Sponsor, on request, with any required study documentation and records generated during examination of participants or analysis of the biological samples obtained during the study. This is particularly important for source data verification or when errors in data transcription are suspected.

In case of governmental or regulatory queries or requests for audits and inspections, it is also necessary to have access to the complete study records. Individuals authorized by governmental and regulatory agencies to audit or inspect studies have the obligation to respect participant confidentiality.

17.2 Monitoring of the Study

The study will be monitored by an unblinded monitor to review randomization and investigational product dispensing and a blinded monitor to review all other activities. Monitoring will occur by on-site visits and/or remotely at a frequency specified in the Monitoring Plan or more frequently, if triggered by observations made during a visit, remote monitoring or as requested by the DSMB.

It is understood that the responsible monitors, as a Sponsor representative, will be fluent in English and French and contact and visit the Investigator in person or electronically regularly and that he/she will be allowed, on request, direct access to the source records as per ICH-GCP guidelines to inspect the various records of the trial (eCRFs, signed consent/assent forms, laboratory test reports, participant records in local health facilities the study participant might contact and other pertinent data, randomization and investigational product dispensing records) provided that participant confidentiality is maintained as required by ICH-GCP.

It will be the monitor's responsibility to inspect such documents to verify the adherence of study conduct to ICH-GCP requirements and the protocol and to verify the completeness, consistency and accuracy of the data entered on the eCRF.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17.3 Audits and Inspections

The Investigator/Institution will also permit trial-related audits, EC review, and regulatory inspection(s), providing direct access to source records to appropriately qualified personnel from the Sponsor or its representative who speak English and French, or to RA or health authority inspectors or EC representatives after appropriate notification. The verification of the eCRF data may be by direct inspection of source records (where permitted by law) or through an interview technique.

Sponsor quality assurance audit(s) may be conducted during the study and/or preceding a planned regulatory inspection.

Inspections by regulatory authorities are at their discretion and cannot be foreseen. It is usual practice for regulatory authorities of foreign countries (e.g. US FDA or the regulatory authorities of other countries considering approval of moxidectin) to contact their counterparts in the RA of the country where the study is conducted when considering an inspection.

18 CONDUCT OF THE STUDY UNDER US FDA INVESTIGATIONAL NEW DRUG APPLICATION

MDGH is conducting Study 3001 under US FDA Investigational New Drug (IND) application 126876. This IND application was opened as part of MDGH's interactions with the US FDA which resulted in the 2018 US marketing approval of moxidectin for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older (US FDA NDA 210867). Study 3001 is a MDGH NDA 210867 postmarketing commitment study.

Consequently, this protocol was submitted to the US FDA by the Sponsor and the Sponsor will ensure all requirements under Title 21 Part 56 of the US Code of Federal Regulations (Institutional Review Boards) are satisfied, or applicable US FDA waiver approved prior to study commencement.

As required by US law, a description of this clinical trial has been made available on http://www.ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03876262). This website will not include information that can identify participants.

US FDA regulations include the following requirement: when seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

While this requirement is applicable to this study, this statement has not been included in the Participant Information Documents for the following reasons:

- The population that will be recruited (e.g. Section 5.5.1) does not know what a Web site is, has no access to the web and is thus not able to access http://www.ClinicalTrials.gov. A study team member could access this for them, but they would not be able to read the entries. Furthermore, since the text on the Web site is not phrased in lay language appropriate for the participant population, a translation of the entries into the local language (see Sections 5.5.1.1 and 5.5.1.2) by a study team member would have no informative value to (potential) participants. Consequently, inclusion of this statement in the Participant Information Document would not have the informative value for the target population intended by the US FDA.
- Elements in this statement intended to inform participants about the confidentiality and deidentification of their data in any reporting of the study results are included in the Information Documents for the (potential) participants.
- All elements of the description of the trial on http://www.ClinicalTrials.gov which are not technical (i.e. not referring to statistical analysis of the data) are included in the Information Documents for the (potential) participants.

18.1 Reporting to US FDA During the Study

As required under the post-marketing commitment, MDGH will provide annual updates on this study to the US FDA. These will describe the study status (e.g. ongoing, delayed), and include information such as the number of participants screened, treated, withdrawn and safety data and any changes to the expected study completion date (noting encountered difficulties if applicable).

Additionally, MDGH will submit the report of the Month 12 analysis of the primary endpoint and associated safety data to the IND (Section 14.11.7).

18.2 Reporting to US FDA After the Study

Upon completion of this study, MDGH intends to submit the final clinical study report to the US FDA in support of a request to update the moxidectin US Prescribing Information with comparative data on the efficacy and safety of moxidectin and ivermectin when given at annual and biannual re-treatment frequencies. If approved, this will provide a US Prescribing Information for moxidectin that is more closely aligned with the anticipated use of moxidectin in the field.

19 PUBLICATIONS

MDGH will update the study entry on www.ClinicalTrials.gov with significant study status updates and to include a summary of the study results when available, which will not contain information that could identify participants.

The Sponsor has also listed the study on the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/).

Once approved by the RA and the ECs, the protocol will be made publicly available.

The results of this study will be published in peer-reviewed open access journals and presented at scientific meetings. Sponsor-initiated publications and/or presentations will be agreed upon between the Investigator and Sponsor. Investigator-initiated publications and/or presentations will be provided for review by the Sponsor at least 30 days before the submission deadline for the manuscript and/or presentation abstract to enable relevant input based on information from other studies that may not yet be available to the Investigator.

Any formal publication of the study in which input of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate 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.

Oral or written presentations or publications will mention "this research is part of the EDCTP2 Programme supported by the European Union (grant NUMBER RIA2017NCT-1843)".

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21 APPENDICES

21.1 Appendix 1: Adverse Events Toxicity Grading Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Major Clinical Conditions: Cardiovascular				
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

[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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)
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)
Dermatologic				
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

[2] As per Bazett's formula.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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] [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
Endocrine and Metabolic				
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)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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
Gastrointestinal				
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)

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	Interventio n 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				
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Neurologic				
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

[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.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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				
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
Psychiatric				
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)	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social &	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with	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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Specify disorder	functional activities	usual social & functional activities		
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				
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				
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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				
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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

[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

[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.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY 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)
Urinary				
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				
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)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 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
Laboratory Values				
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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

[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.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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*

[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.

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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*

[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.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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

21.2 Appendix 2: Overview of Measures to Minimize Risk of Transmission of SARS-CoV-2 virus during study conduct based on national/local guidance as of 30 June 2020

Principal objective (protocol section)	'Target Population'	Physical Distancing possible	Information on physical distancing or measures to be taken to reduce risk of transmission
Across all	Across all		• All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & Maladie de Virus Ebola (MVE)" • All communication about and community engagement regarding COVID-19 (Communication des risques et engagement communautaire en réponse à la COVID-19) will occur in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & MVE" and use their communication material.
Community mobilization (Sections 5.1, 5.2.1, 5.2.2, 5.2.3, 5.3)	Government authorities; Provincial and national parliament members; Provincial and Territory and Health Zone authorities and staff	Yes	• By the time community mobilization is initiated, all members of this 'target population' will have already undergone education on COVID-19, and procedures for screening for COVID-19 symptoms before entering their buildings will have been put in place and everybody will wear masks. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • The offices/meeting rooms of the 'target population' will have already been set up for physical distancing and procedures will have been put in place to refer anybody with COVID-19 symptoms to the designated local health facility/COVID-19 team. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
	Civil society (e.g. associations of different professional, religious groups, non-governmental organizations), Local staff of Local media staff	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • Study team will bring thermometers for temperature measurements and inform, as necessary, participants about COVID-19 related requirements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health /COVID-19 team. They will be excluded from the meeting. • Study team will ensure that all passing this screening will wash hands before entering the room and wear masks throughout the meeting. • Study team will ensure meeting space is set up to allow physical distancing. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Community mobilization (Sections 5.2.4, 5.4)	Religious Leaders, Village/ Community Leaders, Elders, Relais Communautaires (RECOs)	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged per village, and include not more than 20 participants, including not more than 10 chiefs and elders (typically 5), 5-7 RECOs and approximately 3 study team members. • Meetings will be set up in open spaces, a church or a school with study team ensuring seating is arranged for physical distancing. • Study team will bring thermometers for temperature measurements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health facility (or the study team will call the health facility/COVID-19 team on their behalf). They will be excluded from the meeting. • Study team will be bringing megaphones and cloth masks for all meeting participants, and ensure availability of soap and water (or hand sanitizers) for handwashing at the beginning and the end of the meeting. • Study team will ensure that all meeting participants wash hands before entering the meeting space, wear masks all along the meeting and wash hands at the end of the meeting. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents and cloth masks distributed will be left with meeting participants who will be advised to bring the mask to subsequent meetings.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Consultation with village communities and providing information required for village members to decide on participation in the study (Section 5.2.2)	Village inhabitants	Yes	• By the time community mobilization is initiated, the communities will have undergone education on COVID-19. • While the pandemic is ongoing, the community meetings as per protocol section 5.2.2 will be preceded by a meeting with heads of families to provide them with a short overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing, demonstration on proper use and cleaning of cloth masks and the arrangements for further meetings with their family members about the study. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • The 1st and 2nd meeting as per Section 5.2.2 will be arranged to take place with no more than 20 meeting participants including 1 RECO, 1 potential (or selected) literate witness, and up to 16 members of 3-4 families (and two or three study team members). • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs.
Provision of informed consent / assent (Sections 5.2.2, 15.9)	Village inhabitants interested in study participation	Yes	• Meetings between 1 study team member (or 1 study team member plus 1 translator) and an individual wanting to provide informed consent (or a minor with their parent(s)/guardian wanting to provide informed assent and consent) and the literate witness will take place in a setting that will allow physical distancing. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • All will be asked to bring the cloth masks provided to them to the next meeting (study visits).

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
All study visits (Section 7.3)	Screening/study participants	Yes/No	• All study team members will wear masks and gloves during all interactions with study participants. • (Potential) participants will be asked to bring and wear the cloth masks they were provided with during the meetings in which they were informed about the study. • Soap and water (or hand sanitizers) will be brought so that each visit can be initiated and end with hand washing/sanitizing. • Staff members will wash/sanitize hands and change gloves between interactions with different participants. • Areas where screening/study participants can wait will be set up with physical distancing. • At the beginning of each study visit a study team member will measure the temperature of all participants and ask them about COVID-19 symptoms, will advise them to self-isolate and either ask them to call the designated health facility/COVID-19 team or call that health facility/COVID-19 team on their behalf. If they are identified by the health facility/COVID-19 team as not COVID-19 infected, the relevant study visit will be rescheduled. If they are identified as COVID-19 infected, study visits will be arranged to take place after they have been confirmed as recovered by the designated public health staff. • All equipment will be sanitized between use on different participants.

21.3 Appendix 3: Summary of Protocol Amendments

The Summary of Protocol Amendments is provided as a separate document and maintained in the Trial Master File.