Title: Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study

Short Title: RIMDAMAL

Trial Identifiers:

Comité d'Ethique d'IRSS: A03-2015/CEIRES

CSU IRB: 15-5796H

ClinicalTrials.gov: NCT02509481

Sponsor:

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Confidentiality Statement: This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, host institution, relevant ethics committees and regulatory authorities.

Contents

Abbreviations

95% CI	95 percent Confidence Interval
ACD	Active Case Detection (cohort)
ACT	Artemisinin-based combination therapy
AE	Adverse event
AL	Artemether-Lumefantrine
ALB	Albendazole
CHW	Community Health Worker
Cmax	Maximum drug concentration
CM	Centre MURAZ
CRF	Case Record Form
CSPS	Centre de Santé et de Promotion Sociale (Health Center)
CSU	Colorado State University
DDT	Dichlorodiphenyltrichloroethane
DEC	Diethylcarbamazine
DMC	Data Monitoring and Ethics Committee
DRS	Direction Régionale de la Santé
ERC	Ethics Research Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPELF	Global Programme for the Elimination of Lymphatic Filariasis
GMP	Good Manufacturer Practice
Hb	Hemoglobin
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
IRS	Indoor Residual Spraying
IRSS	Institute de Recherche en Sciences de la Santé
ITT	Intention to Treat
ISM	Independent Safety Monitor
IVM	Ivermectin
LF	Lymphatic Filariasis
LLIN	Long-lasting Insecticide Treated Net(s)
MCD	Médecin Chef de District
MDA	Mass drug administration
MoH	Ministry of Health
NMCP	National Malaria Control Program
NTD	Neglected Tropical Disease(s)
PCR	Polymerase Chain Reaction
RCT	Randomized Controlled Trial
RDT	Rapid diagnostic test
REC	Research Ethics Committee
SAE	Serious adverse event
SOP	Standard Operating Procedure
SSA	Sub-Saharan Africa
STH	Soil Transmitted Helminth(s)
TMG	Trial Management Group
WHO	World Health Organization

1. Title of Research Protocol

Repeat Ivermectin Mass Drug Administrations for Control of Malaria: a pilot safety and efficacy study

Short Title: RIMDAMAL study

2. Investigators and Institutions

2.1. Principle Investigators:

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2.3. Institutions:

CSU - Colorado State University, Fort Collins, CO, USA

IRSS - Institute de Recherche en Sciences de la Santé, Bobo Dioulasso, Burkina Faso

CM - Centre MURAZ, Bobo Dioulasso, Burkina Faso

MoH – Ministry of Health, Ouagadougou, Burkina Faso

3. Protocol Summaries

3.1. Trial Registration Data

Data Category	Information
Primary registry and trial identifying number	ClinicialTrials.gov [NCT02509481]
Date of registration	29 / 07 / 2015
Secondary identifying numbers	CSU IRB: 15-5796H; Comite d'Ethique d'IRSS: A03-2015/CEIRES
Source(s) of monetary or material support	The Bill and Melinda Gates Foundation (BMGF)
	Burkina Faso Ministry of Health (MoH)
Primary Sponsor	Colorado State University (CSU)
Secondary Sponsor(s)	NA
Contact for public queries	Dr. Brian Foy, email: Brian.Foy@colostate.edu
Contact for scientific queries	Dr. Brian Foy, email: Brian.Foy@colostate.edu
Public title	Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study
Scientific title	Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study
Countries of recruitment	Burkina Faso
Health condition(s) or problem(s) studied	• Malaria • Lymphatic Filariasis
Intervention(s)	Active comparator (standard treatment): Single mass drug administration of ivermectin (150 µg/kg) + albendazole (400 mg) performed after the start of the rainy season as part of public health efforts to eliminate lymphatic filariasis.
	Experimental: standard treatment, followed by five more mass drug administrations of ivermectin (150 µg/kg) every three weeks thereafter.
Study type	Interventional
	Allocation: cluster (village)-randomized control trial; Intervention model: Parallel assignment with 2 arms; Masking: Single Blind (Outcomes Assessor)
	Primary purpose: Prevention
	Phase 2/Phase 3
Date of first enrollment	17 / 06 / 2015
Target sample size	8 clusters (villages) will receive the treatments, ranging from population sizes of approximately 250-800 persons each, of which usually >70% meet the inclusion criteria for treatment. Sample size of patients within each cluster who are ≤5 years of age and who will be assessed for the primary outcome (clinical malaria incidence) is 69 per cluster or a total of 552 patients.
Recruitment status	Not yet recruiting
Primary objective	To determine the efficacy of repeated ivermectin mass drug administrations (150 µg/kg), given to the population of eligible patients in enrolled villages, for reducing the cumulative incidence of uncomplicated malaria episodes in enrolled village children (≤ 5 years of age) over the course of the treatment
Key inclusion criteria	Patients receiving the mass drug administration(s) (MDA): • Residence in the study site • Able to understand the information and willing to give consent and assent (parent or guardian consent if study participant age is < 18 years)
	Patients monitored for malaria episodes through active case surveillance: • Children who are residents of the study villages and who are ≤ 5 years of age. • Parent or guardian consent
Exclusion criteria	Patients receiving the mass drug administration(s) (MDA): • Residence outside of in the study site • Height ≤ 90 cm • Permanent disability, serious medical illness that prevents or impedes study participation and/or comprehension • Pregnancy • Breast feeding if infant is within 1 week of birth • Known allergy to the study drugs

	Patients monitored for malaria episodes through active case surveillance: • Permanent disability, serious medical illness that prevents or impedes study participation
Primary outcome(s)	• Cumulative incidence of uncomplicated malaria episodes in children ≤ 5 years of age (as assessed by active case surveillance in study villages 2X/week – malaria episode defined as ≥38.0°C fever or history of fever in the last 24 hours + positive rapid diagnostic test for *Plasmodium falciparum*).
Key secondary outcomes	• Incidence of new *P. falciparum* infections acquired (molecular force-of-infection) • Prevalence and intensity (eggs/larvae per gram of feces) of soil transmitted helminth infections in a subset of treated patients between 6-10 years of age. • Indoor-resting *Anopheles* mosquito capture rate • Outdoor-host seeking *Anopheles* mosquito capture rate • Adult mosquito age structure (parity rate) in captured mosquitoes • *Plasmodium* sporozoite rate/entomological inoculation rate in captured mosquitoes • Rate of *Wuchereria bancrofti* in captured mosquitoes
Safety outcomes	• Adverse events • Serious adverse events • Further criteria and monitoring for adverse events may be determined by the Independent Safety Monitor

3.2. Narrative Protocol Summary

3.2.1. **Background and Rationale:** Malaria control efforts that have been implemented across SSA over the last 10 years have significantly curbed infections, morbidity and mortality (1). Efforts towards vector control have primarily been through massive distribution of LLINs and to a lesser extent, increased IRS. However, gains have stagnated in certain regions. In many regions vector mosquitoes are avoiding LLIN and IRS by biting humans outside and in crepuscular hours when people are not in their homes or yet sleeping under LLINs. Additionally, in Burkina Faso and other parts of West Africa, widespread malaria vector resistance to insecticides used on LLIN and for IRS are hampering control efforts (2, 3). Novel tools are needed to circumvent these issues. The implementation of new tools should integrate with existing public health interventions in the same communities for maximal cost savings and logistical benefits. Malaria-endemic communities in Burkina Faso and in other parts of SSA and the world often concomitantly suffer from high rates of NTDs, including LF. Integration of NTD and malaria control efforts, especially with tools that target both, would be ideal. Current LF elimination efforts focus on IVM (150-200 µg/kg) + ALB (400 mg) MDA occurring once per year, but a more intense effort will be needed in places like the Sud-Ouest administrative region of Burkina Faso where >13 rounds of MDA have not yet eliminated the disease (4, 5). We and others have demonstrated that the standard dose of IVM is highly effective at killing malaria vectors that bite treated people for up to 1 week post treatment (6). On a village scale, IVM MDA occurring during the rainy season significantly affects the survivorship and population structure of malaria vectors around treated villages, which significantly reduces their ability to transmit malaria parasites for approximately 2 weeks. We will conduct a pilot trial to determine the safety and efficacy of repeated IVM MDA over the rainy season to sustainably reduce malaria transmission and clinical disease, while simultaneously integrating with and enhancing LF and other NTD control efforts. Such an affect would have profound implications for malaria control and elimination across SSA and the rest of the world. We expect the results of our trial to advance integrated control efforts for these important diseases, and inform national, regional and international health authorities.

3.2.2. **Primary Objective:** To determine the efficacy of repeated ivermectin mass drug administrations (150 µg/kg), given to the population of eligible patients in enrolled villages, for reducing the cumulative incidence of uncomplicated malaria episodes in enrolled village children (≤ 5 years of age) over the course of the treatment.

3.2.3. **Hypothesis:** Repeated IVM MDA starting at the beginning of the rainy season will be well tolerated and safe, and will reduce clinical malaria episodes in children by significantly reducing malaria transmission among treated villages.

3.2.4. **Overview Study Design:** Single-blind (outcomes assessor); parallel assignment with 2 arms; cluster-randomized control trial to determine the effect of repeated IVM MDA on malaria

transmission and clinical malaria episodes. The unit of randomization will be the village (cluster). 8 villages total will be enrolled in two arms. The active comparator arm (4 villages) will receive a single standard MDA (IVM; 150-200 µg/kg + ALB; 400 mg) soon after the start of the rainy season, while the experimental arm (4 villages) will receive the standard MDA on the same date, plus 5 more IVM MDA at 3 week intervals thereafter. The primary endpoint will be the cumulative incidence of clinical malaria episodes in children ≤5 year of age within each village.

3.2.5. **Sites:** This study will be conducted in villages along the main east-west and north-south road corridors in the Sud-Ouest administrative region of Burkina Faso.

3.2.6. **Study Population:** Indigenous Burkinabé from various ethnic groups (Dagara, Bobo, Lobi, Mossi, etc.). The entire eligible population of each enrolled village will receive the MDAs, following the standard inclusion/exclusion criteria of MDA for control of microfilaremia caused by *Wuchereria bancrofti* (LF). Clinical incidence of malaria will be assessed only in children living in enrolled villages who are 0-5 years of age, most of whom will not have received any treatment due to the standard MDA exclusion criteria of children < 90 cm.

3.2.7. **Study Interventions:** 2 arms: 1) Active comparator arm – single standard MDA with IVM (150 µg/kg) + ALB (400 mg) soon after the beginning of the rainy season; 2) Experimental arm, single standard MDA with IVM (150 µg/kg) + ALB (400 mg) plus 5 more MDA with IVM alone (150 µg/kg) at 3 week intervals thereafter. CHW from the CSPS and trained by DRS authority of the Sud-Ouest region will perform the first MDA in both arms with logistical assistance from the study investigators. Repeated MDAs will only occur in the experimental-arm villages, and be performed by the study investigators.

3.2.8. **Outcome Measures:** Primary efficacy outcome – cumulative incidence of uncomplicated clinical malaria episodes in children ≤5 year of age. Primary safety outcome – number and type of adverse events in the treated populations of enrolled villages.

3.2.9. **Follow-up Procedures:** Trained nurses will visit each study village 3 times every 2 weeks over the course of the study to investigate and record any adverse events or severe adverse events communicated by the study population. They will also perform active case surveillance 3 times every 2 weeks on enrolled village children for clinical malaria episodes, defined as ≥38.0°C fever or history of fever in the last 24 hours + positive rapid diagnostic test for *Plasmodium falciparum.* Secondary measures will be collected by the nurses.

3.2.10. **Sample Size:** Assuming an 80% cumulative incidence of malaria episodes in the control arm and an intracluster correlation coefficient of 0.02, 4 clusters are needed per arm and 69 children enrolled per cluster to detect a conservative 40% reduction in incidence in the treatment arm with 80% power and a statistical confidence of 95%.

3.2.11. **Data Analysis:** Primary efficacy analysis will be the cumulative incidence of uncomplicated clinical malaria episodes and will be analyzed using generalized estimating equations (GEE) models using poisson distribution to evaluate differences between 2 arms. The time to malaria espisode will be analyzed using a Cox's proportional hazards model taking into account the censored observations throughout the period of study. The secondary outcome (number of new *P. falciparum* infections acquired over the treatment period) will also be analyzed using a GEE model with Poisson distribution. Odds ratios depicting likelihood of malaria with 95% confidence limits adjusted for repeated measures over time and adjusted for the cluster will be reported to compare the 2 arms. Other potential confounding factors will be considered in a multivariable model based on generalized linear regression models.

3.2.12. **Partner Institutions:** CSU, IRSS, Centre Muraz, Burkina Faso MoH.

3.2.13. **Funding:** The Bill and Melinda Gates Foundation

Table 1. Summary Table of Study Design, Treatment and Assessment Schedule

Month (approx)	1				2					3					4				5					6			
Week (approx)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Phase	Recruitment Phase		Enrollment Phase				Treatment Phase; 2 arms; 1) Single MDA, 2) Repeated MDAs																		Post-treatment Follow-up Phase		
Pretreatment	Community engagement, village		Enrollment, individual consent and baseline measures																								
Blood sample			X	X	X	X																			X	X	X
Stool examination			X	X	X	X																			X	X	X
Treatment by Arm																											
1 – Single MDA (4 villages)							MDA: IVM+ALB																				
2- Repeated MDAs (4 villages)							MDA: IVM+ALB			MDA: IVM			MDA: IVM			MDA: IVM			MDA: IVM			MDA: IVM					
Active malaria case surveillance in children by clinician/nurses							3X			3X			3X			3X			3X			3X					
							Blood sample and treatment with antimalarials (AL) as needed																				
Recording of AE's/SAE's by clinician/nurses							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaires			X	X	X	X																			X	X	X
Sampling by entomology team							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

4. Introduction:

4.1. **Malaria Transmission and Disease in Southwestern Burkina Faso.** Malaria is a major cause of morbidity and mortality in Burkina Faso; it has some of the highest transmission intensities in the world, as assessed by the entomological inoculation rate (http://www.map.ox.ac.uk/), and there has been limited decrease in endemicity of the disease that has been observed in other SSA countries (1). The most prevalent species of parasite is *Plasmodium falciparum*, with less than 20% being *Plasmodium malariae* or *P. ovale* (7). A high proportion of persons living in rural, underdeveloped villages in endemic areas are infected with the malaria parasites throughout the year, but transmission is highly seasonal, beginning with the onset of the rainy season and a subsequent dramatic increase of the malaria vector population (8). As such, the burden of overt clinical disease is on children ≤ 5 years of age who have not developed adequate immunity. In the southwest, clinical incidence is between 2-4 episodes per child per year (9). Clinical incidence in this age stratum spikes at the onset of the rainy season, likely due to a sharp increase in transmission events of new parasite clones accompanying the rise in mosquito populations at the start of rains (10).

4.2. **Malaria Control and Treatment in Burkina Faso.** Treatment options are limited to frontline ACTs because of a high prevalence of resistance to older antimalarial drug combinations such as sulfadoxine-pyrimethamine and quinine (8). Due to prevalent infections, especially in rural, underdeveloped areas, the National Malaria Control policy is to only treat symptomatic cases of malaria in an effort to limit drug resistance to the frontline ACTs. Outside of anti-malarial treatment, most malaria control is achieved through vector control. LLINs are the primary tools employed for limiting vector contact with humans and reducing the vector population through the impregnated insecticides in the nets (pyrethroid insecticides). To a lesser extent, IRS operations using pyrethroid and carbamate insecticide classes are performed in some areas. Unfortunately, mosquito resistance to both of these insecticides is widespread, partially due to their widespread application in agricultural operations that are prevalent in the same afflicted villages, especially cotton and rice production (11). New tools will be critical to achieving malaria control in the country.

4.3. **Lymphatic Filariasis and its Control in Burkina Faso.** Lymphatic filariasis is endemic in much of SSA, and especially prevalent in parts of West Africa, including southern Burkina Faso. In Africa, the disease is caused by infection with the filarioid nematode *Wuchereria bancrofti*. The mosquito vectors that transmit LF in Burkina Faso are the same as those that transmit malaria parasites, primarily *Anopheles gambiae*, *Anopheles arabiensis*, and *Anopheles funestus*. Although a general negative spatial association between malaria and lymphatic filariasis has been reported in West Africa (12), many areas and individual villages are afflicted with both diseases. LF has been targeted by the WHO for elimination by 2020, and GPELF coordinates these elimination efforts with the MoH of endemic countries. The primary method of LF control in Burkina Faso is to perform annual MDAs with IVM (150 µg/kg) + ALB (400 mg) to the population living in endemic villages (5). These MDAs clear the transmissible microfilaria from infected people to limit parasite spread via the mosquitoes vectors, and if performed for at least 5 years, are expected to surpass the estimated fecund life span of the *W. bancrofti* adults worms in infected people. LLINs are also used in LF control to limit contact of the mosquito vectors with people. MDAs have been performed in Burkina Faso since 2001, almost 3 times the recommended number of rounds, yet LF prevalence is still stubbornly high in parts of the south (5). The reasons for this continued prevalence is unclear, but it may partly be due to relatively low LLIN coverage or use in these regions. Furthermore, there is concern that the widespread insecticide resistance observed among the *Anopheles* vectors in Burkina Faso, especially in cotton growing areas, could hamper LF control efforts. A twice-yearly MDA schedule has recently been adopted in 4 health districts of the Sud-Ouest administrative region, which is the study area associated with this proposal (5). However, these MDAs are not specified for a particular time of year, such as the rainy season.

4.4. **Ivermectin and its Efficacy against Blood Feeding *Anopheles* Vectors.** Ivermectin is a semi-synthetic avermectin derivative that was first licensed in 1981 as a veterinary drug. It has a broad spectrum of activity against parasitic nematodes and ectoparasites, high potency, and a relatively long

pharmacokinetic persistence in blood and lymph. The drug is a macrocyclic lactone that targets invertebrate-specific ligand gated ion channels, hyperpolarizing their neurons, and causing them flaccid paralysis and death (13). In 1987, IVM was first approved for human-use to control onchoceriasis. Studies on its activity against mosquitoes began in the early 1980's, where it was soon discovered that *Anopheles* species were particularly sensitive to the drug relative to various *Culex* and *Aedes* species. Since then, many reports by us and others have shown its ability to kill and impair *Anopheles* vectors when they ingest blood either directly or indirectly from treated humans and animals (Table 2). Of particular note, the concentrations of ivermectin that occur in human blood after ingestion of a standard dose (150 µg/kg) are approximately 2 times the lethal concentration needed to kill 50% of *Anopheles gambiae*, the primary malaria vector in SSA.

Table 2. Efficacy of ivermectin against *Anopheles* vectors (adapted from Chaccour *et al*, 2013 Malaria J.)

Publication	Method and Dose	*Anopheles* species	Results
Iakubovich, 1989 (14)	Membrane and feeding on treated rabbits. Dose: 340 µg/kg (once, subcutaneous)	*An. stephensi*	Death rates among *An. stephensi* fed on rabbits 4, 5 and 6 days after administration of the drug were 93, 70 and 79%, respectively.
Gardner, 1993 (15)	Feeding on treated dogs Dose: 6–24 µg/kg (once, orally)	*An. quadrimaculatus*	Significant increase in mortality. LD50= 9.9 µg/kg [6.0, 13.8] Significant decrease in oviposition and egg-hatching from survivors
Bockarie, 1999 (16)	Field collections of engorged wild mosquitoes before and after MDA for LF Dose: 400 µg/kg ivermectin +/- 6 mg/kg DEC (once, orally)	*An. punctulatus* *An. koliensis*	Significant decrease in 9-day cumulative survival rate of *Anopheles* spp. collected 1–3 days post-treatment (0%) vs those collected pre-treatment (67%) The 48-hr survival rate of *An. puctulatus* collected from two houses in the a treated village the morning following MDA was 31% vs 94% from two houses of an untreated village
Foley, 2000 (17)	Feeding on one treated human volunteer Dose: 250 µg/kg (once, orally)	*An. farauti*	12-day cumulative mortality rate of mosquitoes was 100%, 95%, 93%, and 40% for those fed 0, 7, 10 and 14 days post-treatment vs 10% for those fed pre-treatment
Fritz, 2009 (18)	Membrane and feeding on treated cattle Dose: 600 µg/kg (once, subcutaneously)	*An. gambiae* *An. arabiensis*	Membrane feeding: LC50 for *An. gambiae* s.l. was 19.8 ± 2.8 ppb; no oviposition from mosquitoes fed on >10 ppb Cattle feeding: Total cumulative survival of *An. gambiae* s.s. significantly different from controls when fed up to 20 days post-treatment; no or significantly reduced oviposition when fed up to 17 days post-treatment
Chaccour, 2010 (19)	Feeding on randomized, treated volunteers and controls Dose: 200 µg/kg (once, orally)	*An. gambiae*	Mean 12-day survival time of 2.38 days [1.52, 3.24] for mosquitoes fed on treated subjects at 1 day post-treatment vs 5.52 days [4.65, 6.4] for mosquitoes fed on untreated control Subjects No effect on mosquitoes fed on treated subjects at 14 days post-treatment
*Kobylinski, 2010 (20)	membrane feedings Dose: NA	*An. gambiae*	LC50 = 22.4 ng/ml [18.0, 26.9]. At sub-lethal concentrations, significantly reduced mosquito re-blood feeding rates and a second ivermectin blood meal, even at a decreased concentration, further increased mortality
*Sylla, 2010 (21)	Field collections of engorged wild	*An. gambiae*	5-day cumulative survival of *An.*

	mosquitoes before and after MDA for onchocerciasis Dose: 150 µg/kg ivermectin (once, orally)	*An. arabiensis*	*gambiae* s.s. was significantly reduced from 3 treated villages vs pair-matched control villages
*Butters, 2012 (22)	Membrane feeding Dose: NA	*An. gambiae*	Sub-lethal concentrations (LC25 & LC5) caused significant knockdown and reduced recovery rates
Fritz, 2012 (23)	Membrane feeding Dose: NA	*An. arabiensis*	LC50 = 7.9 ppb [6.2, 9.9]; oviposition among survivors was significantly reduced at ≥7 ppb
Bastiaens, 2012	Feeding on treated Swiss mice, Wistar rats and Cynomolgus monkeys Dose: 200–400 µg/kg (different intervals, orally)	*An. stephensi*	3-day cumulative mortality of mosquitoes fed on treated mice, rats and monkeys significantly differed from controls when fed up to 2, 4 and 3 days post-treatment, respectively
*Kobylinski, 2012 (24)	Membrane feeding Dose: NA	*An. gambiae*	Sub-lethal concentrations significantly inhibited *P. falciparum* sporogony when fed prior to, concurrent with, and 6 and 9 days after infection with gametocytes
*Alout, 2014 (6)	Field collections of engorged wild mosquitoes before and after MDA for LF or onchocerciasis Dose: 150 µg/kg ivermectin, +/- 400 mg albendazole (once, orally)	*An. gambiae*	*An. gambiae* s.l. captured in treated villages 1–6 days post-treatment had significantly reduced survival vs. those caught pre-MDA and those caught >7 days post-treatment
* denotes publications from members of the study team LC5, LC25, LC50; the lethal concentrations calculated to kill 5%, 25% and 50% of treated mosquitoes.			

4.5. **Efficacy of Ivermectin MDA to Interrupt Malaria Transmission.** In the two decades following the initial studies demonstrating the efficacy of ivermectin for killing mosquitoes, the concept was mostly limited to ideas centered on total control of a vector population from treating individual hosts and testing direct mortality effects against vectors that ingested the drugs in host blood meals. Over the last 5 years, these ideas around malaria vector control were refined, and experiments were undertaken to test whether MDA of ivermectin in West African villages for onchocerciasis and/or lymphatic filariasis (LF) control, when applied during malaria transmission seasons, could significantly reduce the vectorial capacity of vectors biting the community (6). The effects have been strong and consistent. Single MDAs achieving ≥ 75% drug coverage reduced the daily probability of *A. gambiae* s.l. (indoor-resting, blood fed mosquitoes) survival by ~11% for approximately one week. This mortality effect results in ~25% reduction in parity rate of mosquitoes collected host-seeking outdoors for approximately 2 weeks, which demonstrates that the age structure of the vector population significantly shifts to younger age classes around the village. As young mosquitoes have not lived long enough to become infectious, this results in at least a ≥78% reduction in vectorial capacity, and significant reductions (>77%) in sporozoite rates for two weeks following the MDA (21, 25). While very transient, these reductions are in-line with changes seen in *A. gambiae* populations around SSA villages when IRS has been implemented (26) or LLINs distributed (27) and it is estimated that LLINs reduce, on average, incidence of clinical malaria by ~50% (28). It has been argued that repeated IVM MDAs might achieve sustained malaria control if performed repeatedly and during the rainy season where seasonal transmission is prevalent (29).

4.6. **Modeling of Repeated Ivermectin MDAs for Sustained Effects against Malaria Vectors, Sporozoite Transmission, Malaria Prevalence and Disease.** The first modeling performed on the expected effects of ivermectin on malaria transmission was by Foley *et al* (17). These data were based on experiments showing significantly decreased mosquito survivorship after feeding on a single IVM-treated volunteer, and the modeling focused on changes in the human inoculation rate relative to the proportion of human or animals dosed in the presence of zoophilic or anthropophilic vectors. Ten years later, Sylla *et al* (21) used mortality data from wild mosquitoes observed in the field following a MDA for onchocerciasis control to model the predicted changes in the basic reproductive rate of malaria based on differential MDA coverages and treatment intervals. Both papers predicted significant effects on malaria transmission with only modest drug coverage. Shifts in *Anopheles*

vector population age structure were subsequently modeled in Foy *et al* (29), and field data mirroring this model were then observed and reported in Alout *et al* (6). Most recently, Slater *et al* (30) modeled how IVM MDAs could enhance and shorten malaria elimination efforts when combined with ACT administrations. A primary advance of this modelling effort was that some of the outcomes were clinical measures, namely RDT positivity in ≤5 year olds. Following from this model, Dr. Slater recently used data from Alout *et al* in her model, and with the data on the patterns of seasonal malaria in Burkina Faso, used it to model the anti-malarial effects of repeated IVM MDAs if performed at 2 or 3 week intervals and at different starting dates with respect to the beginning of the rainy season. The output of the model is shown in Figure 1, where it predicts changes in mosquito density, clinical incidence in ≤5 year olds, and cases averted in ≤5 year olds. If IVM MDAs are limited to 6 rounds (as in this pilot study), the most significant effects on predicted clinical incidence is IVM MDAs performed at 3 week intervals and initiated 50-150 days into the rainy season.

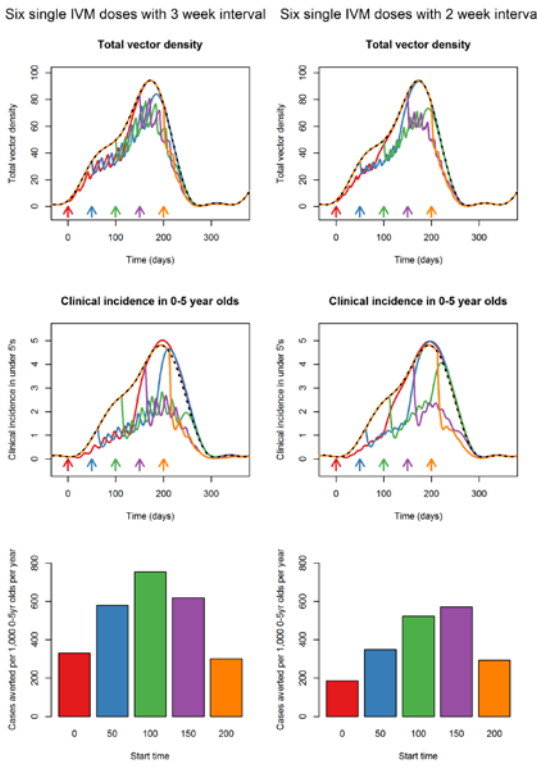


Figure 1. Modelled effect of 6 rounds of IVM MDAs on malaria in Burkina Faso. The left column assumes treatment at 3 week intervals, and the right column assumes treatment at 2 week intervals. Colored arrows and lines in the top 4 graphs and matching colored bars in the bottom two graphs represent the date of the first MDA with respect to the start of the rainy season (Time 0). Model from Dr. Hannah Slater – Imperial College.

4.7. **Safety of Ivermectin in Humans.** Ivermectin binds to the glutamate-gated chloride channel that is present in invertebrates (eg. nematodes and insects), but not present in vertebrates. It can only weakly bind to the distantly-related glycine-gated chloride channel in vertebrates, but these are sequestered in the central nervous system behind the blood-brain barrier, which prevents access to the large macrocyclic lactone drug. These characteristics are likely reasons for ivermectin's exceptional safety profile. Since its approval for human applications in 1987, more than 1.8 billion doses of ivermectin have been administered across the world. The standard indicated dose of ivermectin to control onchocerciasis and lymphatic filariasis is 150-200 µg/kg. Because it is mass administered to impoverished communities in remote locations who often have no scales, dosing in these areas is based on height alone. It is one of a handful of drugs that can be administered to communities via MDA and by community health workers (CHW). Most AEs associated with IVM treatment drug are mild, Mazzotti-type reactions linked to parasite lysis and clearance in heavily-parasitized patients that occurs after their first MDA (31). The drug is contraindicated in persons from areas endemic for *Loa loa* who also take DEC, because some neurological SAE in heavily *Loa*-parasitized persons have been reported exceptionally. Caution and a physician's consult are indicated before IVM is used by pregnant and breast-feeding women. However, in a retrospective MDA study in Liberia, 200 women treated with the drug were determined later to be pregnant; in comparison with untreated mothers in the same population, no significant differences in birth defect rates, development status or disease patterns could be found (32). These findings were later confirmed in hundreds of other women from Cameroon (33), Mali (34), Ghana (35) and Uganda (36), and now pregnant women in highly onchocerciasis-endemic areas who are at risk of loss of sight are no longer excluded from ivermectin treatment (31). Similarly, the concentrations of IVM in milk from breast-feeding mothers is very low, and it now recommended that lactating women from highly onchocerciasis-endemic areas who are at risk of loss of sight take IVM if they are breast-feeding children >1 week of age. Current recommended standard dosing regimens for MDA campaigns is 1 or 2 times/year depending on the severity of the disease in the area, and for individual patients, retreatment may be considered after a 3-month interval (see Appendix V, pg. 50). Studies reporting repeated treatment of communities and individuals are numerous, and all have reported no or limited AEs (Table 3). There are currently two

registered trials in ClinicalTrials.gov who are planning repeated treatment regimens that are more frequent than currently indicated (Table 3).

Table 3. Studies reporting frequent, repeated ivermectin administrations and their safety.

Publication or Trial	Patient Populations	Dose	Frequency	Safety Outcome
Duke, 1990 (37)	36 *O. volvulis*-infected Guatamalan patients	150 µg/kg	every month for either 4, 8 or 12 months	No AEs/SAEs reported
Duke, 1991 (38)	30 *O. volvulis*-infected Liberian patients	~100 µg/kg	every 2 weeks for 10 weeks	No AEs/SAEs reported
Duke, 1992 (39)	36 *O. volvulis*-infected Guatamalan patients	150 µg/kg	every 3 months for either 9, 12 or 31 months	No AEs/SAEs reported
Ismail, 1996	14 *W. bancrofti*-infected Sri Lankan patients	400 µg/kg	11 doses every 2 weeks	Mild AEs in 13 subjects but only after the first dose - suggestive of a link to microfilaria death and clearance; localized inguinal/scrotal reactions linked to a macrofilaricidal effect.
Awadzi, 1999 (40)	85 *O. volvulis*-infected Ghanian patients	150-800 µg/kg, then 400-800 µg/kg	2 doses, administered on days 1 and 4	No AEs/SAEs reported
Kamgno, 2004 (41) & Gardon, 2002 (42)	155 *O. volvulis*-infected Cameroonian patients	150 µg/kg	every 3 months for 3 years (12 doses)	Significantly *fewer* AEs relative to groups receiving one dose annually, including fewer sundry pains, back/wrist pain, headache, fever, pruritis, & oedematous swellings. No SAEs reported.
Guzzo, 2002 (43)	15 healthy American patients	347-594 µg/kg	3 times over 1 week	AEs similar between IVM and placebo and did not increase with dose. No SAEs reported; CNS toxicity not detected.
Multiple versus single dose of ivermectin for the treatment of strongyloidiasis (STRONGTREAT) NCT01570504	strongyloidiasis patients	200 µg/kg	Days 1, 2, 15, 16	Not yet reported
Efficacy and safety of ivermectin against dengue infection NCT02045069	dengue patients	200-400 µg/kg	2-3 times in a 3-day period	Not yet reported

4.8. **Integration of malaria and NTD control efforts globally and in Burkina Faso.** The calls for and efforts to integrate NTD and malaria control programs have been numerous (44, 45) (http://www.malariaconsortium.org/). Integration of these programs is expected to particularly affect anemia in endemic communities, as parasitic worm and malaria parasite infections can cause anemia alone, and co-infections can exacerbate this health problem (46). The most common NTD control platform is MDAs. Ivermectin effectively clears treated persons of *Wuchereria* and *Onchocerca* microfilaria, intestinal roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*) and threadworms (*Strongyloides stercoralis*), while albendazole has strong effects against roundworms and hookworms (47). Integration is not only expected to benefit the health of individuals, but there are expected cost savings and logistical benefits. Integrated control of NTDs in rural Burkina Faso, particularly control of LF and STHs, has been successful in gaining increased financial support and increasing overall NTD MDA coverage (44). However, communities of the south and southwest continue to have high LF prevalence even after 13 rounds of MDA (4), and high rates of infection with STHs (5) (GAHI; www.thiswormyworld.org). A more intense and focused MDA effort for these regions is required. Importantly, these same communities suffer from intense rainy-season malaria transmission from June-October. Further, many STHs critically expand their transmission and prevalence at the beginning of the wet season: STH eggs and preparasitic larvae only survive in moist soils and malaria vectors need the rains to proliferate. Ivermectin and albendazole MDA have a clear potential to integrate control of LF, STH and malaria with a single tool, but a) repeated ivermectin

MDAs will be necessary for maximum effectiveness and b) the repeat MDA timing with respect to frequency and season needs to be optimal. Repeated ivermectin MDA starting at the beginning of the rainy seasonal is expected to a) achieve sustained transmission-blocking when mosquito numbers are low and most vulnerable, b) prevent rapid re-infection of de-wormed people with STH that survive in the soil, and c) achieve maximal MDA coverage, as it is commonly observed that drug administrations are missed to people who are absent on the day of a yearly MDA.

5. Justification for the study

5.1. **Why is this study needed now?** While global malaria control efforts have succeeded in significantly reducing the burden of malaria since the turn of the millennium, these gains have stagnated and are in real danger of reversing. In the Greater Mekong subregion, artemesinin resistance in *Plasmodium falciparum* is rising, and threatens to spread to other regions of the world. As SSA harbors the majority of the global burden of malaria, entry of ACT-resistant parasites into the region would be disastrous; there are currently few registered alternatives to treatment with artemesinin-based therapies (www.mmv.org). Furthermore, SSA, and Burkina Faso in particular, is now dealing with widespread resistance of mosquito vectors to the insecticides used in LLINs and IRS (11). The data are very alarming. A recent study using standard WHO susceptibility assays showed that *Anopheles gambiae* from southwest Burkina Faso are >1000-fold resistant to deltamethrin, permethrin and DDT insecticides used on LLIN and in IRS. Additionally, the latest LLINs, even when new, killed less than half of these mosquitoes in exposure studies, while susceptible reference mosquito strains exhibited nearly 100% mortality (2). New ways to control malaria, especially those that can re-purpose current drugs such as ivermectin, are needed soon. Finally, integration of malaria and NTD control efforts are needed to preserve gains against these diseases and to save in costs and logistical complications of treating these diseases in remote communities.

5.2. **Other relevant ongoing research.** The WHO international Clinical Trials Registry Platform and ClinicalTrials.gov were queried for trials that have or plan to study the effects of ivermectin treatment on malaria transmission or disease. One trial in Burkina Faso has been completed and the results have been published (48). This double-blind placebo-controlled study enrolled individual Burkinabé patients who had uncomplicated *Plasmodium falciparum* infections and treated them with either artemether-lumefantrine alone or in combination with ivermectin (200 µg/kg), given in either one or two doses. The study showed that the combination of these drugs is safe, that the ivermectin combination did not change the efficacy of the AL to clear the patients' infections, and that mosquitoes fed on the treated patients' blood suffered significant mortality compared to controls. These data further support investigating ivermectin for malaria transmission control and elimination. Another study is planned, but not yet registered, in Kenya. Similar to the previous study, the investigators will enroll individual patients who have uncomplicated *Plasmodium falciparum,* but will treat them with higher doses of ivermectin (300 & 600 µg/kg/day for 3 days) plus a different ACT (dihydroartemesinin-piperaquine; DP), and assess safety, treatment efficacy, pharmacokinetics, and mosquito survival when fed on the blood of treated patients. Both of these studies, while important, do not examine the efficacy of ivermectin by itself and do not examine ivermectin's effects when administered to whole village populations in an MDA strategy for malaria transmission and disease control in a natural setting. The current study will research this important advancement.

6. **Hypothesis.** IVM MDAs to the populations of Burkinabé villages (standard clinical dose (150 µg/kg) with standard exclusion criteria), when repeated every 3 weeks and starting at the beginning of the rainy season, will be well tolerated, and result in significant reductions in *Plasmodium* spp. transmission by the local mosquito vectors over the course of the treatment, which will significantly reduce the cumulative incidence of uncomplicated malaria episodes in children ≤5 years of age who live in the treated villages.

7. **Aim & Objectives.** The overall aim of the study is to compare the effect of standard IVM + ALB MDAs given once to Burkinabé village populations at the start of the rainy season, with those same MDAs plus additional MDAs of IVM alone, given every 3 weeks thereafter 5 more times, on reducing clinical uncomplicated malaria episodes in children ≤5 years of age who live in the villages.

7.1. **Primary objective.** To determine the safety and efficacy of one standard IVM + ALB MDA plus 5 additional MDAs of IVM alone, given every 3 weeks, for reducing uncomplicated malaria episodes in children ≤5 years of age who live in the treated villages.

8. Design and Methodology.

8.1. **Overview of Design.** Single-blinded (Outcomes Assessor), cluster-randomized control trial, parallel assignment with 2-arms, to examine the primary objective of repeated IVM MDAs for reducing uncomplicated malaria episodes in children from treated villages. The village will be the cluster unit, and 4 villages with populations between 250-800 persons will be enrolled in each arm. Arm 1 will receive a single MDA; arm 2 will receive repeated MDAs. Secondary objectives will be measured from parasitological data acquired from a subset of treated patients and entomological data acquire from mosquitoes caught in the study villages (secondary objectives 8.2.3 – 8.2.7).

8.2. Secondary Objectives.

8.2.1. To determine the effect of repeated IVM MDAs on the number of new *Plasmodium* clones acquired over time in a subset of treated patients
8.2.2. To determine the effect of repeated IVM MDAs on the prevalence and intensity (eggs/larvae per gram of feces) of soil transmitted helminth infections in a subset of treated patients between 6-10 years of age
8.2.3. To determine the effect of repeated IVM MDAs on the indoor-resting *Anopheles* mosquito capture rate
8.2.4. To determine the effect of repeated IVM MDAs on the outdoor-host seeking *Anopheles* mosquito capture rate
8.2.5. To determine the effect of repeated IVM MDAs on the adult mosquito age structure of captured mosquitoes
8.2.6. To determine the effect of repeated IVM MDAs on the *Plasmodium* sporozoite rate/entomological inoculation rate in captured mosquitoes
8.2.7. To determine the effect of repeated IVM MDAs on the rate of *Wuchereria bancrofti* in captured mosquitoes

8.3. Design Considerations.

8.3.1. **Malaria epidemiology in Burkina Faso.** Understanding the epidemiology of malaria transmission and disease in Burkinabé villages is key to understanding the study design. In rural southwestern Burkina Faso villages, malaria is hyper-endemic, meaning that most people are infected with malaria parasites during the rainy season. A cross-sectional survey of one of the villages in our study area in September, 2014 showed that 52% of people tested were positive for *Plasmodium* trophozoites by slide microscopy, and 78% of children ≤5 years of age tested were positive. These data generally translates to 80-90% infection rates if molecular analyses were used. The Burkina Faso National Malaria Control policy is to only treat symptomatic cases with antimalarial drugs (8) in order to preserve the efficacy of the frontline drugs, although intermittent preventive drug treatment of pregnant women and children is beginning to be implemented in certain regions. Because of the high prevalence of infections, the burden of disease is on children ≤5 years of age who have not yet developed strong immunity from years of exposure to *Plasmodium* infections. This age group experiences a spike in malaria episodes at the start of the rainy season

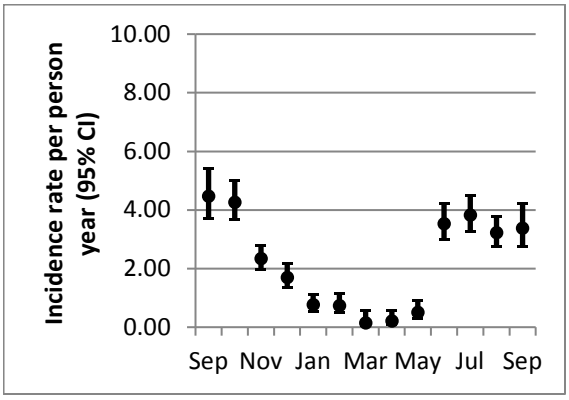


Figure 2. From Tiono *et al*., 2014. PLoS1. The monthly incidence rate of malaria in children ages 0-5 years old from Sept. 2009 to Sept. in 2010 in the Cascades region of Southwestern Burkina Faso.

when mosquito numbers rise, and the higher rate of malaria episodes is sustained until the rains diminish (9) (Figure 2).

Rural villages tend to be populated by farmers and pastoralists, and they are made up of clusters of households surrounded by their fields. Thus, most villages are separated from neighboring villages by ≥1 km, with fields and bush interspaced between them. *Anopheles* vectors breed in and around villages in standing water pools, and they get most of their blood meals from the human population of the village, so they tend not to fly more than 1 km from their breeding sites. In this way, the majority of *Plasmodium* transmission occurs within the village, between neighbors, relatives and family members via the biting mosquitoes, and a minority of transmission is thought to occur from human or mosquito immigration and emigration between villages. It is presumed that the spike in malaria episodes at the start of the rains within the ≤5 year old age group (Fig. 2) coincides with new infections from new *Plasmodium* clones transmitted by biting mosquitoes and acquired from other gametocytemic individuals in the same village.

8.3.2. **The focus on the village as the cluster unit.** The study will enroll entire villages as the cluster unit. This is necessary because patients in each village will have strong intra-cluster associations as most *Plasmodium* transmission occurs between the village residents. Furthermore, IVM MDA is given to all persons of a village who meet the inclusion/exclusion criteria, which generally is ≥70% of the population (6). As we have demonstrated, IVM administered to such a high proportion of people kills many of the mosquitoes who randomly ingest blood from people in the village approximately every 1 or 2 days (6); any one mosquito will have a high probability of ingesting blood from a treated person in the week following the MDA when mosquito-lethal concentrations of IVM are circulating in the blood of the village population. This effect reduces the number of mosquitoes surrounding the village and limits the remainder from transmitting *Plasmodium* between humans within the village because most are too young to have developed infectious parasites in their salivary glands.

8.3.3. **The focus on children ≤5 years of age as the patient population for measuring the primary outcome.** Most village children between ≤5 years of age are not ≥90 cm in height, and so most will not be treated with IVM or ALB. As explained previously, these drugs do not affect *Plasmodium* infections in a patient, rather they are anti-helmintics administered to clear *Wuchereria bancrofti* microfilaremias in patients to help eliminate LF, and also to clear STH infections in patients, however ivermectin also has anti-mosquito effects. The mode of action of ivermectin on malaria is against the mosquito that transmits parasites among the village population. Children ≤5 years of age are the subset of the village population who suffers the most from malaria episodes due to inadequate anti-*Plasmodium* immunity being infected with new *Plasmodium* clones when the rains come and the mosquito population rises and begins to bite them. Thus, this population stratum is expected to benefit the most from the anti-mosquito effects of ivermectin.

8.3.4. **The intervention model - parallel assignment with 2 arms.** This is a pilot study aimed primarily at determining whether repeated ivermectin MDA, occurring at the beginning of the rainy season, can limit *Plasmodium* transmission by mosquitoes and subsequently reduce malaria disease. The broader implementation goal is to achieve integrated control of NTDs and malaria that commonly afflict the same population of patients in Burkina Faso and similar populations across SSA. The current, once-yearly IVM MDAs are being used for LF control, but they have been sub-optimal for eliminating LF in Burkina Faso. It is expected that new and integrated control measures will be needed to achieve both LF elimination and better malaria control in the same villages. Repeated IVM MDAs will inherently be a novel measure that is expected to integrate the control of these two different diseases. The eligible populations of four villages, randomized to the control arm, will receive the active comparator MDA only once, consisting of 150 µg/kg of ivermectin + 400 mg albendazole. At the same time, the eligible populations of four other villages, randomized to the treatment arm, will receive the same MDA. However they will subsequently receive 5 more MDAs in three week intervals after the first, consisting of 150 µg/kg of ivermectin only.

8.4. Study setting

8.4.1. **Study areas.** The study will be conducted in villages along the main east-to-west and north-to-south travel corridors in the northern Sud-Ouest (South-West) administrative region in Burkina Faso that borders Ghana to the east and Cote d'Ivoire to the south. The villages will be located near the town of Diebougou. This region is mostly populated by villages that have mud-brick houses and thatch or corrugated metal roofs, and the population is mostly agricultural workers who grow millet, corn and cotton. The region is endemic for NTDs, including lymphatic filariasis, onchocerciasis, and STHs. The area spans a north-south cline where malaria transitions from being seasonal to perennial, and where malaria is hyper-endemic during the rainy season. Community malaria prevalence is generally >50%, and >70% in children ≤5 years of age during the rainy season.

8.5. Eligibility criteria.

8.5.1. **Population of the study villages for receiving MDAs.** Both Arms; one mass drug administration with IVM (150 µg/kg) + ALB (400 mg); Experimental Arm only: IVM (150 µg/kg) MDA 5 more times every 3 weeks thereafter.

8.5.1.1. Inclusion criteria

- Residence in selected study village
- Able to understand the information and willing to give consent and assent (parent or guardian consent if study participant age is < 18 years)

8.5.1.2. Exclusion criteria

- Residence outside of the study site
- Height ≤ 90 cm
- Permanent disability or serious medical illness that prevents or impedes study participation and/or comprehension
- Pregnancy
- Breast feeding if infant is within 1 week of birth
- Known allergy to the study drugs
- *Loa loa* as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria, and Sudan.
- Enrolled in any other active clinical trials

8.5.2. Active case surveillance cohort

8.5.2.1. Inclusion criteria

- Residence in selected study village
- ≤5 years of age
- Parent or guardian consent

8.5.2.2. Exclusion criteria

- Residence outside of the study site
- Permanent disability, serious medical illness that prevents or impedes study participation

8.6. Interventions

8.6.1. **Mass drug administrations.** In the first phase of the study, 8 villages will be randomized to one of two arms:

1) **Active Comparator Arm:** A single MDA with IVM (150 µg/kg) + ALB (400 mg), given at the beginning of the rainy season (approximately the middle of May)
2) **Experimental Arm:** A single MDA with IVM (150 µg/kg) + ALB (400 mg), given at the beginning of the rainy season (approximately the middle of May). In addition, 5 more MDAs with IVM (150 µg/kg) only, given every 3 weeks after the first MDA.

8.6.1.1. **Ivermectin (IVM)**. 3 mg tablets (Merck Sharpe and Dohme) will be administered by CHWs associated with the CSPS within the Sud-Ouest district who are responsible for distributing MDA for NTD control in this region under the MoH and the DRS. The CHWs will go door-to-door in each village, evaluate which household members are eligible to receive treatment, and administer the dose based on the patient's height as a proxy for their weight, as indicated in the drug package insert: 90-119 cm = 1 tablet, 120-140 cm = 2 tablets, 141-158 cm = 3 tablets, >158 cm = 4 tablets. (see Appendix V, Product characteristics, pg. 50)

8.6.1.2. **Albendazole (ALB)**. One 400 mg tablet (GlaxoSmithKline) will be administered to each patient by the CHWs at the same time as the IVM tablets. The CHWs will go door-to-door in each village, evaluate which household members are eligible to receive treatment, and administer the dose.

8.6.2. **Procedures for Drug Import, Handling and Accountability.** The drugs used in this study are procured by the NTD program within the Burkina Faso MoH, who place orders with the Donors (World Health Organization, Mectizan Donation Program, Global Program for the Elimination of Lymphatic Filariasis). The Burkina Faso MoH covers the administrative, customs and transit costs, receives the drugs at the ports of entry, and stores them in the warehouse of the MoH Disease Control Directorate. The Sud-Ouest DRS, located in the town of Gaoua, receives the drugs from supply trucks sent by the MoH NTD Program office, and stores them in their pharmacy. Each DRS keeps an inventory of the drug supply they have on hand. The drugs for this study will be provided from the stocks maintained by the pharmacy at the Sud-Ouest DRS and supplied to the MCD/CSPS in which the study villages are located. CHWs associated with the MCD/CSPS and affiliated with the study will distribute the first round of drugs, and maintain and share records of the patients who received the drugs with the study investigators. Subsequent IVM MDA in the experimental arm villages will be conducted by the study investigators and nurses with DRS/MCD/CSPS assistance.

8.6.3. **Product Labelling and Storage.** Study drugs are pre-labelled by the manufacturers (IVM – Merck Sharp & Dohme BV, Netherlands, ALB – GlaxoSmithKline) in both French and English. They will be stored in a secure area, with access limited to the MCD staff and study investigators. Products are stored under appropriate product-specific storage conditions as indicted on the drug package label (see Appendix V, Product characteristics, pg. 50).

8.6.4. **Product Accountability.** The site-study investigators will liaise with the MCD & CSPS to ensure correct handling of study drug so that:

8.6.4.1. Deliveries of study drug from the DRS are correctly received by a responsible person (e.g. pharmacist assistant).

8.6.4.2. Accurate records are maintained for the receipt of study drug, for the dispensing of study drug to subjects and for any returned drug.

8.6.4.3. Certificates of delivery and return must be signed preferably by the investigator or authorized personnel and copies retained in the investigator file.

8.6.4.4. Study drug is to be handled and stored safely and properly and in agreement with the given storage instructions.

8.6.4.5. The study drug is to be prescribed only by the authorized DRS medical director, MCD medical director or the study co-investigators that are medical doctors.

8.6.4.6. Study drug is dispensed only to study subjects in accordance with the protocol.

8.6.4.7. At the end of the study, delivery records must be reconciled with records of usage and returned stock. Any discrepancies must be accounted for in writing.

8.6.5. **Removal of Patients from Treatment or Assessment.** Patients can discontinue from the study for any of the following reasons.

1. Screening error resulting in incorrect enrollment (discovery that the subject did not meet the required inclusion/exclusion criteria)

2. Withdrawal of assent/consent at any stage or the subject not willing to continue in the study (or withdrawal of consent by the parent/guardian to keep his or her child enrolled.
3. Suspected or confirmed allergic reaction to the study drugs.
4. Safety reasons as judged by the investigators or the ISM.
5. Other

Patients who discontinue in the study or withdrawal their assent/consent will always be asked about their reason(s) for discontinuing and about any adverse events they may have experienced. If a person discontinues, it should be determined whether:

1. They discontinue treatment, but continue their consent for the data capture and continue follow-up. These subjects will be considered 'off drug study/on study" and follow the same schedule of events except for participation in the interventions
2. They discontinue all future activities in the study, but continue their consent for the data captured up to that point to be used in the research.
3. They discontinue all future activities in the study and withdrawal their consent for any past data captured to be used in the research.

These scenarios will be recorded in Case Record Forms (CRFs). Subjects that have discontinued the study prematurely will not be replaced.

8.6.6. **Discontinue from storage of blood for future studies.** If a subject discontinues, it will also be established whether the subject:

1. Continues their consent for the long-term storage of any blood or fecal samples collected.
2. Withdrawals consent for long-term storage of the blood or fecal sample for any future studies prior to de-identification of the dataset.

When a subject's consent for long-term storage is withdrawn, the stored sample will be destroyed and the withdrawal noted in the CRF. If the request is received after the dataset has been anonymized, the stored sample can no longer be withdrawn.

8.6.7. Adherence to study intervention protocol and strategies for retention.

8.6.7.1. **Adherence to study protocol and MDA.** Study participants will be reminded of upcoming MDA distributions by the study investigators during active case surveillance visits the week prior to the intervention, and asked to be present on the morning of that day in order to receive the study drugs from the CHWs. The week prior to the MDAs is also when nurses will check the pregnancy status of enrolled women of child-bearing age. Similarly, parents whose children are enrolled in the active case surveillance will be reminded of upcoming visits by the study nurse and be given mobile phone contact information should they suspect a malaria episode in their child on days when the nurse is not scheduled to visit. All relevant information will be recorded on the appropriate sections of the CRF.

8.6.7.2. **Strategies for retention.** During screening, potential participants will be asked whether they will be willing and able to comply with the frequent intervention and follow-up schedule, and whether they need to travel out of the study area for an extended period during the follow-up period. Patients referred to the CSPS/hospital for any AE or SAE suspected to be related to the study interventions will be reimbursed for the transportation costs they may incur going to and from the clinic (see Table 4, Expenses reimbursement and incentives, page 38).

8.6.7.3. **Prior and concomitant therapy.** All concomitant medications taken during the study will be recorded in the appropriate sections of the CRF with indication, dose information, and dates of administration.

8.6.7.4. **Permitted medications during active case surveillance.** During active case surveillance in the cohort of enrolled children ≤5 years old, if a subject is diagnosed with malaria, the investigators will prescribe Artemether-Lumefantrine (AL) antimalarial treatment

for uncomplicated cases per the National Malaria Control Program guidelines, or refer complicated cases to the CSPS/MCD.

8.6.7.5. **Self-medications.** Patients will be counseled to avoid self-medicating for malaria, specifically antimalarials that are not prescribed within the trial protocol: chloroquine, halofantrine or mefloquine.

8.7. Endpoints/Outcome Measures.

8.7.1. Primary efficacy outcomes.

8.7.1.1. Cumulative incidence of uncomplicated malaria episodes in enrolled study village children ≤5 years of age. Uncomplicated malaria episodes in this cohort will be assessed by active case surveillance performed by household visits from study nurses, conducted 3 times over each 2 week period during the entire study period. An uncomplicated malaria episode will be defined as axillary temperature ≥38.0°C and/or history of fever in the last 24 hours and a positive rapid diagnostic test (RDT) for *Plasmodium falciparum*.

8.7.2. Secondary outcomes.

8.7.2.1. Incidence of new *Plasmodium falciparum* clones acquired in a subset of patients over the study period.
8.7.2.2. Prevalence and intensity (eggs/larvae per gram of feces) of soil transmitted helminth infections in a subset of treated patients between 6-10 years of age.
8.7.2.3. Indoor-resting *Anopheles* mosquito capture rate
8.7.2.4. Outdoor-host seeking *Anopheles* mosquito capture rate
8.7.2.5. Adult mosquito age structure in captured mosquitoes as assessed by parity rate examination of mosquitoes and near-infrared spectroscopy scanning of mosquitoes
8.7.2.6. *Plasmodium* sporozoite rate/entomological inoculation rate in captured mosquitoes
8.7.2.7. Rate of *Wuchereria bancrofti* in captured mosquitoes

8.7.3. Tolerability and safety endpoints.

8.7.3.1. Tolerability.

- Any adverse events or reactions assessed in general toxicity questionnaires.

8.7.3.2. Safety.

- General toxicity
- CNS effects
- Serious Adverse Events
- Hemoglobin concentrations
- Further criteria for monitoring adverse events may be determined by the ISM.

8.8. Participants Timeline.

8.8.1. **Overview of Study Phases.** The study plan and schedule of assessment is provided in Table 1, page 12. The study timeline consists of 4 Phases: Recruitment, Enrollment, Treatment, and Post-treatment follow-up.

8.8.2. **Recruitment Phase.** As this study is a cluster-randomized control trial with Burkinabé villages being the cluster unit, community engagement and community-wide consent are critical and are the initial method of recruitment. This is especially important as the primary layer of consent because the village population is often tightly interconnected as they are made of extended and intermarried families of the same ethnic group, and many of the older population are illiterate. Potential villages will be pre-analyzed by the study investigators for similar and appropriate characteristics that would make them eligible for the study, such history of malaria and LF (as determined by MCD/CSPS records), location, size, and similarities with regard to the primary occupation of the populations. In general, attempts will be made to enroll small to medium-sized rural villages that are along the primary road corridors and who are mostly inhabited by stationary

agricultural workers. Larger towns and settlements with transient populations, such as gold-mining camps, will be excluded from consideration. The process will involve the study investigators, including the PIs and co-PIs, and may include representative delegates from the MoH NTD control program and the MoH malaria control program, the DRS, the MCD, and CSPS to meet with interested local village chiefs and elders from selected villages in a public meeting in their village. At the meeting, the investigators will explain to the village elders and chiefs the goals, objectives, and interventions of the trial in the local language and in French, and answer any questions they have. It will be made clear that villages will be randomly assigned to one of the 2 arms. The chiefs and elders will be instructed to gather the heads-of-households to discuss their collective interest or opposition to being part of the study. Village leaders who subsequently inform us of their village's initial assent to being part of the study will be brought together for a public randomization of study villages. The names of each of the 8 study villages will be publicly written on a card along with one identification number between 1 and 8. These will then be put in matching envelopes, placed in a transparent container for the drawing, and mixed. Each chief will then be asked to draw one envelope and place it, sequentially, in one of 2 containers labeled for each arm (1 = single MDA; 2 = repeated MDA). At the end of the drawing, 4 envelopes will be in each container. Subsequently, each chief will open a single envelope in each container and publicly reveal the randomization of clusters.

8.8.3. **Enrollment.** Once community consent/assent is affirmed and randomization occurs, consent and enrollment will proceed in each study village. The study investigators will travel to each village and meet publicly with the heads-of-households to inform them of the study goals, objectives, the results of the public randomization meeting, and the interventions specific to their village's randomization and that will occur with family members in their own households. These interventions include the data and sample collection procedures. The heads-of-households will be reminded of the need for them and the family members to be present for any subsequent interventions in their village, and of the active case surveillance in any children of theirs which may be enrolled in the ACD cohort. If they sign a head-of-household consent document (appendix VII), the investigators will walk to each household, take a census of the inhabitants, conduct a questionnaire of inhabitants, survey the houses, enroll adults >18 years of age with their verbal assent, and enroll children <18 years of age with parental/guardian verbal assent. Members of the study team will subsequently map the household and house locations in the village.

8.8.3.1. **Assignment of IDs.** Screened subjects who meet all eligibility criteria will be issued a study subject code, and their picture may be taken and linked to their study subject number during this visit on tablets. Once issued the study subject code, they will be considered as 'enrolled.' This code is the subject's unique identifier and used to identify the subject on the CRFs. Once a code has been assigned no attempt will be made to use that code again, for example if a subject withdrawals their consent.

8.8.3.2. **Clinical assessment of the MDA-eligible population.** After consent is obtained and the subject's eligibility is confirmed, the subject's demographic data, and all relevant clinical information, including previous and current medical history will be recorded in the CRF. Blood samples from finger prick will be obtained from a subset of subjects and spotted onto an FTA card (for subsequent molecular analysis), onto a slide (for subsequent parasitological staining), and put into a Hemocue reader for hemoglobin values. Additionally, a subset of MDA-eligible children between 6-10 years of age, with their parents/guardians assent and assistance, will be asked to provide a stool sample to the study investigators prior to the first MDA.

8.8.3.3. **Pregnant subjects.** All women who are of child-bearing age will be noted and flagged on the CRF at the time of the first MDA by the CSPS CHWs. The CHWs assess exclusion due to pregnancy by questioning the patient on the day of the MDA per their training. Assessment of pregnancy in women of child bearing age (ages 15-49) during subsequent repeated IVM MDAs in the experimental arm villages will be performed within the week prior to the MDAs by the study nurses. Study nurses will directly but privately asked two

questions. 1) “Are you the pregnant.”; 2) “When was your last menstruation?” Subjects responding in the affirmative to question #1 or responding that their last menstruation was more than 28 day prior will be excluded from being administered IVM in the upcoming MDA. Subjects who respond that they are not pregnant or that their last menstruation was within the previous 28 days will be asked to take a pregnancy test (dipstick urine test for HCG). If they refuse the test, fail to provide urine, or if the test returns a positive result, they will be excluded from being administered the study drugs.

8.8.3.4. **Breastfeeding subjects.** All women who are breastfeeding will be noted and flagged on the CRF. On the day of each MDA in their village, these subjects will be asked if they are breastfeeding an infant who is within 1 week of birth. Those who respond in the affirmative will be excluded from receiving the study drug at that time.

8.8.3.5. **Enrollment and clinical assessment of the ACD cohort.** After head-of-household informed consent is gained, parents/guardians of children in enrolled households who are between ≤5 years of age will be asked to give their informed consent to enroll their child(ren) in the ACD cohort. After assent is obtained and the child subject’s eligibility is confirmed, the subject’s demographic data, and all relevant clinical information, including previous and current medical history will be recorded in the CRF. Blood samples from finger prick will be obtained and spotted onto a filter paper card (for subsequent molecular analysis), onto a slide (for subsequent parasitological staining), and put into a Hemocue reader for recording hemoglobin values.

8.8.4. **Treatment Phase.** Approximately eighteen weeks starting at the beginning of the first MDA (Table 1).

8.8.4.1. **Mass drug administration visits.** CHWs and study investigators will go to the study villages in the days prior to the MDAs to remind the populace of MDA occurring in the coming planned day. On the day established for the first MDA, CHWs and study nurses will arrive in the morning and go door-to-door to enrolled households to administer the MDA to all eligible patients per DRS training. MDAs with IVM (150 µg/kg) + ALB (400 mg) will occur on this first day of the study period in all enrolled villages (Arms 1 & 2). MDAs with IVM (150 µg/kg) only will occur 5 more times every 3 weeks thereafter, only in villages previously randomized to study arm 2 (treatment arm), and performed by the study nurses according to this protocol.

8.8.4.2. **Active case detection and adverse events monitoring.** Starting with the week of the first MDA, study nurses will travel to each village 3 times over each 2 week period throughout the study period, keeping a regular schedule, and visit all households with children enrolled in the ACD cohort. When there, they will monitor the children for clinical signs of fever, and if needed sample blood from finger prick, and perform RDTs as needed. Positive, uncomplicated cases will be prescribed AL by the study physician and monitored for recovery. During their visit, nurses will also record any AEs passively reported by the village populace, treat uncomplicated AEs if they are probably associated with the MDA according to published WHO guidelines (see Appendix VIII, pg. 56), refer any SAEs to the CSPS or nearest hospital, and report any SAEs that are determined to be possibly-related to the intervention to the study physician within 24 hours of the nurse becoming aware of it.

8.8.4.3. **Entomology sampling.** Entomology teams will visit the study villages at least 1 time every 3 weeks during enrollment and through follow-up to sample resting mosquitoes from pre-selected sleeping houses of enrolled households. Additionally, they will regularly set up overnight host-seeking mosquito sampling stations in study villages using trained, paid collectors.

8.8.5. **Post-treatment follow-up phase.** Lasting for up to three weeks, starting 3 weeks after the 6th MDA (Table 1).

8.8.5.1. **Post-treatment clinical assessment.** A questionnaire will be administered to all enrolled patients to assess any past or current adverse signs and/or symptoms, including any AEs. In a subset of patients, a brief clinical examination will be performed as before during the enrollment period, whereby blood samples from finger prick will be obtained and spotted onto an FTA card (for subsequent molecular analysis), onto a slide (for subsequent parasitological staining), and put into a Hemocue reader for hemoglobin values. Additionally, the subset of patients who were between 6-10 years of age at the start of the study and who previously provided a stool sample will be asked to provide a follow-up stool sample.

8.8.6. **Unscheduled visits.** At any time, participants displaying signs or symptoms of severe malaria who contact the nurses while they are working in the study sites will be referred to the CSPS or MCD for further evaluation and treatment. If transportation is available, these patients will be transported to the clinic by the study team. Blood samples for malaria smears, parasite genetics (filter paper dried blood spots) and hemoglobin will be taken if clinically indicated.

8.9. Sample size.

8.9.1. **Primary endpoint sample size and recruitment strategy.** The study is powered on the primary endpoint measure, cumulative incidence of uncomplicated malaria episodes in enrolled study village children ages 0-5 years. Assuming a cumulative incidence of malaria episodes in the control arm of 80% and an intracluster correlation coefficient of 0.02, 4 clusters are needed per arm and 69 children enrolled per cluster to detect a conservative 40% reduction in incidence in the treatment arm with 80% power and a confidence of 95%. Importantly, modeling predicts approximately a 80% reduction in incidence (Figure 1). We will attempt to enroll small to medium sized villages that have between 250-800 people. In this region of Burkina Faso, children of this age group usually comprise 25-35% of the village population, which should give us enough children in each village, assuming most parents/guardians enroll their children in the ACD. This is a fair assumption, because the parents in this region observe the impact that malaria has on their children, especially in the rainy season, and usually see the value of having their child monitored regularly for malaria episodes. Tiono et al. (9) had approximately 6% of subjects lost to follow-up in their similarly aged ACD cohort over the course of the rainy season, which would still give us enough subjects in the two initial arms to detect a significant difference in cumulative incidence of malaria episodes.

8.9.2. Secondary endpoints with parasite measures.

8.9.2.1. **Molecular force-of-infection (number of new *Plasmodium* clones acquired over time)**. A subset enrolled patients who live in households at the geographic center of the study villages will have a blood sample taken on spot of filter paper upon enrollment and again at follow-up, including the children enrolled in the ACD. Furthermore, we will obtain regular finger stick blood samples during the treatment phase from children in the ACD cohort when/if they present with a malaria episode. This will give us at least 1400 pre- and post-treatment blood samples from which to score for the number and identify of parasite clones in each person and calculate the molecular force-of-infection over the interval of the study.

8.9.2.2. **Soil transmitted helminths (Prevalence and intensity of STHs in a subset of treated patients between 6-10 years of age).** A subset enrolled patients who live in households at the geographic center of the study villages and who are between 6-10 years of age in the study villages will be asked to provide a stool sample via assent from their parent/guardian, which will be analyzed for larvae/eggs per gram of feces. This age stratum of patients is assumed to have the highest prevalence of infection with *Ascaris lumbricoides* and *Trichuris trichiuria*, both of which are partially sensitive to ivermectin treatment, and have the highest re-infection rates following single MDAs. If the infection rates are low, we will try to increase our sample size by asking patients who are between 11-15 years of age, with assent from their parent/guardian, to provide a stool sample. All of these patients will be

asked to provide a second stool sample in the post-treatment follow-up phase. We estimate his will give us approximately 400 pre- and post-treatment stool samples from which to calculate the change in the prevalence and intensity of STH infections over the interval of the study period.

8.9.3. **Secondary endpoints with entomological measures.** Sleeping houses within enrolled households at the geographic center of the study villages will be sampled one or more times at every 3 weeks over the study period for resting blood fed *Anopheles* mosquitoes. These samplings will be performed by the entomology team in the early mornings using hand-held, battery-powered aspirators. Depending on the month, weather conditions and house, >50 blood fed *Anopheles* mosquitoes can be captured in a single house on a single morning. In general, between 0-20 mosquitoes are caught per house per morning. The mosquitoes will be brought back to the field lab, identified and enumerated, the blood meal contents smashed on an FTA card, and the head+thorax stored in desiccant for subsequent molecular analysis. The blood meals will be subsequently analyzed for the presence of *W. bancrofti* microfilaria, *Plasmodium*, and other potential pathogens, and the head+thorax will be tested for the presence of *Plasmodium* sporozoites.

8.10. Assignment of Interventions

8.10.1. **Allocation.** The allocation process will be public, and involve the study investigators, including the PIs and co-PIs, and some representative delegates from the MoH NTD control program and the MoH malaria control program, the DRS, the MCD, and CSPS to meet with interested local village chiefs and elders from selected villages in public within the village. At the meeting, the investigators will explain with the village elders and chiefs the goals, objectives, and interventions of the trial in the local language and in French, and answer any questions they have. It will be made clear that villages will be randomly assigned to one of the 2 arms. The chiefs and elders will be instructed to discuss with the heads-of-households their collective interest or opposition to being part of the study. Subsequently we will conduct a public meeting with all village leaders who subsequently inform us of their village's initial assent to being part of the study to hold a public randomization of study villages. The names of each of the 8 study villages will be publicly written on a card along with one identification number between 1 and 8. These will then be put in matching envelopes, placed in a transparent container for the drawing, and mixed. Each chief will then be asked to draw one envelope and place it, sequentially, in one of 2 containers labeled for each arm (1 = single MDA; 2 = repeated MDA). At the end of the drawing, 4 envelopes will be in each container. Subsequently, each chief will open a single envelope in each container and publicly reveal the randomization of clusters.

8.10.2. **Blinding.** As this is a pilot safety and efficacy study, and the repeated MDA treatments will be distributed by the CHWs and study nurses and investigators, we will neither blind the patients nor the study investigators at the study sites. Rather, the study outcomes assessor/biostatistician (Dr. Rao), who will not be present at the study site during treatment and data collection, will be blinded when analyzing the data sent to her by the onsite investigators.

9. Data Collection, Management and Analysis.

9.1. Clinical procedures.

9.1.1. **Malaria episode diagnosis in the ACD cohort.** During each village visit, ACD patients will have their axillary temperature taken with a thermometer. Also, parents/guardians will be questioned about whether their child had an apparent fever or showed any signs of illness in the past 24 hours. A temperature of ≥38.0°C and/or history of fever in the last 24 hours will warrant the nurse to perform a finger prick blood collection with a sterile single-use lancet to a) make a thick and thin film blood slide, b) take at least 2 blood spots within 24 hours of each other on filter paper for later molecular analysis, and c) perform a rapid diagnostic test (RDT) for *Plasmodium falciparum*. A positive RDT will warrant antimalarial treatment (AL) as to be dispensed by the nurse under the direction of the study physician.

9.2. Laboratory procedures.

9.2.1. **Thick and thin blood smears for malaria.** Thick and thin blood films for parasite counts will be obtained and examined under a microscope. Malaria parasites will be counted against 300 white blood cells or 100 high power fields before a slide is declared negative.

9.2.2. **Molecular force-of-infection.** Blood samples on filter paper spots will be used for molecular analyses of parasite clonality and population dynamics. Parasite DNA will be extracted using standard molecular kits and polymorphic marker genes will be amplified by PCR with tagged primers and capillary electrophoresed for fragment sizing.

9.2.3. **Hemoglobin testing.** Hemoglobin will be tested using HemoCue® (Angelholm, Sweden) photometers.

9.2.4. **Stool microscopy.** Stool samples will be prepared using the mini-FLOTAC method and examined for presence of STH larvae/eggs and eggs will be counted in positive samples.

9.2.5. ***Plasmodium* sporozoites in the head+thorax of captured mosquitoes.** A subset of desiccant-dried mosquito thoracies will be extracted for their DNA and analyzed with ELISA or by Taqman PCR to detect *Plasmodium* sporozoite DNA.

9.2.6. **Squashed mosquito blood meal spots for detecting *Wuchereria bancrofti*.** A subset of mosquito blood meal spots will be extracted for DNA, and analyzed for the presence of W. bancrofti microfilaria DNA using PCR.

9.2.7. **Aging of captured in *Anopheles* vectors.** Recently-captured live *Anopheles* mosquitoes will be anesthetized with chloroform, scanned on a near-infrared spectrometer, and their ovaries dissected, which will be scored for parity under a microscope via their tracheole skein coiling.

9.3. **Data collection methods and storage.** Patient data will be collected using standardized case reporting forms on tablet computers or paper forms as a backup. Laboratory results will be maintained in paper laboratory books and then entered into an Excel spreadsheet (Microsoft®. Redmond, Washington, USA). All data storage will be encrypted and password protected.

9.4. **Statistical methods.** A detailed study statistical plan for the final analyses, that will supersede that in the study protocol, will be drawn up during the course of the study before the unblinding of data sent to the biostatistician (Dr. Rao).

9.4.1. **Trial profile and flowchart.** A trial profile will be developed and presented as a flow chart following CONSORT guidelines, consisting of the number of villages and their randomization, participants screened, eligible, enrolled, followed through the treatment phases, and number contributing to primary efficacy outcomes. It will also include the number of participants who withdrew or were lost to follow-up.

9.4.2. **Baseline characteristics**. Descriptive statistics of baseline characteristics, overall and by treatment group will be provided in a table consisting of parameters collected at recruitment and enrollment. No statistical comparisons will be made between the groups, but any differences between groups at baseline which are also associated with the outcome variable will be taken into account in subsequent analysis.

9.4.3. Analysis populations.

9.4.3.1. Screening failures.

9.4.3.1.1. **Enrolled population in the clusters who receive the treatments.** It is expected that some heads-of-household or individual subjects in a household will be lost to follow up or may die during the study. This population will be included in both intention-to-treat (ITT) and according-to-protocol (ATP) analyses.

9.4.3.1.2. **ACD cohort.** If the parent/guardian of a subject in the ACD cohort gives informed consent and the subject is provided with a study ID, but then the subject is lost to follow up or dies prior to the first MDA at the start of the Treatment Phase, they will be classified as a screening failure and excluded from the analysis.

9.4.3.2. **Primary endpoint analysis population – ACD cohort.** The population limited to the primary endpoint analysis is defined as all enrolled patients ≤5 years of age who lived in the randomized study villages through the Treatment Phase. These patients will be included in the primary endpoint analysis using the last-observation-carried-forward-method (LOCF), whereby the last available measurement, be that the final measurement of study or at the time point prior to withdrawal or being lost-to-follow, is included in the analysis. Intention-to-treat analysis (ITT) is not appropriate for this population because the majority will not be treated because of their weight/height (MDA is only provided to patients >15 kg/>90 cm). Rather the effects in this population are expected to be derived from the treatment of the older population in the study villages and its effect on malaria transmission.

9.4.3.3. **Safety population.** This population is defined as the population of the study villages who received at least one treatment during the course of the study and were followed-up (ie. provided information on adverse events).

9.4.3.4. **Treated population.** The treated population is defined as all those enrolled patients from the study villages who were treated at least once and lived in the randomized study villages during the Treatment Phase. A subset of this population will be subject to the secondary endpoint analyses, a) incidence of infection with new *Plasmodium* clones and b) prevalence and intensity of infection with STH, both of which require providing at least one sample during the Enrollment Phase and one during the Post Treatment Follow-Up Phase. These secondary analyses will be both ITT and ATP, in order to estimate the effect differences between the per-protocol population and the population with protocol violations (treatment irregularities, non-compliance, early withdrawal, etc.)

9.4.4. **Missing data.** Every effort will be made to minimize the amount of missing data in the trial. Whenever possible, information on the reason for missing data will be obtained. No adjustments will be made for missing outcome data, but missing data may be imputed for co-variates during the analyses.

9.4.5. **Assessment of efficacy.** Primary efficacy analysis will be based on the count variable 'cumulative incidence of malaria episodes'. Generalized Estimating Equations (GEE) based regression models will be constructed to estimate risk ratios and corresponding 95% confidence intervals while taking the cluster design into account. A poisson regression will be used to compare the risk rates between the two treatment groups by considering the cumulative incidence of an individual across the study period as the outcome measure. Proportion of patients experiencing a malaria episode will be compared between arms by odds ratio with corresponding 95% CI; associations between treatment group and continuous variables will be expressed as mean differences and 95% CI. Proportional hazards model will be used to analyze the 'time to first malaria episode' as a secondary outcome.

9.4.6. **Analysis of adverse events.** Adverse reactions will be reported and tabulated for each treatment arm, overall and on per-protocol basis. Adverse reactions are defined as AEs that had an onset day on or after the day of the first dose of study medication and probably related to the treatment. Adverse events that have missing onset dates will be considered to be treatment-emergent. Logistic regression models with random effects will be used to compare the risk of occurrence of each AE in the experimental group with the risk in the control group. Odds ratios with their 95% confidence intervals will be calculated for each AE. All laboratory data will be listed.

9.5. Monitoring

9.5.1. **Data monitoring.** This study is a clinical trial defined at 'Moderate Risk' by the UCH Clinical Translational Research Center Policy on Study Monitoring (http://www.ucdenver.edu/research/CCTSI/programs-services/regulatory/Documents/Study_Monitoring_Policy_2010-01-15.pdf), and from this document, 'Moderate Risk' trials minimally requires an Independent Safety Monitor (ISM). Following this recommendation, an ISM will be contracted for the trial. The ISM will be critical to ensure that the subjects are protected from harm, while also ensuring that the study integrity is not compromised. The ISM will be a person knowledgeable in the conduct of clinical trials, and is expected to be based Burkina Faso. This person will work with the biostatistician (Dr. Rao) to evaluate the nature and occurrence of AEs and SAEs. S/he will make regular assessments (e.g. twice yearly or more frequent if so required) during the data collection period to provide a review of blinded (and if requested, unblinded) data to ensure the safety, rights and well-being of trial participants. The role of the ISM is described in more detail in Appendix II. Terms of Reference Oversight, page 45.

9.5.2. **Interim analysis and criteria for termination of the trial.** Interim analyses of the safety data will be conducted soon after the 3rd MDA. The ISM will be blinded when presented with the interim analysis, unless the ISM judges that for safety reasons the blind should be broken. A detailed plan for interim analysis, any planned statistical adjustments to be employed as a result of interim analysis, the provisional stopping rules and how the stopping rules will be applied, will be drawn up prior to the start of the interim analysis. In addition, regular review of the quality of the study data will be conducted by the ISM.

Following recommendation from the ISM, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the sponsor determines such action is needed, it will discuss this with the investigators. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect. The sponsor will promptly inform the CSU IRB and Comité d'Ethique of the IRSS, and provide the reason for the suspension or termination.

9.6. Safety Monitoring and Reporting.

The principles of Good Clinical Practice require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials.

9.6.1. Definitions.

9.6.1.1. **Adverse Event (AE).** Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

9.6.1.2. **Adverse Reaction (AR).** Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Note: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

9.6.1.3. **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR).** Any adverse event or adverse reaction that results in death, is life-threatening*, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Note: Medical judgment should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.*

9.6.1.4. **Suspected Unexpected Severe Adverse Reaction (SUSAR).** An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.

9.6.1.5. **Intensity.** The intensity of each AE recorded in the case report form should be assigned to a grade (1-5), which will be determined following the definitions set forth in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (Cancer Therapy Evaluation Program, 2006). Use of these standardized guidelines will allow for uniform reporting. The grades are defined as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

9.6.2. **Identifying, managing adverse events.** Participants who develop common adverse events that possibly were a consequence of ivermectin treatment will be identified at follow-up visits and treated by the study nurses according to WHO guidelines for treating common AEs that occur from MDAs (see appendix VIII). All adverse events will be noted in the participant's case report form; in the case of mild AE, no further action will be taken by study staff except in the case of vomiting, in which case the study medication may need to be re-administered. In the case of any severe adverse event (difficulty breathing, convulsions, change in mental status), subjects will be referred to the CSPS/MCD for management. Transportation to the hospital will be provided if available. All hospitalized participants will undergo record review to identify potential adverse consequences of study participation.

9.6.3. **Assessment of causality.** The investigator physician (Dr. Rouamba), in consult with the field physician and the other investigators, is obligated to assess the relationship between the investigational product(s) and the occurrence of each AE/SAE. The physician-investigators will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The physician-investigators will also consult the drug information and the ISM as needed in the determination of their assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report (see 9.6.4.). However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE report to CSU and IRSS. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE case report form accordingly.

9.6.4. **Reporting adverse event procedures.** All SAEs deemed as 'possibly related' to the intervention will be reported to the in-country principal investigator or an assigned representative within 24 hours of the nursing staff becoming aware of it via mobile phone or electronically. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome

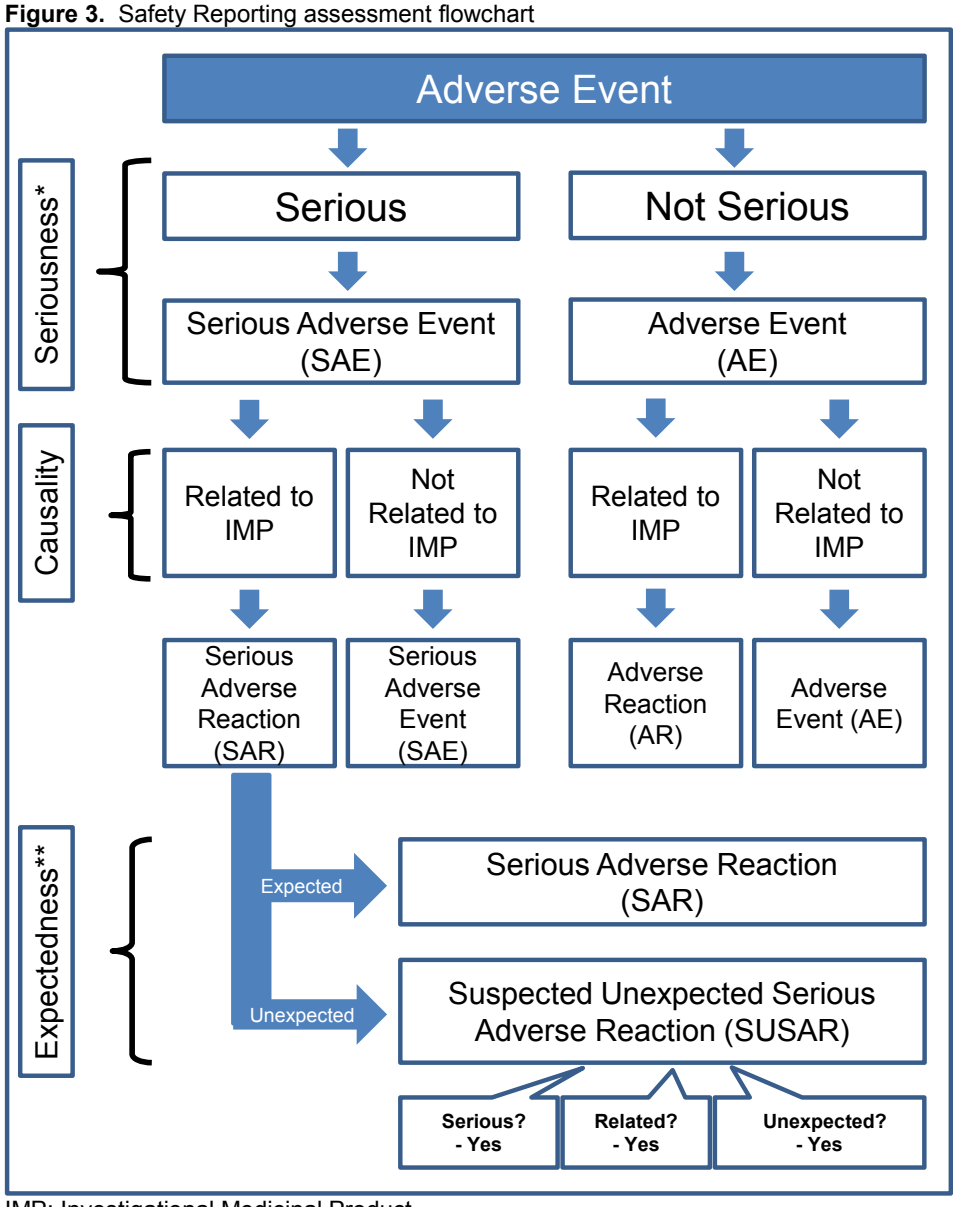
and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible study clinician should ultimately assign the causality of the event.

9.6.4.1. **Expedited reporting.** SAEs that are unexpected and are at least 'possibly related' to the intervention require expedited reporting within 24 hours of nurse becoming aware of it, and reporting within 24 hours to the ISM and sponsor by the country principal investigator or assigned representative becoming aware of it (e-mail notification); i.e. this will be a maximum of 48 hours after the field nurse becomes aware of it (including the 24 hours required for the field staff to report to the principal investigator / representative). Additional information will be sent within 14 additional days (full SAE report) if the reaction had not resolved at the time of e-mail notification.

9.6.4.2. **Regular Reporting.** Other SAEs and AEs will be reported annually in an aggregated report. AEs that will not be reported include common illnesses that do not result in hospitalization, including but not limited to clinical malaria, respiratory, gastrointestinal, and skin diseases, unless they are considered at least possibly related to the intervention.

9.6.4.3. **Recipients of reports.** The study will comply with local regulations pertaining to reporting of SAEs to their local Research Ethics Committee and/or Research & regulatory offices. In addition to the primary ethics committees, we will report safety data to the ISM and to the sponsor. A copy of the final study report will be provided to the ISM, MoH.

Figure 3. Safety Reporting assessment flowchart



IMP: Investigational Medicinal Product
*See definition of SAE in section 9.6.1.3.
**Assessed in line with the current approved Investigator's Brochure (IB)

9.7. Quality Assurance

9.7.1. **Clinical monitoring.** Monitoring of this trial will be conducted to ensure compliance with ICH-Good Clinical Practice and scientific integrity will be managed and oversight retained, by the sponsor. Clinical monitoring will also be performed by the ISM, who will be in-country and familiar with ICH-GCP. At least 3 monitoring visits will be carried out; one at trial initiation, one at close-out and one half-way through the study.

Prior to subject enrollment, the Clinical Trial Monitor (ISM/CTM) will visit the study site to determine the adequacy of facilities, review the protocol and data collection procedures and discuss the responsibilities of the investigator and other study site personnel.

During the study, the CTM will have regular site contacts, including conducting on-site visits to:
1. Confirm that the study is being performed according to the protocol, ICH-GCP and applicable regulations, data are being accurately recorded in the CRFs and that investigational product accountability is being performed.
2. Conduct source data verification
3. Confirm facilities remain acceptable
4. Provide information and support to the investigators
5. Evaluate study progress

Upon completion of the study the CTM will visit the study site to verify that all CRFs are completed and collected, all data queries have been resolved and filed, conduct final accountability, and verify all study site records are complete.

The PIs and relevant staff will be available at monitoring visits and agree to allocate sufficient time to the monitor to discuss any issues and address their resolution.

9.7.2. **Auditing.** The independent clinical monitoring process will be audited remotely by a study staff member from the sponsor's IRB office at CSU in Fort Collins, CO. The auditor will be supplied information from the CTM and study investigators via email. After the audit it will be determined by the sponsor if more auditing visits are required.

9.7.3. **Training.** The principal Investigators are responsible for the conduct of the study at the study sites, including delegation of specified study responsibilities, and training of study staff. The PIs will maintain a record of all individuals involved in the study (medical, nursing and other staff) and will ensure that all persons assisting with the trial receive the appropriate training about the protocol, the investigational product(s) and their trial-related duties and functions. This may include ICH-GCP training when deemed necessary. During the study, regular spot checks will be conducted to assess the performance of study site staff members and re-training provided where necessary.

9.7.4. **Quality assurance/control of laboratory tests.** Regular audits of laboratory procedures will be completed by experienced supervisors according to standard operating procedures. All malaria blood smears and homogenized/fixed stool samples will be read by two different microscopists; any significantly discordant results based on positive/negative results or difference in parasites above a defined threshold will be verified by a third expert microscopist. Similarly, mosquito identifications and age-grading assessments will be regularly cross-checked by at least two technicians during mosquito sample processing.

9.8. **Mitigation and Risk Reduction Plan.** This study is designed to mitigate and reduce the risk to patients. Individual aspects of this plan are:

- Prospective screening of patients (eg. pregnancy) prior to repeat MDAs in experimental arm villages.
- Weekly visits to all villages by trained nurses to enrolled households, which will document any ACD cohort AEs and passively reported AEs on patient CRFs.
- Ongoing physician access to the study site.
- Prompt AE reporting to the study clinician (Dr. Rouamba), and all investigators will determine relationship to the investigational drug.
- Reporting of SAEs possibly related to the study interventions to the sponsor within 48 hours of the investigators becoming aware of it (within 24 hours of the field nurse becoming aware of it)
- Review of the study design, AEs and SAEs by the Burkinabé ISM (also the CTM)
- Clinical monitoring by the Burkinabé ISM/CTM; s/he is familiar with ICH-GCP
- Remote auditing by the CSU IRB (sponsor)
- Quality control of laboratory tests

10. **Timeframe of the study.** The anticipated start time for enrollment is in April 2015.

Activity	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Protocol development	■	■										
IRB review		■	■									
Training staff			■	■								
Recruitment				■								
Enrollment				■	■							
Treatment Phase				■	■	■	■	■	■			
Post treatment follow-up									■			
Data Analysis				■	■	■	■	■	■	■	■	■
Manuscript Preparation							■	■	■	■	■	■

11. Ethical Considerations and Regulatory Approvals.

11.1. **Declaration of Helsinki.** The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996) (http://www.wma.net/en/30publications/10policies/b3/), the principles of ICH-GCP, and in accordance with all applicable regulatory requirements in Burkina Faso.

11.2. **Regulatory Approval and Trial Authorization.** Since the trial is conducted outside the USA, no authorization from an American regulator is required. The trial will be registered with La Direction générale de la pharmacie, du médicament et des laboratoires (DGPML) within the Burkina Faso MoH.

11.3. Research Ethics Approval.

11.3.1. **Review Process.** This protocol, the informed consent documents, and patient information sheets will be reviewed and approved by the IRB at CSU, the Comité d'Ethique d'IRSS.

11.3.2. **Protocol Amendments.** No change will be made to the approved protocol without the agreement of the sponsor.

If it is necessary for the protocol to be amended, the protocol amendment will be submitted to the primary ethics committee for approval before implementation. Any protocol amendments will be submitted to the primary ethics committees (CSU, IRSS) before implementation. Any change to the informed consent form must also be approved by the sponsor and the primary ethics committee in each country before the revised form is used.

The sponsor will distribute amendments to each principal investigator, who in turn is responsible for the distribution of these documents to the staff at his/her study site.

11.4. Informed Consent Procedures.

11.4.1. **Consent Procedures.** Community consent/assent (oral) will first be obtained by public meetings with local village chiefs and elders during the recruitment phase where the study will be explained to them. Following this, in the enrollment period, individual consent/assent (oral) through a public meeting with village heads-of-households will be obtained and at the end of the meeting written informed consent will be obtained from each head-of-household who chooses to have their family participate. Lastly, verbal, witnessed assent from each person in consented households will be obtained by going door-to-door to households (directly from adults, and informed assent will be obtained from children via their parents/guardians). Written, informed consent from each head-of-household will be in French, but also explained in the local language when necessary. The consent process shall be initiated at the time of enrollment into the study and shall continue throughout the patient's participation.

For illiterate participants, an independent witness will be present during the informed consent process and will sign the consent form as a witness, while the participant will be asked to indicate consent or assent by use of thumbprint. Any participant may withdraw their consent at any time throughout the course of the study, and this will be made clear in the informed consent process. All individuals will be informed that there is no requirement to join the study and that the standard medical care they might have through the CHWs and the CSPS will remain the same regardless of study enrollment.

11.4.2. **Consent forms.** There will be one information form, consisting of a printed information sheet to explain the purpose of the trial, what will happen, and the risks and benefits, all in simplified language. This will be given to the enrolled head-of-households. The consent forms for the head-of-household will explain the text of the information form in brief with a place for their signature/fingerprint if they provide consent for themselves and their family to participate, and below that will have a place for the signature of a witness, and the signature of the trial member who is consenting. The form will give the study investigators permission for performing study-related procedures in their household, including consenting to visits by CHWs and trial nurses to distribute MDAs, consenting to regular household visits by the nurses and entomological team, collecting all relevant clinical information from patients in their household and the collection of mosquitoes and biological samples.

The other consent forms (one for all other household adults, and one for all participants <18 years of age), plus the assent form for all participants between 12-18 years of age,

will gain patient consent (and assent for those between 12-18 years of age) to participate in the MDAs, to collect all relevant clinical information, and permission to collect biological samples (including stool samples in household children between 6-10 years of age). It will also gain their consent for regular monitoring of the ACD cohort patients in their household (children ≤ 5 year of age) by the study nurses for malaria episodes, and to collect biological samples including frequent fingerstick blood samples if warranted. Finally, it will gain consent for long-term storage of the blood for future studies as well as for genetic studies on the patient's blood sample related to malaria, LF, and other infectious pathogens, and to drug metabolism. These blood samples shall be stored as dried blood spots in filter papers and analyzed both in Burkina Faso at the IRSS and in the USA at CSU.

All consent forms will be translated into French.

11.5. Protection of Privacy and Confidentiality.

11.5.1. **Privacy.** Personal and medical information relating to research participants will be treated as confidential. The risk of disclosure will be minimized by secure storage of documents on password protected tablets and computers, and use of linked data by replacing personal identifiers with a unique study code to conceal the identity of the patient. The linked list will be destroyed 5 years following the publishing of the study results.

11.5.2. **Privacy of individual.** Tests for malaria and hemoglobin will be reported to the parent/guardian of the participant at point of care, to relevant study staff and where appropriate will be recorded in the patients' medical record book in addition to study CRFs.

11.5.3. **Confidentiality of data.** All information regarding the participants will remain confidential to the extent allowed by law. Unique numerical identifiers will be used for data entry. All screening forms and case report forms will be kept in a secured location with access limited to authorized study staff. Unique numerical identifiers will be used for the computer-based data entry and blood samples. Publications will contain only aggregate data. No identifying information will be included.

11.6. **Declaration of Interest.** None of the principal investigators have paid consultancies with the pharmaceutical companies who manufacture the study drugs, or other competing interests for the overall trial or in each study site.

11.7. **Access to source data/documents.** In addition to the ISM/CTM, authorized representatives of the sponsor, and the CSU IRB and Comite d'Ethique d'IRSS or regulatory authority may visit the study site to perform audits or inspections, including source data verification. The investigators agree to allow the sponsor, including the ISM/CTM, the CSU IRB and Comite d'Ethique d'IRSS direct access to source data and other relevant documents.

11.8. Risk and Benefits.

11.8.1. Risks to Study participants.

11.8.1.1. **Ivermectin.** Ivermectin (Merck Sharp & Dohme) has been shown to be well-tolerated and safe with the standard doses used in this study, including during pregnancy and during breast-feeding when the child is older than 1 week (see Section 4.7 "Safety of ivermectin in humans", page 16). The only confirmed related severe adverse events have been in individuals with *Loa loa* due to lysis of parasites, however *Loa loa* is not present in Burkina Faso, and the patients in the study villages will be questioned about whether they have traveled to countries where *Loa loa* is endemic. Repeated administrations of ivermectin using standard doses in intervals from days to months have been performed numerous times to both individuals and communities, with few reports of AEs or SAEs (Table 3).

11.8.1.2. **Albendazole.** Albendazole (GlaxoSmithKline) has been shown to be well-tolerated and safe within MDA campaigns when administered with ivermectin in the standard doses used

in this study. ALB will only be mass administered in the first MDA of this study along with IVM. While this administration will occur within the timeframe and context of this study, this MDA is scheduled regardless of the presence of this study, in all villages within the Sud-Ouest Administrative Region for LF and STH control and elimination efforts. SAEs are very rare and linked to the presence of *Loa loa* which is not present in Burkina Faso, and the patients in the study villages will be questioned about whether they have traveled to countries where *Loa loa* is endemic. AEs associated with this MDA combination regimen are usually mild and most often include headaches and abdominal cramps and/or diarrhea associated with the expulsion of killed helminths. Other than patient enrollment, sample collection and patient monitoring, MDA with ALB will be conducted by the CHWs associated the Burkina Faso MoH in a manner no different than that would be normally carried out in the study villages in 2015 if they were not enrolled in the study.

11.8.1.3. **Blood sampling by finger prick.** Blood sampling may be inconvenient to the participants, and may cause minor discomfort, fainting (vasovagal syncope), bruising and local infection if not conducted appropriately. The volume of blood collected from each participant will be not more than 1 mL each time. Well-trained clinicians and nurses or laboratory staff employed on the trial will perform blood-sampling. New and sterile disposable single-use lancets, alcohol wipes and cotton gauze will used for blood sample collection. Universal precaution measures for blood handling and disposal will be observed when performing the procedures and used lancets and other waste will be safely discarded immediately after use.

11.8.2. Benefits to study participants.

11.8.2.1. **Anticipated Benefits to study participants.** Ivermectin is an antihelminth drug and may be beneficial to patients who participate in the MDAs with helminth infections and other endoparasites and ectoparasites. Enrolled ACD cohort children will benefit from active surveillance for malaria episodes, and will receive antimalarial treatment free of charge upon having an episode. Patients will also be provided with a superior level of supervision and monitoring than they otherwise would have been.

11.8.2.2. **Benefit to the community.** This project is designed to generate the information required to determine whether repeated ivermectin MDAs during the rainy season can better control malaria transmission and disease than the current standard methods. As such the study helps support science and potential progress towards enhanced options in the arsenal of tools for malaria control and elimination. Subject to the finding, in the longer term, the ultimate beneficiaries of this research could be the populations living in malaria endemic parts of the world, whose quality of life, health, welfare and creative output will be enhanced by reduced malaria transmission.

11.9. Ancillary and Post-trial Care.

11.9.1. **Health care during the trial.** All care directly related to the proper and safe conduct of the trial, and the treatment of immediate adverse events suspected to be related to trial procedures will be provided free of charge by the study in the study health clinics/hospitals. The provision of ancillary care beyond that immediately required for conduct of the trial will not be covered by the trial.

11.9.2. **Trial Insurance.** The sponsor will take out trial insurance such that participants enrolled into the study are covered by indemnity for negligent harm and non-negligent harm associated with the protocol. This will include coverage for additional health care, compensation or damages whether awarded voluntarily by the Sponsor, or by claims pursued through the courts. The liability of the manufacturer of the trial drug ivermectin is limited to those claims arising from faulty manufacturing of the commercial product and not to any aspects of the conduct of the study.

11.9.3. **Post-trial care.** This is only a pilot study and the budget provided by the funder is not designed to fund post-study care or implementation of ivermectin as policy. However, the investigators work in close collaboration with local and international policy makers (e.g. WHO) and funders (e.g. BMGF) to ensure that policy makers and funders are informed early of germane research findings.

11.10. **Expenses Reimbursement and Incentives.** The study will provide payment for all prescribed antimalarials, study procedures, study-related visits and reasonable medical expenses that are incurred in study clinics or hospitals as a result of the study, including expenses for transport for any study related visits including unscheduled visits in between scheduled visits to study clinics. The study will not cover the costs of any non-malaria or non-study related events, including scheduled or unscheduled surgery or trauma-related events (e.g. accidents, burns etc.) if this is not deemed to be related to the study by the principal investigators or their representative.

Table 4. Reimbursement of expenses and incentives provided by the study

To Who	What	Approximate Amount
Regional Hospital/Medical Clinic	Study procedure costs and antimalarials and admission fees for any potential inpatients	~$20 (10,000 XOF) per patient per visit
Patient	Personal travel expenses for any study-related visits to the hospital/medical clinic	~$3 (1500 XOF) per round trip
Patient	Meal or reimbursement for breakfast, lunch or dinner for the participant and any accompanying if required to stay for more than half a day (lunch) or overnight (breakfast and dinner),	~$1 (500 XOF) per person per meal
Patient	New LLIN for each enrolled household	Free of charge from the CSPS/DRS

12. Dissemination and Application of the Results.

12.1. **Results dissemination and publication policy.** At the end of the trial, the results will first be disseminated to national policy makers, government departments, academics from local research institutions and universities, and professional bodies in Burkina Faso. Subject to the findings of the study and based on consensus emerging at these meetings, project partners in Burkina Faso and the USA will support national and international policy makers in deciding whether there is a role for ivermectin in malaria control.

Research results will also be disseminated to the global malaria research community, technical agencies, and international government bodies via peer reviewed journals and at international scientific fora, including the annual American Society of Tropical Medicine and Hygiene (ASTMH) meeting, and via meetings at WHO in Geneva comprised of leading scientists in the field of malaria.

We will also inform other international organizations and funders of large scale malaria control initiatives such as the USAID and the US President's Malaria Initiative (PMI) which aim to improve malaria at regional and local levels and are instrumental in supporting countries to implement malaria control policies in Africa.

12.2. **Impact.** New strategies for malaria control and elimination are critically needed. This protocol explores a research question that is currently highly discussed. In addition to the other known and planned studies occurring in other malaria-endemic countries, this protocol will seek to answer the question as to whether it will be feasible to introduce repeated ivermectin MDAs, timed during the rainy season, for added control of malaria in Burkina Faso. We expect the results of this protocol to stimulate interest and funding for larger, non-pilot trials, as well as to inform national malaria control programs in malaria-endemic countries, to inform WHO guidelines, to be published in high-profile peer-reviewed journals, to be presented at domestic and international conferences, and the data to be shared with other groups for meta-analysis.

12.3. **Training and capacity building.** Research capacity in research partner institutes in Burkina Faso, and reciprocally at CSU in the USA, will be enhanced by provision of training and mentorship for clinic and research staff. By running this trial, capacity in trial management will be enhanced at CSU and the IRSS. The research study will strengthen the clinical and technical skills of IRSS and Centre Muraz health workers in managing patients.

In addition, Burkinabé health workers from the Sud-Ouest Health Administrative region and the IRSS/Centre MURAZ will have the opportunity to learn new assays and techniques in mosquito sampling and age grading.

12.4. **Authorship and publications.** The study will have a publications committee consisting of the PIs (BF and RD). Potential authors include all professionals that have participated in the trial for a minimum of 3 months. Authorship of any presentations or publications arising from this study will also be governed by the principles for authorship criteria of the International Committee of Medical Journal Editors. Disputes regarding authorship will be settled by the publications committee, with further involvement of an independent chair designated by the sponsor if necessary. The manufacturer of the study medication will be provided with a draft of the manuscript but will have no role in review, data interpretation, or writing of the article.

12.5. **Data sharing statement.** The full protocol will be available on request to any interested professional and may be published in a peer reviewed journals or deposited in an online repository. Individual, de-identified participant data will be made available for meta-analyses after the data analysis is completed, with the understanding that results of the meta-analysis will not be published prior to the results of the individual trial without prior agreement of the investigators. No later than 5 years after the publication of the trial a fully de-identified data set will be available for sharing purposes. All requests for data for secondary analysis will be considered by the publication committee.

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14. Financial Aspects and Conflicts of Interest.

14.1. **Funding the trial.** Funding to conduct the trial is provided by a Grand Challenges Explorations grant from the Bill and Melinda Gates Foundation. CSU: the BMGF grant and a grant on ivermectin research from the U.S. National Institutes of Health is providing salary support for BF and HA, while SR is getting salary support only from the BMGF grant. The IRSS is providing salary support of RD, NR and the BMGF grant is supporting IRSS staff salaries, infrastructural support for the field station, transportation, centralized data management and laboratory materials. The Burkina Faso Ministry of Health is providing infrastructural support for the trial conduct in the Burkina Faso Sud-Ouest Health Administrative region.

The funder had no role in the design of this trial and will not have any during the execution, analysis, interpretation of the data, or decision to submit the results

14.2. **Provision of the study drugs.** Ivermectin and albendazole will provided free of charge from the Burkina Faso Ministry of Health from their stocks for NTD control to be used in their country. The study will provide copies of safety reports of SAEs and AEs to the drug manufacturers (expedited where required). The manufacturers will not be involved in the design of the trial.

15. Budget and Budget Justification.

See 16.3 “Appendix III for budget and budget justification”, pg. 46.

16. Appendices.

16.1. Appendix I. Role of Investigators.

16.1.1. **Protocol development: authors' contributions.** Brian Foy (BF) conceived the study. BF and Haoues Alout (HA) wrote the grant proposal that was funded by the BMGF. BF and HA drafted the initial clinical protocol, and Roch Dabire (RD), Noël Rouamba (JR) added revisions and input to construct the final draft. Sangeeta Rao (SR) edited the protocol and provided statistical expertise and verified the sample size calculations. Hannah Slater (HS) provided modeling data in support of the studies hypotheses. All investigators contributed to the refinement of the study protocol and approved the final version.

16.1.2. Role of Investigators.

Noël Rouamba (MD), is a physician working on malaria and NTDs at the IRSS and Centre MURAZ, based in Bobo Dioulasso, Burkina Faso. He will act as a co-Principle Investigator and trial coordinator. He will serve as the senior medical doctor on the study, overseeing clinical aspects.

Brian Foy (PhD), is an associate professor in the Arthropod-borne and Infectious Diseases Laboratory within the Department of Microbiology, Immunology and Pathology at CSU in the USA. He is a Principle Investigator and the grant holder and will carry overall responsibility for the coordination of the trial and for the linkages with the sponsor, funders and with international partners involved with similar transmission reduction research.

Roch Dabiré (PhD), is head of Infectious Disease research at the IRSS, based in Bobo Dioulasso, Burkina Faso. He is a Principle Investigator and will carry responsibility for the coordination of the field and laboratory teams based out of the IRSS and Centre MURAZ. He will also coordinate the linkages with the Burkina Faso MoH, the local village leaders and the regional medical authorities.

Haoues Alout (PhD), is a research scientist in the Arthropod-borne and Infectious Diseases Laboratory within the Department of Microbiology, Immunology and Pathology at CSU in the USA. He is a co-Principle Investigator, and together with the principal investigators, will share overall responsibility for the study, coordination of technicians and staff, and serve as the lead entomologist on the study.

16.1.3. Role of non-engaged collaborators.

Sangeeta Rao (PhD), is an assistant professor in the Department of Clinical Sciences at CSU in the USA. She is biostatistician and epidemiologist and will be the trial statistician/outcomes assessor who will be blinded to the treatment arms.

Roland Bougma (MD), is the coordinator of the LF control program (Le Programme Nationale d'Elimination Filariose Lymphatique) in the Burkina Faso MoH, based in Ouagadougou, Burkina Faso. He will act as the primary contact with the Burkina Faso Ministry of Health, coordinate procurement of the study drugs from the MoH NTD control program, and facilitate our collaboration with the DRS in the Sud-Ouest Region.

16.2. Appendix II: Terms of Reference Oversight Committees

16.2.1. Trial Management Group (TMG)

16.2.1.1. **Purpose.** The TMG is responsible for the administrative management and day to day running of the trial.

16.2.1.2. **Membership.** The TMC will be chaired by one of the Principal Investigators or Co-Investigators.

1. Principal Investigators
2. Co-Principal Investigators
3. Site clinicians
4. Trial Coordinator
5. Administrators
6. Others who are involved in the day to day running of the trial

16.2.1.3. Responsibilities.

- Study planning
- Organization of site visits by the ISM/CTM and supplying them data
- Provide risk report to regulators, manufacturer and ethics committees
- SAE/SAR/SUSAR reporting
- Responsible for trial master file
- Budget administration and contractual issues
- Advice for lead investigators
- Organization of central data management and sample collection

16.2.2. Independent Safety Monitor/Clinical Trial Monitor (ISM/CTM)

16.2.2.1. **Role.** The ISM/CTM is a person with experience in clinical trials and ICH-GCP regulations.

S/he shall review the data and the interim analysis, and monitor the trial documents and safety reports. They are independent and look at the trial from an ethical point of view of the participant safety, future patients and society in general. It is their responsibility to prevent patients being exposed to any excess risks by recommending for the trial suspension or termination early if the safety or efficacy results are sufficiently convincing. The trial statistician will be invited to liase with the ISM/CTM to help analyze the most current data from the trial. This will be blinded, unless the ISM/CTM specifically requests for an unblinded analysis.

16.2.2.2. **Responsibilities.** The ISM/CTM has the following defined responsibilities:

- They will consider the blinded or unblinded interim data from the trial and relevant data from other sources.
- They will consider any requests for unblinding and release of interim data and to recommend to the TMG on the importance of this.
- They will report to the TMG and recommend whether the trial should continue, the protocol be modified, or the trial be stopped.
- The will confirm that the study is being performed according to the protocol, ICH-GCP and applicable regulations, data are being accurately recorded in the CRFs and that investigational product accountability is being performed and confirm facilities remain acceptable

16.3. Appendix III. Budget and Budget Justification

16.3.1. Budget

Description	Cost (USD)
Personnel	$50,000
Laboratory supplies	$15,000
Entomology supplies	$5,000
Logistical supplies and support	$10,000
Transport	$10,000
Travel	$10,000
Total	$100,000

16.3.2. Budget Justification

Personnel $ 50,000

Key staff will be needed to collect vital study information. These include nurses, microscopists, laboratory technicians and entomology assistants. A portion of the PIs and co-PIs salaries are also contained in this part of the budget.

Laboratory supplies $ 15,000

Important laboratory procedures will be critical to realization of study objectives. These include microscopy, RDT tests, AL treatments, hemoglobin testing, stool analysis, and molecular analyses of blood samples. Laboratory consumables are also required for the day to day running of the laboratories.

Entomology supplies $ 5000

Mosquito capturing and processing is essential for the secondary objectives. Supplies include aspirators, batteries, CDC-light traps, tents, mosquito cages, microscopes, dissecting forceps, tubes, desiccant and disposables.

Logistical supplies and support $10,000

Data documentation and storage, and communication in the field will be essential. Supplies include cell phone, internet dongles and minute cards, tablets and printing services for CFRs and other documents, GPS devices and services, and programs for CRF and lab report generation.

Transport $ 10,000

Travel to the study villages by the study staff will be regular throughout the study period for all the activities, including participating the in the MDAs, sampling and clinical monitoring. Additionally, transport reimbursement will be given to study participants that need to attend clinic visits.

Travel $ 10,000

International travel for study investigators based abroad.

16.4. Appendix IV. SPIRIT (Standard Protocol Items. Recommendations for International Trials) 2013 Checklist.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Section/item	Item No.	Description	Addressed on page number
Administrative Information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,8,9
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1,8,9
	2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	19, 42, 46
Roles & Responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 8, 44
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	43
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	45
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	13-18, 19-20
	6b	Explanation for choice of comparators	20
Objectives	7	Specific objectives or hypotheses	18-19
Trial Design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	19-20
Methods: Participants, interventions and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	21
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	21
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	21-23
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	22-23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	23
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	24

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, 24-26
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	27
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	27
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	28
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	28, 36
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	28, 36
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	28, 36, 44
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	28,45
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	28, 36
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	28-29
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23, 29-30
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	29, 33
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	29-30
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	29-30
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	29-30
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.	30
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	30
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	31-32
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	33-34
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	35
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	35
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	36
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	36
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	36-37, 51-53
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	37, 42-43
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	37
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	38
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	39
	31b	Authorship eligibility guidelines and any intended use of professional writers	39
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	39
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	51-53
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	51-53

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17. Appendix V. Product Characteristics.

MECTIZAN® 3mg, tablet
(ivermectin, MSD)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet, you may need to read it again.
- If you have further questions, if you have a doubt, ask your doctor or your pharmacist for more information.

This medicine has been prescribed for you personnelly. You should not pass it on to others even if their symptoms are the same as yours. It may harm them.

1. DRUG IDENTIFICATION

a/ DENOMINATION

MECTIZAN® 3 mg, tablet

b/ QUALITATIVE AND QUANTITATIVE COMPOSITION

Ivermectin ..... 3,00 mg
For a tablet

Excipients: microcrystalline cellulose, pregelatinized corn starch, butylhydroxyanisol, anhydrous citric acid, magnesium stearate.

c/ PHARMACEUTICAL FORM

Tablet.

d/ PHARMACOTHERAPEUTIC CLASS

ANTHELMINTIC

e/ NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER AND RESPONSIBLE FOR PLACING THE DRUG ON THE MARKET

MSD France
34, avenue Léonard de Vinci
92400 Courbevoie
Medical Information : 01 80 46 40 40

f/ NAME AND ADDRESS OF THE MANUFACTURER

Merck Sharp & Dohme BV
Waarderweg 39
2031 BN Haarlem
Netherlands
or
Merck Sharp & Dohme-Chibret Laboratories
Route de Marsat
63200 Riom

2. IN WHICH CASE(S) SHOULD THIS DRUG BE USED?

This drug is an antiparasitic medication.

This drug is indicated:
- for the treatment of onchocerciasis (a disease due to the infection caused by a parasite: the filaria *Onchocerca volvulus*);
- for the treatment of microfilaremia in case of infection caused by *Wuchereria bancrofti* (lymphatic filariasis).

3. CAUTION!

a/ IN WHICH CASE(S) SHOULD THIS DRUG NOT BE USED?

This drug SHOULD NOT BE USED in case of history of allergic reactions to any component of this product.

IN CASE OF DOUBT, IT IS NECESSARY TO ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE.

b/ SPECIAL WARNINGS

In African areas where there are also cases of the human parasitic infection caused by *Loa loa*, it is advisable not to use this medication concomitantly with diethylcarbamazine (DEC) because it may result in increased risk of side effects which may sometimes be serious.

This medicine should only be used when the infestation is proven or highly suspected. It has no efficacy in prophylactic use of the disease (prevention treatment).

IN CASE OF DOUBT, IT IS NECESSARY TO ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE.

c/ PRECAUTION FOR USE

IN CASE OF DOUBT, IT IS NECESSARY TO ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE.

d/ INTERACTIONS WITH OTHER DRUGS AND OTHER INTERACTIONS

IN ORDER TO AVOID POSSIBLE INTERACTION BETWEEN SEVERAL MEDICATIONS, IT IS NECESSARY TO INFORM YOUR PHYSICIAN OR YOUR PHARMACIST IF YOU ARE TAKING ANY OTHER TREATMENT.

e/ PREGNANCY – BREAST FEEDING

Pregnancy:

If you are pregnant, ask your doctor for advice before taking MECTIZAN.

Breast-feeding:

If you are breast-feeding, tell your doctor. If necessary, prescription should be delayed until one week after the birth of the child.

AS A GENERAL RULE, IT IS RECOMMENDED DURING PREGNANCY AND BREAST-FEEDING TO ALWAYS ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE BEFORE USING ANY DRUG.

f/ DRIVING AND USING MACHINES

The effect of MECTIZAN on the ability to drive or use machines has not been studied. In some patients, possible side effects such as dizziness, somnolence, vertigo and tremor that may affect the ability to drive or operate machinery, are not excluded (See section Side effects).

4. HOW SHOULD THIS DRUG BE USED?

a/ DOSAGE

Treatment of onchocerciasis:
The recommended dosage in the treatment of onchocerciasis is a single oral dose of 150 µg/kg of body weight.
For the treatment of individual patients, retreatment may be considered after a 3-months interval.
In mass distribution campaigns for onchocerciasis, the most commonly used dose interval is 12 months. However, in some areas it may be preferable to repeat the administration every 6 months according to the prevalence of the microfilarial density.

For guidance, the dose as established by the patient's weight is:

BODY WEIGHT (kg)	DOSE (Number of 3 mg tablets)
15 to 25	one
26 to 44	two
45 to 64	three
65 to 84	four

Alternatively, and if no scales are available, the dose of ivermectin for use in mass distribution campaigns may be established by the patient's height, as follows:

HEIGHT (cm)	DOSE (Number of 3 mg tablets)
90 to 119	one
120 to 140	two
141 to 158	three
> 158	four

Treatment of microfilaremia caused by *Wuchereria bancrofti* (lymphatic filariasis):
The recommended dosage for mass therapy campaigns of microfilaremia caused by *Wuchereria bancrofti* (lymphatic filariasis) is a single oral dose of 150 to 200 µg of ivermectin per kilogram of body weight once every 6 months.

In endemic areas where treatment can only be administered once every 12 months, the recommended dosage is 300 to 400 µg per kilogram of body weight to maintain adequate suppression of microfilaremia in treated subjects.

For guidance, the dose, as established by the patient's weight, is:

BODY WEIGHT (kg)	DOSE when given once every 6 months (Number of 3 mg tablets)	DOSE when given once every 12 months (Number of 3 mg tablets)
15 to 25	One	two
26 to 44	Two	four
45 to 64	Three	six
65 to 84	Four	eight

Alternatively, and if no scales are available, the dosage for use in mass therapy campaigns may be established by the patient's height as follows:

HEIGHT (cm)	DOSE when given once every 6 months (Number of 3 mg tablets)	DOSE when given once every 12 months (Number of 3 mg tablets)
90 to 119	one	two
120 to 140	two	four
141 to 158	three	six
> 158	four	eight

IN ALL CASES, FOLLOW STRICTLY YOUR DOCTOR'S PRESCRIPTION.

b/ METHOD AND ROUTE OF ADMINISTRATION

Oral route.
For children less than 6 years of age, tablets should be crushed before swallowing.
Treatment is one single oral dose taken with water on an empty stomach.
The dose may be taken at any time of the day but no food should be taken within two hours before or after administration, as the influence of food on absorption is unknown.

c/ FREQUENCY AND TIME WHEN THE DRUG SHOULD BE ADMINISTERED

This medicine is administred in one single dose.

d/ WHAT SHOULD YOU DO IN CASE OF OVERDOSE?

Consult a doctor.

5. UNDESIRABLE AND TROUBLESOME SIDE EFFECTS

AS WITH ANY ACTIVE INGREDIENT, THIS MEDICATION CAN, IN SOME PATIENTS, CAUSE MORE OR LESS TROUBLESOME EFFECTS:

Most often side effects are mild and transient but they may be higher in patients infested with several parasites particularly in case of infestation with *Loa loa*.

Following administration of ivermectin in patients infested with Onchocerca volvulus : itching, redness of the eyes, joint pains, fever, nausea, vomiting, swelling of lymph nodes, diarrhea, hypotension, vertigo, accelerated heart rate, fatigue, rash, headache, visual disturbances, may occur.

Following administration of ivermectin in patients infested with lymphatic filariasis, have been reported: fever, headache, asthenia, feeling of weakness, muscle and joint pains, body pains, digestive disorders such as loss of appetite, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, sore throat, hypotension when getting up, chills, vertigo, sweating, testicular pain or feeling of discomfort.

In patients also heavily infested with the filaria *Loa loa*, serious brain disorders have been reported exceptionally following administration of ivermectin.

Cases of expulsion of adult ascaris worms have been reported following administration of ivermectin.

Very rarely, serious skin reactions have been reported.

INFORM YOUR DOCTOR OR PHARMACIST ABOUT ANY UNDESIRABLE AND TROUBLESOME EFFECT NOT LISTED IN THIS PACKAGE INSERT.

6. CONSERVATION

a/ DO NOT EXCEED THE LIMIT DATE OF USE CLEARLY MENTIONED ON THE PACKAGING

b/ SPECIAL STORAGE PRECAUTIONS

18. Appendix VII. Participant Information Sheets and Informed Consent Forms.
    18.1. Informed consent head-of-household information sheet: English

Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)

Information Sheet

Purpose of research study

People in Burkina Faso get lymphatic filariasis (LF), which causes swollen legs and other sickness. A worm parasite causes the swollen leg sickness, and it is transmitted by mosquitoes. In Burkina Faso, health districts distribute to the population the drugs ivermectin and albendazole to kill this worm parasite. People in Burkina Faso also get malaria, which is caused by a different parasite but which is transmitted by the same mosquitoes. We have found that ivermectin also kills the mosquitoes that spread both of these parasites. We want to test if giving ivermectin more often during the rainy season may stop malaria and lymphatic filariasis from spreading by mosquitoes to other people in the village, especially to the children who can get the most sick from malaria. This is why the Institute de Recherche en Sciences de la Santé (IRSS), the Centre MURAZ (CM), the Burkina Faso Ministry of Health (MoH) and Colorado State University (CSU) are performing this research study.

What we will do

Eight villages of the District Sanitaire of Diébougou have been selected to be part of this study, they are Limania, Kpokologo, Moulé, Tiedia, Djinkargou, Djan-gougourgou, Tempé-gougougré and Kolépar. They have been split in two groups: one experimental and one control with four villages in each. The chiefs and the elders of your village and the others gave their agreement to participate in this study. They were involved in a public draw to determine in which group their village will be.

The study will occur during the rainy season and will have several phases:

1. The first phase consists of enrolling persons that consented to participate. We will ask questions about person information and medical history. Also we will take a sample of blood on the finger (1ml) on selected people and fecal samples on selected children between 6 to 10. These samples will be taken on people living in houses the center of the village.
2. The second phase will start with the mass drug administration of ivermectin and albendazole in the eight villages by the health district of Diebougou. After treatement, active case detection of malaria cases on the children under 5 years old will start. A nurse will visit each child under 5 twice a week. The nurse will check for fever. If one child has fever, the nurse will take a small blood sample to perform a rapid diagnostic test. If the test is positive and there is no other problem (uncomplicated malaria), the nurse will give an anti-malaria treatment according to national guidelines (Coartem^{R}). If the child presents other symptoms he will be referred to the CSPS. During this phase, a team of IRSS/Centre Muraz will come to collect mosquitoes in the houses located in the center of the village. In the villages of the experimental group, the mass drug administration of ivermectin only will repeated five times at three weeks interval. Ivermectin is safe and well tolerated but if you experience adverse events, you need inform the nurse as well as the ASC and you will be referred to the CSPS.
3. The last phase will happen during the three weeks after the last treatment is given to the population. Active case detection and passive monitoring of adverse events will continue. Also we will take a sample of blood on the finger (1ml) on selected people and fecal samples on selected children between 6 to 10. These samples will be taken on people living in houses the center of the village.

Potential risks

The drug ivermectin is well tolerated and safe in single doses. Few side effects have been already described such as:

- fatigue
- Abdominal pain
- loss of appetite
- constipation
- diarrhea
- nausea
- vomiting
- dizziness
- Urticaria, rashes, pruritis

We are not sure what risks may be present in having multiple doses, but we will be monitoring your household closely. Nurses will check on you twice a week. In addition, we will give you a telephone number to call if you are concerned at any time. Ivermectin can give problems to people with *Loa loa*. However, *Loa loa* is not found in Burkina Faso. If you or anyone of your household have travelled to a country with *Loa loa,* you may not participate in the study.

Privacy and confidentiality

Information about yourself and your household will be kept confidential to the maximum extent allowable by law. The data we collect will be stored securely in locked cabinets and on password-protected computers. Only members of the study staff will review the records with the name of you or your family member. We will use the information you give to us only for research. The information collected will be shared with other people, but your name or members of your household will not appear on any reports. At the end of the study, we will remove all names from the data so that no one can identify your or your family's information or your blood sample.

Your rights to participate, say no, or withdraw

We are asking if you and your family are willing to participate in this study. You are free to choose to have your household be part of this study. If you agree, we will ask each member of your family individually to participate. You have the right to refuse. If you do not want your household to go on with this study, you can stop at any time without any prejudice.

Consent for long-term storage of blood samples for future studies

We are asking people who join this study if they will let the researchers' use their blood sample for future studies. These future studies may help find new ways to prevent malaria. If you say yes, we will store the blood we take from you and members of your household with a unique code and not any names in laboratories in Burkina Faso and the US. We may share the test results with researchers at other organizations but we will not give them any names, addresses, or any information that could identify you or your household. After the study period has ended, we will remove any means to link the sample to you and your household, and we will not be able to find the samples connected to your household. If you do not wish to have your blood stored, you and your household may still participate in our study. You and your family will still be provided ivermectin and your children regularly examined for malaria. If they have malaria, we will still treat them.

Costs and compensation for being in the study

The participation is based on volunteering, no one will be paid for his/her participation. Transport reimbursement for sick visits to the health center will be provided to you as per IRSS guidelines.

Contact information for questions or concerns

If you have any questions about this study, you can contact the clinical team in the field, through **Dr Gafar Abdoul Victor COULIDIATY at 70566623.**

You can also contact Dr. Roch Dabire at the IRSS, 399 Ave de la Liberté, Bobo Dioulasso, Houet, Burkina Faso, 10400-000, at 70 73 90 69.

You can also contact the Comité d'éthique of IRSS (CEIRES), or if you want to talk about the study with someone who is not directly involved with this study, please contact **Dr PARE/TOE Léa Mélanie au 70759361.**

If you do not have access to a telephone, or you do not know how to read and write, this will not stop you from participating in this study. You may ask for contact information from the nearest health facility if you wish to talk with one of the listed individuals to raise any concerns.

If you are sick, do not call these numbers. Please go to the nearest health facility.

Thank you very much for your time. If you agree to take part in this study, we will ask you to sign this form.

18.2. Consent documents: English

Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)

Head-of-Household Consent Statement

I have been invited to give approval for my family to participate in the study named **"Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)"**. The objectives and the protocol were provided through the information sheet and have been explained to me.
I agree to have my household take part in the study. I understand that my family and I are free to choose to participate in this study and that refusing will have no effect on my household or me. Every member of my family can ask question whenever they want.

I agree to provide blood and fecal samples that will be sent to IRSS/Centre Muraz in Burkina Faso or to CSU in the USA for detecting malaria and other parasites. I agree to have these blood samples stored for later analysis.

I give my approval to IRSS/Centre MURAZ, Ministry of Health of Burkina Faso and CSU to access and consult the medical history of my family and me. I agree to let those information to be shared with researchers at other organizations if no one could identifiy my family and me. I have been informed that all Information about myself and my household will be kept confidential and that any names, addresses, or any information that could identify my family and me will not be released.

If you have any questions about this study, you can contact the clinical team in the field, through **Dr Gafar Abdoul Victor COULIDIATY at 70566623.** You can also contact Dr. Roch Dabire at the IRSS, 399 Ave de la Liberté, Bobo Dioulasso, Houet, Burkina Faso, 10400-000, at 70 73 90 69. You can also contact the Comité d'éthique of IRSS (CEIRES), or if you want to talk about the study with someone who is not directly involved with this study, please contact **Dr PARE/TOE Léa Mélanie au 70759361.**

Concession number	

	Name	Signature or fingerprint	Date
Head of Household			
Witness			
Study staff			

Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)

Adult consent form

This form is for all family member above the age of 18 years old for which the approval from head of household has been obtained.

I have been invited to participate in the study named **"Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)"**. The objectives and the protocol were provided through the information sheet and have been explained to me.

I agree as an adult family member and after approval of the head of household to participate voluntarily in this study and to follow the protocol. I particularly agree to :

1. Provide a blood sample to detect malaria parasites and other parasites at IRSS in Burkina Faso or at CSU in the USA.

2. Disclose my relevant medical history to IRSS/Centre MURAZ, Ministry of Health of Burkina Faso and CSU I agree to let those information to be shared with researchers at other organizations if no one could identifiy me.

I have been informed that I can stop at any time without any prejudice and without losing the benefit related to this study.

Concession number			
	Name	Signature or fingerprint	Date
Head of Household			
Witness			
Study staff			

Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)

Child consent form

This form concerns all family member under the age of 18 years old for which the approval from head of household has been obtained. It has to be signed by the head of household.

My child/nephew/grand-child/…… (Name) has been requested to participate in the study named : named **"Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)"**. The objectives and the protocol were provided through the information sheet and have been explained to me.

I agree as the head of household that my child/nephew/grand-child will participate voluntarily in this study and will follow the protocol. I particularly agree to :

1. Provide a blood sample to detect malaria parasites and other parasites at IRSS in Burkina Faso or at CSU in the USA.

2. Disclose my relevant medical history to IRSS/Centre MURAZ, Ministry of Health of Burkina Faso and CSU I agree to let those information to be shared with researchers at other organizations if no one could identifiy me.

I have been informed that child/nephew/grand-child can stop at any time without any prejudice and without losing the benefit related to this study.

Concession number			
	Name	Signature or fingerprint	Date
Participant			
Person giving the consent for the child			
Witness			
Study staff			

Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)

Assent form

This form is for all family members between the age of 12 to 18 years old for which the approval from the head of household has been obtained.

I have been invited to participate in the study named **"Repeat ivermectin mass drug administrations for control of malaria: a pilot safety and efficacy study (RIMDAMAL)"**. The objectives and the protocol were provided through the information sheet and have been explained to me.

I agree as an adult family member and after approval of the head of household to participate voluntarily in this study and to follow the protocol. I particularly agree to :

1. Provide a blood sample to detect malaria parasites and other parasites at IRSS in Burkina Faso or at CSU in the USA.

2. Disclose my relevant medical history to IRSS/Centre MURAZ, Ministry of Health of Burkina Faso and CSU I agree to let those information to be shared with researchers at other organizations if no one could identify me.

I have been informed that I can stop at any time without any prejudice and without losing the benefit related to this study.

Concession number			
	Name	Signature or fingerprint	Date
Participant			
Person giving the consent for the child			
Witness			
Study staff			

19. Appendix VIII. Guidelines for study nurses managing AEs and SAEs following MDA that are possibly related to the study treatment.

19.1. These guidelines come from the WHO 2011 publication, 'Assuring Safety of Preventative Chemotherapy Interventions for the Control of Neglected Tropical Diseases: Practical Advice for National Programme Managers on the Prevention, Detection and Management of Serious Adverse Events.' and 'A Handbook for Managing Adverse Events Following Mass Drug Administration (AEs-f-MDA) and Serious Adverse Events (SAEs)', published in August of 2014 by USAID, Envision, RTI International, and the Task Force for Global Health.

19.1.1. Treating patients at home or in the CSPS

- Obtain clinical history including past history and medications used.
- Make rapid clinical assessment. Record and monitor temperature, pulse rate, blood pressure and respiratory rate. Consult with the attending or study physician if possible.
- Explain to the patient that the adverse event is likely not a reaction to the medicine itself, but due to the killing of the parasite by the medicine. Emphasize that it is a sign that the medicine is working and is needed

19.1.1.1. Abdominal pain, vomiting diarrhea

- Put patient at rest, protected from excessive temperature, noise and light.
- Use traditional remedies (e.g. sour fruit juices), if available, to manage nausea and vomiting. Make sure patient can drink water or fruit juices.
- Watch for possible signs of dehydration such as thirst, dry skin, dark colored urine, dry mouth, fatigue, and weakness.
- Administer oral/intravenous fluid if necessary.
- Give antispasmodics and antiemetic, if necessary.

19.1.1.2. Fever, headache, aches in other parts of the body, pain in the joints or inflammation (usually in the inguinal area or scrotum)

- Advise the patient to rest
- Apply cold compress in the affected area when there is localized inflammation.
- Give paracetamol tablets. The recommended doses are:
  - Children 1-5 years: 125-250mg;
  - Children 6-12 years: 250-500mg;
  - from 12 years old: 500mg-1g
  - (these doses can be repeated after 4-6 hours if necessary)

19.1.1.3. Dizziness

- Advise the patient to rest.
- Check the blood pressure to rule out postural hypotension.
- Prop the head up with pillows when in bed to reduce the likelihood of orthostatic hypotension when getting up. Advise the patient to get up slowly from a sitting or lying position.

19.1.1.4. Malaise (feeling unwell), feeling sleepy, tired, weak

- Advise the patient to rest.
- Put patient at rest, protected from excessive temperature, noise and light.

19.1.1.5. Photophobia

- Protect the patient's eyes from light.

19.1.1.6. Urticaria, rashes, pruritis

- Assess the skin signs and symptoms. Be aware that they could be the earliest signs of conditions (e.g. Stevens Johnson Syndrome or Toxic Epidermal Necrolysis) which could be very serious and require rapid response. If Stevens Johnson Syndrome or

Toxic Epidermal Necrolysis are suspected, refer patient to the nearest hospital immediately.

- Give antihistamines. The recommended doses are:
  - Chlorphenamine tablets:
    - children 2-5 years: 1mg;
    - children 6-12 years: 2mg;
    - from 12 years old: 4mg
    - (can be repeated after 4-6 hours if necessary)
  - Promethazine tablets:
    - children 2-5 years: 5-15mg/day in 2 doses;
    - children 6-12 years: 10-25mg/day in 2 doses;
    - from 12 years old: 10-20mg up to 3 times a day

19.1.1.7. Wheezing (occurring in a person that has no history of asthma or other respiratory disease)

- Make sure the administered tablet is not choking the patient.
- Give antihistamines (see dosage schedule above).
- If symptoms are not controlled or worsen, refer patient to appropriate health facility.