

Clinical Trial Protocol

The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against Lymphatic Filariasis and Onchocerciasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

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Trial Design:	Randomized, controlled, parallel-group, open-label, phase II pilot trial
Trial Short Title:	The efficacy of Rifampicin plus albendazole against Lymphatic filariasis and Onchocerciasis
Trial Acronym:	ASTAWOL
Protocol identifying number	TMA2018SF-2451
PACTR Registration Number	PACTR202009704006025
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Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

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Protocol Approval Signatures

With our signatures, we confirm that we are familiar with and understand the protocol and will comply with the principles of Good Clinical Practice (GCP) as determined by the Food and Drugs Authority (Ghana) in the conduct of the trial.

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18/02/2022
Date


Signature

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18/02/2022
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ABBREVIATIONS

AE	Adverse Event
AR	Adverse (Drug) Reaction
ALT	Alanine transaminase
AST	Aspartate Transaminase
ALB	Albendazole
CA	Competent Authority
CDAD	<i>Clostridium difficile</i> Associated Diarrhoea
CFA	Circulating Filarial Antigen
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DEC	Diethylcarbamazine
DOT	Daily Observed Treatment
dpi	Days Post Infection
EC	Ethics Committee
ERC	Ethics Review Committee
eGFR	Estimated Glomerular filtration rate
FDS	Filarial Dance Sign
FPFV	First Subject First Visit
FTS	Filarial Test Strip
GCP	Good Clinical Practice
GHS	Ghana Health Service
γGT	Gamma-glutamyl transferase
Hb	Haemoglobin
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IDA	Individual Drug Administration
IMMIP	Institute for Medical Microbiology, Immunology and Parasitology
IMP	Investigational Medicinal Product
ISF	Trial Specific Investigator Site File

ITT	Intention to Treat
IVM	Ivermectin
KCCR	Kumasi Centre for Collaborative Research in Tropical Medicine
KNUST	Kwame Nkrumah University of Science and Technology
LF	Lymphatic Filariasis
LPLV	Last Subject Last Visit
MDA	Mass Drug Administration
MF	Microfilaria
NTD	Neglected Tropical Disease
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PP	Per Protocol
RIF	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDP	Sponsor Delegated Person
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
UAR	Unexpected Adverse Reaction

Trial Acronym: ASTAWOL

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Trial registration: PACTR202009704006025

1.0 TRIAL ADMINISTRATION STRUCTURE

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Local hospital/ laboratory	<p>War Memorial Hospital</p> <p>Navrongo</p> <p>Upper East Region – Ghana</p> <p>Sefwi Wiawso Municipal Hospital</p> <p>Sefwi</p> <p>Western North Region – Ghana</p> <p>Nana Hima Dekyi Government Hospital</p> <p>Dixcove</p> <p>Western Region – Ghana</p> <p>Axim Government Hospital</p> <p>Axim</p> <p>Western Region – Ghana</p> <p>Essiama Health Center</p> <p>Essiama</p> <p>Western Region – Ghana</p>
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CLINICAL TRIAL SYNOPSIS

Clinical trial title	The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis (LF) and Onchocerciasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.
Phase of trial	Phase II
Trial short title	The efficacy of Rifampicin plus Albendazole against Lymphatic filariasis and Onchocerciasis.
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Trial registration	PACTR202009704006025
Health Conditions	Lymphatic filariasis and Onchocerciasis
Interventions	<p>The following interventions will be compared for both lymphatic filariasis and onchocerciasis trials:</p> <p>Treatment A: Rifampicin 35mg/kg/d plus Albendazole 400mg/d for 7 days</p> <p>Treatment B: Rifampicin 35mg/kg/d plus Albendazole 400mg/d for 14 days</p> <p>Treatment C: Albendazole 400mg/d for 14 days</p> <p>Treatment D: no treatment, except MDA (nodulectomy additionally for the Onchocerciasis trial)</p> <p>All participants (experimental and control groups) will be treated with the standard MDA (mass drug administration) dosage at 6 and 18months' follow-ups after treatment onset. i.e.:</p> <p>Lymphatic filariasis: Ivermectin (Mectizan®/Merck 150 µg/kg orally) plus Albendazole (400mg/d); 6 and 18 months' follow-up and</p> <p>Onchocerciasis: a single dose of Ivermectin 150 µg/kg orally; 6 and 18 months' follow-up</p>

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Investigational medicinal product, Dose and Mode of Application	<p>Experimental (Treatment A and B):</p> <p>1. Trade Name: Rifadin®</p> <p>Substance: Rifampicin®</p> <p>Manufacturer: Sanofi-Aventis</p> <p>Dose: 35mg/kg/day (adapted to body weight)</p> <p>Mode of application: orally</p> <p>Duration of treatment:</p> <p>Treatment A): 7 days</p> <p>Treatment B): 14 days</p> <p>Rifampicin has already been approved for the treatment of tuberculosis and registered in Ghana.</p> <p>2. Trade Name: Zentel®</p> <p>Substance: Albendazole®</p> <p>Manufacturer: Glaxosmithkline</p> <p>Dose: 400mg/day</p> <p>Mode of application: orally</p> <p>Duration of treatment:</p> <p>Treatment A): 7 days</p> <p>Treatment B): 14 days</p> <p>Treatment C): 14 days</p> <p>Albendazole (Zentel®) is an approved and registered drug in Ghana.</p>
Control intervention	<p>Treatment D: No treatment except MDA (nodulectomy for the Onchocerciasis trial)</p>
Trial Population	<p>Healthy adults (18-55 years) with circulating filarial antigen (CFA), with or without worm nests, and with or without microfilariae for Lymphatic filariasis (LF) study, microfilariae-positive for the Onchocerciasis trial (MF+)</p>
Trial Design	<p>Method of allocation: randomized (Blockwise)</p> <p>Masking: open label (patient, caregiver), person responsible for PCR and other</p>

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	<p>laboratory assessment (outcome assessors) will be blinded to treatment assignment</p> <p>Control: standard treatment controlled</p> <p>Assignment: parallel</p> <p>Purpose: Efficacy</p>
Rationale of the trial	<p>The current therapeutic strategy relies on annual mass drug administration (MDA). A major problem with the current MDA, only given twice a year (Ivermectin (IVM) + Albendazole (ALB) or diethylcarbamazine (DEC) +ALB) is that while IVM and DEC efficiently kill microfilariae (MF), and ALB reducing embryogenesis at least in LF, they have limited or no efficacy against adult worms and do not permanently stop MF production.</p> <p>In addition, MDA (IVM + ALB or DEC +ALB) cannot easily be undertaken in regions endemic for <i>Loa loa</i> (primarily in Central Africa) and these places are estimated to cover at least 20% of onchocerciasis-endemic areas. This is because microfilaricidal drugs also kill <i>Loa loa</i> microfilariae and, depending on their number/load, this may elicit loiasis-specific adverse reactions (<i>Loa loa</i> encephalopathy), leading to severe neurological disorders or death. Thus, there is an urgent need for a macrofilaricide, targeting adult worms that can be used for LF and onchocerciasis, particularly in problem areas, such as those with emerging ivermectin resistance or <i>Loa loa</i> co-endemicity [1].</p> <p>Rifampicin (RIF) has been shown to exhibit superior anti- <i>Wolbachia</i> potency in vitro and in vivo in LF and onchocerciasis models compared with the tetracycline class [2-4]. However, these observations have not been translated into superior efficacy in clinical trials at the “standard” 10 mg/kg dose for 2 or 4 weeks to patients with onchocerciasis or LF compared to doxycycline (200mg for 4weeks). This discrepancy has been explained by Liverpool researchers (LSTM) based on RIF Pharmacokinetics and drug exposures recorded in preclinical models compared with humans. They have identified that a minimum dosage of RIF bioequivalent to 30–40 mg/kg in humans is required to deplete <i>Wolbachia</i> beyond the 90% threshold predictive of clinical cure [4, 5, 6]. Reassuringly, fourfold dose elevations of RIF have recently been identified as safe when delivered for periods of 1 month</p>

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	<p>[7] in patients with TB, suggesting that RIF at a high dose could be deployed as a short-course macrofilaricidal drug for human use. The global challenge is to develop a macrofilaricidal treatment that can be delivered in 10 days or less. In a preclinical study, a combination of RIF and ALB confirmed substantial synergy between ALB and rifamycin class of anti- <i>Wolbachia</i> drugs. This synergy leads to long-term sterilizing effects and reduced treatment courses to 7 days. Combining high dose RIF with ALB in a 7-day treatment mediated an accelerated macrofilaricidal effect as well as significantly improving <i>Wolbachia</i> depletion beyond the 90% threshold in surviving adult female filariae, predictive of long-term asymbiotic macrofilaricidal activity [8].</p>
Trial Objectives	<p><u>Primary Objectives:</u></p> <ul style="list-style-type: none"> - To show efficacy (reduction in CFA levels) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and ‘no treatment’ (other than Ivermectin) against lymphatic filariasis using Filarial Test Strip (FTS) method. - To show efficacy (depletion of <i>Wolbachia</i> and interruption of embryogenesis in female adult worms) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and no treatment (other than Ivermectin) against onchocerciasis using the PCR and immunohistology methods. <p><u>Secondary Objectives:</u></p> <p>Lymphatic filariasis</p> <ul style="list-style-type: none"> - To show efficacy (reduction in CFA levels) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and ‘no treatment’ (other than Ivermectin) against lymphatic filariasis using Og4C3 antigen test. - To show macrofilaricidal efficacy of the combination of Rifampicin (RIF) plus Albendazole (ALB) compared to treatment with Albendazole only and “no treatment” using circulating filarial antigen (CFA) with or without ultrasonography examinations.

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	<ul style="list-style-type: none"> - To analyse the safety profile of the combination of RIF plus ALB in the treatment of lymphatic filariasis. - To select the best therapy strategy and dosing regimen with regard to safety and efficacy. <p>Onchocerciasis</p> <ul style="list-style-type: none"> - To show macrofilaricidal efficacy of the combination of Rifampicin (RIF) plus Albendazole (ALB) compared to treatment with ALB only and ‘no treatment’ against onchocerciasis using the PCR and immunohistology methods. • To show <i>Wolbachia</i> depletion efficacy of the combination of Rifampicin (RIF) plus Albendazole (ALB) compared to treatment with ALB only and ‘no treatment’ against onchocerciasis using the PCR and immunohistology methods. • To analyze the effect of the combination of RIF plus ALB on microfilariae (MF) in the skin. • To analyze the safety profile of the combination of RIF plus ALB in the treatment of onchocerciasis. - To select the best therapy strategy and dosing regimen with regard to safety and efficacy.
Trial Endpoints	<p><u>Primary Endpoints (Lymphatic filariasis trial):</u></p> <p>To determine the:</p> <ul style="list-style-type: none"> - The modulation (decline) in CFA levels as a measure of the presence of adult worms assessed by Alere filarial antigen test strips at 18 months after treatment onset (where day 0 is start of drug administration). <p><u>Key Secondary Endpoints (Lymphatic filariasis trial):</u></p> <p>To determine the:</p> <ul style="list-style-type: none"> - Reduction in CFA levels (antigen units) as a measure of the presence of adult worms assessed by the Og4C3 antigen test at 4, 12 and 18 months after treatment onset (where day 0 is start of drug administration).

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	<ul style="list-style-type: none"> - Absence or reduction of filarial dance sign (FDS) detected by scrotal ultrasound 4, 12 and 18 months after treatment onset. - Adverse events (AEs) as well as serious adverse events (SAEs) in response to the different treatments will be assessed and described in the scope of the daily observed treatment (DOT). <p>If SAEs occur, the subject will immediately be referred to the nearest district hospital where medical treatment will be provided. SAEs will be reported to the institutional review boards per guidelines and timelines (see section 10).</p> <p><u>Primary Endpoints (Onchocerciasis trial):</u></p> <p>To determine the:</p> <ul style="list-style-type: none"> - Proportion of dead adult worms and MF assessed by immunohistology 20 months after treatment onset (where day 0 is start of drug administration). - Absence of <i>Wolbachia</i> endobacteria in adult female worms assessed by immunohistology 20 months after treatment onset - embryogenesis in female worms by histology 20 months after treatment onset <p><u>Key Secondary Endpoints (Onchocerciasis trial):</u></p> <ul style="list-style-type: none"> - Determination of number of nodules (onchocercomata) with free living microfilariae assessed by histology 20 months after treatment onset - Normal embryos - Degenerated embryos - no embryos (oocytes only or uterus empty) - Assessment of number of live/ dead worms (macrofilaricidal activity) through histology 20 months after treatment onset - Insemination of female worms assessed by histology 20 months after treatment onset - Absence of <i>Wolbachia</i> bacteria (as a non-quantitative parameter) in adult worms assessed by immunohistology (using antisera against <i>Wolbachia</i> surface protein) as described for our previous trials [9] 20 months after treatment
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	<ul style="list-style-type: none"> - Reduction of <i>Wolbachia</i> bacteria in adult worms assessed by immunohistology 20 months after treatment onset - Reduction of <i>Wolbachia</i> bacteria in adult worms assessed by polymerase chain reaction (PCR) 20 months after treatment onset - Reduction of <i>Wolbachia</i> bacteria in MF assessed by polymerase chain reaction (PCR) 4, 12 and 20 months after treatment onset - Microfilarial load in the skin measured after 4, 12 and 20 months after treatment (but before ivermectin administration), compared to pre-treatment values. - Proportion of study participants with absence of microfilariae in the skin, assessed 4, 12 and 20 months after treatment (but before ivermectin administration), compared to pre-treatment. - Onchocerciasis skin disease after 4, 12 and 20 months, compared to pre-treatment assessment. - Parasite-specific immunoglobulin subclasses and cytokine responses after 4, 12 and 20 months, compared to pre-treatment values. - Adverse events (AEs) as well as Serious Adverse Events (SAEs) in response to the different treatments will be assessed and described in the scope of the daily observed treatment (DOT). <p>For all endpoints: Treatment A, B and C will first be compared to Treatment D and secondly Treatment A and B will be compared to Treatment C. In a last step Treatments, A and B could be compared to each other.</p>
Subject Number	<p>To be assessed for eligibility: n ≈2400 (Lymphatic Filariasis)</p> <p>To be assessed for eligibility: n ≈1900 (Onchocerciasis)</p> <p>To be allocated to (Lymphatic filariasis and onchocerciasis) each trial (after meeting inclusion criteria): n = 120 (n = 30 per intervention group)</p> <p>To be analysed: n ≈ 95 in each trial (calculating a drop-out rate of 30% per group)</p>

<p>Inclusion Criteria</p>	<p>- Lymphatic filariasis</p> <p>Participants will only be included in the study if they meet all of the following criteria:</p> <ul style="list-style-type: none"> • Willingness to participate in the study by signing the Informed Consent Form (ICF) as participation in study is voluntary • 18-55 years in order to enroll adults capable of making an informed decision and with less health conditions • Body weight > 45kg for effective determination of study endpoint • Positive for CFA detected by Filarial Test Strip (FTS) irrespective of the filarial dance sign (FDS) status detected by Ultrasonography (USG) measurement (in men) • with or without MF • Good general health without any clinical condition requiring medication in other to enroll healthy participants • No previous history of tuberculosis to prevent the possible emergence of rifampicin-resistant strains of Mycobacteria. • Participants with the ability to follow study instructions and who are likely to attend and complete all required visits in other to reduce non-compliance and drop-outs from study <p>- Onchocerciasis</p> <p>Participants will only be included in the study if they meet all of the following criteria:</p> <ul style="list-style-type: none"> • Willingness to participate in the study by signing the Informed Consent Form (ICF) as participation in study is voluntary • 18-55 years in other to enroll adults capable of making an informed decision and with less health conditions
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	<ul style="list-style-type: none"> • Body weight > 45kg for effective determination of study endpoint • Presence of at least 1 medium-sized onchocercoma detected by palpation as an indicator of ongoing infection • MF-positive as a measure of active infection • Good general health without any clinical condition requiring medication in other to enroll healthy participants • No previous history of tuberculosis to prevent the possible emergence of rifampicin-resistant strains of Mycobacteria. • Participants with the ability to follow study instructions and are likely to attend and complete all required visits in other to reduce non-compliance and drop-outs from study
Exclusion Criteria	<p>Participants will not be included in the study if any of the following criteria applies:</p> <p>General Exclusion Criteria:</p> <ul style="list-style-type: none"> • Participants not able to give consent • Participants who are unable to understand the nature, scope, significance and consequences of this clinical trial • Participants taking concomitant medication that interferes with study drugs (For Albendazole, the concomitant medications are: – Dexamethasone, Praziquantel, Cimetidine, Theophylline and Phenytoin. For Rifampicin, the concomitant medications are: – Atazanavir, Darunavir, Fosamprenavir, Saquinavir, Tipranavir, Praziquantel and Tenofovir) • Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure (rifampicin or any member of the rifamycins) • Simultaneous participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning • Participants with a physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in this clinical trial • Known or persistent abuse of medication, drugs or alcohol

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	<ul style="list-style-type: none"> History of neurological, cardiac or pulmonary, disease History of acute Hepatitis A and acute or chronic Hepatitis B or C <p>Laboratory Exclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory evidence of liver disease (AST, ALT and γGT greater than 1.5 times the upper limit of normal i.e., 44.0U/L, 40.0U/L and 55.0U/L respectively) Laboratory evidence of renal disease (eGFR <60ml/min/1.732M2) Laboratory evidence of leukopenia (leukocytes < 3000/μl) Laboratory evidence of anaemia (Hb < 8.0)
Trial Procedures for LF	<p>Screening Visit 1: informed consent for screening, demographic data, Medical examination, laboratory assessments and urine / pregnancy test</p> <p>Screening Visit 2: informed consent for treatment from all eligible volunteers, enrolment, medical history, concomitant medication, prior therapies/medication, physical examination, vital signs, Ultrasonography to detect worm nests in male participants (adult worm) and review of inclusion / exclusion criteria.</p> <p>Randomization</p> <p>Visit 1 (Treatment Day 1): review of inclusion/ exclusion criteria, concomitant medication, urine / pregnancy test, application of IMP(s) (treatment groups A, B and C)</p> <p>Visit 2 - Visit 7: concomitant medication, application of IMP(s) (treatment groups A, B and C), AE and SAE assessment (all treatment groups).</p> <p>Visit 8: concomitant medication, pregnancy testing (before 8th treatment), laboratory assessment of ALT, AST, γGT, creatinine and leukocytes (before 8th treatment for all groups), application of IMP(s) (treatment groups B and C), application of IMP(s) (treatment group A in case of patients who missed one or more treatment days {range days}), AE and SAE assessment (all treatment groups).</p> <p>Visit 9 – Visit 14 (Treatment day 9-14): concomitant medication, pregnancy testing</p>

	<p>(before 14th treatment, range: + 2 days) application of IMP(s) (treatment groups B and C), application of IMP(s) (treatment group A in case of patients who missed one or more treatment days {range days}), AE and SAE assessment (all treatment groups).</p> <p>Visit 15: concomitant medication, application of IMP(s) (treatment group B and C in case of patients who missed one or more treatment days {range days}), AE and SAE assessment (all treatment groups).</p> <p>Visit 16 – Visit 21: concomitant medication, application of IMP(s) (treatment groups B and C in case of patients who missed one or more treatment days {range days}), AE and SAE assessment (all treatment groups).</p> <p>Visit 22 (End of treatment): concomitant medication, AE and SAE assessment (all treatment groups).</p> <p>Visit 23 (4 months' follow-up, 4 months \pm 2 weeks (range) after treatment): Medical examination, blood sampling, urine sampling.</p> <p>Visit 24 (6 months after treatment): treatment with Ivermectin 150μg/kg and Albendazole 400mg/d (MDA standard dose) and care of side effects if any.</p> <p>Visit 25 (12 months (-2/+4 weeks range) after treatment): Ultrasonography to detect worm nests in male participants, medical examination, blood sampling, urine sampling, AE and SAE assessment (all treatment groups), and concomitant medication.</p> <p>Visit 26 (18 months after treatment onset): Ultrasonography to detect worm nests in male participants, medical examination, blood sampling, urine sampling, AE and SAE assessment (all treatment groups), and concomitant medication.</p> <p>Visit 27 (any day after visit 26) – IVM and ALB distribution</p>
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	<p>Visit 28 – visit 29): Follow-up after IVM + ALB distribution, care of side effects if necessary.</p> <p>Visit 30: End of trial, information to participants about trial results.</p> <p>Subsequently patients will be treated according to clinical routine with the best treatment regimen resulting from the trial.</p>
Trial procedures for Onchocerciasis	<p>Screening Visit 1: informed consent for screening, demographic data, palpation of onchocercomata, skin snipping and skin examination</p> <p>Screening Visit 2: informed consent for treatment, medical history, concomitant medication, prior therapies/ medication, physical examination, vital signs, blood and urine sampling, laboratory assessments, review of inclusion/ exclusion criteria</p> <p>Randomisation</p> <p>Visit 1 (Treatment Day 1): review of inclusion/ exclusion criteria, pregnancy testing, concomitant medication, application of IMP(s) (treatment groups A, B and C).</p> <p>Visit 2 – Visit 7: concomitant medication, application of IMP(s) (treatment groups A, B and C), AE and SAE assessment (all treatment groups).</p> <p>Visit 8: concomitant medication, pregnancy testing (before 8th treatment), laboratory assessment of ALT, AST, γGT, creatinine and leukocytes (before 8th treatment for all groups), application of IMP(s) (treatment groups B and C), application of IMP(s) (treatment group A in case of patients who missed one or more treatment days (range days)), AE and SAE assessment (all treatment groups).</p> <p>Visit 9 – Visit 14 (Treatment day 9-14): concomitant medication, pregnancy testing (before 14th treatment, range: + 2 days) application of IMP(s) (treatment groups B and C), application of IMP(s) (treatment group A in case of patients who missed one or more treatment days (range days)), AE and SAE assessment (all treatment groups).</p>

	<p>Visit 15: concomitant medication, application of IMP(s) (treatment groups B and C in case of patients who missed one or more treatment days (range days)), AE and SAE assessment (all treatment groups).</p> <p>Visit 16 – Visit 21: concomitant medication, application of IMP(s) (treatment groups B and C in case of patients who missed one or more treatment days (range days), AE and SAE assessment (all treatment groups)</p> <p>Visit 22 (End of treatment): concomitant medication, AE and SAE assessment (all treatment groups)</p> <p>Visit 23 (4 months' follow-up, 4 months \pm 2 weeks (range) after visit 1): AE and SAE assessment (all treatment groups), concomitant medication, palpation of onchocercomata, skin snipping, blood sampling, urine sampling.</p> <p>Visit 24 (6 months after treatment): treatment with Ivermectin 150μg/kg (MDA standard dose) and care of side effects if any.</p> <p>Visit 25 (18 months follow-up, 18 months \pm 2 weeks (range) after visit 1): AE and SAE assessment (all treatment groups), concomitant medication, palpation of onchocercomata, skin snipping, urine sampling, treatment with Ivermectin 150μg/kg (MDA standard dose)</p> <p>Visit 26-27 (before and during nodulectomy, 20 months (-2/+4 weeks range) after visit 1, baseline): informed consent (nodulectomy), AE and SAE assessment (all treatment groups), concomitant medication, prior therapies (medication, blood and urine sampling, pregnancy testing, vital signs, palpation of onchocercomata, skin snipping, skin examination, Nodulectomy, concomitant medication, AE and SAE assessment.</p> <p>Visit 28 (1 day after visit 27) – Visit 33 (10 days after visit 27): Wound dressing, concomitant medication, AE and SAE assessment.</p> <p>Visit 34: End of trial, information to participants about trial results</p>
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	Subsequently patients will be treated with the best treatment regimen resulting from the trial.
Trial Specific Measurements for LF	<ul style="list-style-type: none"> • Laboratory assessments • Application of trial drug(s) • Blood and Urine samples: For CFA measurement, microfilarial load and PCR analyses, blood and urine samples are taken at pre-treatment, 4, 12 and 18 months after treatment onset. • *Ultrasonography: At baseline, 12 and 18 months after treatment onset. <p><i>*See section 9.1.1-page 54</i></p>
Trial Specific Measurements for Onchocerciasis	<ul style="list-style-type: none"> • Laboratory assessments • Application of trial drug(s) • Skin snips: To assess skin microfilarial load, skin biopsies are taken pre- treatment, as well as at 4, 18 and 20 months after treatment onset • Nodulectomies: 20 months after treatment onset, all accessible onchocercomata will be removed (surgical intervention as described above)
Investigational trial sites	<p>This is a mono-centre trial carried out by the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), Kwame Nkrumah University of Science and Technology (KNUST), Kumasi (see http://kccr-ghana.org/?page_id=238). The LF and onchocerciasis trial patients will be recruited from selected communities in Bawku West, Builsa South, Nabdam, Fumbisi, Garu-Tempene, Kayoro, Kassena Nankana Municipal, Kassena Nankana West District all in the Upper East Region of Ghana, the Sefwi Akontombra District in the Western North Region of Ghana, which is endemic for onchocerciasis, Ahanta West Municipal, Nzema East Municipal and Ellembelle Districts all in the Western Region of Ghana, which are endemic for lymphatic filariasis (LF).</p>

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<p>Statistical Rationale</p>	<p>Primary statistical Analysis:</p> <p>For the primary endpoint frequencies of worms without <i>Wolbachia</i> and their confidence intervals (95%) will be estimated from linear regression models taking the dependency between worms found in one patient into account. Blood and worms from participants who finished the study according to protocol will be analysed for primary efficacy. Secondly, efficacy will also be analysed per Intention to treat analysis.</p> <p>Secondary Endpoints:</p> <p>Secondary endpoints will be described as estimators with confidence intervals (95%) for each intervention group and analysed with adequate statistical methods.</p> <p>Safety Analysis:</p> <p>Frequency of Adverse events and Serious Adverse Events will be analysed. In this analysis all patients who took the drugs at least for one day will be included.</p>
<p>Time Schedule</p>	<p>Per Subject:</p> <p>The treatment will have a duration per patient of:</p> <ul style="list-style-type: none"> • 7 days (Rifampicin 35mg/kg/d plus Albendazole 400mg/d) in Treatment A • 14 days (Rifampicin 35mg/kg/d plus Albendazole 400mg/d) in Treatment B • 14 days (Albendazole 400mg/day) in Treatment C. <p>All Participants, regardless of the treatment arm they are assigned to (Treatment A, B, C or D (no treatment)), will be asked to come to the daily treatment visits for at least 14 days for safety assessment by the trial clinician.</p> <p>The nodulectomy will take 10-14 days (incl. wound dressing).</p> <p>Each participant will remain in the study for approximately 24 months, including recruitment, treatment and nodulectomies.</p> <ul style="list-style-type: none"> • Trial duration: 40 months • Recruiting Period: 2-3 months • Planned Start Date (FPFV): December 01, 2020 • Planned End Date (LPLV): March 31, 2024

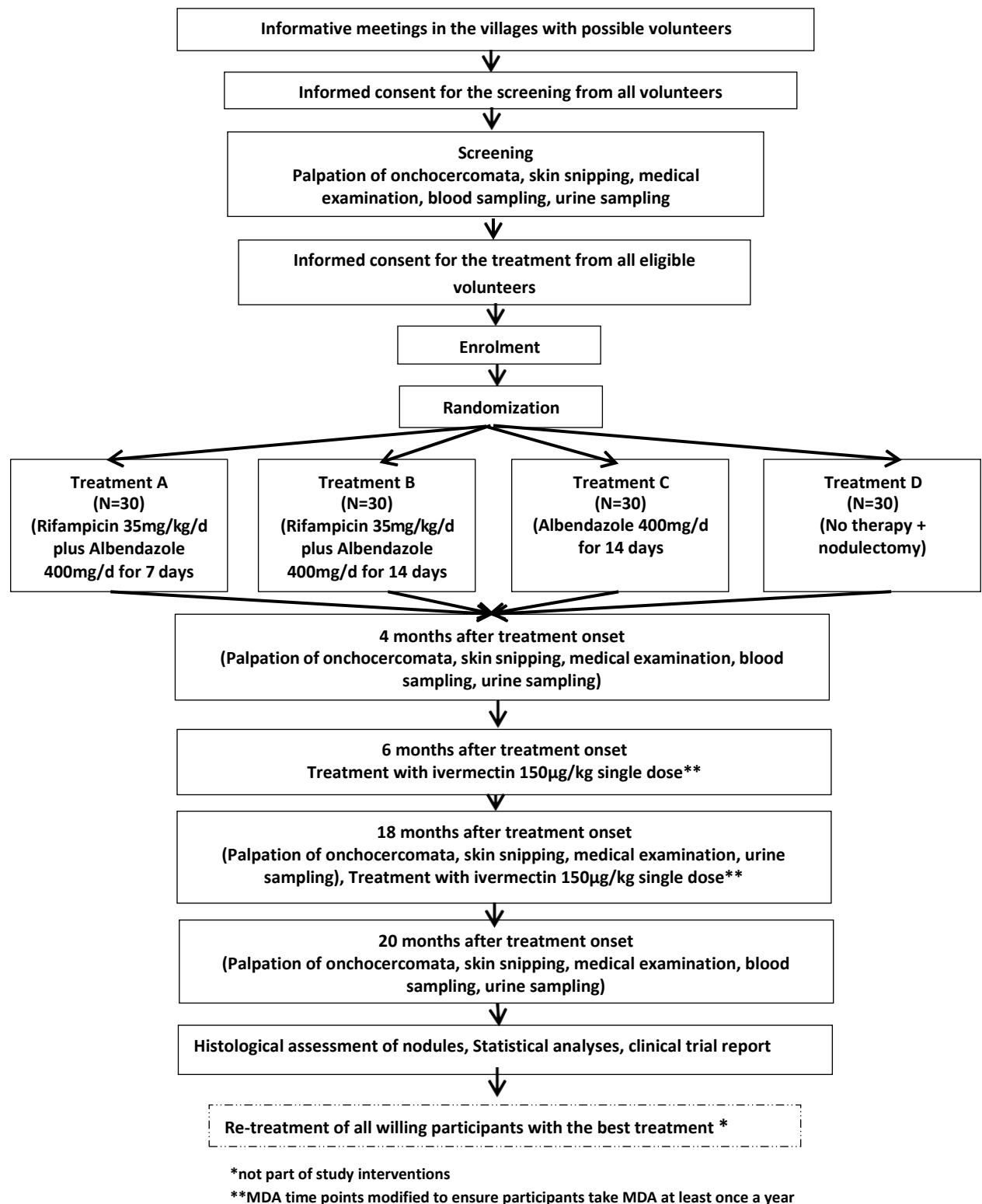


Figure 1: Flowchart summary of the planned onchocerciasis trial procedures.

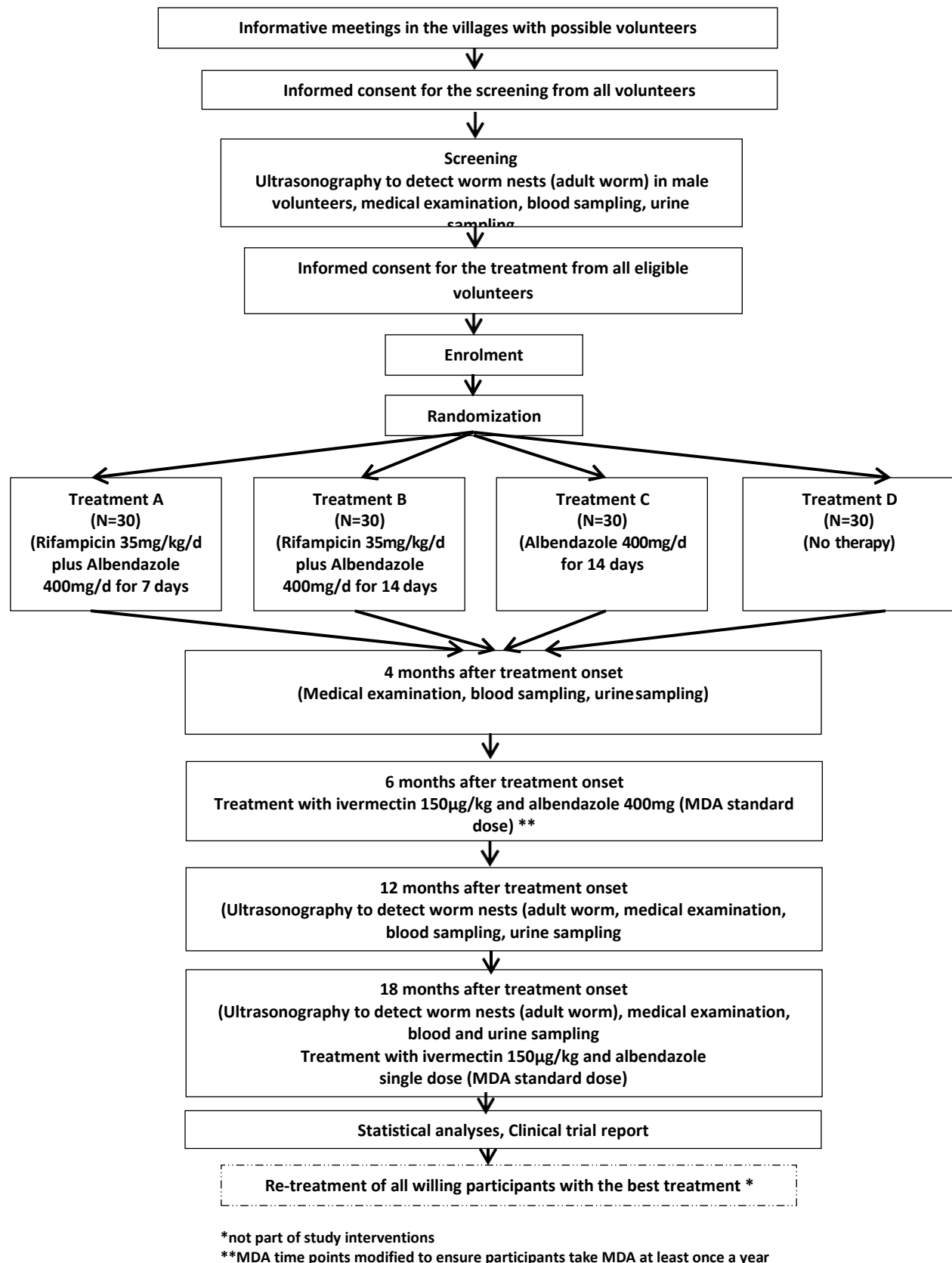


Figure 2: Flowchart summary of the planned LF trial procedures

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

Trial Acronym: ASTAWOL

Trial Code: TMA2018SF-2451

Trial registration: PACTR202009704006025

SCHEDULE OF ACTIVITIES

3.1 Schedule of activities for LF trial

	Screening Visit 1	Screening Visit 2 (within 4 weeks after screening visit 1)	Visit 1* Baseline Day 1 (range +4 weeks after screening visit 2)	Visit 2 – Visit 7 (Day 2 – Day 7)	Visit 8 (Day 8)	Visit 9 – Visit 14 (Day 9 – Day 14)	Visit 15 (Day 15)
Informed Consent	√ (screening)	√ (treatment)					
In-/Exclusion Criteria		√	√				
Demographic data	√						
Medical History		√					
Physical Examination		√					
Ultrasonography		√					
Prior therapies/medications		√					
Concomitant Medication		√	√	√	√	√	√
Laboratory (blood)		√(leukocytes, ALT, AST, γGT and creatinine, before treatment)			√(leukocytes, ALT, AST, γGT and creatinine, before 8 th treatment, all groups)	√(leukocytes, ALT, AST, γGT and creatinine, before 8 th treatment, if not done on visit 8, all groups)	
Laboratory (Urine)	√						
Pregnancy test	√		√		√ (before 8 th treatment, range + 2 days)	√(before 14 th treatment, range + 2 days)	
Microfilarial load	√						
Vital Signs		√					
Randomisation		√					
Trial Drug (Treatment A)			√	√	(√) (range days for missed treatment days)	(√) (range days for missed treatment days)	
Trial Drug (Treatment B)			√	√	√	√	(√) (range days for missed treatment days)
Trial Drug (Treatment C)			√	√	√	√	(√) (range days for missed treatment days)
Group D (Treatment D)		√	√	√	√	√	
AEs and SAEs				√	√	√	√
IVM + ALB distribution							

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

Trial Acronym: ASTAWOL

Trial Code: TMA2018SF-2451

Trial registration: PACTR202009704006025

	Visit 16 – Visit 21 (Day 16 – Day 21)	Visit 22 End of treatment	Visit 23 4 months' follow-up (4 months ± 2 weeks(range) after treatment onset	Visit 24 IVM and ALB 6 months' follow-up (6months ± 2 weeks (range) after treatment onset	Visit 25 12 months (± 2 weeks range) after treatment onset	Visit 26 18 months (± 2 weeks range) after treatment onset	Visit 27** IVM and ALB (every other day after Visit 26)
Informed Consent							
In-/Exclusion Criteria							
Demographic data							
Medical History							
Physical Examination			√		√	√	
Ultrasonography					√	√	
Prior therapies/medications					√	√	
Concomitant Medication	√	√	√	√	√	√	√
Laboratory (blood)			√		√	√	
Laboratory (Urine)			√		√	√	
Pregnancy test			√		√	√	
Microfilarial load			√		√	√	
Vital Signs			√		√	√	
Randomisation							
Trial Drug (Treatment A)							
Trial Drug (Treatment B)	(√) (range days for missed treatment days)						
Trial Drug (Treatment C)	(√) (range days for missed treatment days)						
Group D (Treatment D)							
AEs and SAEs	√	√	√	√	√	√	√
IVM + ALB distribution				√		√	√

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

Trial Acronym: ASTAWOL

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	Visit 28 – visit 29 IVM+ALB follow-up (Visit 28- visit 29 can be done a day after IVM +ALB distribution)	Visit 30 End of Trial
Informed Consent	Care of side effects, if necessary	Information to patients about trial results – Initiation of re-treatment
In-/Exclusion Criteria		
Demographic data		
Medical History		
Physical Examination		
Ultrasonography		
Prior therapies/medications		
Concomitant Medication		
Laboratory (blood)		
Laboratory (Urine)		
Pregnancy test		
Microfilarial load		
Vital Signs		
Randomisation		
Trial Drug (Treatment A)		
Trial Drug (Treatment B)		
Trial Drug (Treatment C)		
Group D (Treatment D)		
AEs and SAEs		
IVM + ALB distribution		

*All other procedures can be done on either day. Informed consent for treatment has to be obtained before randomization.

**Visits 27 – 29 are not part of the study interventions but will be done due to ethical considerations.

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

Trial Acronym: ASTAWOL

Trial Code: TMA2018SF-2451

Trial registration: PACTR202009704006025

3.2 Schedule of activities for Onchocerciasis trial

	Screening Visit 1	Screening Visit 2 (within 4 weeks after screening visit 1)	Visit 1 Baseline Day 1 (range +4 weeks after screening visit 2)	Visit 2 – Visit 7 (Day 2 – Day 7)	Visit 8 (Day 8)	Visit 9 – Visit 14 (Day 9 – Day 14)	Visit 15 (Day 15)
Informed Consent	√ (screening)	√ (treatment)					
In-/Exclusion Criteria		√	√				
Demographic data	√						
Medical History		√					
Physical Examination		√					
Palpation of onchocercomata	√						
Skin snipping	√						
Skin examination	√						
Prior therapies/medications		√					
Concomitant Medication		√	√	√	√	√	√
Laboratory (blood)		√(leukocytes, ALT, AST, γGT and creatinine, treatment group A)			√(leukocytes, ALT, AST, γGT and creatinine, before 8 th treatment, all groups)	√(leukocytes, ALT, AST, γGT and creatinine, before 8 th treatment, if not done on visit 8, all groups)	
Laboratory (urine)		√					
Pregnancy test		√	√		√ (before 8 th treatment, range + 2 days)	√ (before 14 th treatment, range + 2 days)	
Vital Signs		√					
Randomisation		√					
Trial Drug (Treatment A)			√	√	(√) (range days for missed treatment days)	(√) (range days for missed treatment days)	
Trial Drug (Treatment B)			√	√	√	√	(√) (range days for missed treatment days)
Trial Drug (Treatment C)			√	√	√	√	(√) (range days for missed treatment days)
Group D (Treatment D)							
AEs and SAEs			√	√	√	√	√
Nodulectomy							
Wound healing							
IVM distribution							
Wound healing							
IVM distribution							

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

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	Visit 16 – Visit 21 (Day 16 – Day 21)	Visit 22 End of treatment	Visit 23 [4 months ±2 weeks (range) after treatment onset]	Visit 24 IVM [6months ±2 weeks (range) after treatment onset]	Visit 25 IVM (18 months ± 2 weeks (range) after treatment onset)	Visit 26-27 Before and during Nodulectomy (20 months (± 2 weeks (range) after treatment onset)	Visit 28-33 Wound dressing (every other day after Visit 26)
Informed Consent						√	
In-/Exclusion Criteria							
Demographic data							
Medical History							
Physical Examination			√		√	√	
Palpation of onchocercomata					√	√	
Skin snipping			√		√	√	
Skin examination					√	√	
Prior therapies/medications					√	√	
Concomitant Medication	√	√	√	√	√	√	√
Laboratory (blood)			√			√	
Laboratory (urine)			√		√	√	
Pregnancy test			√		√	√	
Vital Signs			√		√	√	
Randomisation							
Trial Drug (Treatment A)							
Trial Drug (Treatment B)	(√) (range days for missed treatment days)						
Trial Drug (Treatment C)	(√) (range days for missed treatment days)						
Group D (Treatment D)							
AEs and SAEs	√	√		√	√	√	√
Nodulectomy						√	
Wound healing						√	√
IVM distribution				√	√		

Title: The efficacy of Rifampicin 35mg/Kg/d plus Albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis– a randomized, controlled, parallel-group, open-label, phase II pilot trial.

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	Visit 34 End of Trial
Informed Consent	Information to patients about trial results – Initiation of re-treatment
In-/Exclusion Criteria	
Demographic data	
Medical History	
Physical Examination	
Palpation of onchocercomata	
Skin snipping	
Skin examination	
Prior therapies/medications	
Concomitant Medication	
Laboratory (blood)	
Laboratory (urine)	
Pregnancy test	
Vital Signs	
Randomisation	
Trial Drug (Treatment A)	
Trial Drug (Treatment B)	
Trial Drug (Treatment C)	
Group D (Treatment D)	
AEs and SAEs	
Nodulectomy	
Wound healing	
IVM distribution	

4.0 INTRODUCTION

More than 200 million humans are parasitized by filarial nematodes, causing the neglected tropical diseases: lymphatic filariasis, loiasis and onchocerciasis. The lymphatic, ocular and dermatological damages have severe economic and social consequences including poor school performance, low productivity, higher health related costs among infected adults, and a reduced life span [10, 11].

The achievements of onchocerciasis and lymphatic filariasis (LF) mass drug administration (MDA) programmes have considerably reduced transmission and led to the formulation of the goal to eliminate these diseases [1]. The development and implementation of new drugs or improved regimens will increase cost effectiveness by avoiding unnecessary treatments of uninfected individuals within the mass drug administration (MDA) schemes.

A major problem with the current MDA is that while ivermectin (IVM) and diethylcarbamazine (DEC) efficiently kill microfilariae (MF) and albendazole (ALB) (at the low dose used) reduces embryogenesis at least in LF, they have limited (DEC and ALB in LF) or no (IVM) efficacy against adult worms and do not permanently stop MF production. Simulation studies have suggested that administering IVM at shorter intervals of 6 instead of 12 months' intervals have a higher likelihood of eliminating the infection, but incur large logistical costs on health infrastructures of the endemic countries. Given the longevity of adult worms (>10 years), a high-coverage (>80%) and many rounds of treatment required, the set goal of elimination in a majority of endemic countries will not be feasible by 2020.

Immigration of infected persons into areas where filariasis is considered eliminated and where treatment has ceased may also occur. Not only could this lead to re-emergence of the infection, however, these populations may not have been exposed to challenge and hence may be more susceptible to the parasites. Consequently, new infections may present higher worm burdens and microfilarial loads. Equally important is the fact that indication of IVM suboptimal efficacy is emerging, which has alerted experts in the filariasis community since there is currently no alternative treatment suitable for MDA.

In addition, MDA (IVM + ALB or DEC +ALB) cannot be undertaken in onchocerciasis regions co-infected with *Loa loa* (primarily in Central Africa) and which are estimated to cover at least 20% of onchocerciasis- endemic areas. This is because these microfilaricidal drugs also kill *Loa loa* microfilariae and, depending on their number/load, this may elicit loiasis-specific adverse reactions (*Loa loa* encephalopathy), leading to severe neurological disorders or death. Thus, there is an urgent need for a macrofilaricide, targeting adult worms that can be used for onchocerciasis and LF, particularly in problem areas, such as those with emerging ivermectin resistance or *Loa loa* co-endemicity [1].

4.1 Background

Wolbachia endosymbiotic bacteria are found in most of the filarial worms and are essential for worm fertility and survival [12]. Doxycycline has been shown to deplete *Wolbachia* leading to long-term sterility and possesses a characteristic macrofilaricidal effect, the extent not observed in current drugs used against onchocerciasis and LF [13, 14]. **In an LF study conducted by our research group, it was observed that treatment with doxycycline showed continues decline of Circulating Filarial Antigen (CFA) levels beyond a 12 month period. This phenomenon was observed when an ultrasonography (USG) examination showed clearance of adult worm from worm nests [6].** Current recommendations for individual drug administration (IDA) are: Doxycycline 200mg/d for 4 weeks or 100mg/d for 5 weeks if interruption in embryogenesis is wanted and Doxycycline 200mg for 6 weeks if a macrofilaricidal effect is desired [13].

Although the application of Doxycycline shows efficacy superior to ALB+IVM, treatment with Doxycycline is not recommended for MDA because of the long treatment duration [15]. Therefore, the aim is to find a drug or a drug combination with long-term sterilizing or macrofilaricidal activity given for a shorter treatment period [16]. Within the A-WOL consortium (<http://www.a-wol.net>), which was funded by the Bill and Melinda Gates Foundation, three clinical trials were conducted by our group. One placebo controlled double-blind phase II trial was carried out in Lymphatic filariasis (LF) (ISRCTN15216778). The other two trials were carried out in Onchocerciasis, one placebo controlled double-blind phase II trial (ISRCTN68861628) and one open label pilot trial (ISRCTN06010453). These trials had the aims to use new drugs (Rifampicin, Minocycline) or combinations of drugs (Rifampicin plus Doxycycline, Albendazole plus Doxycycline) to shorten the treatment period from 6 to 3 weeks, 2 weeks or 10 days and to reduce the dosage of Doxycycline from 200mg to 100mg. The trial in LF showed long-term sterilizing (absence of MF) and macrofilaricidal effects in the Doxycycline 100mg groups (given for 4 and 5 weeks) and a long-term sterilizing effect after 12 months in the 2 weeks Doxycycline plus Rifampicin group. Thus, this pilot study showed that rifampicin might have a synergetic effect with doxycycline at shorter treatment duration [9, 17].

The open label pilot trial confirmed earlier studies that Doxycycline 200mg given for 4 weeks is sufficient for *Wolbachia* depletion with desired parasitological effects. The data further suggest that there is an additive/synergistic effect of Albendazole (3 days) on top of Doxycycline 200mg given for 3 weeks, and that Minocycline 200mg given 3 weeks has a stronger potency than Doxycycline given for 3 weeks. These latter two results are preliminary and need confirmation in a full randomized controlled phase 2 trial [18]. Interestingly, sterilization of female filariae without significant macrofilaricidal activity (assessed up to 2 years after treatment) has been demonstrated clinically with a reduced treatment duration of DOX (3 weeks vs. 4 weeks), where *Wolbachia* was depleted >80% but <90% from nematode tissues (5). This suggests that a lower threshold depletion level of *Wolbachia* may still mediate sustained transmission-blocking activity in the

treatment of LF and onchocerciasis.

The global challenge is to develop a macrofilaricidal treatment that can be delivered in 10 days or less. In a preclinical trial, a combination of RIF and ALB confirmed substantial synergy between ALB and rifamycin class of anti- *Wolbachia* drugs. This synergy leads to long-term sterilizing effects and reduced treatment courses to 7 days. Combining high dose rifampicin with albendazole in a 7-day treatment mediated an accelerated macrofilaricidal effect as well as significantly improving *Wolbachia* depletion beyond the 90% threshold in surviving adult female filariae, predictive of long-term asymbiotic macrofilaricidal activity. These observations provide a strong rationale for immediate clinical evaluation of these synergistic combinations in LF and onchocerciasis patients. Reassuringly, no evidence of drug–drug interaction was observed when ALB+RIF were co-administered [8].

4.2 Trial Rationale

LF and onchocerciasis are 2 NTDs targeted for elimination by the World Health Organization (WHO). Progress has been made in some parts of the world such as Latin America and elsewhere, but control and elimination is facing some challenges in Africa due to the vectors involved in transmission and the large geographical areas. MDA programmes have been effective and have considerably reduced transmission and led to the formulation of the goal to eliminate these diseases. However, there are some problematic areas in Africa referred to as “Hotspots” where despite many rounds of ivermectin, transmission is still high, suggestive of possible resistance to the drug [19]. **LF surveys conducted by our group in some LF endemic communities in the Western region (Ahanta West, Nzema East and Ellembele Districts) and Upper East region (Nabdam District) (unpublished data) showed marked reduction in MF prevalence (0.07%) and (0.5%) respectively. Notwithstanding, CFA levels remain proportionally high (7.8% and 12.8% respectively) being an indication of the presence of adult worms. These findings suggest that MDA will have to continue in those seemingly high CFA prevalent areas which might not be necessary due to low MF prevalence (<1%), posing logistic and financial burdens on the MDA programme. It has however been shown that mf levels in blood circulation do not typically correlate with adult worm numbers in LF as most people in endemic areas where MDA is ongoing are usually amicrofilaremic (25) Therefore, drug(s) which target the adult worm leading to a reduction or clearance of CFA in the blood is / are needed to complement the efforts of programme managers in LF disease elimination. Thus, a method to quantify the adult worm burden independent of microfilariae is required, especially in infected individuals residing in endemic areas where MDA is ongoing and as a result there exist many people without mf (25).**

Also, there are other areas where the current drugs, IVM and DEC cannot be administered due to co-endemicity with *L. loa* infection. Therefore, the development of new drugs or improved regimens is urgently needed to achieve the WHO goal of eliminating these two diseases[20].

Rifampicin (RIF) has been shown to exhibit superior *anti- Wolbachia* potency in vitro and in vivo in models of LF and onchocerciasis compared with the tetracycline class [2–4]. However, these observations have not been translated into superior efficacy in clinical trials compared to doxycycline (DOX) when administered at the “standard” 10 mg/kg dose for 2 or 4 weeks to patients with onchocerciasis [9, 21]. This discrepancy has been explained by Liverpool researchers (LSTM) based on RIF pharmacokinetics (PKs) and drug exposures recorded in preclinical models compared with humans. They identified that a minimum dosage of RIF bioequivalent to 30–40 mg/kg in humans was required to deplete *Wolbachia* beyond the 90% threshold predictive of clinical cure [4, 5, 6]. Reassuringly, fourfold dose elevations of RIF have recently been identified as safe when delivered for periods of 1 month [7] in patients with TB, suggesting that RIF at a high dose could be deployed as a short-course macrofilaricidal drug for human use.

Rifampicin (Rifadin®) and Albendazole (Zentel®) are both registered antibiotics in Ghana. Rifampicin is a registered and an approved drug for the treatment of tuberculosis in Ghana. Similarly, Albendazole is an approved and registered drug in Ghana.

Both drugs (Rifampicin and Albendazole) are already registered drugs for human use with detailed safety profiles. The Safety-profile for the use of the combination of Rifampicin plus Albendazole in the treatment of onchocerciasis have been proved in animal model (10). Rifampicin and Albendazole are both registered for use in Ghana and readily available so will be purchased locally.

It would be a great success and benefit to all LF and onchocerciasis infected individuals if it were possible to shorten the treatment period from 4 weeks to 14 or even 7 days. Additionally, the trials would provide parameter estimators for the sample size calculation of a subsequent confirmatory randomized controlled double blind phase II trial.

The trials will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

Potential risks and benefits of study participation

4.2.1. Side effects of trial drugs

4.2.1.1. Rifampicin:

Very frequent (> 10%) side effects:

Hematologic: Lymphopenia (12.7%), neutropenia (12.5%), anemia (12.2%)

Metabolic and Nutritional: Hyperuricemia (31.9%) - most likely related to pyrazinamide as only 2 cases were reported during the continuation phase, when pyrazinamide was no longer part of the regimen.

Renal and Urinary: Pyuria (21.6%), hematuria (17.7%), proteinuria (13%), urinary tract infection (13.3%)

Frequent (1-10%) side effects:

Hematologic: Leukopenia (6.6%), thrombocytosis (5.5%), leukocytosis (3%), neutrophilia (2.5%), thrombocytopenia (2.5%), polycythemia (2.2%), lymphadenopathy (1.1%)

Metabolic and Nutritional: Hypoglycemia (10%), hyperkalemia (9.1%), increased nonprotein nitrogen (3.9%), hyperglycemia (3.6%), increased lactate dehydrogenase (1.4%), hyperphosphatemia (1.4%)

Renal and Urinary: Urinary casts (8%), cystitis (1.7%)

Respiratory: Hemoptysis (8.3%), coughing (8%), upper respiratory tract infection (4.7%), bronchitis (2.5%), pharyngitis (1.9%), epistaxis (1.4%), pleuritis (1.1%)

Infections and Infestations: Influenza (7.8%), tuberculosis infection (2.5%), infection (1.4%), herpes zoster (1.1%)

Hepatic and Biliary: ALT increased (6.9%), AST increased (5.8%)

Body as a whole – general: Back pain (6.9%), pain (6.1%), chest pain (5.5%), accident injury (4.7%), abdominal pain (1.9%), fever (1.4%), fatigue (1.1%), dependent edema (1.1%)

Dermatologic: Increased sweating (6.4%), rash (6.1%), pruritus (3.6%), acne (2.5%), maculopapular rash (1.7%), skin disorder (1.4%), and eczema (1.1%)

Gastrointestinal: Anorexia (5.8%), dyspepsia (2.8%), nausea (2.5%), vomiting (2.5%), constipation (1.9%), diarrhea (1.9%), hemorrhoids (1.4%)

Nervous system: Headache (3.9%), dizziness (1.7%), tremor (1.4%), insomnia (1.1%)

Musculoskeletal: Arthralgia (4.4%), arthritis (1.1%), arthrosis (1.1%), gout (1.1%)

Cardiovascular: Hypertension (1.7%)

Ocular: Conjunctivitis (2.5%)

Occasionally (< 1%) side effects:

Hematologic: Lymphocytosis, hematoma, purpura, hypochromic anemia, normocytic anemia, thrombosis

Metabolic and Nutritional: Weight decrease, Blood Urea Nitrogen (BUN) increased, diabetes mellitus, alkaline phosphatase increased, hypophosphatemia, hypercalcemia, hypovolemia, weight increase

Renal and Urinary: Urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder

Reproductive Disorders: Penis disorder, vaginitis, vaginal hemorrhage, positive cervical smear test, leukorrhea, male mastitis, prostatic disorder, abortion

Respiratory: Abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnea, pneumonitis, sinusitis, increased sputum, pulmonary fibrosis, upper respiratory congestion, asthma, abnormal chest x-ray, bronchospasm, laryngeal edema, laryngitis, respiratory disorder

Infections and Infestations: Fungal infection, parasitic infection, protozoan infection

Hepatic and Biliary: Bilirubinemia, hepatomegaly, jaundice, hepatitis

Body as a whole – general: Abnormal laboratory test, legs edema, asthenia, face edema, abscess, peripheral edema, malaise, ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation

Dermatologic: Skin ulceration, urticaria, dry skin, furunculosis, skin discoloration, fungal dermatitis, nail disorder, alopecia, erythematous rash

Gastrointestinal: Tooth disorder, gastroenteritis, gastritis, esophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified

Nervous system: Somnolence, seizure not specified, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor, and taste loss

Musculoskeletal: Myalgia, myositis, bone fracture, muscle weakness, muscle spasm

Cardiovascular: Syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis, deep thrombophlebitis, vascular disorder, vasodilation

Ocular: Eye pain, eye abnormality

Psychiatric: Anxiety, confusion, drug abuse, aggressive reaction, agitation

Oncologic: Pulmonary carcinoma, neoplasm not specified, carcinoma, lipoma

4.2.1.1.1 Precautions to mitigate drug specific risks (Rifampicin)

Hepatotoxicity:

Elevations of liver transaminases may occur in patients receiving rifampicin. Patients on Rifampicin should be monitored for liver injury. Therefore, patients with abnormal liver tests (ALT, AST, γ -GT, bilirubinemia) and/or liver disease will be excluded from this clinical trial. Serum transaminase and bilirubin levels will be obtained during the screening in all participants and during the course of treatment. Treatment will be discontinued if evidence of liver injury occurs.

Hypersensitivity and Related Reactions:

Hypersensitivity reactions may occur in patients receiving rifampicin. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis. Therefore, participants in this clinical trial will be monitored for signs and symptoms of hypersensitivity reactions. The drugs will be administered in the morning directly in the village by the trial clinicians in the form of daily observed treatment. In case of emergency the trial clinicians will be reachable via mobile phone at any time. In case of any suspected hypersensitive reaction the treatment will be stopped immediately and the patient will be treated for the symptoms until full recovery.

Discoloration of Body Fluids:

Rifampicin may produce a red-orange discoloration of body tissues and/or fluids (e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become

permanently stained. Participants of this trial will be informed about this effect in detail during the Informed Consent procedure.

Porphyria:

Porphyria has been reported in patients receiving rifampicin, attributed to induction of delta aminolevulinic acid synthetase. Therefore, participants with known porphyria will be excluded from this trial and in any suspected case during treatment the treatment will be immediately stopped and the patient will be treated for the symptoms until recovery.

Drug interactions:

Rifampicin is an inducer of CYP450 enzymes. Concomitant use of rifampicin with other drugs metabolized by these enzymes, such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception may cause a significant decrease in plasma concentrations and loss of therapeutic effect. Therefore, participants with chronic medication will be excluded from this trial.

4.3.1.2 Albendazole:

Headache, nausea, stomach pain and vomiting are most common, and usually associated with heavy geohelminth infections. Severe allergic reactions occur rarely, and include rash, hives, itching, difficulty breathing, and tightness in the chest, swelling of the mouth, face, lips, or tongue, dark urine, mild elevation in liver transaminases can occur, but normalize with cessation of treatment. These side effects are usually associated with prolonged ALB therapy.

4.3.2 General precautions and warnings

Pregnancy and breastfeeding:

To avoid any complications, pregnant or breastfeeding women will be excluded from the clinical trial. Pregnancy tests will be carried out during the screening and right before the first treatment. Additionally, pregnancy tests will be repeated every week of treatment. In case of pregnancy in any group, treatment will be stopped immediately. All women will be informed in detail about the risks of getting pregnant during the informed consent procedure and their obligation and responsibility to use effective contraception with other methods than hormonal contraception as the trial drugs can reduce their efficacy. Women who become pregnant during treatment will be followed up monthly by the trial clinician who is also Family Physician until one year after delivery. In the events of pregnancy-related complications, pregnant women will be referred to appropriate health facilities by the clinician. Babies born to such mothers will be referred by the trial clinician to the nearest health facility to see a pediatrician for up to a year

4.3.3 Risk Benefit Assessment

All participants will benefit from this trial even if they do not belong to the experimental intervention groups or the control group. They will be treated immediately after the study with Ivermectin plus Albendazole (LF) or IVM alone (onchocerciasis) at the standard MDA dosage. Additionally, all participants will be treated with the regimen which has shown best efficacy after termination of the trial.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

Wolbachia endosymbionts, present in most of the human filariae, are essential for worm fertility and survival. In this trial, the combination of Rifampicin plus Albendazole given for 7 and 14 days will be tested and compared to albendazole 400mg for 14 days and to a group receiving no therapy. Both experimental interventions will be subsequently tested for superiority compared to no therapy, and secondly, for non-inferiority compared to albendazole only. Efficacy is given if superiority to no therapy and non-inferiority to albendazole only therapy is proven.

5.1 Primary Objectives

- The primary objective of the LF trial is to show efficacy (**reduction in CFA levels**) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and 'no treatment' (other than Ivermectin) against lymphatic filariasis using the **FTS** method.
- The primary objective of the Onchocerciasis trial is to show efficacy (depletion of *Wolbachia* and interruption of embryogenesis in female adult worms) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and no treatment (other than Ivermectin) against onchocerciasis using the PCR and immunohistology methods.

5.2 Primary Endpoint

LF trial:

To determine:

- The **modulation (decline) in CFA levels as a measure of the presence of adult worms assessed by Alere filarial antigen test strips** at 18 months after treatment onset (where day 0 is start of drug administration).

Onchocerciasis trial:

To determine the:

- Proportion of dead adult worms and MF assessed by immunohistology 20 months after treatment onset (where day 0 is start of drug administration).
- Absence of *Wolbachia* endobacteria in adult female worms assessed by immunohistology 20 months after treatment onset
- Assessment of embryogenesis in female worms by histology 20 months after treatment onset
- Evaluation of worm embryogenesis assessed by histology 20 months after treatment onset
 - a) Normal embryos
 - b) Degenerated embryos
 - c) no embryos (oocytes only or uterus empty)

5.3 Secondary Objectives

- Lymphatic filariasis
 - **To show efficacy (reduction in CFA levels) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and ‘no treatment’ (other than Ivermectin) against lymphatic filariasis using Og4C3 antigen test 18 months after treatment onset (where day 0 is start of drug administration).**
 - To show macrofilaricidal efficacy of the combination of RIF plus ALB using CFA with or without ultrasonography compared to no treatment and treatment with albendazole.
 - To show macrofilaricidal efficacy of the combination of RIF plus ALB using Filaria dance sign (FDS, ultrasonography) compared to no treatment and treatment with albendazole.
 - To analyse the safety profile of the combination of RIF plus ALB in the treatment of lymphatic filariasis
 - To select the best therapy strategy and dosing regimen with regard to safety and efficacy
- Onchocerciasis
 - To show macrofilaricidal efficacy of the combination of RIF plus ALB using PCR and immunohistology compared to no treatment and treatment with albendazole.
 - To show *Wolbachia* depletion efficacy of the combination of RIF plus ALB using PCR and immunohistology compared to no treatment and treatment with albendazole.
 - To analyse the effect of the combination of RIF plus ALB on microfilariae (MF) in the skin.
 - To analyse the safety profile of the combination of RIF plus ALB in the treatment of onchocerciasis.
 - To select the best therapy strategy and dosing regimen with regard to safety and efficacy.

5.4 Secondary Endpoints

- Lymphatic filariasis

To determine the:

- **Reduction in CFA levels (antigen units) as a measure of the presence of adult worms assessed by the Og4C3 antigen test at 4,12 and 18 months after treatment onset (where day 0 is start of drug administration).**
- Absence or reduction of filarial dance sign (FDS) detected by scrotal ultrasound 4, 12 and 18 months after treatment onset
- Adverse events (AEs) as well as serious adverse events (SAEs) in response to the different treatments will be assessed and described in the scope of the daily observed treatment (DOT).

If SAEs occur, the subject will immediately be referred to the nearest district hospital where medical treatment will be provided. SAEs will be reported to the institutional review boards per guidelines and timelines (see section 10).

- Onchocerciasis

- Determination of number of nodules (onchocercomata) with free living microfilariae assessed by histology 20 months after treatment onset
- Assessment of number of live/ dead worms (macrofilaricidal activity) through histology 20 months after treatment onset
- Insemination of female worms assessed by histology 20 months after treatment onset
- Absence of *Wolbachia* bacteria (as a non-quantitative parameter) in adult worms assessed by immunohistology (using antisera against *Wolbachia* surface protein) as described for our previous trials [9] 20 months after treatment
- Reduction of *Wolbachia* bacteria in adult worms assessed by immunohistology 20 months after treatment onset
- Reduction of *Wolbachia* bacteria in adult worms assessed by polymerase chain reaction (PCR) 20 months after treatment onset
- Reduction of *Wolbachia* bacteria in MF assessed by polymerase chain reaction (PCR) 4, 18 and 20 months after treatment onset
- Microfilarial load in the skin measured after 4, 18 and 20 months after treatment (but before ivermectin administration), compared to pre-treatment values.
- Proportion of study participants with absence of microfilariae in the skin, assessed 4, 18 and 20 months after treatment (but before ivermectin administration), compared to pre-treatment.
- Onchocerciasis skin disease after 4, 18 and 20 months, compared to pre-treatment assessment.
- Parasite-specific immunoglobulin subclasses and cytokine responses after 4, 18 and 20 months, compared to pre-treatment values.
- Adverse events (AEs) as well as Serious Adverse Events (SAEs) in response to the different treatments will be assessed and described in the scope of the daily observed treatment (DOT).

For all endpoints: Treatment A, B and C will first be compared to Treatment D and secondly Treatment A and

B will be compared to Treatment C. In a last step Treatments, A and B could be compared to each other.

5.5 Further Variables

Additionally, the effect of the drugs on microfilariae will be evaluated by PCR and immunohistology.

6.0 TRIAL DESIGN

6.1 Trial Design

The study is a prospective, randomized, controlled, monocentric, open-label, parallel-group, interventional phase II pilot trial with blinded endpoint evaluation as the ultrasonography, immunohistology and the persons responsible for PCR assessment and other outcome analyses will be blinded to treatment assignment. Patients with lymphatic filariasis and onchocerciasis who meet the inclusion/exclusion criteria will be allocated to participate in this clinical trial and finally randomized to one of the four following treatment groups for each trial.

6.2 Treatment Groups

Treatment A: Rifampicin (Rifadin®) 35mg/kg/d (adapted to body weight) plus Albendazole (Zentel®) 400mg/d for 7 days

Treatment B: Rifampicin (Rifadin®) 35mg/kg/d (adapted to body weight) plus Albendazole (Zentel®) 400mg/d for 14 days

Treatment C: Albendazole 400mg/d for 14 days

Treatment D: No therapy (only nodulectomy for onchocerciasis trial)

All participants (experimental and control groups) will be treated at 6 and 18 months after treatment onset with standard MDA (mass drug administration), that is, Ivermectin (150 µg/kg) and a single dose of albendazole (400mg/d) for LF; and Ivermectin (150 µg/kg) for onchocerciasis.

6.3 Trial centres

These trials will be monocentric. It will be conducted by the Kumasi Centre for Collaborative Research (KCCR) in Tropical Medicine of the Kwame Nkrumah University for Science and Technology (KNUST), Kumasi Ghana. The Filariasis research group under the leadership of Prof. Alexander Yaw Debrah is very experienced with the implementation of clinical trials in the field of Filariasis and meets all structural and personnel requirements for performing the planned regular trial-related investigations (see <http://kccr-ghana.org/?page id=238>).

The LF and onchocerciasis trials will be set up in communities of Bawku West, Builsa South, Nabdam, Fumbisi, Garu-Tempane, Kayoro, **Kassena-Nankana Municipal and Kassena Nankana District** all in the Upper East

Region of Ghana where lymphatic filariasis and onchocerciasis are endemic, communities in Sefwi Akontombra District in the Western North Region of Ghana, which is endemic for onchocerciasis and Ahanta West Municipal, Nzema East Municipal and Ellembelle Districts all in the Western Region of Ghana, which are endemic for lymphatic filariasis (LF).

A preliminary survey done in about 10 study villages (see Figure 2) of the Nabdam District showed CFA prevalence between 19.8% to 38.5% and MF prevalence between 1.7% to 3.8% in the examined volunteers. The district capital of Nabdam District is Nagodi, which is about 20-45 minutes' drive to the study villages where the patients will be recruited.

A preliminary study also conducted in some communities in the Bawku West District and the Kayoro Sub-district showed a nodule prevalence of 5.9-35.5% and 9.3-23.4%, both in the Upper East Region of Ghana where onchocerciasis is endemic.

A prevalence assessment conducted in about 10 communities in the Sefwi Akontombra District showed a nodule prevalence of between 15.9-47.2% and microfilaridermia prevalence of between 10.0-48.7%, respectively.

According to the Ghana Neglected Tropical Diseases Control Program (NTDCP), the Ahanta West Municipal, Nzema East Municipal and Ellembelle Districts, are endemic hotspots for LF disease and transmission is still ongoing in these Districts.

Despite IVM+ALB MDA, transmission is ongoing and our recent rapid preliminary assessments for other trials have identified many patients who were CFA-Positive and MF-positive (Figure 2C). Participants will be recruited and treated directly in their villages.

Safety measures such as the use of facemasks, washing hands, the use of alcohol-based sanitizers, etc. would be employed with staff and participants to avoid transmission of any viral disease such as coronavirus. These measures are effective in reducing transmission. We would provide these materials to both participants and research staff.

The laboratories where the lab analyses will be done are located in the War Memorial District Hospital in Navrongo, the Sefwi Wiawso Municipal Hospital, Nana Hima Dekyi Government Hospital – Dixcove, the Axim Government Hospital - Axim and the Essiama Health Center - Ellembelle. The research team will stay in Bolgatanga, Sefwi Wiawso, Dixcove, Axim and Essiama, respectively, during the trial periods for continuous contact and monitoring of the trial participants. Bolgatanga is 30 minutes' drive from Navrongo and about 60 minutes' drive from some of the study communities. Sefwi Wiawso is approximately 45 minutes' drive from the study communities in Sefwi Akontombra. Dixcove, Axim and Essiama are also about 45 minutes' drive from the study communities.

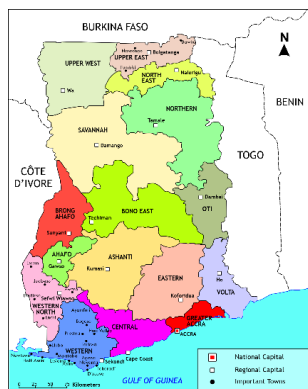


Figure 3A: Map of Ghana



Fig. 3B

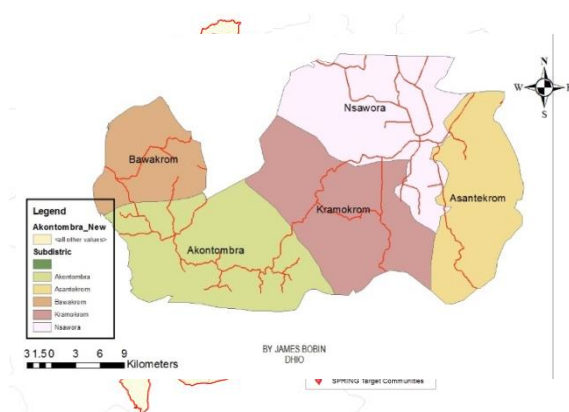


Fig. 3C

Fig. 3D

Figure 3B: Map of Ghana showing regions (red) where selected study communities are located.

Figure 3C: Map of the Bawku West District showing the study communities.

Figure 3D: Map of the Sefwi Akontombra District showing Sub-districts.

6.4 Number of subjects

The study is planned to enroll a total number of 120 participants in each trial (LF and Onchocerciasis).

Participants will be randomized as follows:

30 participants will be randomized in treatment A,

30 participants in treatment B,

30 participants in treatment C and

30 participants in treatment D

6.5 Recruitment

Recruitment will be carried out directly in the villages. Before start of recruitment the research team will visit the village elders to explain the planned study in detail. At the next visit, all villagers will be invited to come to a public meeting where the study will again be explained in detail. After this meeting all interested volunteers, who are from 18 to 55 years old and have signed the Informed Consent Form for screening, will

be invited for the first screening (LF: Medical examination, ultrasonography, blood and urine sampling; Onchocerciasis: Medical examination, palpation, skin snipping, blood and urine sampling) which will be carried out by trained members of the research team under the supervision of Dr. Linda B. Debrah and/or Prof. Alexander Debrah. The screening will be carried out directly in the villages. The research team will use rooms provided by the village or will bring tents that guarantee the privacy of the volunteers during examination.

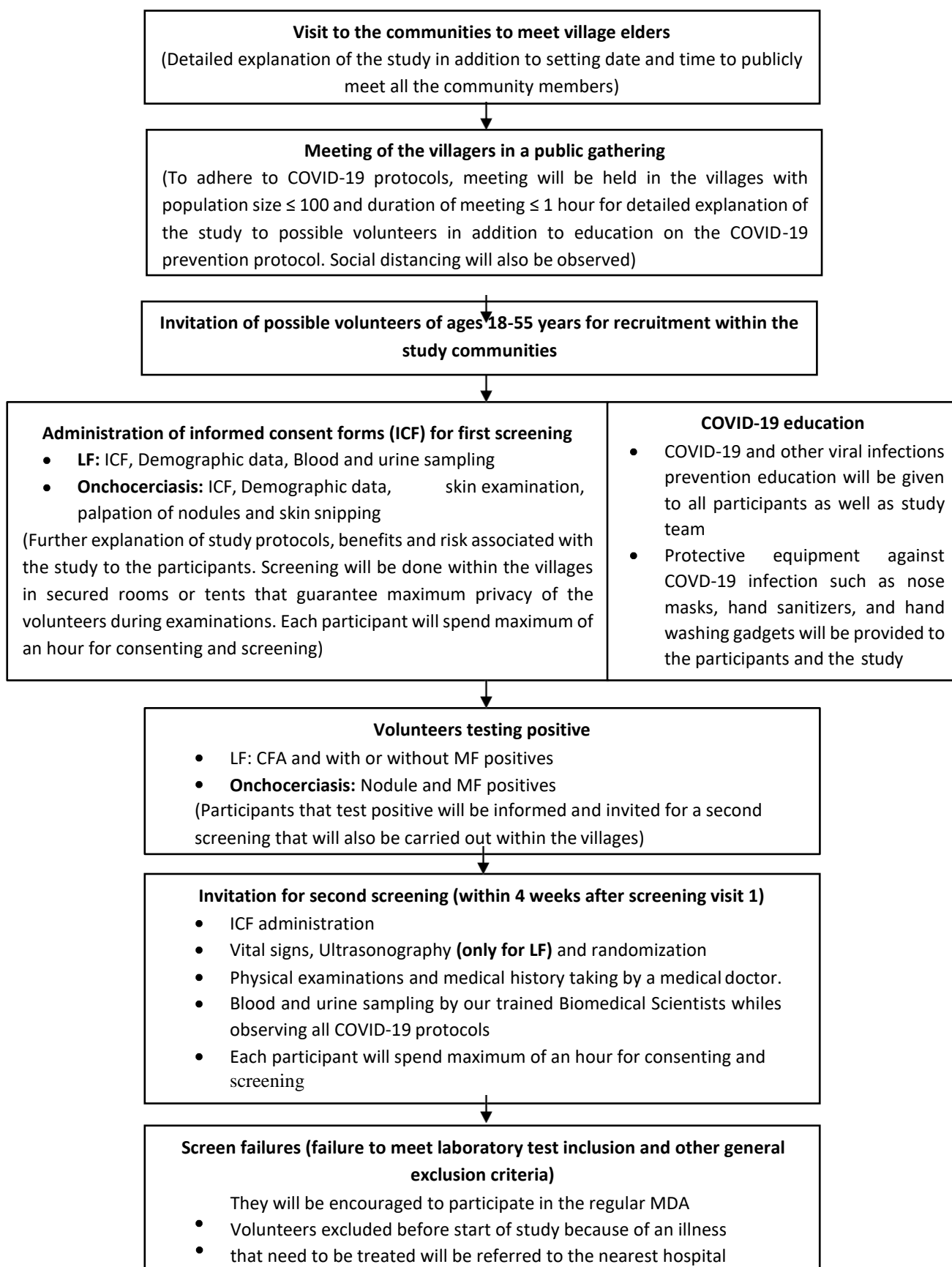
All volunteers who tested positive for CFA during the first screening **with or without MF** will be invited to come to the second part of the screening which will also be carried out directly in the villages.

During the onchocerciasis survey, volunteers who had palpable nodules during the first screening and were also MF-positive will be invited to come to the second part of the screening. During the second screening a medical doctor will be present to do the physical examination and to take the medical history of the volunteers. The blood sampling will be done by trained research personnel/phlebotomists.

Screen failures will be encouraged to take part in the regular MDA (“standard of care”). In case volunteers are excluded before study start because of an illness that has to be treated they will be referred to the nearest hospital.

Safety measures such as the use of facemasks, washing hands, the use of alcohol-based sanitizers, social distancing, etc. would be employed with staff and participants to avoid transmission of any viral disease such as coronavirus. These measures are effective in reducing transmission. We would provide these materials to both participants and research staff.

COMMUNITY ENGAGEMENT



RECRUITMENT PLAN

Activity	Screening Timelines	
	Visit 1	Visit 2
Informative meetings with village elders	1 week before 1 st Screening	Not Applicable (N/A)
Informed Consent for 1 st Screening and Demographic data collection	1 week after meeting with village elders	(N/A)
Informed Consent for 2 nd Screening, and Treatment (Medical History, Physical Examination, Ultrasonography (for only LF) , Prior therapies/medications, Concomitant Medication, Vital Signs, and Randomization)	(N/A)	4 weeks after first screening visit 1
FTS for CFA and Mf testing (for LF studies)	Within the period of 1 st Screening	(N/A)
Skin examination, Nodule Palpation and Skin snipping for Mf (for Onchocerciasis studies)		

SUMMARY OF LABORATORY TESTS

No.	Laboratory Test	Normal Reference	Availability of Test Results
1	Filarial Test Strip (FTS) for CFA test	Positive	Same day after sampling
2	Microfilarial Count a) Sedgewick-rafter chamber b) Filtration Procedure (Giemsa Staining)	Not applicable	
3	Haemoglobin level (Hb)	8.0 – 17.0 g/dL	
4	Leucocyte count (Total WBC)	3.0 – 15.0 x10 ³ /L	
5	Neutrophils%	37.0 – 72.0 %	
6	Lymphocytes%	20.0 – 50.0 %	
7	Monocytes%	0 – 14 %	
8	Eosinophils%	0 – 6 %	
9	Basophils%	0 – 1 %	
10	Platelet count	50 – 400 x10 ³ /L	
11	Urine Pregnancy Test	Negative	
12	AST (GOT)	0 – 44 U/L	
13	ALT (GPT)	0 – 40 U/L	
14	γGT	0 – 55 U/L	
15	Creatinine	53 – 124 μmol/L	
16	Skin Snipping (Microscopy)	Not applicable	Next day after sampling
17	TropBio ELISA for CFA test	Positive	72 hours after sampling
18	Urine Glucose	Negative	Same day after sampling
19	Urine Protein	Negative	
20	Blood (Urine)	Negative	

6.6 Time Schedule

Per participant:

The treatment will have a duration per patient of:

- 7 days (Rifampicin 35mg/kg/d plus Albendazole 400mg/d) in Treatment A
- 14 days (Rifampicin 35mg/kg/d plus Albendazole 400mg/d) in Treatment B,
- 14 days (Albendazole 400mg/d) in Treatment C.

However, participants, regardless of the treatment arm they are assigned to, will be asked to come to the daily treatment visits for at least 14 days for safety assessment by the research team asking for adverse events and performing physical examination or other diagnostic procedures as necessary. USG, blood and urine samples will be taken at 4, 12 and 18 months after treatment onset for LF. For onchocerciasis, urine and blood samples will be taken at 4, 18 and 20 months after treatment onset. Each participant will remain in the study for approximately 18 and 22 months for LF and onchocerciasis respectively.

For onchocerciasis patients, after an initial follow-up period at 4 and 18 months after treatment, nodulectomies will be carried out finally at 20 months after treatment onset. The nodulectomy will take 10-14 days (including wound dressing). Beginning from recruitment, treatment, follow-up periods and nodulectomies, each participant will remain in the study for approximately 22 months.

During recruitment and treatment participants will be able to work. Treatment visits will take place early in the morning.

Trial duration:

- Screening/Recruiting Period: 2-3 months
- Planned Start Date (FPFV): December 01, 2020
- Planned End Date (LPLV): **March 31, 2024**

Different to most clinical trials, treatment of all 120 participants for each trial (both LF and Onchocerciasis) will be carried out at the same time.

7.0 TRIAL POPULATION AND SELECTION CRITERIA

These trials can fulfill their objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular participant.

Only patients with lymphatic filariasis and Onchocerciasis will be included in these trials. LF will be assessed by CFA and/or USG and blood draw for microfilarial load from volunteers and Onchocerciasis will be assessed by palpation for nodule and skin snip from volunteers from endemic areas. Children and persons not capable

of giving adequate informed consent will not be included.

7.1 Study population

The Lymphatic Filariasis and Onchocerciasis trials will be set up particularly in communities of Bawku West, Builsa South, Nabdam, Fumbisi, Garu-Tempane, **Kassena-Nankana Municipal, Kassena-Nankana West District** and Kayoro districts all in the Upper East Region, Sefwi Akontombra in the Western North Region, Ahanta West Municipal, Nzema East Municipal and Ellembelle Districts all in the Western Region of Ghana, where lymphatic filariasis and onchocerciasis are still endemic.

The Upper East Region of Ghana is a guinea savanna woodland area, with an annual rainfall of approximately 100 cm, most of which falls between May and September. Temperatures range between 16°C and 41°C. The area is contiguous with the border of Burkina Faso and has a typically Sahelian ecological setting. About 20% of the region has had any formal education and they are relatively poor. There are numerous small dams in the area, and consequently, many favorable breeding sites for mosquitoes and other insects. The people are mostly occupied with farming, livestock and handicrafts including straw hats, baskets, cloth and jewelry. Only 21 percent of the population live in towns, it is mainly rural with dispersed settlements of extended family compounds surrounded by their farm lands. Villages have distinctive building styles that have evolved through the generations (24).

Preliminary surveys done in about 10 study villages (see Figure 2) of the Nabdam District showed CFA prevalence between 19.8% and 38.5% and MF prevalence between 1.7% to 3.8% in the examined volunteers. A preliminary study also conducted in some communities in the Bawku West District and the Kayoro Sub-district showed a nodule prevalence of 5.9-35.5% and 9.3-23.4%, both in the Upper East Region of Ghana. Our recent rapid preliminary assessments identified many patients who were CFA-Positive and MF-positive. Despite IVM+ALB MDA, transmission is clearly ongoing. The district capital of Nabdam District is Nagodi, which is about 20-45 minutes' drive to the study villages where the patients will be recruited.

The Nabdam district where the LF trial will be conducted has a population of about 40,718 (2019 projected population, Ghana statistical service) and the Bawku District where the Onchocerciasis trial will be conducted has a population of about 49,907 adults who are 18 years and above (2019 projected population, Ghana statistical services) all of which leaves no doubt about the feasibility of the 120 number of patients proposed for LF and Onchocerciasis in this trial.

7.2 Gender Distribution

No gender ratio has been stipulated in this trial as the results of preclinical and clinical studies or medical literature did not indicate any difference in the effect of the trial treatment in terms of efficacy and safety.

7.3 Inclusion Criteria

- Lymphatic filariasis

Participants must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

- Willingness to participate in the study by signing the Informed Consent Form (ICF) as participation in study is voluntary
- 18-55 years in other to enroll adults capable of making an informed decision and with less health conditions
- Body weight > 45kg for effective determination of study endpoint
- Positive for CFA detected by Filarial Test Strip (FTS) irrespective of the filarial dance sign (FDS) status detected by Ultrasonography (USG) measurement **(in men)**
- **with or without MF.**
- Good general health without any clinical condition requiring medication in other to enroll healthy participants
- No previous history of tuberculosis to prevent the possible emergence of rifampicin-resistant strains of Mycobacteria.
- Participants with the ability to follow study instructions and who are likely to attend and complete all required visits in other to reduce non-compliance and drop-outs from study

- Onchocerciasis

Participants will only be included in the study if they *meet all* of the following criteria:

- Willingness to participate in the study by signing the Informed Consent Form (ICF) as participation in study is voluntary
- 18-55 years in other to enroll adults capable of making an informed decision and with less health conditions
- Body weight > 45kg for effective determination of study endpoint
- Presence of at least 1 medium-sized onchocercoma detected by palpation as an indicator of ongoing infection
- MF-positive as a measure of active infection
- Good general health without any clinical condition requiring medication in other to enroll healthy participants
- No previous history of tuberculosis to prevent the possible emergence of rifampicin-resistant

strains of *Mycobacteria*.

- Participants with the ability to follow study instructions and are likely to attend and complete all required visits in order to reduce non-compliance and drop-outs from study

7.4 Exclusion Criteria for both LF and Onchocerciasis

Participants presenting with any of the following exclusion criteria may not be included in the trial:

General Exclusion Criteria:

- Participants not able to give consent
- Participants who are unable to understand the nature, scope, significance and consequences of this clinical trial
- Participants taking concomitant medication that interferes with study drugs (at the discretion of trial clinician)
- Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure (Rifampicin or any member of the Rifamycins)
- Simultaneous participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning
- Participants with a physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in this clinical trial
- Known or persistent abuse of medication, drugs or alcohol.
- History of neurological, cardiac or pulmonary, disease
- History of acute Hepatitis A and acute or chronic Hepatitis B or C

Laboratory Exclusion Criteria:

- Laboratory evidence of liver disease (AST, ALT and γ GT greater than 1.5 times the upper limit of normal i.e., 44.0 U/L, 40.0 U/L and 55.0 U/L respectively)
- Laboratory evidence of renal disease (eGFR <60ml/min/1.73m²)
- Laboratory evidence of leukopenia (leukocytes < 3000/ μ l)
- Laboratory evidence of anaemia (Hb < 8.0)

Exclusion criteria regarding special restrictions for females:

- Pregnant women
- Breastfeeding women

- Females of childbearing potential, who are not willing or able to use methods to prevent a pregnancy for the entire treatment duration in addition to hormonal contraception (e.g., condoms) unless they are surgically sterilized/hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases.

7.5 Subject Information

The informed consent procedure will mainly be carried out in two steps for both LF and Onchocerciasis with a third step for only participants in the Onchocerciasis trial:

Step 1: Screening

It is a requirement that written consent is obtained prior to any trial-specific procedures. Since it is necessary to perform trial-specific procedures (Ultrasonography, palpation, skin examination, skin snipping blood and urine sampling) prior to the decision of eligibility, all volunteers will be informed about the trial and specifically about these trial-specific screening procedures by the investigator and will be asked for his/her written or thumb print consent prior to the screening. The investigator will record the details of all examined volunteers on trial specific lists provided.

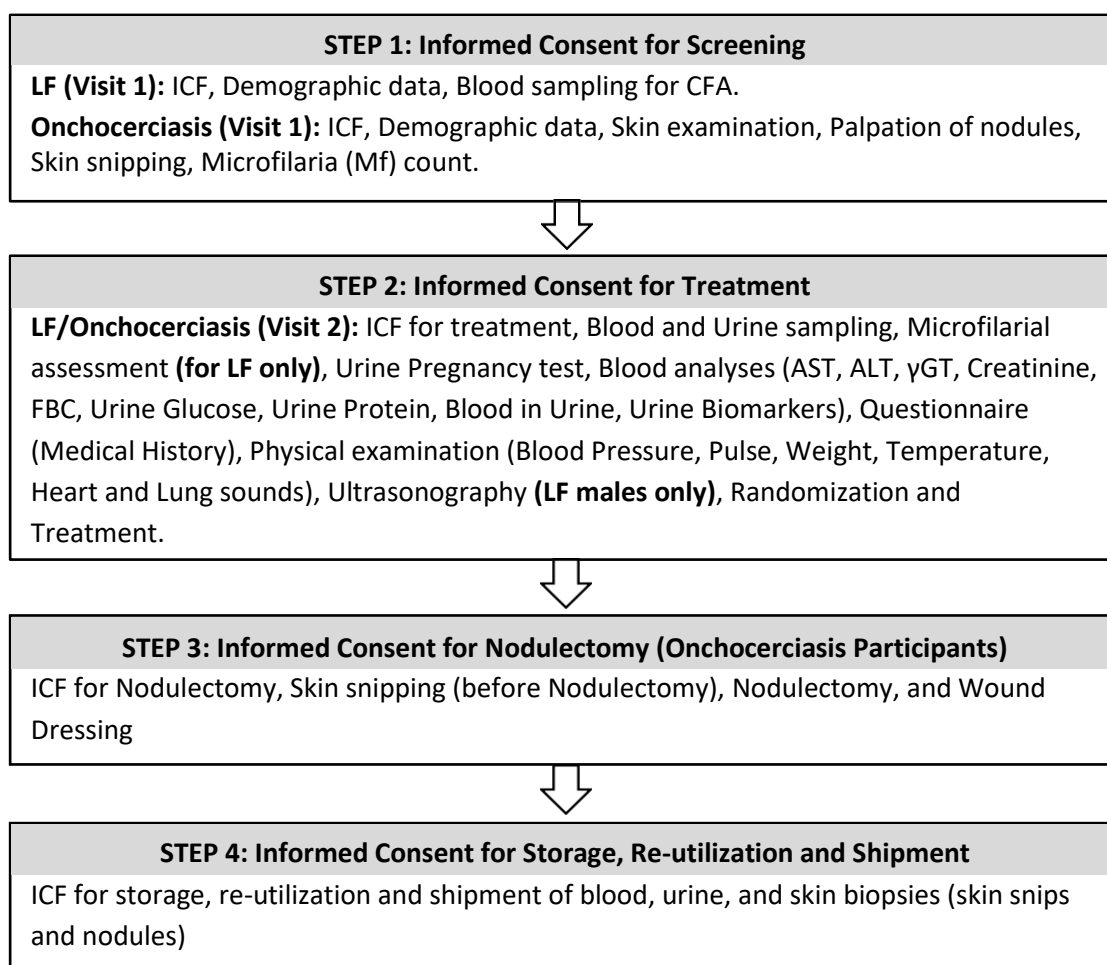
Step 2: Enrolment

If a volunteer appears to be eligible for the trial, the investigator will inform the volunteer again about the trial and about the interventions and therapeutic regimen in more detail and ask the volunteer for his/her written or thumb print consent.

Third Step: Surgical intervention (Nodulectomies)

The informed consent for the surgical intervention will be part of the informed consent in step 2, but the surgeon will inform the participant again in detail about the intervention and the following procedures (wound dressing, etc.) prior to the nodulectomy and ask the volunteer for his/her written or thumb print consent as part of the clinical routine.

There will be a fourth informed consent form for “Sample storage, re-utilization and shipment”. With this consent form the participant will be asked to give his/her consent for the storage and re-use of the samples taken during and after the clinical trial to find new ways to better diagnose or treat lymphatic filariasis and Onchocerciasis. Since the development of new methods also takes place at the IMMIP Bonn, Germany, the participants will also be asked for their consent to have the samples shipped to Germany



7.6 Randomization

These trials are randomized controlled trials. Between screening visit 1 and treatment visit 1 all subjects eligible for randomization will be randomly assigned to one of the following treatment groups in each trial:

Treatment group A: 30 subjects

Treatment group B: 30 subjects

Treatment group C: 30 subjects

Treatment group D: 30subjects

Randomization to the treatment groups will be conducted by central randomization. Randomization is carried out according to a predefined randomization list. The randomization list will comprise treatment codes from 1 to 150 (for the 120 patients plus 30 spare codes) and the name of the respective treatment for each code, respectively. In case a participant is eligible for treatment his/her ID will be sent to the data management team in KNUST and the next treatment number in the list will be assigned to the patient.

This procedure assures that the assignment of the participants to the respective treatment groups will not be biased by any personal involvement.

All persons involved in data handling and the statistical analyses at the end of the trial as well as the USG, immunohistology and PCR outcome assessors will stay blinded to the nature of the treatment. After randomization, the treatment can be initiated according to the treatment code.

8.0 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

8.1 Specification of IMP

IMP 1:

Trade name	Rifadin®
Name of manufacturer	Sanofi-Aventis
Substance name (if applicable, give substance code)	Rifampicin
Name and dose of active ingredient per unit	Rifampicin 35mg
Pharmaceutical form	tablet
Mode of administration	oral
Storage conditions	25°C – excursions permitted 15-30°C, dry and away from heat

IMP 2:

Trade name	Zentel®
Name of manufacturer	Glaxosmithkline
Substance name (if applicable, give substance code)	<u>Albendazole</u>
Name and dose of active ingredient per unit	<u>Albendazole 400mg</u>
Pharmaceutical form	film-coated tablets
Mode of administration	oral
Storage conditions	below 25°C, dry

8.2 Rifampicin (IMP 1)

Rifampicin (Rifadin®) is an already marketed product for the treatment of tuberculosis. It is used only in treatment combinations. The treatment of filarial diseases (lymphatic filariasis and Onchocerciasis) is an off-label treatment and was never used for these diseases in humans before.

Rifampicin will be supplied for this trial by Sanofi-Aventis for the duration of the whole trial.

The IMP 1 will not be modified from its usual commercial status.

8.3 Albendazole (IMP 2)

Albendazole (Zentel®) is an already approved and registered drug in Ghana and is the current standard of care in Ghana used in combination with Ivermectin for lymphatic filariasis mass drug administration.

This IMP will be obtained in collaboration with the Ghana Health Service or if the need be it will be purchased locally from Glaxosmithkline official distributor.

8.4 Adverse Reactions of IMP

See section 4

8.5 Packaging and Labelling of IMP

Only licensed and marketed IMPs will be used in the clinical trial without additional modifying. All IMPs will be labeled for the conduct of clinical trials only. The packaging and labeling of the IMPs will be done by the pharmacist.

8.6 Transport of IMP

All IMPs are available in Ghana (Rifampicin and Albendazole) and will be purchased locally.

8.7 Storage requirements

The IMP(s) will be stored under the following conditions:

IMP 1 (Rifampicin): below 25°C, dry and away from heat

IMP 2 (Albendazole): below 25°C, dry

The investigator will be responsible for ensuring the correct storage and sufficient stocks of the IMP(s) at the centre. The temperature in the storage room should not pass under 15°C or over 25°C. To control the temperature, it will be measured at least twice daily (using a calibrated thermometer) and documented in a temperature log by the responsible person.

The investigator bears the responsibility for the proper storage in a secure location at the site with restricted access to the investigators and authorized site staff. Personnel who have access to the trial drug will be listed (name and responsibilities) on the Authorization and Delegation Log in the trial specific Investigator Site File (ISF).

The investigator should ensure that the IMP is only used according to the protocol.

8.8 Dosage, Mode of Application and Dose Schedule

IMP 1: Rifampicin will be administered orally once daily at a dosage of 35mg/kg/d as suggested by the manufacturer Sanofi-Aventis. Prior experience in humans showed that an intake of this dosage is safe. The dosage of Rifampicin will be reduced to 750mg/d if the participant has a body weight < 50kg. In total 7560 tablets of Rifampicin will be distributed in the study (both LF and Onchocerciasis).

IMP 2: Albendazole will be administered orally once daily at the standard dosage of 400mg which is also used for mass drug administration. Rifampicin and Albendazole will be given as a combination treatment. There will be three treatment arms with this combination. Treatment A is Rifampicin plus Albendazole given for 7 days; Treatment B is Rifampicin plus Albendazole given for 14 days and Treatment C Albendazole given for 14 days.

An adaption of the dosage of either drug to concomitant diseases will not be necessary since this is already captured by the in- and exclusion criteria. The IMPs will be distributed by the trial clinician/pharmacist directly in the villages of the participants in the form of directly observed treatment (DOT). Participants will be encouraged to eat before swallowing the tablets with water. Doses vomited within 15 minutes after intake will be repeated.

8.9 Handling of IMP at the Site and Drug Accountability

The investigator/pharmacist, or an individual who is designated by the investigator/pharmacist, will explain the correct use of the investigational medicinal product to each subject prior to administration of the product. In accordance with all applicable regulatory requirements and depending on the type of IMP and its mode of application, the investigator/pharmacist, or another appropriate individual who is designated by the investigator/pharmacist, will maintain records to document receipt of the IMP, the stocks of IMP at the trial centre, the dispense and use by the individual subject (drug accountability), the reconciliation, and the return of unused investigational medicinal products to the sponsor or their disposal on appropriate forms filed in the investigator site file.

All the forms relevant for the documentation of drug handling will be confirmed by signature of the investigator/pharmacist, or another appropriate individual who is designated by the investigator/pharmacist.

The investigator may only dispense the investigational medicinal product to subjects who have signed the informed consent and who have been enrolled in the trial. The dispensing of the investigational medicinal product to subjects outside of this clinical trial is not permitted.

8.10 Subject Compliance

The IMP will be administered by the trial clinician/pharmacist in the form of directly observed treatment (DOT), meaning that the drugs will be taken with water in presence of the research team. The intake of the drugs will be individually documented by the research team in treatment sheets and the CRF. In case a patient is not present for the DOT, efforts will be made by the study team to reach the patient through phone call and if this fails, the patient will be recorded as being absent for the particular treatment day. In some cases, patients have to travel for a few days. When they proved their compliance before, the IMP for the travel days will be handed out to the patient and compliance will be reviewed by getting back the empty packages when the patient comes back from travel. In this case the patient will be reminded by the designated investigator to take their drugs through phone calls and also advised to immediately report any adverse reactions or problems with the trial drugs to the trial clinician. Everything will be documented in detail in the treatment sheets (source data) and the CRF.

8.11 Return and Disposal of IMP

All unused IMP will be destroyed as per FDA guidelines. The destruction will be supervised by the FDA and a destruction form has to be completed with the information about date and location of destruction, sort and amount of IMP.

Copies of relevant forms completed at the trial site will be returned to the Principal Investigator at the end of the trial and will be collected by the monitor during the close out visit or have to be sent to the Principal Investigator on request.

8.12 Unblinding

This is an open label study; therefore, participants and the field team will not be blinded to the different regimen. However, to avoid bias during the evaluation of the USG, immunohistology and PCR, the outcome assessors will be unaware of the assigned treatment regimens.

As a matter of principle, unblinding is therefore only performed after the closing of the database for the final analysis.

8.13 Prior and Concomitant Therapy/Medication

Every concomitant medication (other than the trial drugs) during the treatment period should be discussed with the trial clinician/trial pharmacist and will be documented in subject's medical record and the CRF with mentioning of the reason and dosage.

8.13.1 Previous therapy / medication of trial specific illness

All previous treatments for managing the trial specific illness (e.g., Mass drug administration, previous rounds of Ivermectin + Albendazole, last intake of Ivermectin + Albendazole) and applied medications will be documented in the subject's medical record and the CRF according to the memory of the patient.

8.13.2 Previous therapy / medication with Rifampicin

All previous treatments and medications with Rifampicin during the last year before starting the trial will be documented in the subject's medical record and CRF according to the memory of the patient.

8.13.3 Concomitant therapy / medication for other indications

All concomitant therapies/medications other than the trial therapy/investigational medicinal product applied during the trial will be documented in the subject's medical record and in the appropriate CRF.

The above-mentioned therapies/medications have to be recorded in the subject's medical record and CRF including the following information:

- brand name,
- indication,
- dose per intake and units,
- route of administration,
- time /duration of treatment (start and stop date of treatment or ongoing instead of the stop date if treatment is still persisting at subject's termination visit)

8.13.4 Prohibited therapy / Concomitant medication

The following therapies / medications are not allowed to be applied during the trial because of interaction with the trial drugs:

- Interaction with Rifampicin: NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
- Interaction with Rifampicin: corticosteroids

- Interaction with Rifampicin (induction of CYP450 enzymes): protease inhibitors, reverse transcriptase inhibitors, hormonal contraceptives

Every effort should be made to avoid the use of any of the listed prohibited therapies/medications during the entire of the trial.

All participants will be asked not to take part in the mass drug administration (MDA with Ivermectin) during screening, before treatment and 20 months after treatment. There will be no harm or disadvantage for the participants if they take part but since it may affect the outcome parameters of the study, these participants will then be excluded from the per protocol analyses. Ivermectin will be distributed to every participant following the 18 months follow-up for LF and 20 months follow-up for onchocerciasis

8.13.5 Rescue/Escape/Salvage Therapy

Not applicable

9.0 TRIAL PROCEDURES

9.1 Methods of Assessment for LF trial

The following section will give an overview and adequate explanations for the examinations and procedures to be performed in this trial.

9.1.1 Ultrasonography

Scrotal ultrasound **may** be done on every male volunteer to detect worm nests (adult worm) by an experienced member of the research team. **Prior to the advent of the COVID-19 pandemic, it was planned that** Dr. Inge Kroidl from Munich University will come to Ghana and go to the field with the team to teach the PhD students on the use of ultrasonography for worm detection as a capacity building for future projects. **This was initially planned** for pre-treatment, 12 months and 18 months after treatment time points. **However, this procedure is currently in jeopardy due to travel restrictions resulting from COVID-19 and other unforeseen circumstances that may arise. If circumstances allow,** a SonoSite M-Turbo S Series hand-carried ultrasound system (SonoSite Inc.; Washington, USA) equipped with an L 38 mm 7.5 MHz linear array transducer will be used. Male volunteers will be examined in a supine position in order to reduce interference by movements of the patients themselves. The examiner, Dr Inge Kroidl will document detected worm nests and scrotal findings using print outs (thermo- printer) and digital video sequences. The Pulse Wave Doppler (PWD) mode will be used as an additional tool to differentiate FDS of adult worms in lymphatic vessels from blood flow in veins and arteries. The worm nests locations if found will be documented in the case report form for each time point (pre- treatment, 12 months and 18 months) of USG examination. This will be done only in male volunteers since it is difficult to detect FDS in females [22].

This procedure is not invasive nor will it harm the volunteer. In case there is a detection of worm nest the volunteer will undergo the following procedures (see 9.1.2, 9.1.3).

9.1.2 Blood sampling

Blood samples (2 tubes, 9ml each) will be taken before treatment to examine microfilarial load, creatinine, liver and kidney enzymes at the War Memorial hospital, Nana Hima Dekyi Government Hospital, Axim Government Hospital and Essiama Health Center, as well as disease-specific immunoglobulins, TropBio® ELISA test, assessment of immunological and vascular endothelial growth factors (VEGFs) using ELISA test kits, cytokines and other potential biomarkers at the KCCR and IMMIP. Before treatment visit 8, 2x5ml of blood will be taken to assess possible changes caused by the drugs on liver enzymes, creatinine and leukocytes. Additional blood sample (2 tubes, 9ml) will be taken at 4, 12 as well as 18 months after treatment onset to assess possible changes caused by the drugs on microfilarial load. If any of these values show clinical significance (range of exclusion criteria) measurements will be repeated and the participants will be monitored and treated at the discretion of the trial clinician.

9.1.3 Urine sampling

Urine samples will be taken before treatment, 4, 12 and 18 months after treatment onset to assess potential diabetes or, in case of a female participant, pregnancy using the HCG accurate pregnancy test kit (Registration number FDA/D. 18-6072) as well as disease-specific biomarkers.

9.1.4 PCR

Deoxyribonucleic acid (DNA) will be extracted from blood according to the manufacturers' instructions (QIAamp DNA Mini Kit). The gene will be quantified from the purified DNA by real-time duplex PCR (qPCR). Genes will be amplified in a Rotor gene 3000 (Corbett Research, Sydney, Australia). Fluorescence will be acquired on the FAM and JOE channel. Copy numbers for each gene will be calculated using a modification of the comparative quantification formula.

Source documents regarding the different assessment methods will be stored and be available for subsequent review. Respective printouts will be stored in the subject medical file, including the trial number. The PCR will be done at KCCR and that of CFA analyses at War Memorial hospital, Nana Hima Dekyi Government Hospital, Axim Government Hospital and Essiama Health Center. The PCR technology has recently been transferred to Ghana (KCCR) with the purchase of a RotorGene 6500 (Corbett Research, Sydney, Australia) as part of the expansion of the facilities in Ghana.

9.1.5 Laboratory examinations / Biological Specimens

Laboratory blood analyses will be done on the same day of the blood sampling by the research team at a designated laboratory at the War Memorial Hospital in Navrongo, Nana Hima Dekyi Government Hospital, Axim Government Hospital and Essiama Health Center. Analyses will be done by using the validated Chemistry analyzer- Selectra Pro S from ELITechGroup. All parameters tested in this trial can be tested in Serum or Heparin-Plasma.

The scientific analyses of immunoglobulins, cytokines and biomarkers will be done at baseline and following the treatment (4, 12 and 18 months after treatment) at the KCCR and IMMIP. Therefore, the blood samples will be frozen and stored, labelled with the trial specific ID of the patient as well as date of sampling.

The total amount of blood drawn per subject during the entire trial will be approximately 85-90 ml.

For detailed list of parameters determined in the blood refer to 9.1.2, blood sampling.

Pregnancy tests will be carried out in the urine using the HCG accurate pregnancy test kit (Registration number FDB/D16-11170) at the field site during the screening period, on the first day of treatment (before intake of the first dosage of the IMP), and weekly during treatment period and after treatment or before treatment with Ivermectin and Albendazole.

All other urine-analyses will be done at the field site using Roche Combur 9-Test® strips. Urine samples will also be taken before treatment, after 4, 12 and 18 months for assessment of potential biomarkers at the KCCR and IMMIP. For the Scientific analyses of the urine, samples will be labeled with the trial specific patient ID as well as the date of sampling, frozen and stored until analyses can start.

Data from the screening visit which describe the baseline status of the subjects will be documented in the source data and in the CRF.

All additional clinically significant findings will as well be documented in the source data and in the CRF.

9.2 Methods of Assessment for Onchocerciasis trial

The following section will give an overview and adequate explanations for the examinations and procedures to be performed in this trial.

9.2.1 Palpation of onchocercomata

Every volunteer will be palpated manually for subcutaneous nodules (onchocercomata) by an experienced member of the research team – Dr. Linda Batsa Debrah. This procedure is not invasive nor will it harm the volunteer. If the volunteer has nodules, he/she will undergo the following procedures:

9.2.2 Assessment of microfilariae load (skin snipping)

Skin snips will be taken 4 times during the trial period (during the screening period, 4 months after treatment, 18 months after treatment and 20 months after treatment but before the nodulectomies to assess the MF load in the skin. Two skin biopsies 1-3 mg will be taken from the right and the left iliac crest. Each biopsy will be immersed in 100 ml of 0.9% NaCl solution in a well of a microtiter plate. The skin biopsies will be incubated overnight at room temperature to allow MF to emerge. The solution will then be transferred onto a slide for microscopic examination and MF count done by two independent investigators according to the local SOP. In case of doubt, a third opinion will be sought. The wet biopsies will be weighed using an electronic balance and the MF load will finally be calculated per mg skin. After the readout of the number of MF, the MF will be stored in isopropanol to be later analysed by using a newly established PCR method for the detection of *Wolbachia* at the KCCR.

9.2.3 Blood sampling

Blood samples (2 tubes, 9ml each) will be taken before treatment to assess liver and kidney enzymes and leucocytes at the War Memorial hospital in Navrongo and the Sefwi Wiawso Municipal hospital, as well as disease-specific immunoglobulins, cytokines and other potential biomarkers at the KCCR and IMMIP. Before treatment visit 8, 2x5ml of blood will be taken to assess possible changes caused by the drugs on liver enzymes, creatinine and leukocytes. If a study participant has elevated liver function test (LFT) during treatment, treatment will be stopped if it's ongoing and participant will be monitored with appropriate clinical care. Biochemistry tests will also be performed to check if participants' LFTs have returned to acceptable and manageable levels. Additional blood sample (2 tubes, 9ml) will be taken at 4 months, 18 months and 20 months (before nodulectomies) to assess changes in disease-specific immunoglobulins, cytokines and other potential biomarkers vascular endothelial growth factors (VEGFs).

9.2.4 Urine sampling

Urine samples will be taken before treatment, at 4 months, 18 months and 20 months (before nodulectomies) to assess potential diabetes or, in case of a female participant, pregnancy as well as disease specific biomarkers.

9.2.5 Nodulectomies

Nodulectomies (surgical extirpation of onchocercomata) will be done under local anaesthesia in the local district hospital to assess *Wolbachia* in the adult worms, embryogenesis in female adult worms and worm vitality. The nodules will be fixed in ethanol or formaldehyde solution. Samples will be embedded in paraffin and several sections will be stained with hematoxylin and eosin, Gomori's method for iron, and

immunostained using antibodies for worm vitality. The nodulectomies will be performed 20 months after anti-*Wolbachia* drug administration. All participants will be operated 20 months after the start of drug administration since the blockage of embryogenesis (primary outcome) or even worm death can be shown at this time point. Patients will be kept in hospital for the day of operation or one day longer (depending on their recovery) for observation before being discharged. Patients will be compensated for the 1 to 2 days hospitalization. They will be provided with 3 square meals worth GHS 20.00 per meal. In addition, GHS 25.00 will be given per day as compensation for lost of wages. Wound dressing will continue in the villages until all the wounds are healed (at least for 10 days after nodulectomy). Part of the nodule samples will be shipped to the Institute for Medical Microbiology, Immunology and Parasitology (IMMIP) of University Hospital Bonn, Germany for quality control.

9.2.6 PCR

For DNA extraction 8 nodule paraffin sections of 4 µm will be placed in microcentrifuge tubes and DNA will be extracted according to the manufacturers' instructions (QIAamp DNA Mini Kit). The *Wolbachia* *ftsZ* and *O. volvulus* actin gene will be quantified from the purified DNA by real-time duplex PCR (qPCR). Genes will be amplified in a Rotorgene 3000 (Corbett Research, Sydney, Australia). Fluorescence will be acquired on the FAM and JOE channel. Copy numbers for each gene will be calculated using a modification of the comparative quantification formula. To do the histological assessment and the PCR, the nodules will be stored in plastic containers and labelled with the trial specific ID of the patient as well as date of extirpation and the number of the nodule removed. The histological assessment and PCR will be done at the IMMIP and KCCR respectively.

All participants (experimental and control interventions) will be treated with a single dose of Ivermectin (Mectizan®/Merck) at the standard MDA (mass drug administration) dosage of 150µg/kg orally at 6 months and again at 18 months before nodulectomies 20 months after study onset. This Ivermectin dose is currently the standard of care for the treatment of Onchocerciasis in the region where the study will take place.

9.2.7 Laboratory examinations / Biological Specimens

Laboratory blood analyses will be done on the same day of blood sampling by the research team in a designated laboratory at the War Memorial Hospital in Navrongo and the Sefwi Wiawso Municipal

Hospital. Analyses will be done by using the validated Chemistry analyzer Selectra Pro S from ELITechGroup.

All parameters tested in this trial can be tested in Serum or Heparin-Plasma.

The scientific analyses of immunoglobulins, cytokines and biomarkers will be done at baseline and following treatment (4, 18 and 20 months after treatment) at the KCCR and IMMIP. Therefore, the blood samples will be frozen and stored, labelled with the trial specific ID of the patient as well as date of sampling.

The total amount of blood drawn per subject during the entire trial will be approximately 85-90 ml.

For detailed list of parameters determined in the blood refer to 9.2.3, blood sampling.

Pregnancy tests will be carried out in the urine using the HCG accurate pregnancy test kit (Registration number FDB/D16-11170) at the field site during the screening period, on the first day of treatment (before intake of the first dosage of the IMP), and weekly during treatment period and after treatment or before treatment with Ivermectin.

All other urine-analyses will be done at the field site using Roche Combur 9-Test® strips. Urine samples will also be taken before treatment, after 4, 18 and 20 months for assessment of potential biomarkers. For the Scientific analyses of the urine, samples will be labeled with the trial specific patient ID as well as the date of sampling, frozen and stored until analyses can start.

Data from the screening visit which describe the baseline status of the subjects will be documented in the source data and in the CRF.

All additional clinically significant findings will as well be documented in the source data

9.3 Time schedule of Measurements for LF trial

9.3.1 Screening period

All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the trial.

All subjects must have the following procedures completed prior to enrollment:

Screening Visit 1

- Subject information and informed consent (screening)
- Demographic data
- CFA analysis using Alere® Filariasis test kits according to the manufacturers' protocols

Screening Visit 2 (within 4 weeks after screening visit 1)

- Subject information and informed consent (treatment)

- Review of inclusion and exclusion criteria, Medical history and concomitant/prior therapies/medication
- Physical examination including height and weight
- Vital signs: blood pressure, pulse, temperature
- Specific investigations (blood (microfilarial load and CFA analysis) and urine sampling)
- Pregnancy test
- Laboratory assessments
 - CFA level determination using Alere® Filariasis test kit according to the manufacturers' protocols
 - Measurement of liver and kidney function parameters (creatinine, γ GT and AST/ALT levels) leukocytes count (leukocytes < lower limit of normal)
- Ultrasonography

- Randomization

9.3.2 Treatment period

The treatment period will include maximum 22 visits from day 1/week 1 until day 22/week 4.

All visits will be performed according to the flow chart (see figure 2).

Visit 1 - Baseline (day 1)

In the morning:

- Review of inclusion / exclusion criteria
- Change of medication since last visit
- Occurrence of any new concomitant diseases
- Pregnancy test
- Application of IMP(s) (only treatment groups A, B and C)

Visit 2 – Visit 7 (day 2– day 7)

In the morning:

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (only treatment groups A, B and C)

Visit 8 (day 8)

In the morning:

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Pregnancy test
- Application of IMP(s) (only treatment groups B and C, in case of missed treatment days also group A)
- ALT, AST, γGT, creatinine and leukocytes, before 8th treatment (all groups).

Visit 9 – Visit 14 (day 9 – day 14)

In the morning:

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (only treatment groups B and C, in case of missed treatment days also group A)
- Pregnancy test

Visit 15 (day 15)

In the morning:

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (groups B and C in case of missed treatment days)

Visit 16 – Visit 21 (day 16 – day 21)

In the morning:

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (groups B and C in case of missed treatment days)

Visit 22 (End of treatment)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit

9.3.3 Follow-ups

- Visit 23 (4 months \pm 2 weeks after treatment onset)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - Physical Examination and Vital Signs (Blood pressure, pulse, weight, temperature)
 - Laboratory assessment (blood and urine)
 - Microfilariae loads (Whatmann® Nucleopore filters)
 - CFA level determination (TropBio® ELISA test and Alere® Filariasis test kits)
 - *Wolbachia* loads (RotorGene®, real time-PCR)
 - Levels of VEGF (ELISA test kits)
 - Urine to measure disease specific biomarkers
 - Pregnancy test
- Visit 24 (6 months \pm 2 weeks after treatment onset)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - IVM + ALB distribution (Treatment with a single dose of Ivermectin (150 µg/kg) + Albendazole (400 mg) will be given)
- Visit 25 (12 months \pm 2 weeks after treatment onset)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - Physical Examination and Vital Signs
 - Laboratory assessment (blood and urine)
 - Microfilaria loads (Filtration Whatmann® Nucleopore)
 - CFA level determination (TropBio® ELISA test and Alere® Filariasis test kits)
 - *Wolbachia* loads (RotorGene 3000® PCR-real time)
 - Levels of VEGF (ELISA test kits)
 - Urine to measure disease specific biomarkers
 - USG examination to determine reduction/absence of worm nests in scrotal lymphatic vessels by detection of FDS.
 - Pregnancy test
- Visit 26 (18months \pm 2 weeks after treatment onset)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Physical Examination and Vital Signs
- Laboratory assessment (blood and urine)
 - Microfilaria loads (Filtration Whatmann® Nucleopore)
 - CFA level determination (TropBio® ELISA test and Alere® Filariasis test kits)
 - *Wolbachia* loads (RotorGene 3000® PCR-real time)
 - Levels of VEGF (ELISA test kits)
 - Urine to measure disease specific biomarkers
- USG examination to determine reduction/absence of worm nests in scrotal lymphatic vessels by detection of FDS.
- Pregnancy test
- IVM + ALB distribution (Treatment with a single dose of Ivermectin (150 µg/kg) + Albendazole (400 mg) will be given)

9.3.4 Ivermectin and Albendazole distribution

Visits 27 (Every other day after visit 26)

- Distribution of IVM+ALB
- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit

Visit 28 – Visit 29 (IVM + ALB follow-up, visit 28- visit 29 can be done a day after IVM + ALB distribution)

- Follow up of Ivermectin and Albendazole, care of side effects if necessary

9.3.5 Final Visit/Re-treatment

Visit 30 (after 18 months follow up – End of trial)

- Information of the participant about the best performing treatment

- Subsequently patients will be treated according to clinical routine at the discretion of the treating physician.

9.4 Time schedule of Measurements for Onchocerciasis trial

9.4.1 Screening period

All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the trial.

All subjects must have the following procedures completed prior to enrollment:

Screening Visit 1

- Subject information and informed consent (screening)
- Demographic data
- Specific investigations (palpation of onchocercomata, skin snipping, skin examination)

Screening Visit 2 (within 4 weeks after screening visit 1)

- Subject information and informed consent (treatment).
- Medical history and concomitant/ prior therapies/ medication.
- Physical examination including height and weight.
- Vital signs: blood pressure, pulse, temperature.
- Laboratory assessments.
- Pregnancy testing (urine) for female subjects.
- Measurement of liver and kidney function parameters (creatinine, γ GT and AST/ALT levels).
- Leukocytes count (leukocytes < lower limit of normal).
- Review of inclusion and exclusion criteria.

- Randomization

9.4.2 Treatment period

The treatment period will include maximum 22 visits from day 1/week 1 until day 22/ week 4.

All visits will be performed according to the schedule of activities (see figure 1).

Visit 1 - Baseline (day 1)

- Review of inclusion / exclusion criteria.
- Pregnancy testing (urine) for female subjects.
- Change of medication since last visit.
- Occurrence of any new concomitant diseases.
- Application of IMP(s) (only treatment groups A, B and C).

Visit 2 – Visit 7 (day 2– day 7)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (only treatment groups A, B and C)

Visit 8 (day 8)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Pregnancy testing (urine) for female subjects (before 8th treatment)
- Application of IMP(s) (only treatment groups B and C, in case of missed treatment days also group A)
- ALT, AST, γ GT, creatinine and leukocytes before 8th treatment (all groups).

Visit 9 – Visit 14 (day 9 – day 14)

- Assessment of AEs / SAEs (all treatment groups).
- Change of medication since last visit.
- Application of IMP(s) (only treatment groups B and C, in case of missed treatment days also group A).
- Pregnancy testing (urine) for female subjects (before 15th treatment, range: +2 days)

Visit 15 (day 15)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (groups B and C in case of missed treatment days)

Visit 16 – Visit 21 (day 16 – day 21)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Application of IMP(s) (groups B and C in case of missed treatment days)

Visit 22 (End of treatment)

- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit

9.4.3 Follow-ups

- Visit 23 (4 months \pm 2 weeks after treatment onset)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - Physical Examination and Vital Signs (Blood pressure, pulse, weight, temperature)
 - Laboratory assessment (urine and blood)
 - Specific investigations (palpation of onchocercomata, skin snipping, skin examination)
- Visit 24 (6 months \pm 2 weeks after treatment onset)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - Distribution of Ivermectin
- Visit 25 (18 months (\pm 2 weeks after treatment onset)
 - Subject information and informed consent (nodulectomy)
 - Assessment of AEs / SAEs (all treatment groups)
 - Change of medication since last visit
 - Laboratory assessments (urine only)
 - Pregnancy testing (urine) for female subjects
 - Specific investigations (palpation of onchocercomata, skin snipping, skin examination)
 - Distribution of Ivermectin
- Visit 26 - Visit 27 (20 months, (\pm 2 weeks after treatment onset)

All participants will be screened for eligibility before nodulectomy. Only eligible subjects will be operated.

All subjects must have the following procedures completed prior to nodulectomy:

- Subject information and informed consent (nodulectomy)
- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit
- Physical Examination and Vital Signs (Blood pressure, pulse, weight, temperature)
- Laboratory assessments (urine and blood)
- Pregnancy testing (urine) for female subjects
- Specific investigations (palpation of onchocercomata, skin snipping, skin examination)
- Nodulectomy

9.4.4 Wound dressing

Visit 28 – Visit 33 (day 1- day 10 after nodulectomy)

- Wound dressing will be performed by the trial clinician and his team every other day directly in the village. If the wound healing process is good, sutures will be removed on day 10 after operation. If there are any problems with the wound healing process, visits may be done on a more frequent basis until all wounds are healed.
- Assessment of AEs / SAEs (all treatment groups)
- Change of medication since last visit

9.4.5 Final Visit/ Re-treatment

Visit 34 (approximately 8 months after nodulectomy)

- Information to the study participants about the best performing treatment
- Subsequently patients will be treated according to clinical routine at the discretion of the treating physician.

10.0 SAFETY, DATA COLLECTION, RECORDING AND REPORTING

Adverse Event (AE)

Any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product(s).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product. An unexpected AE is an experience not reported in the current Investigators Brochure or elsewhere.

Adverse (Drug) Reaction (AR)

In the pre-approval clinical experience with a new medicinal product or its new usages, (particularly as the therapeutic dose(s) may not have been established), all noxious and unintended responses to the medicinal product in relation to any dose should be considered an adverse drug reaction. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse (Drug) Reaction (UAR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

Serious Adverse (Drug) Reaction (SAR)

This is defined as an adverse drug reaction that is serious and at least possibly related to the IMP (see SAE criteria above).

Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)

Any UAR that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

10.1 Criteria to be evaluated by the investigator (1st assessment)

Special attention is to be paid to the occurrence of adverse events (AE) throughout every stage of the clinical trial. The investigator should evaluate all adverse events according to the criteria and steps mentioned below.

10.1.1 Assessment of Intensity

Any adverse event has to be graded regarding its intensity.	
MILD (Grade 1)	Does not interfere with subject's usual activities or is transient, easily tolerated.
MODERATE (Grade 2)	Interferes to some extent with subject's usual activities (which patient is still able to perform).
SEVERE (Grade 3)	Interferes significantly with subject's usual activities (which patient is not able to perform)

10.1.2 Assessment of Seriousness

Determination of the seriousness of the adverse event according to the definitions for a serious adverse event (SAE) given in section 10.

10.1.3 Assessment of Causality

Determination of the relationship of the adverse events to the medicinal product(s) being studied after having evaluated all accessible data according to the following classification:

The relationship of adverse events to the investigational products being studied should be determined as follows:

- Suspected: there is a “reasonable possibility” that the SAE is related to the study drug (a causal relationship is possible, probable, or definite, or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event).
- Not suspected: there is a “no reasonable possibility” that the SAE is related to the study drug (a causal relationship is unlikely or impossible (i.e., not related), or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event).

10.2 Criteria to be evaluated by the Sponsor Delegated Person (2nd assessment)

In addition to the first evaluation of an adverse event that is performed by the investigator, a second evaluation with respect to seriousness, causality and expectedness and a risk-benefit assessment is performed by the Sponsor Delegated Person to process safety evaluation according to the four-eyes principle.

10.3 Documentation and Reporting of Adverse Events

Any AE relevant for the evaluation and analysis of the clinical trial has to be documented in the source data and in the CRF on the respective Adverse Event Report Form.

Documentation and evaluation of each AE occurring between:

- Visit 1 (first day of treatment) and
- the last visit with the last individual specific examination of the subject (Visit 34)

10.4 Documentation and Reporting of Serious Adverse Events

Any SAE occurring after the subject has received the trial drug for the first time until the last visit with the last individual specific examination of the subject (Visit 34) will be documented and reported within 48 hours after investigator awareness of the event to the FDA, the GHS and to the sponsor represented by the Sponsor informally via email containing at least the minimal criteria (the name of the clinical trial, an identifiable patient, an identifiable reporter, a reaction/event, a causality assessment). The Sponsor will add missing information in consultation with the investigator including the sponsor’s 2nd assessment and submit the completed SAE form to the FDA and the GHS:

FDA: clinicaltrials@fda.gov.gh

GHS: ethics.research@ghsmail.org

10.5 Follow-up of Adverse Events and Serious Adverse Events

Every AE or SAE will be treated according to clinical standards at the discretion of the investigator and followed up until it is resolved. Costs for treatment of AEs/SAEs will be covered by the research team.

10.6 Handling of Emergency Cases

The study clinicians/physicians will visit the participants in their villages twice a day during the first two weeks of treatment to closely supervise possible AEs or SAEs. Additionally, the phone numbers of the trial clinicians will be handed to the village health workers as well as to the participants. In case of an emergency between the visits, the clinicians have to be called and will come to the participants whenever needed. In case the participant has to go to a hospital for further examinations and treatment, the transport and medical care will be paid by the research team.

10.7 Deaths

All fatal cases during the treatment period and follow-ups will be accompanied by a formal autopsy report. Deaths occurring in the period between treatment and follow-ups will be evaluated in detail and, if reported immediately to the research team, would be accompanied by a formal autopsy.

10.8 Pregnancy

Women of childbearing potential are required to have a negative urine pregnancy test to exclude a pregnancy before being enrolled in the clinical trial.

Pregnancy testing will be conducted on the first day of treatment prior to the first dose of the trial drug and will be repeated every **2** weeks of treatment.

10.8.1 Actions to be taken if pregnancy occurs to female subjects or partners of malesubjects

If a female subject becomes pregnant or is suspected to be pregnant (including a positive pregnancy test regardless of age or disease state) while participating in this trial and being on study drugs, or within 14 days of the last dose of the study drug, the investigator has to be informed immediately about this event. Likewise, if the partner of a male trial subject becomes pregnant or is suspected to be pregnant while the subject participates in this trial, the investigator has to be informed immediately by the male subject about this suspected or confirmed pregnancy. The investigator will then provide this information to the sponsor for follow-up as necessary.

If a woman becomes pregnant during the treatment period, treatment with the IMP will be immediately stopped. She will be treated according to clinical routine at the discretion of the treating medical doctor supported by the investigator. The woman will remain in the trial as a participant (Intention-to-treat collective).

To ensure the safety of female subjects, each pregnancy that becomes known to the investigator during the trial, must be reported as an event similar to an SAE. Therefore, the investigator will record and report pregnancy information on the appropriate pregnancy reporting form as an initial report and send it immediately (latest within 24h) to the Clinical Study Core Unit.

The pregnancy itself is not considered to be an AE or SAE but must be followed up until delivery or until pregnancy termination and the outcome of pregnancy should be notified to the Sponsor to determine the outcome of the pregnancy regarding maternal or newborn complications. The investigator will seek and provide this follow-up information after the planned date of delivery. For this purpose, the pregnancy reporting form will also be used as a follow-up report. The timeframe to follow up the details of birth will be one year after treatment start.

If the outcome of the pregnancy includes:

- Spontaneous, therapeutic abortion or voluntary termination,
- stillbirth,
- neonatal death,
- presence of birth defects, or
- congenital anomaly (including that in an aborted fetus, stillbirth or neonatal death),

The investigator should report either of these outcomes as an SAE.

11.0 DATA MONITORING AND SAFETY COMMITTEE (DMSC)

A Data safety monitoring board (DSMB) will be established that will review the data for all work packages. The DSMB will comprise five members: two from Ghana and three from abroad who will be pulled from a pool of experienced members who have all served as DSMB members on our previous studies. The following people will be proposed to Ghana FDA for consideration:

1. Dr. Sabine Specht, Head of Filarial Clinical Programme, Drugs for Neglected Diseases Initiative, Geneva

2. Prof. Samuel Wanji, Head of Department, University of Buea Faculty of Science, Department of Microbiology and Parasitology
3. Dr. Nick Opoku, MD, School of Public Health, University of Health and Allied Sciences, Ho, Ghana
4. Dr. Alex Owusu-Ofori, MD, Senior lecturer, School of Medicine and Dentistry of the Kwame Nkrumah University of Science and Technology
5. Dr. Philip Budge, MD and senior scientist, the Task Force for Global Health/ Assistant Professor of Medicine and Infectious Diseases Washington University, USA

12.0 STATISTICS AND ANALYSIS

12.1 Trial Design

See also section 6.

12.2. Target Variable/Endpoints

12.2.1 Primary Target Variables

- **Reduction or absence of CFA in the blood assessed by FTS 18 months after treatment onset.**
- Absence of *Wolbachia* endobacteria in female adult worms assessed by immunohistology 20 months after treatment onset.

12.2.2 Secondary Target Variables

- **Reduction or absence of CFA in the blood 18 months after treatment onset using the Og4C3 antigen test.**
- Reduction or absence of microfilariae in the skin after treatment onset.
- Assessment of safety

12.2.3 Sample Size Calculation

Since the study is a non-confirmatory pilot study to gain first experience regarding the primary and secondary endpoints under the intended treatment regimens, the sample size is not justified by a statistical argumentation. It is based on the experience from previous trials. Therefore, a sample size of 30 participants (30% drop-out rate) per treatment arm was chosen which is in line with the sample sizes normally taken for pilot trials.

12.2.4 Achievement of sample size for the LF trial

With 120 participants for the trial and a mean CFA-prevalence rate of 30.0% and an MF prevalence of 3.1% in the selected trial site (outcome from a preliminary survey in the Nabdam district), the research team will have to screen approximately 2400 volunteers. The Nabdam district where the trial will be conducted has a population of about 40,718 (2019 projected population, Ghana statistical service). Therefore, the number of 120 LF patients proposed in this trial is feasible.

12.2.5 Achievement of sample size for the onchocerciasis trial

With 120 participants for the trial, a mean nodule prevalence rate of 17.0% and 16.4% in the selected trial sites (outcome from a preliminary survey in the Bawku West district and Kayoro Sub-district respectively), and an estimated MF prevalence of 5%, the research team will have to screen approximately 1900 volunteers. The Bawku District where the trial will be conducted has a population of about 49,907 adults who are 18 years and above (2019 projected population, Ghana statistical services).

12.2.6 Definition of Populations Included in the Analysis

Different analysis sets will be prepared before de-blinding (Safety set (SAF), Intention-to-treat set (ITT), Per-Protocol set (PP)). The exclusion of participants from the analysis sets will be finally decided together during the blind data review before the unblinding of the histological and PCR assessments and will be described in detail in the blind data review report.

Since this is a non-confirmatory pilot-trial the Per-Protocol (PP) analysis will be carried out for all parameters. The Intention-to-treat (ITT) set will be used to describe the baseline data and for the confirmation of the results of the PP analysis.

12.2.6.1 Intention-to treat set (ITT)

The ITT set will include all participants that were randomized to one of the four treatment arms.

12.2.6.2 The Safety set (SAF)

The SAF set will include all patients who were randomised to one of the 4 treatment regimens and who took the drugs at least once. This analysis set will be used for adverse event reporting only.

12.2.6.3 Per Protocol set

The PP set will include all patients who completed the whole treatment without any violations of the protocol and who will be present for all follow-up at 4, 12 and 18 months for LF and 4, 18 and 20 months for onchocerciasis.

12.2.7 Methods of Analysis

For all analyses: a p-value of $p < 0.05$ will be considered significant.

12.2.7.1 Analysis of the primary endpoint

For the primary endpoint frequencies of worms without *Wolbachia* and their confidence intervals (95%) will be estimated from linear regression models taking the dependency between worms found in one patient into account. The female worms from all participants who finished the study according to protocol will be analysed for primary efficacy. Secondly, efficacy will also be analysed per Intention to treat analysis.

12.2.7.2 Analysis of secondary endpoints

Secondary endpoints will be described as estimators with confidence intervals (95%) for each intervention group and analysed with adequate statistical methods. For more details, see statistical analysis plan.

12.2.7.3 Analysis of Safety

Frequency of Adverse events and Serious Adverse Events will be analysed. In this analysis all patients will be included who took the drugs at least for one day.

12.2.8 Interim Analysis(es)

Not applicable

12.2.9 Protocol Violations

Protocol violations are major deviations from the procedures outlined in this document like:

- non-compliance with investigational medicinal product (missing treatment days at the end of the treatment period (the treatment period should be prolonged for all days the patient was absent or did not get the trial drugs by decision of the trial clinician).
- the intake of medications not allowed (intake of Ivermectin, Doxycycline, Albendazole or Rifampicin during the 20 months between treatment and time point follow-ups)
- any non-adherence to the protocol that would have an impact to the subject's rights, safety or welfare,
- Absence from treatment for more than 3 consecutive days (participants who are absent for more than 3 consecutive treatment days will be requested to finish the whole treatment).
- Absence from treatment for more than 7 treatment days (treatment will be stopped if participants are absent for more than 7 treatment days, but the patients will be asked to come for the follow-ups at 4, 12 and 18 months for LF and 4, 18 and 20 months for onchocerciasis).

After a subject has been enrolled, it is the investigator's responsibility to make a reasonable effort to prevent and correct any protocol violations if necessary and to continue the subject's participation in the trial, if possible.

Protocol violations will be reported to the sponsor/sponsor delegated person during the course of the trial in the monitoring reports and reported to the Ethics Committees after completion of the trial.

All protocol violations will be listed and the impact on the evaluation of the subjects concerned will be discussed prior to statistical analysis.

12.2.10 Handling of Drop-outs, Withdrawal, and Missing Data

- Subjects dropping out of the trial prior to randomization will be listed as screening failures including the reason.
- Subjects dropping out of the trial after randomization but before start of treatment will be reported including the reason. In case of subjects dropping out in the period between randomization and treatment start additional subjects will be included in the trial. The new participants will be randomized consecutively.
- Subjects dropping out of the trial after randomization and also during treatment will be analysed using all available data (ITT analysis). This includes subjects who have elevated liver function tests (LFTs) during treatment. Treatment will be stopped for a subject with elevated LFT if it's ongoing, and subject will be monitored with appropriate clinical care. Biochemistry tests will also be performed to check if subjects' LFTs have returned to acceptable and manageable levels.
- Subjects missing more than 3 consecutive treatment days will be analysed using all available data (ITT analysis)
- In case of subjects dropping out during the first 3 days of treatment, additional subjects may be included in the trial. The new participants will be randomized consecutively. All available data from the participants who dropped out will still be used for the ITT analysis.

Taking into account a drop-out rate of approximately of 30%, 120 subjects need to be enrolled in order to obtain 84 evaluable subjects for analysis.

The trial has the limitation that only data from participants who were present can be analysed for all outcomes assessed in the nodules and a replacement of missing values is restricted. A check of a possible treatment effect on the frequency of missing values will be done.

13.0 DATA COLLECTION, HANDLING AND RECORD KEEPING

13.1 Documentation of Trial Data

13.1.1 Documentation of Trial Data in the Medical Record

The investigator will record the participation in the trial, the frequency of the trial visits, the relevant medical data, the concomitant treatment and the occurrence of adverse events in the medical record of each subject. Data collected on the CRFs must match the source data.

13.1.2 Case Report Form (CRF)

The investigator has ultimate responsibility for the accuracy, authenticity, timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs. All these data may only be entered into the CRF by authorized trial personnel as promptly as possible.

In this clinical trial a hard copy CRF will be used. A standardized CRF will be used to document the subject's data during the course of the trial. The hard copy of the CRF consists of no carbon required (NCR) paper or if normal paper is used, the pages have to be copied later and the conformity with the original data has to be confirmed.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, signed and explained (if necessary) and should not obscure the original entry. The copies of the completed CRF pages, and a copy of query forms, if any, will be stored per subject CRF in an extra file locked and secure. More information in detail regarding CRF documentation, CRF corrections, CRF collections (e.g. at each monitoring visit, at the end of the trial) and subsequent changes (queries) will be given in a separate CRF manual at the trial site.

13.2 Data Coding

Coding of adverse events and concomitant diseases will be done according to the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

13.3 Data Management

Study data will be managed using Research Electronic Data Capture (REDCap) tools hosted at the Kwame Nkrumah University of Science and Technology (KNUST). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [23]. Details on data management (procedures, responsibilities, data corrections, if any, which may be made by Data management staff themselves, etc.) will be described in a data management plan prior to the trial.

During the trial, the performance of data management and any deviations from the data management plan will be documented in a data management report. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented in a variable plan.

Processing of data is done via Double-Data-Entry. Double data entry will be performed by two different persons in Ghana (with the exception of free text). The two entries will then be compared with each other and verified. An audit trail will be created to provide an electronic record of which data were entered or subsequently changed, by whom and when.

Statistical Analysis System (SAS) software will be used to review the data for completeness, consistency and plausibility. The checks to be programmed will be specified beforehand in a data validation plan, as required by the subject protocol. After running the check programs, the resulting queries will be sent to the investigator for review of his/her data. Answered queries will also be entered twice, verified and the updated data will then be transferred to the database. All programs which can be used to influence the data or the data quality will be validated (e.g. check programs, programs used for the input of external data, etc.).

All data will be checked for consistency and plausibility by the monitor and by the data management. Inconsistencies will be queried and discussed with the investigator. After data clearance, the database will be locked and data will be used for statistical analysis.

13.4 Trial site File

The Trial site will be provided with a trial specific investigator site file (ISF) containing all sponsor-specific essential and trial specific documents. The monitor will regularly check the ISF for accuracy and completeness. The trial site file has to be stored locked and secure. After end of trial or early termination of the trial the trial site file should be retained for 10 years at the site.

The ISF includes the subject identification list, where the investigator has to record the trial participation of each subject. This list allows identification of each subject and contains the subject number, the name, telephone number (if applicable) and the date of inclusion of the subject into the trial, and will be reviewed by the monitor for completeness. After end of the trial the subject identification list remains with the trial site.

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. This list will be provided with the ISF, too.

Furthermore, trial personnel responsible for any task or duty within the trial should be identifiable. Therefore, a signature list with the name, signature, initials/abbreviation and trial responsibilities of all persons will be filed in the investigator's site file.

13.5 Archiving

13.5.1 Sponsor

All clinical and experimental data (electronic or paper) and all essential documents inclusively the case report forms (Subject Master File) shall be kept in a secured place (metallic safety cabinets under lock) for a period of 15 years after completion of the trial and be made readily available for review upon request by the Authority and the Ethics Committees. The sponsor will archive all trial related documents according to regulatory requirements.

13.5.2 Investigator

The investigator will maintain all subject documents as specified in the Essential Documents for conduct of a clinical trial (see ICH-GCP, section 8) and as required by the applicable regulatory requirement(s) after completion of the clinical trial so that they will be available for audits and inspections by the authorities. The investigator will be responsible for the storage.

The following retention periods will apply after completion or stop of the clinical trial:

- all essential documents and trial related data must be retained securely for at least 15 years
- the subject identification list for at least 15 years
- medical records and other source documents for the longest possible period allowed by the institution

The investigator/institution would make arrangements to prevent accidental or premature destruction and illegitimate access to these documents.

To enable evaluations and/or audits from the sponsor or inspections from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e. g. CRFs and other records), all original signed informed consent forms, copies of all CRFs, serious adverse event reports, source documents, and detailed records of treatment disposition, drug accountability and adequate documentation of relevant correspondence (e. g. letters, meeting minutes, telephone calls reports).

The trial site will maintain a file of essential subject documentation (Trial site File). It is the responsibility of the site to retain copies of all completed CRFs for the subject and their trial file on site.

14.0 STATISTICAL REPORT

The statistical evaluation and the statistical report are performed, evaluated and signed by the responsible biometrician. All data in this report are strictly confidential.

15.0 DEFINITION OF END OF TRIAL

15.1 Regular End of the Trial

The regular end of trial is defined as Last Subject Last Visit, meaning, the trial ends when the last patient will be informed about the best performing treatment. At this visit re-treatment will be offered to patient which is not part of the clinical trial but will be performed by the KCCR trialclinician.

After regular end or early termination of the trial, patients will be treated according to clinical routine at the discretion of the treating physician.

15.2 Termination of the Trial for Individual Subjects

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial participants and ensure appropriate therapy and follow-up for the participants.

The competent authority and the ethics committees will also be informed by the sponsor delegated person. Details of the criteria for premature termination can be found below.

15.2.1 Termination by the Participant

Participants may withdraw from the trial at any time (before, during or after treatment) at their own request without stating the reason(s) for withdrawal. They will experience no disadvantage as a result of this decision and no alternative therapy will be withheld by the investigator. This means also that the participant will be encouraged to come for subsequent follow-ups.

The investigator is urged to ask the participant to return for an early termination visit and to document information as much as possible in the CRF. However, after unrestricted withdrawal no data can be collected from the patient.

15.2.2 Termination by the Investigator

Participants may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, e. g.:

- Occurrence of intolerable adverse events and which would constitute an unacceptable high risk for the participant
- Medically indicated e.g., because it is found that inclusion/ exclusion criteria were violated

- Continuation is unacceptable because risks outweigh the benefits
- Pregnancy
- Lack of compliance of the participant (e.g., alcohol abuse, absence from treatment)
- Significant protocol violations
- Logistical reasons (e.g., participant moves to another location)

Whenever a participant is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the CRF and a final examination should be conducted if possible.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. The investigator should inquire about the reason for withdrawal and the participant has to be followed-up regarding any unresolved adverse events, if possible.

In any circumstance, every effort should be made to document the participant's outcome, if possible. Therefore, all participants, even if the participant discontinued trial treatment, will be encouraged to come for the subsequent follow-ups.

15.3 Termination of One of the Treatment Arms / or the Entire Trial

The sponsor/Principal Investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial.

A treatment arm or the entire clinical trial must be terminated prematurely if:

New toxicological or pharmacological data or SAEs invalidate the earlier benefit-to-risk ratio for the subject.

Adverse events occurring in such severity and frequency that the proposed schedule can no longer be adhered to.

The sponsor/Principal Investigator considers that the termination of the trial is necessary.

Indications arise that the subjects' safety is no longer guaranteed.

An insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible. The reasons for such a decision will be documented in written form.

Premature termination of one of the treatment arms does not automatically mean a termination of the other treatment arms. A separate decision on further treatment must be made for each participant, depending on the overall situation. So, it has to be clarified that:

An adequate further treatment and follow-up of already enrolled participants must be ensured.

The documentation of already enrolled participants will be reviewed for completeness and plausibility.

Queries may be raised for further clarification before the centre is closed. These queries must be answered properly.

Even if the trial or a treatment arm will be terminated prematurely, all enrolled participants will be invited to take part in the planned follow-ups.

15.4 Statistical argument for termination of the trial

The trial will be completed after all statistical analyses are finalized. All participants will be treated at the same time and follow-ups will be done 4, 12 and 18 months after treatment onset for LF and 4, 18 and 20 months after treatment onset for onchocerciasis. The evaluation of the primary outcome as well as most of the secondary outcomes will be done at the same time for all patients. Therefore, a statistical argument for a premature termination of the trial cannot be provided.

15.5 Report of termination of the trial

When the trial is prematurely terminated, the sponsor should submit a report to the FDA, the GHS-ERC and institution within 30 (thirty) days. This report will include:

Justification for the premature ending or of the temporary halt of the trial; Number of patients receiving treatment at the time of the study termination;

Proposed management of patients receiving treatment at the time of halt or study termination;

Implications of the discontinuation on the evaluation of the final results.

16.0 MONITORING, AUDITS AND INSPECTIONS

During the clinical trial, quality control and quality assurance will be ensured through monitoring, auditing and inspections by the authority.

16.1 Monitoring

To ensure accurate, complete, consistent, reliable data, and ensure patients' safety, the investigator's site and trial procedures will be monitored by a representative of the sponsor. The sponsor's representative will visit the site:

- to evaluate the progress and recruitment of the trial
- to review the source documents and CRFs for protocol compliance, accuracy and validation
- to assess facilities and equipment
- to check protocol compliance
- to assure AE/SAE reporting
- to verify proper handling and dispensing of the IMP(s), and other factors

Frequency and scope of monitoring visits will be defined in the Monitoring Plan for this trial which also includes the extent of source data verification that is required as a risk-adapted strategy rather than a full monitoring will be conducted.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, thereby ensuring the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial.

16.2 Source Data Verification (SDV)

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the access to the medical records for the performance of SDV.

Source data as defined by ICH-GCP include data such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, or magnetic media, x-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

16.3 Audits and Inspections

In accordance with GCP this trial may be selected for audit by representatives of the sponsor or for inspection by site responsible representatives of the competent authority.

The investigator agrees to give the auditor access to all relevant documents for review and to support the sponsor to solve possible audit findings concerning the trial conduct at the site.

After every audit, the auditee(s) will receive an audit confirmation by the auditor. This document has to be filed together with the trial documentation and has to be made available also to the authorities in case of an inspection. At the end of the trial, a copy of the audit certificate(s) will be included in the final report.

17.0 ETHICS AND GOOD CLINICAL PRACTICE

The trial will be conducted in accordance with the FDA Guidelines for Good Clinical Practice and for conducting clinical trials of medicines, food supplements, vaccines and medical devices in Ghana, the relevant national regulations and the Declaration of Helsinki.

17.1 Responsibilities of the Sponsor

The sponsor is responsible for obtaining the approval from the FDA Ghana, the national ethics approving body, Ghana Health Service and the respective main ethical review committee (Committee on Human Research Publication and Ethics, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana) before initiation of the trial.

17.2 Responsibilities of the Investigator

By signing this protocol, the local investigator declares his/her commitment:

- to not enroll any person dependent on him/her or the sponsor in accordance with the principles of GCP
- to inform the subjects of the transmission of their pseudonymized data and to make sure that subjects unwilling to give consent to the processing of their data are not included into the trial
- to certify that he/she was informed of the pharmacological – toxicological issues and risks of the clinical trial
- to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
- to be thoroughly familiar with the appropriate use of the trial drug(s), as described in the protocol, the product information and other information sources provided by the sponsor
- to be aware of, and comply with GCP and the applicable regulatory requirements
- to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties.

17.3 Ethics Committee and Competent Authority

The clinical trial protocol and amendments have to be approved by the Competent Authority (CA), in addition to the subject information and informed consent, and any other written information to be provided to the trial subjects have to be approved by the respective national ethics approving body, Ghana

Health Service and the respective main ethical review committee (Committee on Human Research Publication and Ethics, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana).

A copy of the written approval must be received by the sponsor before recruitment of subjects into the trial and shipment of trial drug.

Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol must also be sent to the EC/CA. Records of the EC review and opinion of all documents pertaining to this trial must be kept on file by the investigator and are subject to regulatory authority and / or sponsor inspection during or after completion of the trial.

The sponsor delegated person will submit quarterly progress reports to the FDA providing information about the recruitment and safety of the clinical trial.

17.4 Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the sponsor and the investigator. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/authority/ethics committee (unless subject safety is at risk, see below).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the subjects. An amendment if necessary, should subsequently be reported to the ethics committee, the sponsor or sponsor delegated person and the competent authority, giving reasons.

17.5 Notification of General Amendments to the Protocol

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change:

- the safety of the persons concerned,

- the interpretation of the scientific trial documents or the scientific informational value of the trial results,

- the nature of management or conduct of the clinical trial (e.g., change of Principal Investigator, sponsor or sponsor's deputy),

the pharmaceutical quality or safety of the investigational medicinal products, the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical trial with drugs consisting of or containing genetically modified organisms.

The clinical trial may only be continued when a favourable opinion has been obtained from the competent ethics committee and if the competent authority has not raised any objections accompanied by reasons.

Amendments which only have to be approved by the EC (e.g., changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial, also will be notified to the CA with the comment “For information only”. Similarly, the EC will be informed of any substantial amendments for which only the CA is responsible (e.g., quality data).

If administrative protocol changes (e.g., change of monitoring, telephone numbers) or purely editorial changes or more detailed definitions of already approved procedures are necessary, the EC and CA will be notified only.

17.6 Notification of the end of the trial

The end of the clinical trial is the date of the last visit of the last participant undergoing the trial. At the end of the trial, the sponsor delegated person will notify the EC(s)/CA about the trial completion and submit a preliminary report on the ethical evaluation within 30 days and a final report within 90 days after completion of the trial.

17.7 Participation in study

Your participation in the study is entirely voluntary and you may withdraw at any time and for any reason without penalty or loss of benefits. However, your participation in this study may be discontinued by the investigators if you keep getting serious side effects of the trial drugs or if you keep missing the visits appointments and do not follow the directions of the study doctors.

You will be involved in the study for approximately 18 or 20 months including screening, treatment and follow-ups. However, the results of the study will only be available around 6 months after the last follow-up (20 months after treatment). You will be informed about the outcome and offered the best treatment regimen needed as soon as all analyses are done.

17.8 Subject Information and Informed Consent

Every participating subject will be informed about nature, importance, treatment methods, risks and consequences of the trial by the investigator. Details of indemnity and insurance are also stated.

The local investigator is responsible for obtaining written/ thumb print consent from a subject before any protocol-specific screening procedures will be performed or any investigational products will be administered. The written/ thumb print consent documents will be prepared and provided in English and the preferred local language (Twi, Nabit and Kusaal) during the informed consent procedure.

Subjects must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, subjects must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The subject will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the subject. On the other hand, by signing the consent form subjects give their consent to the evaluation, recording and usage of their personal data. The written consent form will be personally dated and signed by the subject, or thumb printed by the subject and dated by a witness. Additionally, it will be signed by an independent witness from the participant's village. The informed consent forms will be filed in the Trial Site File at each site.

The acquisition of informed consent should be documented in the subject's medical record. A copy of the signed and dated informed consent form will be given to the subject and a copy will be held in the subject's medical notes. The existence of written/ thumb print consent will have to be confirmed before any trial-specific test/treatment has been performed. Please see detailed explanation of the informed consent procedure in patient information sheet.

In the case of substantial amendments, the subject must be informed about relevant changes.

17.9 Subject Insurance

There will be no cost to the participants in this study. Participants will receive no payment for taking part in the study. Participants will be compensated for their time loss with incentives such as milo, sugar, tins of milk worth GHS50.00 per visit.

Every subject participating in the trial will be insured against any trial-related illness/injuries pursuant to the legal requirements which may occur during the trial. For the whole study period, participants will be insured by a Ghanaian insurance company (Hollard Insurance Ghana) in case of any harm caused by the study drugs or study interventions. The insurance coverage is valid until **October 31, 2022**. The duration for the insurance coverage is 2 years from the start of recruitment to the last follow-up visit. So, participants will be asked to inform the research team immediately about any complaints or symptoms in particular if any harm is suspected to be caused by the study procedures.

Excluded from this, however, are injuries to health and deterioration of illnesses already in existence which would have continued to exist even if the subject had not taken part in the clinical trial. The participants will be afforded access to insurance documents and provided with a copy of the general conditions of insurance on request. The insurance cover is jeopardized if the subject fails to immediately report to the investigator or responsible physician any injury to health which might have resulted from the participation in the clinical trial, or if she/he undergoes any other medical treatment (except for emergency treatment) without the investigator's knowledge before her/his participation in the clinical trial has officially ended.

In case of any health impairment, the subject is obliged to notify the investigator as soon as possible. The investigator is then obliged to notify the insurance and additionally to make a report to the sponsor.

The subject insurance will be arranged by the sponsor delegated person. The insurer will be:

Hollard Insurance Ghana

P. O. Box 1481

Harper Road, Adum

Kumasi - Ghana

Email: info@hollard.com.gh

Website: www.hollard.com.gh

This insurance covers trial related injuries to health up to a maximum of **10,000** Ghana Cedis per subject.

17.10 Data Protection and Subject Confidentiality

The representatives of the KCCR, the Ethics Committees and the Food and Drug Authority (FDA) Ghana will be allowed to look at original medical records of all study subjects adhering to data confidentiality. Participants will give permission by signing a written informed consent form or by thumb-printing. Records giving study subjects' identity will be kept confidential and not made public. All data will be stored electronically and analyzed. However, participants' data will be assigned to individual numbers instead of their names (pseudonymized). Also, during publication of trial results, identities will be made confidential.

The pertinent provisions of the legislation in Ghana on data protection will be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to the Data Protection Act 2012. Prior to trial participation each subject must be informed by the investigator about the purpose and extent of the collection and use of personal data, particularly medical data and must give written/ thumb print consent.

The subjects must be informed that:

1. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial, age) and will only be transmitted to
 - i. the Principal Investigator/sponsor/sponsor delegated person for scientific and adverse event evaluation
 - ii. the responsible regulatory authority, the ECs of the trial for verifying the proper conduct of the trial and for assessment of trial results and adverse events
2. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the regulatory authority must have direct access to personal data. In this case, the investigator is released from confidential medical communication.

17.11 Financing of the Trial

The present trial is an investigator initiated subject (IIT). This study is fully funded by the European and Developing Countries Clinical Trials Partnership.

17.11.1 Trial Agreement / Investigator Compensation

According to GCP 3.3.13, a trial agreement on the conduct of the clinical trial will be signed between the sponsor (donor) of the clinical trial and the investigators including their heads of administration (donee). No compensation will be paid to the investigators.

17.11.2 Reimbursement of Participants

Participants will be given incentives such as milo, sugar, tins of milk, etc., worth approximately GHS 50 per person per visit as compensation for their time loss.

18.0 TRIAL REPORTS

Quarterly reports of the progress of a clinical trial starting from the date of issuance of the clinical trial certificate will be submitted to the CA in the recommended format within 21 days after the end of the previous quarter (a quarter will be considered as three months beginning from the date of initiation of the clinical trial).

If the trial does not begin or is delayed as per the date of commencement on the Clinical Trial Certificate issued, the CA will be informed of the new date of commencement within ninety (90) days of issuance of the Clinical Trial Certificate.

18.1 Final Report

In addition to the reports referred to above, the Principal Investigator/Sponsor delegated person who conducted the trial will, not later than 90 days after the completion of the trial, compile and submit a comprehensive formal report to the CA conforming to the ICH Guideline.

The report (hard and soft copies (1 each)) will include a short but comprehensive summary of the essential findings of the trial and of its methodology and course.

19.0 PUBLICATION

19.1 Publication Policy

The results of the trial will be published by the Principal Investigator under participation of all institutions taking part. The manuscript will be provided to every co-author before publication. The publication of partial results after the main publication is possible depending on the approval by the sponsor-delegated person. To maintain the scientific integrity of the subject, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the sponsor- delegated person. All participant-related data need to be published in a pseudonymous form.

The right of publication rests primarily with the Principal Investigator, its representative and the senior coordinating physician. All data collected in connection with the clinical trial will be treated in confidence by the sponsor/Principal Investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the Principal Investigator, its representative and the senior coordinating physician.

According to the Declaration of Helsinki all participants have the right to be informed about the study results. The information will be given to the participants after all analyses are completed during a final visit (Visits 30 and 34 for LF and onchocerciasis respectively).

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