Clinical Trial Protocol

Trial Title: **Impact of increased praziquantel frequency on childhood fibrosis in persistent schistosomiasis morbidity hotspots. A phase IV CTIMP trial.**

Protocol Number: FibroScHot18

ISRCTN Number: 16994599

Investigational Product : Praziquantel

Protocol Version: 4.22

Chief Investigator: Dr Shona Wilson

CI Address: Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QP, UK

Telephone: +44 (0)1223 333338

Maternity Cover

Chief Investigator: Dr Caroline Trotter

Director Cambridge-Africa

Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QP, UK

Telephone: +44 (0)1223 333690

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust
Box 277, 1 Hills Road,
Cambridge,
CB2 0QQ
UK

Joint-sponsored by The Chancellor, Masters and Scholars of the University of Cambridge,
The Old Schools, Trinity Lane,
Cambridge,
CB1 1TS
UK

SAE Reporting: Dr Edridah Tukahebwa, Vector Control Division, Uganda Ministry of Health, edmuheki@gmail.com

and

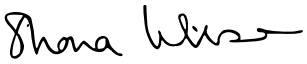
Dr Shona Wilson, University of Cambridge, UK. sw320@cam.ac.uk (or Dr Caroline Trotter, University of Cambridge, UK. clt56@cam.ac.uk when acting as CI maternity cover)

1. Protocol Signatures:

I give my approval for the attached protocol entitled "Impact of increased praziquantel frequency on childhood fibrosis in persistent schistosomiasis morbidity hotspots. A phase IV CTIMP trial". Dated 23-11-2022

Chief Investigator

Name: Dr Shona Wilson

Signature: 

Date: __16th February 2022_____

Site Signatures

I have read the attached protocol entitled "**Impact of increased praziquantel frequency on childhood fibrosis in persistent schistosomiasis morbidity hotspots. A phase IV CTIMP trial**" dated 26/10/2022 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name: Dr. Edridah Tukahebwa

Signature: 

Date: 16/02/2023

2. Trial Management Committee(s) and Protocol Contributors

Dr Shona Wilson, Department of Pathology, University of Cambridge, UK. Chief Investigator (TMG/TSC).

Dr Edridah Tukahebwa, Vector Control Division, Ministry of Health, Uganda. National Principal Investigator and Trial site co-ordinator (TMG).

Prof Birgitte J Vennervald, University of Copenhagen, Denmark. Principal Investigator, Clinical advisor (TMG).

Dr Stella Neema, Department of Sociology and Anthropology, Makerere University. Principal Investigator, Anthropological advisor (TMG).

Mr Eliot Tegyeza Kanyesigye, Department of Public Health, Makerere University, Uganda. Trial Site Manager and Site Principle Investigator (TMG).

Prof Fred Nuwaha, Department of Public Health, Makerere University, Uganda. Principal Investigator, Clinical Trial oversight (TSC).

Dr Caroline Trotter, Department of Pathology, University of Cambridge, UK. Chief Investigator Maternity Cover (TMG/TSC).

Dr Simon Bond, Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, UK. Trial Statistician.

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3. Abbreviations

AE/AR	Adverse event/Adverse Reaction
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
UCam	University of Cambridge
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
MDA	Mass Drug Administration
NHS	National Health Service
NTD	Neglected Tropical Disease
PIS	Participant Information Sheet
PZQ	Praziquantel
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SCORE	Schistosomiasis Consortium for Operational Research and Evaluation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VCD	Vector Control Division

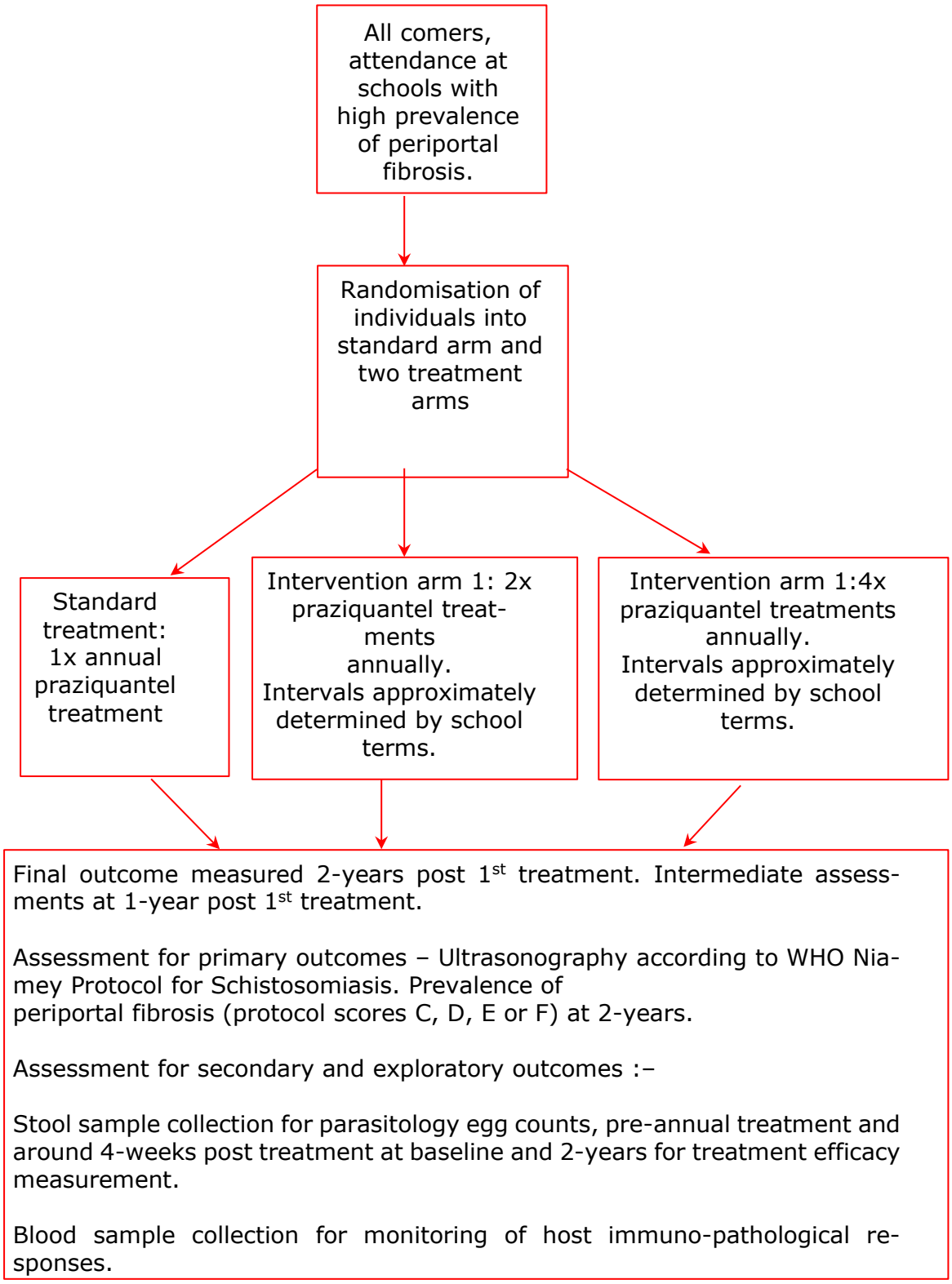
4. Trial Synopsis

Title of clinical trial	Impact of increased praziquantel frequency on childhood fibrosis in persistent schistosomiasis morbidity hotspots. A phase IV CTIMP trial.
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
ISRCTN Number	16994599
Medical condition or disease under investigation	Periportal fibrosis of the liver caused by schistosomiasis mansoni
Purpose of clinical trial	To ascertain the most effective treatment frequency for morbidity control
Primary objective	To compare the effect of 2x and 4x treatments annually with praziquantel to the standard 1x annual treatment on the prevalence of *Schistosoma mansoni* associated periportal fibrosis of the liver.
Secondary objective (s)	To compare the effect of 2x and 4x treatments annually with praziquantel to the standard 1x annual treatment on the mean infection intensity of *Schistosoma mansoni*.
Trial Design	Phase IV, single centre, randomised, trial, single blinded to the primary outcome assessors, but open label to all other investigators and participants.
Trial Outcome Measures	Ultrasound periportal fibrosis pattern scores.
Sample Size	600

Summary of eligibility criteria	Inclusion Criteria: • Aged 6-14yrs • Resident in study village for at least 2years • Parental/Guardian consent granted • Child assent granted Exclusion Criteria • Previous facial oedema after praziquantel treatment • Known neurocysticercosis or ocular cysticercosis
Investigational medicinal product and dosage	Praziquantel, ~40mg/kg according to standardised WHO dose pole.
Active comparator product(s)	Standard annual treatment with praziquantel
NIMPs and Challenge Agents	—
Route(s) of administration	Oral
Maximum duration of treatment of a participant	One oral dose per treatment round
Procedures: Screening & enrolment	Demographic data - age, sex, length of residency, history of severe praziquantel side effects
Procedures: Baseline	Ultrasonography - WHO Niamey Protocol Faecal parasite egg counts Urine samples Blood sample
Procedures: Treatment period	Control arm – PZQ treatment annually Intervention arm 1 – treatment with PZQ twice annually Intervention arm 2 – treatment with PZQ 4 times annually Treatment schedule based around Ugandan school terms, at approximate but not exactly equal intervals. At time of 1-year treatment of all arms: Faecal parasite egg counts on sub-set of children (n =120, split approximately equal across treatment arms) Urine samples

Procedures: End of trial	Ultrasonography - WHO Niamey Protocol Faecal parasite egg counts Blood sample Urine sample Final treatment
Procedures for safety monitoring during trial	Treatment observed and managed for AEs for at least one hour after administration. 24-hour post-treatment follow-up of participants by health professional. Treatment side effects recorded. Severe adverse effects reported to Dr Edridah Tukahebwa, VCD-Ministry of Health and Dr Shona Wilson, University of Cambridge (Dr Caroline Trotter, University of Cambridge, CI maternity cover) for notifications
Criteria for withdrawal of participants	Severe Adverse Event/Reaction Withdrawal of assent/consent

5. Trial Flow Chart



6. Introduction

6.1. Background

Periportal fibrosis is the severest pathology caused by schistosomiasis mansoni. Large fibrotic deposits in the liver can lead to portal hypertension, and death by haematemesis (1). The cornerstone of disease control is annual preventative chemotherapy (PC) through mass administration (MDA) of the safe and efficacious drug praziquantel (PZQ).

Elimination of schistosomiasis as a public health problem is promoted as global health priority in the WHO Roadmap to Neglected Tropical Disease (NTD) Control. The Roadmap stipulates annual treatment with praziquantel of 75% of all school-aged children living in schistosome endemic areas by the year 2020. This is the age-group that carries the greatest burden of infection. Community treatment is recommended in areas of intense transmission (2). The WHO roadmap has been strengthened by World Health Assembly Resolution 65.21. The resolution calls for a concerted effort to achieve the target of 75% treatment coverage, and a highly ambitious target of moving towards elimination of infection where possible.

Working with the Schistosome Control Initiative, Uganda was one of the first countries to introduce MDA of PZQ, with the first communities receiving treatment in 2003 located on the shores of Lake Albert (3). The inhabitants of these fishing communities had very high infection intensities, and a record in the 20th century scientific literature of highly prevalent severe schistosomiasis (4–6). Responding to more recent reports in this area of high numbers of individuals attending health clinics with end-stage schistosomiasis, we recently conducted a parasitological and ultrasound screen in these fishing communities and found periportal fibrosis to be commonplace. Worryingly fibrotic patterns are not restricted to those of the older generation, ruling out the scenario that the fibrosis is present due to childhood exposure amongst those too old to have received treatment through MDA when they were school-aged. Amongst the 910 school-aged children (aged 7-15yrs) examined in Hoima District, 82% were found to have ultrasound detectable periportal fibrosis and 31% had central fibrosis, the manifestation most likely to lead to increases in portal pressure. The longstanding current intervention strategy is therefore not preventing morbidity in this region, with an unacceptably high percentage of children presenting with severe periportal fibrosis, and those children with mild periportal fibrosis being at risk of progression towards more severe disease. Highlighting this is the finding that amongst the adults screened, 56% had central periportal fibrosis, 24% with grades considered very severe and likely to respond poorly to treatment with PZQ. This is despite concerted efforts to treat annually, with the latest reported community MDA coverage rates for the district being 81%.

Large-scale cluster intervention trials on optimal treatment have been implemented by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE), their design focusing on annual treatment, comparing either a community or school-based approach, with treatment holidays (to free resources for other public heath activities) (7). Spatial analysis of the Kenyan SCORE trial shows annual interventions failing to decrease infection intensity in transmission hotspots over the 5-years of the trial (8). A similar result of persistent hotspots was also found in the Tanzanian SCORE trial. Here hotspots were found to be independent of treatment coverage, and likely caused by an underlying high intensity of transmission and a consequent high force of infection (9). As periportal fibrosis is a focal manifestation due to transmission patterns and underlying host-parasite interactions, other areas where annual treatment fails to control infection levels, and are hotspots of morbidity such as Hoima

District, are likely to exist. While undoubtedly annual MDA has been a major public health advancement, the current strategies are falling short of the goal of Sustainable Development Goal 3, which promotes good health for all and indeed of the specific control targets for schistosomiasis articulated by the WHO.

6.2. Clinical Data

Praziquantel – tablet, ~40mg/kg according to WHO dose pole (10), maximum of 5 tablets. Registered for children aged 4-years or more. Listed on WHO Model List of Essential Medicines.

6.2.1. Efficacy

A tentative threshold of 90% egg reduction rate has been set by WHO as an indicator of optimal efficacy.

6.2.2. Safety and tolerability

Praziquantel: side-effects increase with dose and duration of treatment with the more severe reactions being associated with longer and heavier doses that are required for non-schistosome platyhelminth infections e.g. neurocysticercosis (50mg/kg/day for 15 days).

Neurological
Headaches – very common (>10%)
Dizziness – very common (>10%)
Vertigo, drowsiness – common (1-10%)
Seizures – very rare (<0.01%)

Gastro-intestinal
Gastrointestinal and abdominal pains– very common (>10%)
Nausea – very common (>10%)
Vomiting – very common (>10%)
Anorexia – common (1 – 10%)
Diarrhoea – common (1 – 10%)
Bloody diarrhoea - very rare (<0.01%)

Dermatological
Urticaria – very common (>10%)

Cardiovascular
Unspecified arrhythmias – very rare (<0.01%)

Immune system disorders
Allergic reaction – very rare (<0.01%)
Polyserositis – very rare (<0.01%)
Eosinophilia – very rare (<0.01%)
Jarisch-Herxheimer reaction - very rare (<0.01%)

Hepatobiliary disorders
Liver function tests increased – rare (0.01 – 0.1 %)

Musculoskeletal and connective tissue disorders
Myalgia – common (1 – 10%)

General disorders
Fatigue–very common (>10%)
Feeling unwell (asthenia, malaise) – common (1 – 10%)
Fever– common (1 – 10%)

Adverse reactions with food, over the counter drugs or commonly prescribed drugs are not reported.

6.2.1. Pharmacokinetics & pharmacodynamics

Half-life (serum) 0.8-1.5 hours.
Extensive first-pass effect for metabolism. Renal metabolism.
Excretion 80% within 4-days, mostly within urine.

7. Rationale for Trial

An alternative to the standard annual treatment for areas of high persistent morbidity is desperately required if the target of good health for all and schistosomiasis control is to be met. Integrated approaches of MDA, WASH (water, sanitation and hygiene) (11) and where appropriate, intermediate snail host control (12), are proposed long-term strategies to drive down transmission in hot-spots. However, where persistent morbidity occurs, disease control strategies that will have a more immediate effect are required to prevent further generations progressing to severe, difficult-to-treat schistosomiasis with potentially irreversible sequelae.

Although a range of morbidity indicators are included as outcomes of ongoing trials, there exist no published controlled intervention trials specifically examining the effect of treatment frequency on ultrasound detectable periportal fibrosis in high morbidity areas; the SCORE Gaining Control studies are being conducted in Lake Victoria transmission areas where the prevalence of school-aged periportal fibrosis is very low (<1%) (13). This low prevalence is in agreement with previous observation studies on Lake Victoria (14). The published literature on the resolution/regression of periportal fibrosis with treatment solely covers single intervention strategies, mostly annual (15–19) but also biannual treatment (20). They examine different aged cohorts and have varying follow-up periods, stretching from 7-months (15) to three years (16,19,21) and show clear geographical differences that will represent both transmission and host-parasite interaction dynamics. This previous literature indicates that regression of central fibrosis occurs at a faster rate than complete resolution of fibrosis, the former being detectable by 7-months in school-aged children (15), and the latter at 2-years (17). None achieve 100% disease resolution, with some individuals within the cohorts showing progression in severity of morbidity under the interventions.

Autopsy studies have shown conclusively that periportal fibrosis is solely attributable to schistosomiasis and is associated with high worm burdens (1). With the introduction of portal ultrasound machines, community studies have shown, however, that the highest *S. mansoni* infection intensities are not always significantly associated with periportal fibrosis: infection intensities peak in adolescence and the prevalence of fibrosis peaks in adulthood (22). Severe periportal fibrosis therefore seems to result from cumulative exposure to high infection intensities throughout childhood, and if

untreated increasing in severity towards adulthood (6). Correspondingly, when community-based PZQ treatment interventions are paired with monitoring of disease regression, periportal fibrosis is found to resolve more readily both in younger members of cohorts and those with milder fibrosis scores (16,18,23).

While in our Hoima District screen there is no significant increase in infection intensities between children without fibrosis and those with peripheral fibrosis (fibrosis of the segmental branches of the portal vein, but no fibrosis around the central portal vein), the PZQ intervention literature supports the resolution of this milder form of periportal fibrosis through chemotherapeutic intervention (16,20). In addition, in agreement with studies of school-aged children (23), a clear association between increased infection intensities and presentation with central fibrosis and worsening of this central fibrosis was observed. By implication, if we can drive down the infection burden amongst children, the prevalence of central fibrosis, that most likely to cause the severe manifestation of PHT, should also decrease. The link between infection intensity and the severest patterns suggests that resolution, even in this small subset of children may be achievable, contrary to the evidence linking severity of periportal fibrosis to poor resolution in adulthood (20).

Increasing PZQ dosage to 60mg/kg results in no significant difference in egg reduction rate (24,25), and 2 doses 2 weeks apart, although increasing cure rate, fails to have a long-term effect on infection intensities (26). Alternative annual treatment regimens therefore are unlikely to provide valid solutions. However, while not directly relating *S. mansoni* infection intensities to morbidity, increased PZQ treatment frequency is successful at reducing the infection burden amongst school children (27). Where periportal fibrosis is found to still occur, targeting increased frequency of intervention at school-aged children is likely to be a successful strategy to resolve much of the periportal fibrosis observed and prevent disease progression for others amongst these younger generations. However, this change in treatment regime requires evaluation, including validation of the required frequency of treatment, prior to recommendation for implementation.

Aim: *To evaluate whether increasing treatment frequency with praziquantel through school- based /school-community based delivery strategies reduces the prevalence of childhood periportal fibrosis in schistosomiasis morbidity hot-spots after two years of intervention.*

8. Trial Design

8.1. Statement of Design

This is a phase IV, randomised superiority trial that is blinded to the primary outcome assessors, but open label to all other investigators and participants.

8.2. Number of Centres

1

8.3. Number of Participants

We plan to include 600 participants in this trial. . Given the disruption caused by the COVID-19 pandemic to the communities from which the participants for this trial are identified, we anticipate this may require up to 750 participants to be enrolled; however we will continue to recruit participants until target participant completion is achieved.

8.4. Participants Trial Duration

Participants will be enrolled prior to the start of any other trial visits/treatments. The active treatment phase will last 2-years. All participants will be enrolled for the duration of the 2-year follow-up post 1st treatment. The time the participants will be enrolled in the trial has been elongated due to COVID-19 restrictions. Please see Diagram 'Chronological Trial Plan' in Section 12.6

8.5. Trial Objectives

8.5.1. Primary objective

To compare the effect of 2x and 4x treatments annually with praziquantel to the standard 1x annual treatment on the prevalence of *Schistosoma mansoni* associated periportal fibrosis of the liver.

8.5.2. Secondary objective

To compare the effect of 2x and 4x treatments annually with praziquantel to the standard 1x annual treatment on the mean infection intensity of *Schistosoma mansoni*.

8.6. Trial Outcome Measures

8.6.1. Primary outcome measure

The primary outcome is prevalence of periportal fibrosis, defined as Niamey Protocol pattern scores of C, D, E or F, measured at 2-years post 1st treatment follow-up.

8.6.2. Secondary outcome measure

The secondary outcome is *Schistosoma mansoni* infection intensities as measured by Kato-Katz faecal egg counts (28), measured at 2-years post 1st treatment follow-up.

8.6.3. Exploratory outcome measure

An exploratory secondary use of the trial data will be mathematical modelling of predicted long-term success of trial strategy. One year interim assessments of infection levels are to be taken to improve the fit of these models.

An exploratory outcome measure is the *S. mansoni* egg reduction rate, measured post treatment at baseline + 4 weeks and 2-years + 4 weeks, with accompanying parasite genetic/genomic characterisation. Processing of stool samples for parasite isolation will solely be conducted on samples received from participants who tested positive for *S. mansoni* infection using a point-of-care urinary dipstick that detects circulating cathodic antigen (CCA).
An exploratory outcome measure is host immuno-pathological responses to the eggs of the parasite. This will be measured at baseline, and if local conditions permit at the 2-year follow-up.

9. Community, School and Trial Team COVID-19 precautions

All Trial activities carried out by the trial team members will be performed following the COVID-19 precaution national guidelines and the trial Risk Mitigation Plan for the duration of the pandemic in Uganda. Any future national guidelines issued by the Ugandan Government will be reviewed by the Sponsor alongside the trial Risk Mitigation Plan and implemented as required.

10. Selection and withdrawal of participants

10.1. Inclusion Criteria

To be included in the trial the participant must:

- Have a parent/guardian who has given written/marked informed consent for the child to participate
- Have given written/marked informed assent to participate
- Be aged 6-14-years of age.
- Be born or resident within the community in which their school is situated for >=2 years.

10.2. Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

- History of facial oedema after treatment with praziquantel
- Known neurocysticercosis or intraocular cysticercosis

10.3. Treatment Assignment and Randomisation Number

Prior to enrolment trial participant identification numbers will be generated and these numbers assigned an intervention arm via simple computer generated random number randomisation. This paper-based list will be provided to the trial site team and upon enrolment children will be assigned to the ordered participant identification numbers, class-by- class and school-by-school or household or household if schools are not open and school-by-school. Randomisation will be stratified by school.

10.4. Method of Blinding

Open label to participants and the investigators, with the exception of the ultrasonographers who are undertaking the scoring for the primary trial outcome. Scoring will be undertaken remotely from the participant being examined, via a video link of the structured ultrasound examination, without audio, and the technicians who are undertaking the egg counts for the secondary outcome.

10.5. Participant Withdrawal Criteria

- Severe Adverse Reaction to praziquantel
- Withdrawal of consent/assent

11. Trial Treatments

11.1 Treatment Summary

Praziquantel, ~40mg/kg, dependent on standardised and verified dose pole, which was developed by WHO in 2001 for the administration of praziquantel without the use of weighing scales (29,30). Maximum dose 4x600mg tablets. Total treatments detailed below include an end of trial final treatment.

Control arm: 3 treatments (1x per annum for 2-years + final treatment)
Intervention arm 1: 5 treatments (2x per annum for 2-years + final treatment)
Intervention arm 2: 9 treatments (4x per annum for 2-years + final treatment)

11.1.1 Name and description of IMP X

Praziquantel. Anti-helmintic drug specific for trematode infections. It is distributed through MDA programmes in endemic countries through trained non-clinical community drug distributors. WHO estimates that 151M doses were dispensed through MDA programmes in 2017.

11.1.1.1 Legal status

Licensed for use in those over the age of 4-years. Licensed in Uganda. On the WHO Model List of Essential Medicines.

11.1.1.2. Supply

Praziquantel, the IMP, in the trial will be standard commercial stock as used by MDA programme, allocated by Vector-Control Division, Ministry of Health, from the praziquantel donated by Merck Healthcare KGaA for preventative chemotherapeutic treatment of school-aged children. Where possible this will be from a single manufacturing batch. The batch number and Certificate of Analysis, of all praziquantel donated by Merck Healthcare KGaA for use in this trial, along with manufacturing and expiry dates will be submitted for Clinical Trial Authorisation (CTA) to the National Drugs Authority (NDA) – Uganda, prior to its administration to trial participants.

In the event of supply interruption of the praziquantel, dontated by Merck Healthcare KGaA to the MDA, biosimilar praziquantel preparations, used by the MDA programme in Uganda are permitted for use in this trial.

11.1.1.3.Packing and Labelling

Provided in clearly labelled packages of tablets, as provided by the manufacturer, ready for dispensing according to a standardised dose pole. Administration will be observed.

11.1.1.4. Storage conditions

Praziquantel tablets are stable when stored at room temperature.

11.1.1.6.Maximum duration of treatment of a participant

At each treatment time-point participants will receive a single dose of praziquantel.

11.1.1.6.Dose

Praziquantel treatment will be assigned according to the WHO dose pole for praziquantel, a standardised and validated pole that assigns treatment according to height to facilitate mass-drug administration. The pole is designed to assign treatment doses of approximately 40mg/kg. The tablet is scored for easy breakage as doses include treatment with half tablets. The maximum dose dispensed for treatment of schistosomiasis is four 600mg PZQ tablets.

11.1.1.7.Administration

Oral, after provision of food.

11.1.1.8 Known drug reactions

Neurological
Headaches – very common (>10%)
Dizziness – very common (>10%)
Vertigo, drowsiness – common (1-10%)

Seizures – very rare (<0.01%)

Gastro-intestinal
Gastrointestinal and abdominal pains– very common (>10%)
Nausea – very common (>10%)
Vomiting – very common (>10%)
Anorexia – common (1 – 10%)
Diarrhoea – common (1 – 10%)
Bloody diarrhea - – very rare (<0.01%)

Dermatological
Urticaria – very common (>10%)

Cardiovascular
Unspecified arrhythmias – very rare (<0.01%)

Immune system disorders
Allergic reaction – very rare (<0.01%)
Polyserositis – very rare (<0.01%)
Eosinophilia – very rare (<0.01%)
Jarisch-Herxheimer reaction – very rare (<0.01%)

Hepatobiliary disorders
Liver function tests increased – rare (0.01 - 0.1%)

Musculoskeletal and connective tissue disorders
Myalgia – common (1 – 10%)

General disorders
Fatigue–very common (>10%)
Feeling unwell (asthenia, malaise) – common (1 – 10%)
Fever– common (1 – 10%)

Adverse reactions with food, over the counter drugs or commonly prescribed drugs are not reported.

11.1.1.9. Dose modifications

N/A

11.1.1.10. Procedures for monitoring treatment compliance

Treatment will be observed by a member of the study team trained in dispensing praziquantel. If the individual refuses treatment this will be entered into the treatment log.

11.2. Accountability and dispensing

11.2.1.Pharmacy responsibilities

The Vector Control Division – Ministry of Health, Uganda are responsible for ensuring adequate stocks of praziquantel. Praziquantel will be stored out of direct sunlight, with restricted access, prior to transport to the trial site. A trial team member will observe provision of treatment, which will be conducted in each participating school, local community trial site location or house-hold to house-hold by either the

teacher in each participating school who is the National Control Programme trained drug dispenser, an appropriately trained VHT or trial team member

11.2.2 Drug accountability

A log of drug treatments will be kept, including batch number, dose received, and date of treatment.

11.2.3 Returns and destruction

All praziquantel not used within the trial will be returned to Trial site co-ordinator, Dr Edridah Tukahebwa, Vector Control Division – Ministry of Health, Uganda.

12 Procedures and assessments

All procedures will be undertaken within the communities. Ultrasonography examinations and phlebotomy will be conducted within the schools or local community trial site location, when the schools are not available due to COVID-19 restrictions or any other government restrictions, including other infectious diseases. Stool and urine samples will be collected in a sensitive manner from participants in the school setting or house-hold to house-hold dependent upon COVID-19 or other government restrictions. Annual treatments will be dispensed after scheduled sample collection and ultrasonography examinations in the school setting, local community trial site location or house-hold to house-hold dependent upon COVID-19 or other government restrictions. Intervening treatments will be dispensed by the trial team during visits to the participating primary schools, community trial site location or house-hold to house-hold dependent upon COVID-19 or other government restrictions. Treatment will be observed by trained members of the trial team, and a 24-hour post-treatment follow-up will be conducted by a trained health worker to record treatment side-effects. The collected blood and stool samples will be processed as initially planned. Dependent upon COVID-19 or other government restrictions, and where possible, samples may be frozen for analysis at a later date.

When COVID-19 or other government restrictions are lifted it is intended that trial activities which directly involve the participants will be carried out in the participating primary schools as initially planned. The alternative locations for trial activities are to facilitate the conduct of trial activities whilst adhering to the COVID-19 or other government restrictions, the National Guidelines for Conduct of Research during coronavirus Disease 2019 (COVID-19) Pandemic, July 2020, UNCST, Government of Uganda and the FibroScHot Risk Mitigation Plan.

12.1. Participant identification

Children attending primary schools in Hoima District, Uganda will be enrolled. Participating schools will be selected from already collected ultrasound screening data, to ensure high morbidity schools are involved, and their enrolment numbers for primaries 1 to 4, to limit the number of participating schools. Advocacy meetings will be held with District officials, including local government, Health and Education officials and with school-teachers prior to commencement of enrollment. Information meetings will be held with members of the community to explain the purpose and procedures of the trial to parents/guardians of the children. The study will also be explained to the school children themselves.

12.2. Consent

The Informed Consent form will be approved by the Vector-Control Division, Ministry of Health REC and will be in compliance with GCP, local regulatory requirements and

legal requirements. The investigator or designee will ensure that the legally acceptable representative of each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written/marked informed consent from each participant's legally acceptable representative before any trial-specific activity is performed. If the participant's legally acceptable representative is unable to read or write, the trial documentation will be read to them in the local language and their questions addressed, prior to their marking of the consent form. An independent observer will witness consent procedures for those who can't read and write. Written assent will be obtained from all children who participate in the trial, after age-appropriate description of the procedures involved. Those seeking written assent must be particularly sensitive to and prevent any pressures being applied to the children regarding their decision to participant in the trial or not. The trial information sheets and consent/assent forms will be translated into the local language, and back translated into English. All sections of the approved documents must appear in the translation. The translated version will be appropriately dated and include version control.

The informed consent form used for this trial and any change made during the course of this trial, will be prospectively approved by the REC. The Trial site co-ordinator, Dr Edridah Tukahebwa, will retain the original of each participant signed/marked informed consent and assent forms.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant and their legally acceptable representative at the next visit by a member of the trial team. We do not expect any new information as this drug has been available for 40 years post licensure and is not being used for any unintended purposes.

12.3. Screening evaluation

12.3.1. Screening Assessments

Trial specific assessments will only be conducted after participants and their legally acceptable representative have given their written/marked informed consent/assent.

The primary outcome of the trial will be obtained from ultrasonography examinations. They will be conducted according to the WHO Niamey Protocol for Schistosomiasis.

The secondary outcome of the trial will be obtained by collection of stool samples for egg counts by Kato-Katz.

12.3.2. Exploratory outcomes

Sample collections for the exploratory outcomes to be carried out where local conditions permit and involve:

Stool samples	4-week post-treatment egg reduction egg counts
Urine samples	Pre-treatment and 4-week post-treatment CCA urinary dip-stick diagnosis of *S. mansoni*. Parasites to be hatched from stool samples for those positive by CCA.
Blood sample	8ml by phlebotomy for cellular and cytokine response measurement.

All assessments are non-invasive (ultrasonography and stool collection), or considered of minor risk (phlebotomy).

12.3.3. Participant Registration/Randomisation

Participants will be enrolled prior to any other visits/treatment can be scheduled. Individuals will be randomised on a 1:1:1 ratio into the control or intervention arms.

12.3.3.1 Participant Photograph

A photograph of each participant is to be taken at enrolment or as soon as possible after enrolment and kept by the trial team to assist with participant identification throughout the trial. Photograph to be destroyed or handed to participant at end of trial.

12.4. Baseline Assessments

The following data points are to be recorded:

a) Sex
b) Age and date of birth
c) WHO ultrasonography score
d) *Schistosoma mansoni* infection intensity by faecal egg count
e) Praziquantel dose according to standardised WHO dose pole (no later than 12 months after the 1st ultrasonography score collection)

12.4.1 Baseline Assessment Assurance following COVID-19 pause

All school-based trial activities were paused on the 19 March 2020 in accordance with the Ugandan government announcement concerning COVID-19. At the time baseline assessments were completed at Buhirigi School except the administration of Praziquantel.

The following data points are to be repeated in at least 10% of the participants from the Buhirigi school cohort to ensure data integrity.

c) WHO ultrasonography score
d) *Schistosoma mansoni* infection intensity by faecal egg count

12.5. Trial assessments following the 1st treatment dose

12.5.1.Timing of assessments

Annual assessments for two years, including treatment efficacy eggs counts at baseline and two-years +4 weeks.

12.5.2. Assessments at time point

The following is to be recorded at around 4-weeks:

Schistosoma mansoni infection intensity by faecal egg count

The following are to be recorded at around 1-year:

a) *Schistosoma mansoni* infection intensity by faecal egg count (for a subset of 120 participants, 60 per school/community)

The following are to be recorded at around 2-years:

a) WHO ultrasonography score (primary outcome assessment)

b) *Schistosoma mansoni* infection intensity by faecal egg count (secondary outcome assessment).

12.5.3. Assessments at the end of trial visit

To be recorded at around 2-years + 4-weeks:

Schistosoma mansoni infection intensity by faecal egg count.

12.6 Schedule of Assessments

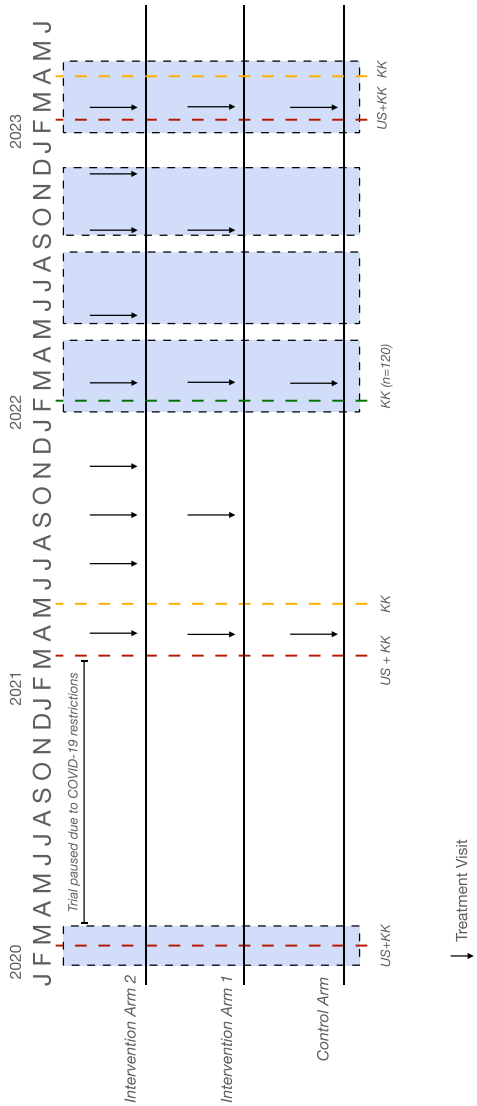


Figure: Chronological Trial Plan

12.7. End of Trial Participation

Participants will return to the standard care of once per annum treatment at the end of the trial.

12.8. Trial restrictions

None

13. Assessment of Safety

13.1. Definitions

13.1.1. Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a participant has yet received a medicinal product.

13.1.2. Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

13.1.3. Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI).

When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant /event outcome or action criteria.

13.1.4. Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening - The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- requires inpatient hospitalisation
- results in persistent or significant disability or incapacity

- is an important medical event - Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalisation.

13.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

13.1.6. Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC) and is the information used for assessing whether an adverse reaction is expected.

For this trial the Reference Safety Information is:
contained in the Table in Section 4.8 of the Summary of Product Characteristics (SmPC) for Praziquantel 600mg tablets (Medopharm Private Ltd) dated May 2021 published by WHOPAR Part 4, available at
https://extranet.who.int/pqweb/WHOPAR/nt008

13.2. Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are as specified in section 12.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 12.5.

13.3. Expected Adverse Events/Serious Adverse Events (AE/SAE)

The following adverse events are not reported as SAEs

- Adverse events due to malaria.
- Adverse events due to contemporaneous outbreaks of epidemic prone diseases/conditions, including COVID-19 symptoms, occurring from the time of consent to the end of the trial.

13.4. Evaluation of adverse events

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product.

Individual adverse events should be evaluated by the investigator. This includes the evaluation of its severity, and relationship to IMP(s)/study treatment (causality).

13.4.1. Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

13.4.2. Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

13.4.3. Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

13.4.4. Recording of adverse events

Adverse events and adverse reactions should be recorded in the appropriate section of the AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.5.

13.5. Reporting serious adverse events

The Trial Site Manager will record all adverse events, ensure potential serious adverse events are referred to the trial clinical officer at Kigorobya Health Centre IV and upon confirmation the trial clinical officer report serious adverse events to the Principle Investigator, Chief Investigator, Trial Site Manager and Trial Site co-ordinator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor and Merck KGaA (for IMP donated by Merck KGaA) or the manufacturer of biosimilar IMP as required, immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team. The Principal Investigator is responsible for ensuring the onward notification of all SAEs to the Research Ethics Committee in Uganda within 24-hours of first notification.

The Trial Site Co-ordinator is responsible for prompt reporting of all serious adverse event findings to the competent authority of the concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

The completed SAE form can be faxed or emailed. Details of where to report the SAE's can be found on the 'FibroScHot' SAE form and the front cover of the protocol.

Please see Appendix 25.3 at the end of this document for the Safety reporting flow chart.

13.6. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 12.1.6 for the Reference Safety Information to be used in this trial.

13.6.1. Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor

The Principle Investigator in the trial site must report all the relevant safety information previously described, to the:

- Competent authorities in the concerned member states
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

13.6.2. When to report?

13.6.3. Fatal or life-threatening SUSARs

All parties listed in 12.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed

as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

13.6.2.2. Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 12.6.1 as soon as possible but no later than **14 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

13.6.3. How to report?

13.6.3.1. Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source

and, when available and applicable:
- an unique clinical trial identification
- an unique case identification (i.e. sponsor's case identification number)

13.6.3.2. Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

13.6.3.3. Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

14. Toxicity – Emergency Procedures

Development of facial oedema, an extensive urticarial rash or severe stomach cramps within the first 48-hours post-treatment will be considered as a severe adverse reaction, and the child will be referred to the local health centre IV at Kigorobya for care by the trial clinical officer. A follow-up visit from the nursing qualified Trial Site Manager will be conducted once the child has returned home. In the event of facial oedema as a result of treatment the child will be permanently removed from further participation in the trial.

15. Evaluation of Results (Definitions and response/evaluation of outcome measures)

15.1. Response criteria

15.1.1. Prevalence of periportal fibrosis of the liver

A WHO Niamey Protocol for Ultrasound in Schistosomiasis pattern score of C, D, E or F will be considered as presence of periportal fibrosis. This will be measured during baseline activities, and at 2-years. A 20% difference in prevalence between the control and intervention arm at 2-years of intervention will be considered a success.

15.1.2. Schistosoma mansoni infection intensity

S. mansoni faecal egg counts as determined from Kato Katz smears will be used to calculate infection intensity. A statistically significant difference between control and intervention arm, with an alpha of 0.05, and 80% power will considered a success.

16. Storage and Analysis of Samples

Stool samples will be collected and processed for egg counts by Kato Katz. Stool samples will also be processed for hatching of the miracidial stage of the parasite for genetic characterisation, the exploratory outcomes.

Urine samples will be collected and tested using a point-of-care rapid diagnostic test for *Schistosoma mansoni*.

Blood is to be drawn into EDTA, heparin anti-coagulants and for sera by a skilled phlebotomist. Whole blood cell cultures will be set up from the heparin aliquot and plasma harvested from the EDTA aliquot. Plasma and culture supernatants will be stored between -15°C and 25°C in the trial site laboratory. Sera will be stored between -60°C and -80°C. Shipment to the analysing laboratory will be on dry ice or in liquid nitrogen vapour. Upon receipt, plasma and cell culture supernatants will be stored at between -60°C and -80°C in a specialised freezer until assays are to be processed.

Peripheral blood mononuclear cells (PBMC) will be cryopreserved in liquid nitrogen vapour at the study laboratory situated within Hoima District, and shipped to the analysing laboratory where they will be stored in liquid nitrogen tanks.

Blood products, urine and stool samples will be collected for future pathogen specific research, and host-pathogen research. Unprocessed stool samples will be stored in at VCD-Uganda, blood products, urine and one aliquot of stool sample products will be shipped to University of Cambridge. They will remain the property of VCD-MoH Uganda. Participating laboratories will be able to request access to these samples. Researchers outside of the trial will have access on a case-by-case basis. These requests will only be granted if the research questions is in line with the participant information sheet. Transfer will be considered by a Material Transfer Committee, including an independent researcher. These samples will be held for a maximum of 15-years, after which they will be destroyed. They will be stored according to UK Human Tissue Act regulation standards, irrespective of where they are stored. All samples will be linked anonymised.

17. Statistics

17.1. Statistical methods

The primary analysis will estimate the absolute difference between the arms in terms of the rate of periportal fibrosis using logistic regression on the absolute difference scale, adjusting for baseline covariates, including school, fibrosis score and egg count. Treatment effect estimates and 95% confidence intervals will be reported; formal hypothesis testing will compare the two-sided p-values for all three pairwise comparisons to a nominal significance level of 1.66%, as a Bonferroni correction to preserve the overall significance level at 5%.

Secondary endpoints will be analysed using regression tools to compare arms, adjusting for covariates, but tailoring the model to the form of the endpoint (continuous, binary, time-to-event) as required.

17.2. Number of Participants to be enrolled

Berhe et al 2008 (20) reported a 47.7% resolution rate of grade C to non-periportal fibrosis scores of A and B and 24.6% resolution rates of D scores to scores A and B. Extrapolating this success rate onto our preliminary data, we would expect 35% less of the children in a successful intervention arm to have periportal fibrosis after 2-years intervention than those in the control arm. However, Berhe et al also reported geographical differences in resolution, with higher transmission villages having poorer resolution. We therefore propose a minimum 20% absolute difference in prevalence of periportal fibrosis between the control and intervention arms to be a clinically significant outcome. Based on preliminary data we assume an incidence rate of scores C-F of 80% in the control arm. With a Bonferroni correction to allow any pairwise comparison between the three arms, testing at a 1.66% significance level, a total sample size of 450, 150 per arm, would provide 92% power to detect an absolute reduction of 20%. In previous Lake Victoria fishing community observation studies, failure to follow-up has been as high as 35%. The communities on Lake Albert are more stable (NB Kabatereine, pers. comm.) but to minimise failure to follow-up, selection is restricted to children in P1 to P4, retaining the cohort within the primary school structure over the two years of the study, and an inclusion criteria of born or resident in the village for >2yrs, displaying stability of their household within the village is included. A failure to follow-up of 25% is included in the final study numbers. Six hundred primary school-aged children will be enrolled into the study, with 200 randomised into each of the three intervention arms. Given the disruption caused by the COVID-19 pandemic to the communities from which the participants for this trial are identified, we anticipate this may require up to 750 participants to be enrolled to obtain the sample size of 600; however we will continue to recruit participants until target participant completion is achieved.

17.3. Criteria for the premature termination of the trial

The trial site has become too dangerous for trial staff to work, either through an infectious disease outbreak or civil unrest.

17.4. Procedure to account for missing or spurious data

The power calculation contains a 25% failure to follow-up rate to account for the inherent instability of Ugandan fishing communities. A principled approached will be undertaken to quantify how robust the study conclusions are in the presence of missing data, by considering a range of assumptions about the distribution of the missing data and translating these into the equivalent estimates of treatment effect.

17.5. Definition of the end of the trial

The end of trial will be the date of the last patient's provision of the final stool and urine sample for parasitology.

18. Data handling and record keeping

18.1. CRF

All data will be transferred into a Case Report Form (CRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial co-ordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

All CRF pages must be clear and legible. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialed by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

18.2. Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., CRFs and samples), all original signed informed consent forms and copies of the CRF pages.

Source Data:
Signed/marked informed consent forms by parents/guardians.
Signed/marked assent forms by participants.
Parasitology raw data egg count sheets
Ultrasonography Protocol Mark Sheets
Treatment log
Sample log
AE reporting form

18.3. Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the General Data Protection Regulation 2018, Uganda National College of Science and Technology Policy and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

19. Data Monitoring Committee/Trial Steering Committee

A trial steering committee will be set up with 1) a minimum of one clinically qualified, independent expert, 2) a second independent expert, 3) a community representative for the parents/guardians and Dr Shona Wilson and Prof Fred Nuwaha on behalf of the trial investigators. CCTU investigators will be invited to observe proceedings on behalf of the sponsor for trial audit purposes.

Due to the well-established safety profile of PZQ, a full DMC is not required. Safety data will be monitored by independent experts (one of whom will be clinically qualified), who are members of TSC.

20. Ethical & Regulatory considerations

20.1. Ethical committee review

Before the start of the trial or implementation of any amendment approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents will be attained from the Vector Control Division, Uganda Ministry of Health Research Ethics Committee (REC). All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Ethical Clearance will be sought from the Ugandan National Council for Science and Technology.

Annual reports will be submitted to the REC. It is the Chief Investigator's responsibility to produce the annual reports as required.

20.2. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the National Drugs Authority (NDA) – Uganda. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

20.3. Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC.

The only circumstance in which an amendment may be initiated prior to REC approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures).

20.4. Peer Review

The trial protocol has been reviewed by the Ethics Committee of the funder, The European and Developing Countries Clinical Trial Partnerships (EDCTP). It has also been reviewed by an independent expert on behalf of Trial Sponsors (CUH).

20.5. Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

20.6. GCP Training

All trial staff must hold evidence of appropriate GCP and/or GCLP training as appropriate or undergo GCP/GCLP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years.

21. Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The trial will be funded by The European and Developing Countries Clinical Trial Partnership (EDCTP).

Cambridge University Hospitals NHS Foundation Trust, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, and where no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial. Vector Control Division will arrange comparable insurance within Uganda.

22. Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for the trial site. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

23. Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator, The REC and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor and REC without any delay.

24. Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

Participating investigators will have rights to publish the trial data.

The EDCTP will be acknowledged as the funder in all publications resulting from the trial data.

Community meetings will be held to report the results of the trial to the participants and their parents/guardians upon analysis of the trial data.

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26. Appendices

26.1. Appendix 1 - Trial Management / Responsibilities

26.1.1. Participant registration/ Randomisation procedure

Receive parent/guardian consent for participation, and conduct the assent process within the school or village community environment. Eligible children will then be assigned class-by-class and school-by-school or household-by-household if the schools are not open and school-by-school to listed identification numbers. These identification numbers will have previously been assigned to an intervention arm. Randomisation will be stratified by school.

26.1.2. CRF Completion & Data management

Data entered from hard copy field generated data entry sheets, will be signed and dated upon entry, prior to storage in a locked fire proof filing cabinet for the duration of the trial.
A dedicated trial database (MACRO) will be designed, constructed and managed by the Cambridge Clinical Trials Unit (CCTU). The latest up-grade to MACRO was successfully validated and UAT in our hosted environment in January 2017.

Programmers make the MACRO database live by following specific steps of a checklist. Trial staff are then contacted by email to inform them that database has gone live. Database access is limited to selected and trained users as specified by the trial team. MACRO allows unlimited data points and fields. During the trial period, data required for specific project objectives, is available to consortium members upon request. Requests and data downloads for consortium members will be logged.

Data Entry Clerks employed by VCD, and the Data Manager (VCD) will be responsible for receipt of completed paper case report form (CRF) pages from the trial site, cleaning the data and the entry of these data into the trial database within pre-defined timelines outlined in the data management plan. The data manager will assist with preparation of the interim safety data reports with unblinded data in response to formal requests. Hence the data manager has access to all data, but will not contribute to analysis. CCTU will provide oversight of data management procedures on behalf of the sponsor.

All CCTU data collected from the clinical trial will be stored electronically, backed up daily and secured on a database hosted at the School of Clinical Medicine, University of Cambridge. The data backup services are in accordance with the security policy for Secure Data Hosting Service 2014 of the School of Clinical Medicine. All data are held in scalable file systems or parallelized databases with redundancy and backup, along with disaster recovery protocols. All changes to systems or configuration within the application environment are handled by service team under ITIL-based change protocols. Industrially supported EMC hardware is used including DCA (Data Computing Appliance) hardware with Pivotal HD (Hadoop) and Pivotal DB software (PostgreSQL compatible), as well as the Isilon clustered file system for semi- or un-structured data.

Exploratory data will be stored independently of the main clinical trial forms. This data will be linked to samples and, upon request trial data, via the trial generated identification codes. Investigators requesting trial data for analysis of exploratory outcomes will not contribute to the analysis of the primary trial outcomes. This trial

data will be maintained under strict password protection, and only accessible to the requesting investigators.

26.1.3. Data protection/ confidentiality

Data is stored in a secure, remote, professionally managed database accessed by two methods (1) for data entry by co-ordinator / data manager via secure https website (2) via encrypted Remote Desktop thin client connections for administration, security setup, design, reports, data downloads and archiving.
Exploratory outcome data will be stored independently on secure data platforms by the generating participants. All exploratory data will be stored separately from files containing personal identifiers. Electronic exploratory data will be protected by robust passwords, and regularly backed-up to password protected hard-drives and stored in fireproof data safes. Hard copy data generated will be stored in locked fire-proof study files.

Access to the data linking trial identification numbers to personal identifiers will only be granted to investigators who require them for trial site activities. All data acquisition, storage and transmission will comply with the Data Protection Act.

26.1.4. Trial documentation & archiving

All individual consent and assent files will be archived at Vector Control Division – Ministry of Health, Uganda for a period of 5-years after the end of the trial. Primary and secondary trial data will be archived by CUH. The data will be stored for a minimum of 10 years; backup and business continuity are all in accordance with policies implemented by the University of Cambridge. Exploratory outcome data will be archived by the generating investigator. In compliance with Horizon 2020 data directives, anonymised meta-data will be deposited within an open access data repository with linkage for data sharing requests to the raw data.

26.2. Appendix 2 – Authorisation of Participating Sites

26.2.1. Required Documentation

Ethical Approval from Vector Control Division – Research Ethics Committee.
Ethical Clearance from Uganda National Council for Science and Technology
Trial Certificate from Uganda National Drug Authority.
Insurance Certificates for the trial.
Fully executed trial contracts
Completed delegation log and signed CVs and dated and GCP certificates for the trial staff. Completed training logs for trial staff.

Confirmation of receipt of the Investigator Site File.
Confirmation of receipt of the trial Data Logs and paper CRFs.
An example of the participant information documentation (Consent and assent) in both languages.

26.2.1. Procedure for initiating/opening a new site

Regional health and education authorities are informed of the trial.
Headmasters and teachers have agreed for the trial to be undertaken in their school.
Community leaders and parents/guardians are informed of the trial and their children invited to participate.
The drug will be released to the site by Dr Edridah Tukahebwa, Vector Control Division – Ministry of Health.
A site activation letter from Sponsor

26.2.3. Principal Investigator Responsibilities

Attendance at the initiation teleconference.
Training of new members of the trial team in the protocol and its procedures.
Delegation of activities to appropriately trained staff
Appropriate recruitment and care of participants in the trial
Timely completion of the paper and electronic CRF data
Dissemination of important safety or trial related information to all stakeholders at the trial site
Safety reporting within the timelines and assessment of causality and expectedness of all SAEs
Sample Management.
Archiving of the Investigator Site File on confirmation of Sponsor post end of trial.

26.3. Appendix 3 - Protocol and amendment history

Amendment No.	Protocol version no.	Date	Details of changes made
1	1.4	10 Oct 2019	Submitted to VCD REC; pre NDA approval. -Addition of exclusion criteria of neurocysticercosis or ocular cysticerosis. -Clarification of safety data collection (Section 12) -Specification of the trial Reference Safety Information as Praziquantel 600mg tablets (Cipla Ltd) dated January 2017 published by WHOPAR Part 4. (Section 12.1.6) -Update on side effects of PZQ (Section 6.2 and 10.1.1.3) -Addition of ISRCTN number -Updating of trial management committee -Clarification of trial design (Section 4) -Clarification of urine sample collection (Section 11.3.1) - Administrative updates

2	2	08 Sept 2020	- Updated CI Maternity Cover (Front page, Section 2 Trial Management Committees and Section 26.3 Safety Reporting Flow Chart) - Addition of 'school-community based' to aim (Section 7) to enable trial activities to be carried out whilst schools are closed due to COVID-19 National Guidelines - Addition Section 9 Community School and Trial Team COVID-19 precautions. - Section 11.1.1.2 removal of IMP expiry date of 31/01/2022, as trial will run beyond this date due to COVID-19 pause of trial activities. - Addition of 'local community trial site location' and 'house-hold to house-hold' throughout the protocol to enable trial activities to be carried out in the appropriate locations whilst the schools are not permitted to be used for trial activities due to COVID-19 restrictions. (Section 12) - Explicit statement that trial activities to return to the participating school location when allowed. (Section 12) - Clarification of exploratory outcome sample collection (Section 12.3.3). - Addition of participant photograph to enhance participant identification for community based trial activities (Section 12.3.3.1) - Widening of window between baseline assessments and IMP administration so that baseline data may be used. Delay between activities caused by COVID-19 pause to trial activities. (Section 12.4) - Addition Section 12.4.1 Baseline Assessment Assurance following COVID-19 Pause. Text added to allow repeat collection of primary and secondary endpoint data from Buhirigi School participants to verify data integrity despite time delay between first collections and IMP administration caused by COVID-19 pause. - Section 12.5.3 Addition of footnotes to the Schedule of assessments to allow for wider window between ultrasound examination and first IMP administration at baseline visit, due to COVID-19 pause. - Widening of temperature storage range for collected samples (Section 16)

			- 26.3 Safety Reporting Flow Chart updated to include CI Maternity Cover - Administrative updates
3	3	31 Oct 2021	Submitted VCD REC prior to NDA approval - Update of 1-year procedures in trial synopsis (section 4) to reflect removal of ultrasound examination and reduction in sampling for egg counts. - Update of trial flow chart (section 5) to reflect removal of 1-year+4-week egg count for exploratory outcome of egg reduction rate - Update of section 8.6. Trial outcome measures to reflect altered examinations/sampling schedule detailed above for changes to sections 4 and 5, plus removal of blood sampling at 1-year. - Update of section 12.5 to reflect altered examinations/sampling schedule detailed above for changes to sections 4 and 5. - Update of Schedule of assessment (Section 12.6) to reflect altered examination/sampling schedule detailed above for changes to sections 4 and 5. - Update of Response Criteria (Section 15.1) to reflect removal of ultrasound examinations at 1-year. - Update of appendix 1 to reflect changes in Data Management responsibilities -

4	4	17th May 2022	Submitted to VCD REC prior to NDA approval - Update of Trial Management Committee (section 2) to reflect change in Trial Management Group - Update of Trial Synopsis (section 4) with clarification of AE monitoring procedure - Update of Reporting Serious Adverse events (section 13.5) to reflect new SAE reporting structure - Update of Toxicity (section 14) to reflect change in qualification required for the Trial Site Manager - Update of Participant registration/ Randomisation procedure (section 26.1.1) to correctly reflect procedure that took place - Update of Safety Reporting Flow Chart (Section 26.4) to reflect changed qualification requirement of Trial Site Manager and where the medical oversight is provided.
5	4.1	26th June 2022	Administrative change, submitted to VCD REC prior to NDA approval (note – submitted prior to review of version 4) - Update of Trial management committee (section 4) to include name of Trial Site manager - Update of Safety Reporting Flow Chart (Section 26.4) to include name of Trial Site manager.

6	4.21	18th November 2022	Submitted to VCD REC prior to NDA approval. Clarification of numbers of participants enrolled into the trial. - Update of Number of Participants (Section 8.3) - Update of Number of Participants to be enrolled (Section 17.2) Addition of text to enable use of biosimilar praziquantel preparations as the IMP for this trial. - Update of Supply (Section 11.1.1.2 - Update of Reporting Serious Adverse Events (Section 13.5) - Update of Safety Reporting Flow Chart (Section 26.4) Amendment to RSI – update to SmPC to be used in this trial. - Update to Reference Safety Information (Section 13.1.6) - Update to Safety & tolerability (Section 6.2.2) Correction to Schedule of Assessments - Update of Treatment Visit, corrected to September 2022 (Section 12.6) Administrative changes to clarify text. - Update of Number of Participants (Section 8.3) - Update to Participants Trial Duration (Section 8.4) - Update to Participants identification (Section 12.1) - Update to Participants Registration/ Randomisation (Section 12.3.3) - Addition of text to enable community based trial activities in the event of school closures due to government restrictions for reasons other than COVID-19 (Section 9.0 and Section 12)

7	4.22	23rd November 2022	Administrative change to clarify SAE reporting - Addition of text to clarify that the PI will report SAEs to the REC within 24-hours of notification (section 13.5).

26.4. Safety Reporting Flow Chart