

Praziquantel for children under age four years:

A Phase II PK/PD driven dose finding trial (PIP trial)

NIH/NICHD Funding Mechanism: R01 HD095562

Pharmaceutical Support Provided by *Tedor Pharma, Cumberland, RI (non-financial) & International AIDS Vaccine Initiative (IAVI) Pharmacy, Entebbe, Uganda*

Lead Principal Investigator (US): *Dr. Jennifer Friedman*

Lead Principal Investigator (UK): *Dr. Amaya L. Bustinduy*

Site Principal Investigator (Uganda): *Dr. Patrice Mawa*

Site Principal Investigator (Philippines): *Charissa Borges-Tabora, MD*

Trial Statistician and Co-investigator: *Dr. Emily Webb*

Clinical Project Manager (Uganda): *Dr. Andrew Edielu*

External Study Monitor: *Nampijja Proscovia*

Independent Safety Monitor: *Dr. Zacchaeus Anywaine*

Draft or Version Number: *5.4*

Day Month Year

March 03, 2022

1 STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

2 SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

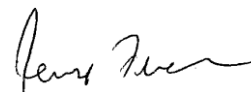
I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Dr Jennifer
Friedman

Lead Principal
Investigator (US)

Jennifer_friedman@brown.edu



Dr Amaya
Bustinduy

Lead Principal
Investigator (UK)

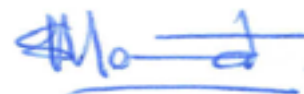
Amaya.Bustinduy@lshtm.ac.uk



Dr Patrice
Mawa

Site Principal
Investigator
(Uganda)

pmawa@uvri.go.ug



3 TABLE OF CONTENTS

| | |
|--|----|
| STATEMENT OF COMPLIANCE | 2 |
| SIGNATURE PAGE..... | 3 |
| TABLE OF CONTENTS..... | 4 |
| LIST OF TABLES..... | 9 |
| LIST OF FIGURES..... | 10 |
| LIST OF ABBREVIATIONS | 11 |
| PROTOCOL SUMMARY | 14 |
| 1. KEY ROLES | 19 |
| 2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE | 23 |
| 2.1. Background Information..... | 23 |
| 2.2. Rationale | 24 |
| 2.3. Potential Risks and Benefits | 26 |
| 2.3.1. Potential Risks..... | 26 |
| 2.3.2. Known Potential Benefits | 27 |
| 3. OBJECTIVES AND OUTCOME MEASURES..... | 29 |
| 3.1. Study Objectives | 29 |
| 3.1.1. Primary..... | 29 |
| 3.1.2. Secondary | 29 |
| 3.2. Study Outcome Measures | 30 |
| 3.2.1. Primary..... | 30 |
| 3.2.2. Secondary | 31 |
| 4. STUDY DESIGN | 32 |
| 5. STUDY ENROLLMENT AND WITHDRAWAL | 39 |
| 5.1. Subject Inclusion Criteria | 39 |
| 5.2. Subject Exclusion Criteria | 39 |

| | | |
|--------|--|----|
| 5.3. | Treatment Assignment Procedures | 40 |
| 5.3.1. | Randomization Procedures..... | 40 |
| 5.3.2. | Masking Procedures | 40 |
| 5.3.3. | Reasons for Withdrawal and Discontinuation of Study Product Administration | 40 |
| 5.3.4. | Handling of Withdrawals and Discontinuation of Administration | 41 |
| 5.3.5. | Subject Replacement | 41 |
| 5.3.6. | Termination of Study | 42 |
| 6. | STUDY INTERVENTION/INVESTIGATIONAL PRODUCT | 43 |
| 6.1. | Study Product Description | 43 |
| 6.1.1. | Acquisition of Praziquantel..... | 43 |
| 6.1.2. | Formulation, Packaging, and Labeling..... | 43 |
| 6.1.3. | Product Storage and Stability | 44 |
| 6.2. | Dosage, Preparation and Administration of Study Intervention/Investigational Product | 44 |
| 6.3. | Modification of Study Intervention/Investigational Product for a Subject..... | 45 |
| 6.4. | Accountability Procedures for the Study Intervention/Investigational Product(s)..... | 45 |
| 6.5. | Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device | 46 |
| 6.6. | Concomitant Medications/Treatments | 46 |
| 7. | SCHEDULE | 47 |
| 7.1. | Recruitment | 47 |
| 7.2. | Screening | 47 |
| 7.3. | Enrollment/Baseline | 47 |
| 7.4. | Follow up at 4 weeks | 49 |
| 7.5. | Follow up at 6 months | 49 |

| | | |
|--------|--|-------------------------------------|
| 7.6. | Follow-up and close out at 12 months | 50 |
| 7.7. | Final Study Visit..... | 51 |
| 7.8. | Early Termination Visit (if needed) | 51 |
| 7.9. | Unscheduled Visit (if needed)..... | 51 |
| 8. | STUDY PROCEDURES/EVALUATIONS | 52 |
| 8.1. | Clinical Evaluations | 52 |
| 8.2. | Laboratory Evaluations | 52 |
| 8.2.1. | Clinical Laboratory Evaluations..... | 52 |
| 8.2.2. | Special Assays or Procedures..... | 52 |
| 8.2.3. | Specimen Preparation, Handling, and Shipping | 53 |
| 9. | ASSESSMENT OF SAFETY..... | 54 |
| 9.1. | Specification of Safety Parameters..... | 54 |
| 9.2. | Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters..... | 54 |
| 9.2.1. | Adverse Events | 54 |
| 9.2.2. | Serious Adverse Events..... | 56 |
| 9.2.3. | Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings | 57 |
| 9.3. | Reporting Procedures | 57 |
| 9.3.1. | Serious Adverse Events..... | 57 |
| 9.3.2. | Regulatory Reporting for Studies Conducted Under Investigator-Sponsored IND | Error! Bookmark not defined. |
| 9.3.3. | Reporting of Pregnancy | 57 |
| 9.4. | Type and Duration of Follow-up of Subjects after Adverse Events..... | 58 |
| 9.5. | Halting Rules | 58 |
| 9.6. | Safety Oversight (ISM plus SMC or DSMB) | 59 |
| 9.6.1. | Independent Safety Monitor (ISM) | 59 |

| | | |
|---------|--|----|
| 9.6.2. | Data and Safety Monitoring Board (DSMB)..... | 60 |
| 10. | CLINICAL MONITORING | 62 |
| 10.1. | Site Monitoring Plan | 62 |
| 11. | STATISTICAL CONSIDERATIONS | 63 |
| 11.1. | Study Hypotheses | 63 |
| 11.2. | Sample Size Considerations | 64 |
| 11.3. | Planned Interim Analyses | 66 |
| 11.3.1. | Interim Safety Review..... | 66 |
| 11.4. | Final Analysis Plan..... | 66 |
| 12. | SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS | 69 |
| 13. | QUALITY CONTROL AND QUALITY ASSURANCE..... | 70 |
| 14. | ETHICS/PROTECTION OF HUMAN SUBJECTS..... | 71 |
| 14.1. | Ethical Standard | 71 |
| 14.2. | Institutional Review Board | 71 |
| 14.3. | Informed Consent Process..... | 72 |
| 14.3.1. | Informed Consent/Assent Process (in Case of a Minor)..... | 73 |
| 14.4. | Subject Confidentiality..... | 73 |
| 14.5. | Study Discontinuation..... | 74 |
| 14.6. | Costs, Subject Compensation, and Research Related Injuries | 74 |
| 14.7. | Future Use of Stored Specimens and Data..... | 75 |
| 15. | DATA HANDLING AND RECORD KEEPING | 76 |
| 15.1. | Data Management Responsibilities | 76 |
| 15.2. | Data Capture Methods | 77 |
| 15.3. | Types of Data | 78 |
| 15.4. | Timing/Reports | 78 |
| 15.5. | Study Records Retention | 79 |

| | | |
|-------------|---|----|
| 15.6. | Protocol Deviations..... | 79 |
| 16. | PUBLICATION POLICY | 81 |
| 17. | LITERATURE REFERENCES | 82 |
| 18. | SUPPLEMENTS/APPENDICES | 85 |
| APPENDIX A. | SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS..... | 86 |

4 LIST OF TABLES

| | | |
|-----------------|-----------------------|----|
| Table 1: | Treatment Arms* | 17 |
|-----------------|-----------------------|----|

5 LIST OF FIGURES

Figure I Schematic of Study Design

Figure II. Conceptualization of Specific Aims

6 LIST OF ABBREVIATIONS

| | |
|---------|--|
| AE | Adverse Event/Adverse Experience |
| BLA | Biologics License Applications |
| CAR | Clinical Agents Repository |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DMID | Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHs |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| EED | Environmental Enteric Dysfunction |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FWA | Federal Wide Assurance |

| | |
|---------|---|
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IEC | Independent or Institutional Ethics Committee |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| JAMA | Journal of the American Medical Association |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| N | Number (typically refers to subjects) |
| NDA | New Drug Application |
| NEJM | New England Journal of Medicine |
| NIAID | National Institute of Allergy and Infectious Diseases, NIH, DHHS |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |

| | |
|--------------------|--|
| OHSR | Office for Human Subjects Research |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PSAC | Preschool aged children |
| PZQ | Praziquantel |
| iaQA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| <i>S.</i> | <i>Schistosoma</i> genus |
| <i>S.mansoni</i> | <i>Schistosoma mansoni</i> |
| <i>S.japonicum</i> | <i>Schistosoma japonicum</i> |
| SMC | Safety Monitoring Committee |
| SOP | Standard Operating Procedure |
| UK | United Kingdom |
| US | United States |
| UVRI | Uganda Virus Research Institute |
| WHO | World Health Organization |

Protocol Summary

| | |
|---------------------------------------|--|
| Title: | Praziquantel for children under four: A Phase II PK/PD driven dose finding trial |
| Phase: | 2 |
| Population: | <p>Sample size N=600</p> <p>Sex: Male:Female (1:1)</p> <p>Ages: 12 – 47 months old inclusive</p> |
| Number of Sites: | Two: Uganda (N=300) and Philippines (N=300) |
| Study Duration: | 36 months |
| Duration of Subject participation | 13 months |
| Description of Agent or Intervention: | <p>Baseline: Children will receive either</p> <p>1-Praziquantel 40 mg/kg given as a single dose and placebo 3 hours later</p> <p>or</p> <p>2-Praziquantel 80 mg/kg (40 mg/kg followed by 40 mg/kg 3 hours later)</p> <p>Six months post baseline: Praziquantel given at the child's baseline dose or placebo</p> <p>Oral route – crushed tablets</p> <p>12 months post baseline: Praziquantel only to children positive by any diagnostic test at same baseline dose.</p> |
| Objectives: | <p>Primary:</p> <ul style="list-style-type: none"> To assess parasitologic cure and egg reduction rate of praziquantel (PZQ) at two different doses (40 mg/kg or 80 mg/kg split as two doses over three hours) among children aged 12-47 months. |

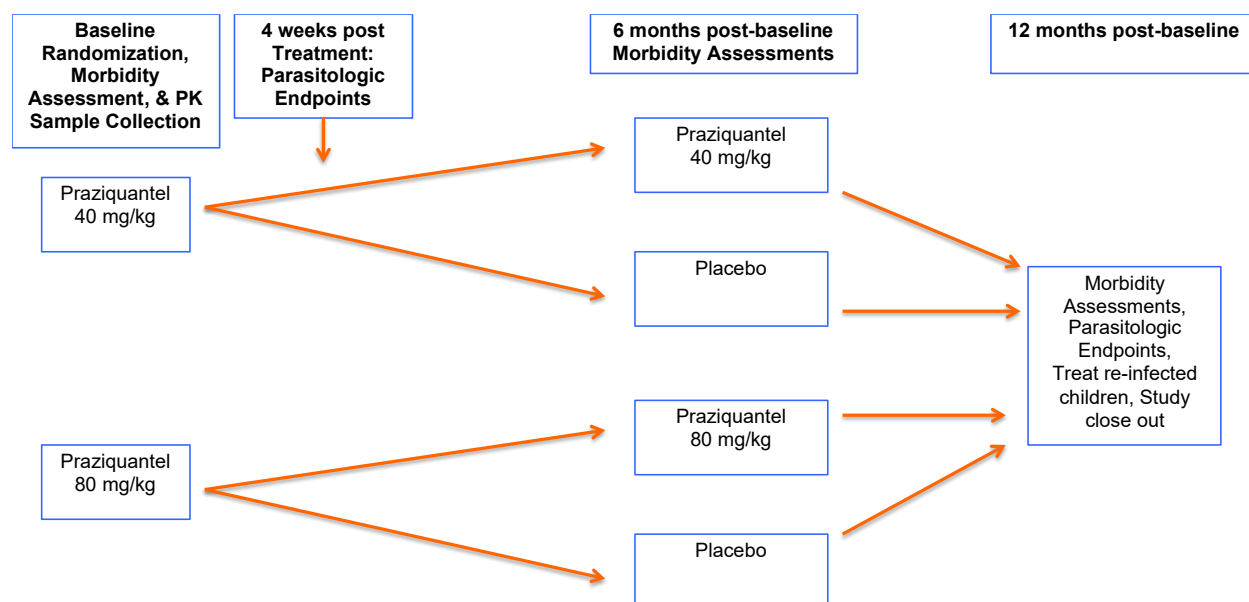
| | |
|-------------------|--|
| | <p>Secondary:</p> <ol style="list-style-type: none"> 1. To assess the safety and efficacy and PK/PD of PZQ administered at different dose regimens. 2. To evaluate the PK/PD of both PZQ enantiomers given the concern that this has varied in studies of <i>S. mansoni</i>. 3. To expand PD endpoints for drug efficacy to include state-of-the art antigen tests to accurately capture residual worm burden (Circulating Cathodic and Anodic Antigens (CCA and CAA)). 4. To assess the safety and impact of PZQ treatment (dose and interval) on key measures of morbidity 6 and 12 months after initial treatment and mechanisms mediating morbidity 5. To further evaluate the safety of higher PZQ dosing (80 mg/kg) including bone marrow, renal, and liver toxicity as captured before dosing and 12 hours after. 6. To evaluate the mechanisms mediating the effect of varying treatment doses and frequencies on growth and nutritional morbidity 7. To evaluate the mechanistic role of Environmental Enteric Dysfunction (EED) in the pathogenesis of schistosomiasis related morbidities. 8. To explore immune responses to <i>S. mansoni</i> infection and treatment 9. To determine the prevalence and the pattern of schistosomiasis-related morbidity as determined by ultrasound scan. |
| Outcome Measures: | <p>Primary:</p> <p>Drug efficacy as per standard parasitological endpoints (Cure Rate and Egg Reduction Rate) at +/- 1 weeks post-PZQ</p> <p>Secondary:</p> |

| | |
|--|---|
| Description of Study Design: | <ol style="list-style-type: none"> 1. Drug efficacy assessed by novel antigenic endpoints (CCA and CAA) among all children, and in relation to PK/PD parameters associated with cure (Area-Under-the Curve (AUC)) at 4 +/- 1 weeks post-PZQ in a subset of children. 2. 12 hour clinical monitoring for safety including active capture of adverse events and assessment of toxicity through serum chemistries and hematologic parameters. 3. Iron status, hemoglobin, and age and gender adjusted longitudinal growth and nutritional status 4. Biomarkers of inflammation and EE including fecal calprotectin, urine lactulose:mannitol ratio, serum endotoxin, serum endotoxin core antibody, and proinflammatory cytokines 5. Inter-individual variability in PZQ AUC as modified by Environmental Enteric Dysfunction (EED) 6. Immune responses to <i>S. mansoni</i> infection and treatment 7. Prevalence and the pattern of schistosomiasis-related morbidity as determined by ultrasound scan. <p>Four parallel arm randomized quasi-double blinded placebo-controlled trial with a 4 week, 6 months and 12 month follow up. Interventions will be given at baseline and at 6 months. Parasitological endpoints will be measured at 4 weeks. Morbidity endpoints will be measured at 6 and 12 months.</p> |
| Estimated Time to Complete Enrolment: | 24 months |

Table 1: Treatment Arms*

| | Number of subjects | Baseline Dose | 6 months post baseline dose |
|-------|--------------------|---|---|
| ARM 1 | 150 | 40 mg/kg dose PZQ (40 mg/kg followed by Placebo 3 hours later) | Placebo followed by Placebo 3 hours later |
| ARM 2 | 150 | 40 mg/kg dose PZQ (40 mg/kg followed by Placebo 3 hours later) | 40 mg/kg dose (40 mg/kg followed by Placebo 3 hours later) |
| ARM 3 | 150 | 80 mg/kg split dose PZQ (40 mg/kg followed by 40 mg/kg 3 hours later) | Placebo followed by Placebo 3 hours later |
| ARM 4 | 150 | 80 mg/kg split dose PZQ (40 mg/kg followed by 40 mg/kg 3 hours later) | 80 mg/kg split dose (40 mg/kg followed by 40 mg/kg 3 hours later) |

*** These numbers represent subject totals across both sites. At each site, approximately N=75 subjects will be enrolled in each of the 4 arms providing N=300 subjects at each site.**

Figure 1: Schematic of Study design

1. KEY ROLES

A. Individuals

US Principal Investigator:

Jennifer Friedman, *MD, PhD, MPH*

Director, Center for International Health Research (CIHR)

55 Claverick Street, Suite 101, Rhode Island Hospital

Providence, RI 02903

Phone: 401 444 4779

Fax: 401 444 7854

Email: Jennifer.Friedman@Brown.edu

UK Principal Investigator:

Amaya L. Bustinduy, *MD, MPH, PhD*

London School of Tropical Hygiene and Medicine, Room 358

Keppel Street, London, UK WC1E 7HT

Phone: +44 020 79272642

Email: Amaya.Bustinduy@lshtm.ac.uk

Uganda Site Lead Investigator:

Patrice Mawa, *PhD*

Uganda Medical Research Council/Virus Research Institute

P.O. Box 49, Entebbe-Uganda

Plot 51-59 Nakiwogo Road, Entebbe

Phone: +256 (0) 417704000

Email: Patrice.Mawa@lshtm.ac.uk

Philippines Site Lead Investigator

Charissa Borges-Tabora, *MD*

Research Institute of Tropical Medicine

| | |
|-----------------------------------|---|
| | <p>9002 Research Drive, Filinvest Corporate City, Alabang Muntinlupa City, Metro Manila Philippines, 1781</p> <p>Telephone: +63 (02) 8807-2631/ 8807-2632/ 8807-2637</p> |
| Trial Statistician | <p>Emily Webb, <i>PhD</i></p> <p>London School of Tropical Hygiene and Medicine, Room G12 Keppel Street, London, UK WC1E 7HT</p> <p>Phone: +44 (0)207 9272012</p> <p>Email: Emily.Webb@lshtm.ac.uk</p> |
| Co-investigator | <p>Professor William Hope</p> <p>Antimicrobial Pharmacodynamics and Therapeutics Department of Molecular and Clinical Pharmacology University of Liverpool, Sherrington Building Liverpool L69 3GE, United Kingdom</p> <p>T: +44 (0)151 794 5941</p> <p>E: william.hope@liverpool.ac.uk</p> |
| Uganda Site Project Leader | <p>Andrew Edielu, <i>MBChB, MSc</i></p> <p>MRC/UVRI & LSHTM Uganda Research Unit P.O. Box 49, Entebbe-Uganda. Plot 51-59 Nakiwogo Road, Entebbe, Uganda</p> <p>Phone: +256 (0) 417704000</p> <p>Email: Andrew.Edielu@mrcuganda.org</p> |

| | |
|--|--|
| Philippines Site Project Leader | <p>Veronica Tallo, <i>PhD</i></p> <p>Research Institute of Tropical Medicine</p> <p>9002 Research Drive, Filinvest Corporate City, Alabang Muntinlupa City, Metro Manila Philippines, 1781</p> <p>Telephone: +63 (02) 8807-2631/ 8807-2632/ 8807-2637</p> <p>Email: veronica.tallo@gmail.com</p> |
| External Study Monitor | <p><u>Nampijja Proscovia</u></p> <p>Email: pnampijja@yahoo.com</p> <p>Phone: +256 702 966109</p> |

A. Institutions:**Rhode Island Hospital****Center for International Health Research**

Providence, RI

London School of Hygiene and Tropical Medicine

Keppel Street, London, UK

Research Institute of Tropical Medicine

9002 Research Drive, Filinvest Corporate City, Alabang
Muntinlupa City, Metro Manila Philippines, 1781

Vector Control Division, Ministry of Health

Kampala, Uganda

University of Liverpool

Liverpool, UK

Pharmacy of International AIDS Vaccine Initiative (IAVI)

Entebbe, Uganda

Data Coordinating Center:

London School of Hygiene and Tropical Medicine

Keppel Street, London, UK

Study Agent Repository:

Tedor Pharma, Cumberland, RI

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

The overall goals of the proposed trial are to address the significant gaps with respect to our understanding of best approaches to treatment of children 1-4 years of age with intestinal schistosomiasis. This age window coincides with the current “praziquantel treatment gap,” which highlights the fact that this age group remains excluded from preventive chemotherapy campaigns, which represent the primary approach to reducing infections in endemic regions globally.^{1,2}

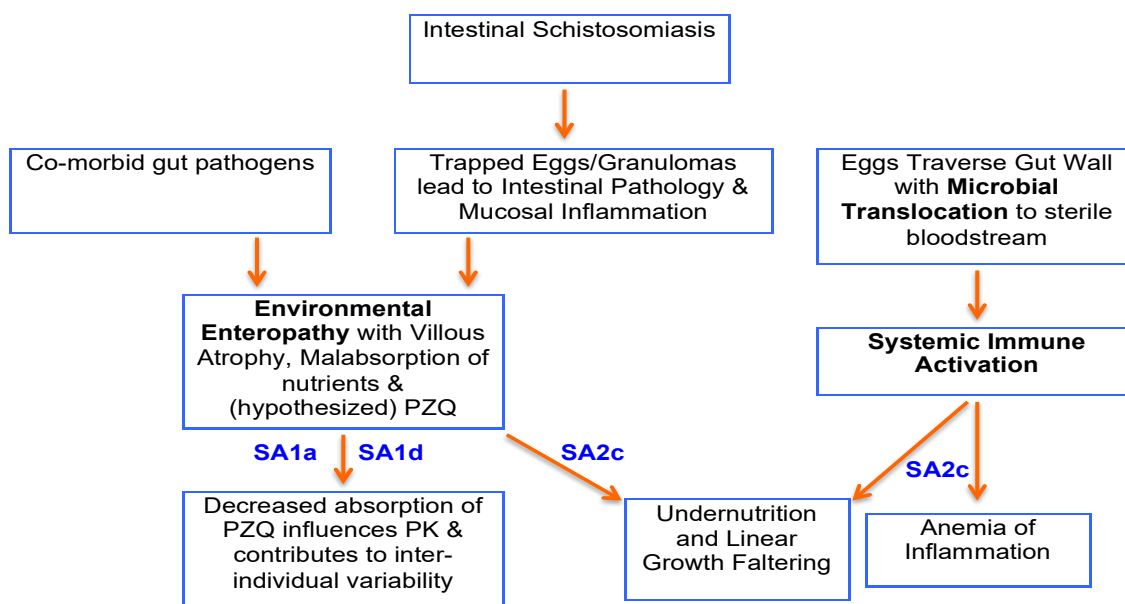


Figure II. Conceptualization of Specific Aims

One of the main reasons for this persistent treatment gap is that praziquantel (PZQ) has not been extensively evaluated in children under the age of 4 globally, despite its recent US FDA approval down to one years of age. A key goal of the proposed trial would be to provide data in support of a change in the “labeling” or indications for PZQ to include young children. To achieve these goals, we propose a randomized, quasi-double blind, trial of PZQ at two baseline doses (40 and

80 mg/kg) with placebo or re-treatment provided at 6 months employing the baseline dose given (**Figure I**). Though we will utilize a placebo (dextrose) tablet that is matched for color and size as closely as possible, it is possible that study staff administering the drug will be able to distinguish the two based on appearance or odour as they will need to crush the tablets. Subjects may be able to notice the bitter taste of praziquantel as opposed to placebo, though subjects in this trial are very young and less likely to mark this. This will also allow us to evaluate optimal treatment intervals (6 versus current 12 months) for intestinal schistosomiasis. Finally, we will assess the impact of treatment on key indicators of morbidity that have been implicated in schistosomiasis, yet never studied among children under the age of four. Demonstrating efficacy with respect to morbidity will support the prioritization of treatment for this vulnerable age group and will significantly contribute to the impetus to provide treatment, even in resource constrained settings.

Schistosomiasis, caused by three main species of tissue-invasive parasitic trematodes, affects over 200 million individuals globally.³ A significant proportion of the global burden of disease due to schistosomiasis, includes key morbidities that disproportionately affect children.⁴ Specifically, the primary disabilities attributed to schistosomiasis including undernutrition, linear growth stunting, anemia, and cognitive impairment largely affect children who have limited, crucial windows to achieve these key growth and developmental milestones. Importantly, children aged 1-4 years are most vulnerable to these morbidities given this period coincides with peak velocities of somatic and brain growth, with the highest global prevalence of anemia, linear growth stunting, and undernutrition occurring in this age group worldwide.^{5,6} Despite this vulnerability and likely increased risk of morbidity due to schistosomiasis, few if any studies have evaluated the effect of treatment on these key indicators of early childhood well-being.

2.2. Rationale

The latest WHO recommendation to treat with 40 mg/kg was **not informed by PK/PD studies**; rather it relied solely on differences in cure and egg reduction rates. Despite the fact that an estimated 25 million children are treated with PZQ annually, only one very recent study conducted by co-PI Bustinduy and co-investigator Hope has evaluated PK/PD among children of any age.⁷

The current recommended dose of 40 mg/kg is extrapolated from the relatively few PK/PD studies of healthy adults as well as adults with varying degrees of liver failure. Despite the known flaws of this approach, including evidence from quantitative pharmacological methods that an extrapolation approach does not achieve accurate pediatric dosing, this continues to define dosing regimens for children.^{8,9} This is of significant concern given the many differences in drug absorption, metabolism, and distribution among children compared to adults.¹⁰ A specific and relevant issue for this proposal is that weight alone does not capture age-dependent nonlinearities in drug metabolism.⁸ Specifically, body weight-normalized drug clearance in children exceeds that of adults for many drugs,¹⁰ suggesting children may require a higher dose per unit of bodyweight.

Concerns regarding the use of 40 mg/kg dosing are further highlighted by the PK/PD study conducted by Co-PI Bustinduy in Uganda.⁷ In that study, 60 children aged 3-8 years living in an *S. mansoni* endemic region of Uganda were randomized to receive 40 versus 60 mg/kg of PZQ. Importantly, the investigators found that the total PZQ area under the curve was a significant predictor of both cure rate and egg reduction rate, while administered dose was not a significant predictor. **Figure III** demonstrates expected individual cure rates at two different weights for children aged 3-5 years as modelled in 5,000 patients. These models suggest that doses much higher than 40 mg/kg are necessary to achieve cure rates of 85% as recommended by the World Health Organization. This was particularly true for younger children. Specifically, it is likely that 80 mg/kg is necessary to achieve recommended cure rates.

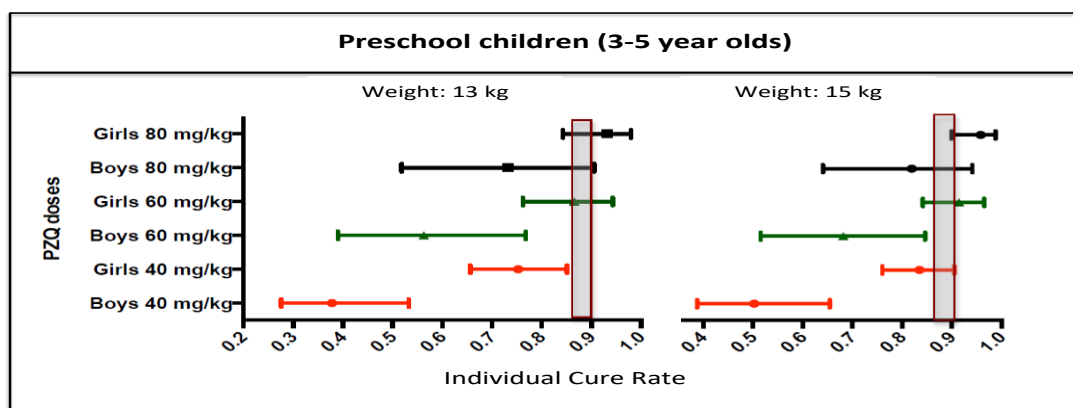


Figure III Individual cure rate by different PZQ doses as modelled in 5,000 patients in scale 0.0 (total failure) 1.0 (complete cure) 24 days post single doses PZQ. Median weight for age were used to calculate the plots. Adapted from Bustinduy et al ⁷

CONFIDENTIAL

Immunity in schistosome infections has been mainly studied in school-age children (SAC, ≥ 6 years old), and adults ¹¹, yet infection occurs early in preschool-age ¹². Immune responses in PSAC are therefore understudied and not understood. Infections in early life have potent effects on the infant's developing immune system and thus may determine later life outcomes including responses to childhood routine vaccinations. It is essential that these responses are probed and understood since PSAC is a vaccine-target population and a key age for establishing morbidity.

Recent modeling of the impact of *S. mansoni* vaccine and MDA to achieve morbidity control and transmission elimination suggests a combination of vaccination and MDA is needed to control or eliminate schistosomiasis ¹³. Lack of a pediatric formulation for PZQ and current treatment guidelines restrict research in this area leading to poor knowledge of immune responses promoted by treatment. It is important to profile immune responses following PZQ treatment of infants to inform future vaccine development/deployment that would include the PSAC.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

PZQ is safe in preschool children as evidenced by a large number of published studies. The investigators, however, recognize that the study population constitutes a vulnerable population of very young children. This vulnerable population is studied because the objectives are to understand the safety and efficacy of praziquantel, a drug that benefits people globally, in very young children. Currently, these children are not included in preventive chemotherapy campaigns due to lack of data with respect to optimal dosing, PK/PD, safety at varying doses, and efficacy. The two PIs for the planned trial are both pediatricians with significant experience leading pediatric studies of helminthiasis in LMICs.

The primary risk is exposure to a higher dose of praziquantel than is routinely given. This is necessary and informed by a study conducted by co-PI Bustinduy that demonstrated that standard 40 mg/kg dosing in young children is likely too low given lower cure rates in this age group and that 80 mg/kg is the necessary dose based on modelling. Children experienced minimal side effects in that study at 60 mg/kg. Further, a 60 mg/kg dose has been routinely given for *S. japonicum* to children over the age of four. Finally, a study addressing treatment for *S. mekongi* employed a dose of 75 mg/kg (split 50/25 mg/kg over 4 hours) for children aged 10-15 years.¹¹

Three events were denoted “severe” (vomiting (2) and vertigo) in the 75 mg/kg dose group which had N = 45 children; no Serious Adverse Events as defined by death, life threatening event, need for hospitalization, or persistent morbidity/incapacity, were reported in either group. The reported rates of adverse events were slightly higher in the 75 mg/kg group than the 40 mg/kg comparison group. In a separate recently published study in Cote D’Ivoire, escalating doses of praziquantel (20, 40, 60 mg/kg) were examined in a cohort of children including pre-school age children (PSAC) aged 2-6 years.¹² Among PSAC, adverse events were mild with fewer adverse events observed three hours post-treatment compared to pre-treatment. Importantly, the number of adverse events was similar among the three praziquantel treatment doses, with fewer adverse events observed in the placebo-treated groups. Only mild expected adverse events were reported with the exception of one moderate grade adverse event 3 hours after the first praziquantel dose in one PSAC (diarrhea). No serious adverse events were noted at any dose. We will minimize risk by “admitting” children for observation with active and passive assessment for adverse events for 12 hours. We will also provide children with a meal to minimize side effects. **Finally, we will administer the 80 mg/kg dose as two doses of 40 mg/kg split over three hours.**

There is also a small risk to young children from blood draw, which is due to iron deficiency anemia as a blood draw removes red blood cells and iron. This risk is minimal given the small amount (7 – 12 ml) that will be drawn at each of three time points, representing 20 – 25 ml in a year. For the immunology study subpopulation, an extra blood draw of 7ml will be made at 4-week follow up time point. Very minimal risks are associated with venipuncture itself, which will be performed by trained medical personnel.

2.3.2. Known Potential Benefits

- 2.3.2.1. **Pediatric Care.** Children are likely to receive better pediatric care as many do not ever have a history and physical examination by a healthcare provider. Children will be examined by the study physician and be referred for care provided by the study as needed including iron and nutritional interventions. The same procedures will be followed for children at baseline and follow up.
- 2.3.2.2. **Parasitological results and treatment.** For all screened children, parents will be provided with results of stool screening for both schistosomiasis and soil transmitted

helminths, which is not part of standard care in the study area. For all schistosomiasis infected children recruited into the main study, we will provide praziquantel (40 or 80 mg/kg at baseline and 12 months after treatment if re-infected) with half of the children receiving a second dose at six months. In addition, albendazole treatment will be provided at baseline for children infected with soil-transmitted helminths and again at 12 months post-treatment if they are re-infected.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Study Objectives

3.1.1. Primary

To assess the efficacy of PZQ administered at different dose regimens.

- 3.1.1.1. To measure drug efficacy as per standard parasitological endpoints (Cure Rate and Egg Reduction Rate) at 4 +/- 1 weeks post-PZQ.

3.1.2. Secondary

To assess the **safety and** efficacy and PK/PD of PZQ administered at different dose regimens.

- 3.1.2.1. To evaluate the PK/PD of both PZQ enantiomers given the concern that this has varied in studies of *S. mansoni*.
- 3.1.2.2. To expand PD endpoints for drug efficacy to include state-of-the art antigen tests to accurately capture residual worm burden (Circulating Cathodic and Anodic Antigens (CCA and CAA)).
- 3.1.2.3. To assess the safety and impact of PZQ treatment (dose and interval) on key measures of morbidity 6 and 12 months after initial treatment and mechanisms mediating morbidity
- 3.1.2.4. To further evaluate the safety of higher PZQ dosing (80 mg/kg) including bone marrow, renal, and liver toxicity as captured before dosing and 12 hours after.
- 3.1.2.5. To evaluate the impact of different doses (40 vs. 80 mg/kg) and varying dosing intervals (every 6 or 12 months) on iron status, hemoglobin, and age and gender adjusted longitudinal growth and nutritional status as captured by height and weight for age, and weight for height z-scores as determined by WHO Anthro.
- 3.1.2.6. To evaluate the mechanistic role of *Environmental Enteric Dysfunction (EED)* in the pathogenesis of schistosomiasis related morbidities. We will capture state of the art biomarkers of EE including fecal calprotectin, urine lactulose:mannitol ratio, serum

endotoxin, serum endotoxin core antibody, and pro- inflammatory cytokines and employ Path Modeling techniques to identify mechanistic pathways.

- 3.1.2.7. To assess the role of Environmental Enteric Dysfunction (EED) in inter-individual variability in PZQ area under the curve (AUC) PK parameters demonstrated in this age group.
- 3.1.2.8. To explore immune responses to *S. mansoni* infection and treatment
- 3.1.2.9. To assess the prevalence and the pattern of schistosomiasis-related morbidity as determined by ultrasound scan.

3.2. Study Outcome Measures

3.2.1. Primary

To measure **drug efficacy** as per standard parasitological endpoints including a) Cure Rate as defined by the proportion of children who have zero eggs per gram of stool as assessed by Kato-Katz four weeks following treatment and b) Egg reduction Rate as defined by the percent reduction in egg burden from baseline to four weeks post treatment as assessed by Kato-Katz.

3.2.2. Secondary

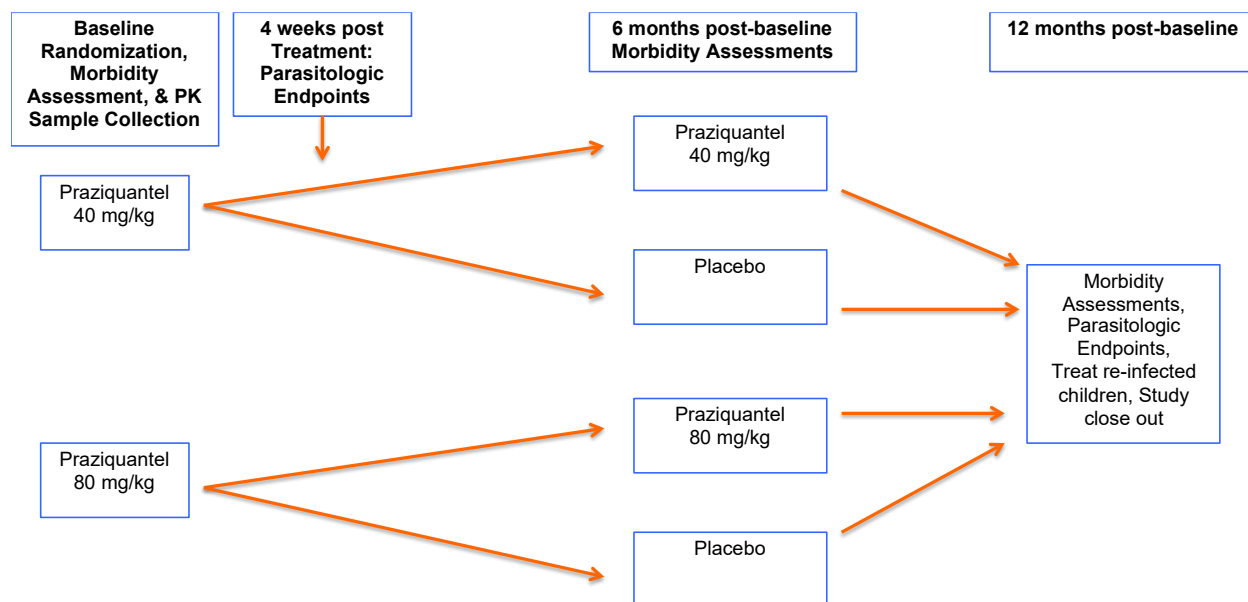
- 3.2.2.1. To assess novel antigenic endpoints (CCA and CAA) in all children and in relation to PK/PD parameters associated with cure (Area-Under-the Curve (AUC)) at 4 +/- 1 weeks post-PZQ in a sub-set of children.
- 3.2.2.2. To monitor adverse events in children for 12 hours post-PZQ dosing.
- 3.2.2.3. To assess bone marrow, renal, and liver toxicity as captured before dosing and 12 hours after.
- 3.2.2.4. To measure iron status, hemoglobin, and age and gender adjusted longitudinal growth and nutritional status at different varying doses and dosing intervals (every six or 12 months)
- 3.2.2.5. To evaluate the mechanisms mediating the effect of varying treatment doses and frequencies on growth and nutritional morbidity including measures of Environmental Enteric Dysfunction (EED) and inflammation (fecal calprotectin, urine lactulose:mannitol ratio, serum endotoxin, serum endotoxin core antibody, and pro-inflammatory cytokines).
- 3.2.2.6. To evaluate inter-individual variability in PZQ AUC as modified by EED
- 3.2.2.7 To assess immune responses to *S. mansoni* infection and treatment
- 3.2.2.8 To quantify the prevalence and evaluate the pattern of schistosomiasis-related morbidity as determined by ultrasound

4. STUDY DESIGN

4.1 Trial design

Four arm randomized double blind placebo-controlled trial with a 4 week, 6 months and 12 month follow up (Figure I). Half of the cohort will receive an additional PZQ dose (at the same dose given at baseline) at 6 months and half placebo. Parasitological endpoints will be measured at 4 weeks and at 6 months urine stored for future antigen testing. Morbidity endpoints will be assessed at 6 and 12 months.

Figure I Schematic of Study Design



4.2 Study population

4.2.1 PSAC with Schistosomiasis

We will recruit approximately 600 children aged 12 to 47 months inclusive at two field sites with approximately N=300 at each site. Subjects will be recruited from *S. japonicum* endemic rice farming villages in The Philippines and *S. mansoni* endemic villages along Lake Albert, Uganda. In

Uganda, the prevalence of infection in children is very high in the proposed villages along Lake Albert, where a recent study led by co-PI Bustinduy found a prevalence of 57% by Kato -Katz among children aged 3-5 years.¹³ In a community survey conducted as part an NIH funded study in May of 2016 at the proposed site in Leyte, The Philippines, the prevalence of infection among individuals ages 7-30 was 51.9%. The community survey was extended to include an assessment of the prevalence of infection among children ages 1-4 and was found to be 42%. This high prevalence is likely due to the fact that young children had not been included in annual preventive chemotherapy campaigns.

Given the population size per village ranges from approximately 578 to 1878 individuals at both sites, about 10% of the population is under four (57-187 per village) and we expect the prevalence of schistosomiasis in young children can conservatively be estimated at 40%, (23-75 infected children under four per village), we will need to recruit in 15-20 villages across the two sites which is entirely feasible. The investigative teams have worked in the proposed villages, including numerous studies involving children, and communities have always participated without concern.

In addition, the general health of children in both study areas is poor. In our recent studies from The Philippines, 31.7% of subjects aged 8-30 were anemic; of these, anemia of inflammation was the primary cause among 67%.¹⁴ In addition, 67.1% of children were chronically under-nourished as assessed by HAZ < -2 and 14.9% were wasted as captured by BMI-Z.¹⁵ Importantly, we expect these prevalences to be higher among children under four who disproportionately bear the burden of these morbidities in the LMIC setting. The under-five population in the Lake Albert region of Uganda also experiences high rates of undernutrition with approximately 38% stunted and 16% underweight.¹⁶ Thus, we expect there to be variability in the morbidity outcomes assessed such that treatment may be impactful and mechanisms mediating them captured.

Trial Phase: II multicenter (two centers)

Study Arms: The study will have four arms as follows:

Arm 1: 40 mg/kg dose at baseline & Placebo 3 hours later//Placebo & Placebo 3 hours later at six months post baseline (N = 150). N=75 will be recruited in this arm at each site.

Arm 2: 40 mg/kg dose at baseline & Placebo 3 hours later //40 mg/kg dose & Placebo 3 hours later at six months post baseline (N = 150). N=75 will be recruited in this arm at each site.

Arm 3: 80 mg/kg dose split at baseline as 40 mg/kg and 40 mg/kg 3 hours later// Placebo & Placebo 3 hours later at six months post baseline (N = 150). N=75 will be recruited in this arm at each site.

Arm 4: 80 mg/kg dose at baseline split as 40 mg/kg and 40 mg/kg 3 hours later //80 mg/kg dose split as 40 mg/kg and 40 mg/kg 3 hours later at six months post baseline (N = 150). N=75 will be recruited in this arm at each site.

Study Enrollment timeline: Subject screening and recruitment will occur over 24 months.

Duration of participation: Individual subject participation will be approximately 13 months

Study agent and administration: For study agent conformity and quality, we will obtain PZQ tablets from a single source, Macleods Pharmaceuticals. Children will be randomized and receive either 40 mg/kg or 80 mg/kg (split as 2 doses of 40 mg/kg over 3 hours) at baseline. Children randomized to the 40 mg/kg arm will receive placebo 3 hours post treatment while children randomized to the 80 mg/kg arm will receive two split doses of 40 mg/kg over 3 hours. At the six months post initial treatment time point, children will be randomized to receive the same dose as they received at baseline or to receive placebo. The research pharmacy, *Tedor Pharma, Cumberland, RI*, will compound a placebo tablet matched for the active agent's excipients, color, shape, and size.

The research pharmacy, International AIDS Vaccine Initiative (IAVI) pharmacy will allocate the study agent and placebo into pre-labelled vials. The vials will be pre-labelled with the study name, “investigational use only”, the study ID, and either A, B, C, or D to denote first and second doses at baseline or 6 months as per Table I below. Prior to study initiation, the study biostatistician, Dr. Webb, will share the randomization code with IAVI. Using this, they will fill each vial with 3 tablets of either Praziquantel or Placebo based on the study ID assignment. This allows sufficient dose for the range of weights expected and in case of vomiting within an hour of dose with a need to repeat. This includes reference to both the study timepoint and whether it is the first or second dose at that timepoint as a subject may, for example, receive praziquantel for the first dose and placebo for the second dose at baseline OR praziquantel for both doses based on his/her randomization status.

Table I

| Baseline Visit | Study Drug Vial Letter |
|-------------------|------------------------|
| Dose 1 | A |
| Dose 2 | B |
| Visit at 6 months | |
| Dose 1 | C |
| Dose 2 | D |

For both arms, we will crush the study agent and give with juice as per the Ugandan and other studies.^{7,17} This will be a quasi-double blind approach as we will not be able to fully mask taste for participants. About 30 minutes prior to dose administration, a meal consisting of local foods will be provided as this increases PZQ bioavailability.

Trial periods/timepoints:

1. *Screening* We propose to employ a two stage screening process. The first phase is a village - based survey to identify children who are infected using rapid point of care testing (urine Circulating Cathodic Antigen (CCA)). CCA provides a highly sensitive and efficient means to screen children, with high sensitivity demonstrated in young children.^{18,19 20,21} Two stool samples (taken on consecutive days) will also be collected from every child who is CCA positive prior to the start of the study, at four weeks +/-1 week after treatment, and at 12 months post-treatment to provide a measure of infection intensity. Fecal smears will be prepared from each sample in duplicate applying the thick Kato-Katz technique for the detection of *S. mansoni*, *S. japonicum* and soil-transmitted helminths. Mean egg counts per gram of stool (epg) will subsequently be calculated and three intensity categories will be considered for *S. mansoni* and *S. japonicum* infection: light (1-99 epg), medium (100 – 399 epg) and heavy (>400 epg) as per World Health Organization Guidelines.²²

The second phase of screening will occur at the field laboratories in Palo, Leyte, The Philippines and in Lake Albert, Uganda. Prior to study enrollment, each child will undergo a physical exam and medical history to determine eligibility. Children who are not eligible based on severe malnutrition (WHZ < -3.0), severe anemia (hemoglobin < 7.0 g/dL) or chronic medical condition as defined by a disease lasting longer than three months and impacting a child's daily function or normal activities will be excluded at this stage.²³

1. *Study visit 1/Baseline.* After determination of eligibility, subjects will be enrolled following all screening assessments. Both field stations have a patient intake area with private areas for consenting and physical examinations. At this visit, a small blood drawing catheter will be placed to minimize the number of times children need to have a needle stick. Blood will be drawn for baseline morbidity studies (5 ml). In depth measures of nutritional status will be made, and children will be randomized to receive either 40 mg/kg or 80 mg/kg of Praziquantel either annually or six-monthly (4 arms).

In addition, children will be randomly split into two groups, half will have an extra 7 ml of blood drawn at the time of the morbidity studies (N=150) for immunologic studies and half will take part in pharmacokinetic studies (N=150, further details below).

To test gut permeability and absorptive capacity, lactulose-mannitol solution (containing 250 mg/mL lactulose and 50 mg/mL mannitol in purified water) will be administered to study participants orally at a

dose of 2ml/kg up to a maximum of 20 ml. Prior to administration of the solution, the child will be fasted for 30 minutes. Breast feeding will continue. A urine bag will be strapped to ensure all the urine is collected. The first urine sample voided will be considered as baseline. A new bag will then be put in place to continue urine collection for 2 hours. Once collected, an aliquot of 2 ml of urine will be stored between 2°C and 8°C having added 2 drops of chlorhexidine. Two hours after ingestion of LM solution, the test will be stopped. If the child has not passed any urine, the test time will be extended until the next urine is voided.

Following the LM test, two doses of PZQ will be administered three hours apart. After receiving praziquantel, all children will stay at the study premises for 3-6 hours with a guardian monitoring side effects. After administration of the second dose of the study product, children will undergo ultrasound scan to determine presence or absence of any pathology related to schistosomiasis. The Niamey Protocol will be used to grade severity of disease.

The subset of children (approximately N=150) who will be randomly selected for PK sampling (four blood draws in total) children will stay at the premises for at least 6 – 8 hours after administration of the initial dose of praziquantel. At the time of discharge, children who will be found to be infected with soil-transmitted helminths will be treated with albendazole 200 mg (12 – 24 month old children) or albendazole 400 mg (children over age two). Blood Chemistry to ascertain renal and liver function will be repeated 6 – 8 hours after administration of the first dose of praziquantel, before discharge.

2. *Study Visit 2.* Stool will be collected 4 weeks (+/- 1 week) after treatment. Two stools will be collected on consecutive days to quantify egg counts by Kato Katz. Field workers will be responsible for picking up cups at this timepoint. No visit to the field laboratories will be required. Urine will be collected for CCA/CAA. Blood (7 ml) will be collected for the same subset of N=150 subjects for studies of immunological responses as at baseline.

3. *Study Visit 3 (6 months post enrolment)* Six months (+/- 2 weeks) following visit one, subjects will return to the respective field laboratories. They will receive either the same dose of Praziquantel as received at Visit 1 or placebo as determined at baseline randomization. At this

visit, and before the study drug or placebo is received, blood will be drawn for follow up assessment of morbidity, and in depth measures of nutritional status. An ultrasound scan will be performed. Blood (7 ml) will be collected for the same subset of N=150 subjects for studies of immunological responses. Urine will be stored at this visit for future processing of CAA to monitor re-infection.

4. Study Visit 4, Close out. (12 months post enrollment) Twelve months (+/- 2 weeks) post enrollment and initial treatment, study subjects will return to the field laboratory. Prior to this visit they will be asked to provide three stool samples and one urine. At this visit, blood will be drawn for follow up morbidity studies and in-depth measures of nutritional status will be made. All children will be treated with Praziquantel and those infected with soil-transmitted helminths will be treated with albendazole 200 mg (12 – 24 month old children) or albendazole 400 mg (children over age two). A repeat ultrasound scan will be done before the participant is discharged from the study. If however, the ultrasound scan at six months revealed resolution of any pathology detected at baseline, there will be no repeat at discharge. Blood (7 ml) will be collected for the same subset of N=150 subjects for studies of immunological responses.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Subject Inclusion Criteria

- *S. mansoni* (Uganda) or *S. japonicum* (Philippines) infection of any intensity as determined by Kato-Katz
- Otherwise healthy as determined by history and physical examination conducted by the study physician at the second stage screening
- Age 12-47 months inclusive
- Parental consent to participate.

5.2. Subject Exclusion Criteria

- Parental inability to provide informed consent
- Significant disease/illness as determined by history or physical exam. This includes a severe acute illness or chronic disease as defined by greater than 3-months duration and significantly impacting a child's daily activities.
- Grade 3 or higher laboratory abnormality of BUN, Creatinine, bilirubin, white blood cell count, or platelet count will warrant exclusion. Grade 2 or higher abnormality of ALT or AST will warrant exclusion. Children with severe anemia as defined by hemoglobin less than 7.0 g/dl will be excluded.
- Severe wasting as defined by WHZ < -3SD
- Exposure to immuno-modulatory therapeutics such as steroids e.g. dexamethasone, prednisone and other medications such as chloroquine.
- Confirmed diagnosis of ocular cysticercosis.

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

Prior to study inception, the study biostatistician (Emily Webb) will use a random number generator with randomly permuted block sizes, to assign study numbers to each of the four study arms. We will work with the pharmacist at International AIDS Vaccine Initiative (IAVI) who will pre-fill two vials per child for each study visit's two doses and the assigned study number. As a child is enrolled, they will be assigned the next study number. The arm to which they are randomized will determine both baseline dose and repeat dose versus placebo at the six-month visit.

5.3.2. Masking Procedures

At baseline, all subjects will be treated with 40 mg/kg followed by placebo or 80 mg/kg (40 mg/kg followed by 40 mg/kg). Study subjects and parents will not be informed of the dose received in the form of crushed tablets. Placebo will consist of tablets matched for size, shape, and color with the excipients from the active drug.

At the six month visit, subjects will receive either the same baseline dose or placebo, according to the group to which they were randomized at baseline.

5.3.3. Reasons for Withdrawal and Discontinuation of Study Product Administration

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

The reasons, might include, but are not limited to the following:

- Subject no longer meets eligibility criteria
- Subject becomes noncompliant
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with

the subject's successful completion of this study, or interfere with the evaluation of responses

- Subject lost to follow-up
- Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure subject's health and well-being (or treatment failure, if applicable)
- Voluntary withdrawal

If the subject consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research are included in the informed consent.

Investigators will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study, unless they withdraw consent.

5.3.4. Handling of Withdrawals and Discontinuation of Administration

If subjects are withdrawn by study investigators due to newly diagnosed medical condition, they will be referred for treatment at the respective district hospitals. Subjects who voluntarily withdraw consent will be offered follow up screening for schistosomiasis and soil transmitted helminths and treatment provided as needed. No other nutritional or morbidity studies will be conducted as these are research only. In the unlikely event that a subject needs to discontinue product administration at later time points due to an AE or SAE, he/she will be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care for symptoms of any AE until resolved or the subject's condition becomes stable.

5.3.5. Subject Replacement

Subjects withdrawn will not be replaced. Our sample size calculations allowed for withdrawal and expected rates of loss to follow up.

5.3.6. Termination of Study

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

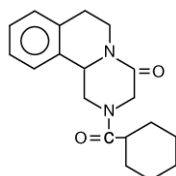
6.1.1. Acquisition of Praziquantel

Praziquantel will be purchased from Macleods Pharmaceuticals, Marol Church Road, Andheri (East), Mumbai, India. The study drug will be shipped by Thermo Fisher Scientific to the Tedor Pharmaceuticals in Rhode Island for compounding into vials. These will then be shipped by Thermo Fisher Scientific to the two study sites.

The study drug will be shipped at regular intervals to ensure doses do not expire.

6.1.2. Formulation, Packaging, and Labeling

Praziquantel is a trematodicide provided in tablet form for the oral treatment of schistosome infections and infections due to liver fluke. is 2-(cyclohexylcarbonyl)-1,2,3,6,7, 11b-hexahydro-4H-pyrazino [2, 1-a] isoquinolin-4-one with the molecular formula; C₁₉H₂₄N₂O₂. The structural formula is as follows:



Praziquantel is a white to nearly white crystalline powder of bitter taste. The compound is stable under normal conditions and melts at 136-140°C with decomposition. The active substance is hygroscopic. Praziquantel is easily soluble in chloroform and dimethylsulfoxide, soluble in ethanol and very slightly soluble in water.

Praziquantel tablets contain 600 mg of praziquantel. Inactive ingredients are corn starch, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, polyethylene glycol, titanium dioxide and hypromellose.

6.1.3. Product Storage and Stability

Praziquantel is stable when stored below 86 °F (30° C). It will be stored at room temperature at the field laboratory with rigorous temperature monitoring. The field sites at Lake Albert, Uganda and Leyte, The Philippines have generators in case of electrical outage.

6.2. Dosage, Preparation and Administration of Study Intervention/Investigational Product

Praziquantel dosing will be calculated by study participant's weight as follows:

Arm 1: 40 mg/kg dose at baseline & Placebo 3 hours later//Placebo & Placebo 3 hours later at six months post baseline (N = 150)

Arm 2: 40 mg/kg dose at baseline & Placebo 3 hours later //40 mg/kg dose & Placebo 3 hours later at six months post baseline (N = 150)

Arm 3: 80 mg/kg dose at baseline split as 40 mg/kg and 40 mg/kg 3 hours later// Placebo & Placebo 3 hours later at six months post baseline (N = 150)

Arm 4: 80 mg/kg dose at baseline split as 40 mg/kg and 40 mg/kg 3 hours later//80 mg/kg dose split as 40 mg/kg and 40 mg/kg 3 hours later at six months post baseline (N = 150)

The pharmacy will provide single use vials with study numbers based on randomization group with sufficient study drug for the highest expected weight (4 year old at 80 mg/kg dose). Subjects will receive praziquantel at either 40 or 80 mg/kg at baseline based on the arm to which they are randomized. At six months, subjects will receive either 40 mg/kg or 80 mg/kg or placebo based on study arm.

Participant specific dose will be calculated and the adequate amount of 600mg tablets will be crushed for both praziquantel and placebo. The powder will then be mixed with a small amount of fruit juice for optimal suspension and delivery to the study participant. The dose will be given with a meal to improve absorption.

6.3. Modification of Study Intervention/Investigational Product for a Subject

Children who experience emesis within one hour of dosing will receive a repeat dose. This will be done only once per subject.

6.4. Accountability Procedures for the Study Intervention/Investigational Product(s)

Praziquantel and Placebo will be stored and shipped from the United States. Once received, Praziquantel and placebo tablets will be stored in locked cabinets and dispensed by the Project leader. Unused product will be locked and disposed of at the study sites following local guidelines.

The Investigator will be responsible for ensuring that a current record of product disposition is maintained and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records will be available for inspection by monitoring contractors, and will be subject to inspection by relevant regulatory agencies at any time. An assigned Study Monitor will review the pharmacy records.

Unused reconstituted investigational product vials will be stored at room temperature at each site until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed in accordance with the MOP following complete drug accountability and monitoring.

6.5. Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Subjects will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer the study product. Administration will be documented on the Treatment Case Report form and entered into the eCRF.

6.6. Concomitant Medications/Treatments

Study participants should not be on any concomitant immune-modulatory treatment, rifampicin, chloroquine, antiepileptic drugs and grape juice all of which are known to alter PZQ metabolism and/or efficacy.

7. SCHEDULE

7.1. Recruitment

Philippines site: Meetings will be arranged with community leaders including village mayors, village health workers and directors of relevant municipal health centers. Field staff will arrange village level information sessions about the study. Flyers will be made available and field workers will additionally contact families with young children in target villages to provide information about the study. Field workers will identify families who are willing to learn about phase one screening activities for the study. Information sheets will be delivered in the households and the screening informed consent will ensue delivered by GCP certified field staff.

Uganda site: Fishing communities along Lake Albert will be approached through organizing community wide meetings. Prior to these, the village chiefs will be contacted to inform them about the project and obtain permission. The meetings will be announced publicly with flyers distributed by community mobilisers who will be in charge of contacting the interested parents after the information sessions have taken place. Information sheets will be delivered in the households and the screening informed consent will ensue delivered by GCP certified community workers.

7.2. Field Based Screening

Both study sites: Screening will take place in two phases. The first phase will occur at the village level with field staff after informed consent for only the initial screening activities (urine sample for CCA testing). Children with a positive antigen test will be considered positive for schistosomiasis and eligible for potential enrolment. Parents will be given two cups (three in the Philippines) to provide stool samples collected on different days to quantify intensity of infection at baseline. Work will be performed by Ministry of Health personnel (Vector Control Division).

7.3. Laboratory Based Screening, Enrollment/Baseline

Philippines site: If children are deemed eligible based on both screening phases, they will be “admitted” to the Palo Field Laboratory for 12 hours. There will be one medical technologist assigned to four children.

Uganda site: If children are deemed eligible based on both screening phases, they will be “admitted” to the Kabatereine Schistosomiasis Research Center in Buliisa District for 12 hours. There will be one nurse assigned to four children. Technical work in this phase will be performed by Ministry of Health personnel (Vector Control Division).

Phase two screening will take place at the field laboratories to ensure other inclusion/exclusion criteria are met prior to enrollment. Specifically, information will be provided which will detail the second phase of screening as well as the full procedures, and informed consent obtained. Phase two screening includes capture of weight and height to determine nutritional status (weight for height z-score), laboratory studies

to rule out severe anemia, physical examination and history to rule out a chronic medical condition that might make deem a child ineligible.

At both sites, the following activities will take place in **ALL** participants:

- History and physical exam
- Weight and height
- A catheter will be placed for blood draws
- Blood collection (5 mL) for complete blood count (CBC) and renal/liver toxicity measures. Serum will also be used for morbidity studies (EED biomarkers, iron biomarkers, and pro-inflammatory cytokines). Before discharge, another blood sample will be removed between 6 – hours after administration of the first dose of the study drug. This enables monitoring for possible toxicity.
- HIV testing and malaria testing
- Lactulose/Mannitol beverage. Children will take a small volume of a lactulose/mannitol at a dose of 2 ml/kg up to a maximum of 20 ml beverage as a measure of gut permeability and gut absorptive capacity and we will collect urine for 2 hours afterwards. They will fast 30 minutes before the lactulose:mannitol administration.
- Ultrasound scan for detection of schistosomiasis-related morbidity.
- **Stool** collection for parasitology by Kato-Katz if two stools not provided prior to enrollment, fecal calprotectin and fecal occult blood (performed on site).
- **PZQ** administration at the study assigned dose after a meal consisting of local foods.
- Final blood collection (3 ml) for CBC, renal, and liver toxicity 12 hours post dosing (all participants)

To participants further randomly selected for pharmacokinetics and immunology sub-studies:

- At each site participants will be randomly allocated into two groups with different blood sampling frequency but similar overall volume (an extra 5 ml)
 - Pharmacokinetic sub-study:
 - In a sub-set of children (N= 150 in both sites) the indwelling cannula will be used to obtain four blood samples of approximately 1 ml for PK/PD studies at respective intervals. Participants who will be sampled for PK/PD studies **will not** participate in the immunology sub-study
 - Immunology sub-study:

- In a sub-set of children in Uganda, 7 ml of whole blood will be collected for immunology assays (such as flow cytometry, Luminex, ELISpot and ELISA).
- Participants who will be sampled for the immunology sub-study **will not** participate in the PK/PD study
- A subset of children without schistosomiasis will be recruited and will provide urine before and after ingesting lactulose-mannitol solution. Stool and 4ml of blood will also be taken for study of gut microbiota/EED biomarkers and morbidity markers.

7.4. Follow up at 4 weeks

Stool will be collected 4 weeks (+/- 1 week) after the baseline visit from parents at their home. Three stools will be collected to quantify egg counts by Kato Katz. Field workers will be responsible for picking up cups at this timepoint for microscopy. Technical work in this phase will be performed by Ministry of Health personnel (Vector Control Division). They will also perform the urine CCA test. **Urine** collection for:

- 2 ml tube collection for CCA/CAA testing
- **Stool** collection for:
 - Parasitology (Kato Katz assessment for schistosomiasis and geohelminths (hookworm, Ascaris, Trichuris).
- Blood- only to those children in the immunology sub-study. 7 ml of whole blood will be collected for immunology assays (such as flow cytometry, Luminex, ELISpot and ELISA).

7.5. Follow up at 6 months

The following activities will take place at the respective research laboratory. This visit will take approximately three hours with no overnight admission. Technical work in this phase will be performed by Ministry of Health personnel (Vector Control Division).

- **Admission** weight, height, clinical history
- **Stool** collection for:
 - Calprotectin and fecal occult blood (performed on site).
- **Urine** collection and storage for future processing of CAA. This will allow for monitoring of re-infection in the cohort.
- **PZQ or Placebo** administration at the study assigned dose after a meal consisting of local foods and monitoring for AE post-treatment

- **Blood:** Five ml for morbidity studies including CBC, iron biomarkers, EED biomarkers, pro-inflammatory cytokines and further 7 ml from the sub-group of N=150 children who were selected at baseline for immunology assays (such as flow cytometry, Luminex, ELISpot and ELISA). Before discharge, another blood sample will be removed between 6 – hours after administration of the first dose of the study drug. This enables monitoring for possible toxicity.
- **Ultrasound** to determine possible changes in baseline morbidity patterns

7.6. Follow-up and close out at 12 months

The following activities will take place at the respective research laboratories. This visit will take approximately 5-6 hours with no overnight admission. Technical work in this phase will be performed by Ministry of Health personnel (Vector Control Division).

- Weight, height, clinical history
- Lactulose/Mannitol beverage. They will take 2ml/kg of lactulose-mannitol solution (containing 250 mg/mL lactulose and 50 mg/mL mannitol in purified water, in aliquots of 20ml) up to a maximum of 20 ml. Urine will be collected for 2 hours after ingestion of the solution. 2ml aliquots of each of the urine samples will be collected and stored between 2 – 8°C for lactulose-mannitol assay.
- **Urine** test for CAA/CCA assay
- **Stool** collection for:
 - Calprotectin and fecal occult blood (performed on site).
 - Kato Katz (two samples in Uganda and three in Philippines) with some collected prior to visit
- **Urine** collection for CCA and CAA
- **Blood:** Five ml for morbidity studies including CBC, iron biomarkers, EED biomarkers, pro-inflammatory cytokines and further 7 ml from the sub-group of N=150 children who were selected at baseline for immunology assays (such as flow cytometry, Luminex, ELISpot and ELISA).
- **PZQ** administration at the study assigned dose after a meal consisting of local foods for children infected with schistosomiasis based on Kato-Katz or urine CCA
- **Albendazole** administration for any child infected with soil-transmitted helminths

- **Ultrasound** to determine persistence of morbidity

7.7. Final Study Visit

This visit will occur with the 12 month follow up visit as above. Technical work in this phase will be performed by Ministry of Health personnel (Vector Control Division). All children will be treated for schistosomiasis as per Uganda DOH and WHO recommendations.

7.8. Monitoring PZQ resistance

Stool samples will be obtained at all visits from a sub-sample of the participants to do PZQ resistance testing. Briefly, eggs from participant's stool will be hatched and individual miracidia will be picked up using a micropipette under a microscope and transferred onto Whatman FTA[®] indicator cards. The Whatman FTA[®] cards will be allowed to dry in the shade for one hour. Up to 100 miracidia should be collected per participant, dependent on the intensity of infection.²⁴

7.9. Early Termination Visit (if needed)

A participant may, at any time point, voluntarily withdraw from the study based on their personal judgement. In the event that this arises, efforts will be made to understand the reasons for the participant's decision. If the concerns are within the means of the study team to manage, proper attention will be given with the aim of maintaining participation to completion.

7.10. Early Termination Visit (if needed) Unscheduled Visit (if needed) Early Termination Visit (if needed) Unscheduled Visit (if needed) Early Termination Visit (if needed) Unscheduled Visit (if needed)

Participants may visit the research center or contact the research team at any time outside the stipulated scheduled visits. This may be due to concerns regarding safety.

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

- Medical history
- Medications history
- Physical examination height and weight.
- Abdominal ultrasound of liver and spleen

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

We will obtain the following:

- Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.
- Renal and liver function tests
- Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic is required.
- Stool assay: Kato-Katz, Calprotectin, Fecal Occult Blood
- CCA/CAA-urine based point of care antigen tests for schistosomiasis

8.2.2. Special Assays or Procedures

- Lactulose:Mannitol assays
- Calprotectin Stool
- Fecal occult blood
- Alpha-1 antitrypsin
- Endocab antibody
- Myeloperoxidase
- Neopterin

- Pharmacokinetic assays from serum
- Immunologic assays using cells, whole blood and plasma

8.2.3. Specimen Preparation, Handling, and Shipping

Samples will be spun down with centrifuge. The CBC will be run and serum will be placed in three aliquots at each site. The aliquots will be stored in -80 freezer until shipment. Every six months, two aliquots will be shipped from the field laboratories to MRC in Entebbe and RITM in Manilla. From there, one aliquot will be stored in -80 and the other shipped to Rhode Island Hospital for multi-plexed assays (markers of EED and iron status).

8.2.3.1. Instructions for Specimen Preparation, Handling, and Storage

8.2.3.2. Specimen Shipment

Samples will be transported from Lake Albert to Entebbe UVRI by road and stored there at -80 C and from Leyte to Manilla by air until further shipment to the United States (serum aliquot and urine for lactulose-Mannitol) and to Liverpool (serum for Pharmacokinetics). International shipment will be done by World Courier which has extensive experience in the transport of biologic specimens.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Safety will be assessed by the frequency and severity of actively monitored and passively captured adverse events continuously in the 12 hours after every investigational product administration given throughout the duration of the trial. Parent reported adverse events during that time period will also be captured. This is made possible due to the continuous onsite presence of the trial doctor. The 12 hour duration is deemed sufficient monitoring since praziquantel is a moderately fast acting drug with elimination in less than 24 hours.

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

Adverse Event:

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs, including solicited local (injection site) and systemic (subjective and quantitative) reactions, will be captured on the appropriate data collection form and eCRF. Information to be collected for unsolicited non-serious AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis, date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product (see definitions). Adverse events characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

Severity of Event:

AEs will be assessed by the investigator using a protocol-defined grading system (toxicity table included as an appendix). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The assessment of the relationship of an AE to the administration of study product is made only by those with the training and authority to make a diagnosis based on all available information at the time of the completion of the eCRF. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- **Not Related** – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.2. Serious Adverse Events

Serious Adverse Event (SAE):

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event¹,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

¹ Life-threatening adverse event. An adverse event is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology.

- Recorded on the appropriate SAE data collection form and eCRF.
- Followed through resolution.
- Reviewed and evaluated by an Independent Safety Monitor (ISM) (as deemed necessary), the DSMB (periodic review unless related), and the IRB.

9.2.3. Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Children who are noted to have an acute or chronic medical condition at enrolment or follow up will be referred for appropriate treatment if the issue cannot be managed by the study paediatrician. This may include referral for severe undernutrition or chronic disease such as asthma. For any child found to be anemic (hgb < 11.0 g/dL) we will provide iron supplements.

9.3. Reporting Procedures

9.3.1. Serious Adverse Events

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to both study Principal Investigators, the study clinical officer, and the independent safety monitor described below.

SAE Email Address: Jennifer.Friedman@Brown.edu and Amaya.Bustinduy@lshtm.ac.uk

In addition to the SAE form, select SAE data fields must also be entered into the electronic data capture system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DSMB and should be provided as soon as possible.

9.3.2. Reporting of Pregnancy

Not applicable

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

For subjects who are excluded based on chronic or acute medical condition or undernutrition, we will ensure follow up was secured at the community health center. The study field workers will re-visit the homes of these families to ensure follow up occurred.

For children found to have mild or moderate anemia, we will provide a 2-month supply of iron (mild) or 4 month supply (moderate) and we will recheck CBC at 6 month visit and repeat this approach based on laboratory findings.

We expect that adverse events related to drug dosing will resolve prior to discharge at 12 hours (enrollment) or 3-4 hours after dose (6 month visits).

9.5. Halting Rules

Safety findings that would lead to temporary suspension of enrolment include:

- 1) A greater than expected number of total serious adverse events deemed associated with the study product as defined by two or more SAEs associated with the study product among the first 20 children enrolled and then five or more serious adverse events among children, associated with the intervention per 100 children enrolled (5%).
- 2) 15 subjects per 100 enrolled experiencing adverse drug events as defined by a) an unexpected adverse event, as defined by a clinical adverse event (not a laboratory defined adverse event) that is not listed as expected with treatment, that occurs within 2 days after dosing, If the total number of unexpected adverse drug events occurs among 15 children per 100 enrolled or 15% or more of children, halting rules would apply.

If either of the above occurs, this would lead to temporary suspension of enrolment and a safety review (either routine or ad hoc), the objective of which is a decision as to whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group or for the entire study) is another potential outcome of a safety review.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, DSMB, IEC/IRB, the sponsor(s), or relevant local regulatory authorities may also result in suspension of further trial interventions/administration of study product at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

Individual Halting Rules

A child will be discontinued from the study if he/she experiences a severe allergic/anaphylactic reaction to any dose of Praziquantel given during the study (enrolment or six months).

9.6. Safety Oversight (ISM plus SMC or DSMB)

Independent safety oversight will be under the direction of a DSMB composed of individuals with expertise in clinical pediatrics, schistosomiasis, biostatistics, and clinical trials methodology. The DSMB will be engaged until the last patient is enrolled and treated at baseline. We expect this will be about 18-24 months. An independent safety monitor (ISM) will be identified in Uganda and The Philippines. The individuals will be physicians, independent of the trial, and live in close proximity to the study activities. The DSMB will operate under the rules of an IRB-approved charter that will be written at the organizational meeting of the DSMB. The DSMB will set the frequency of planned meetings and establish safety criteria for additional ad hoc meetings. The DSMB will advise PIs and IRBs of its findings. The DSMB had a first meeting to review the protocol and develop the charter on June 14, 2019. DSMB suggestions for changes to the protocol are reflected in this protocol.

9.6.1. Independent Safety Monitor (ISM)

The ISM will be a physician with relevant expertise whose primary responsibility will be to provide to the PI and DSMB an independent safety assessment in a timely fashion. Participation is for the duration of the study and is a voluntary position that does not receive payment. The ISM will meet the requirements of the NIH conflict of interest policy.

The ISM:

- Is in close proximity to the study site and has the authority and ability to readily access study participant records in real time.

- May be a member of the participating institution's staff but preferably be from a different organizational group within the institution.
- Will not be in a direct supervisory relationship with the investigator.
- Will have no direct involvement in the conduct of the study.

The ISM will:

- Sign a Conflict of Interest (COI) certification at the time they are asked to participate and provide updates to this information as needed.
- Receive reports of Serious Adverse Events (SAEs) from the site investigator and will be notified by email when the PI is notified of the SAE.
- Evaluate the SAE and report their clinical assessment to the PIs, through in a timely manner using the attached report form and email the report.
- Communicate with the investigator at the participating site as needed.
- Review additional safety related events at the request of NIH.
- Provide additional information to the PIs and/or the DSMB by teleconference as requested.

9.6.2. Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises the PIs and study staff. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will operate under the rules of an approved charter that will be written and agreed upon at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrolment and demographic information, medical

history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

The DSMB will conduct the following reviews:

- Interim analysis
- Ad hoc when a halting rule is met: DSMB chair may convene an ad hoc meeting if there are immediate concerns regarding observations during the course of this trial.
- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by PIs.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by PIs or other study staff. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study procedures and to continue, modify, or terminate this trial.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. The sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by the study team and may be made more frequently as directed by the PIs. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken, and will document site visit findings and discussions.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

Primary outcome

The null hypothesis that there is no difference in cure rate assessed by microscopy at 4 weeks between children who received 40 mg/kg praziquantel and children who received 80 mg/kg praziquantel. This will be tested against the alternative hypothesis that there is a difference in cure rate at 4 weeks between children who received 40 mg/kg praziquantel and children who received 80 mg/kg praziquantel, and will be a superiority comparison.

Secondary outcomes

All secondary outcomes will be superiority comparisons, with alternative hypothesis of a difference in the outcome between the two sets of participants being compared.

For outcomes 1 to 5 below, the null hypothesis is that there is no difference in the outcome between children in the 40 mg/kg praziquantel group and children in the 80 mg/kg praziquantel group.

1. Mean egg reduction rate at 4 weeks
2. Schistosomal antigenic clearance assessed by CCA at 4 weeks
3. Schistosomal antigenic clearance assessed by CAA at 4 weeks
4. Prevalence of any adverse event within 3 hours of dosing

Adverse events will be classified by type. Adverse event types that occur with overall prevalence >5% or at prevalence >5% in either setting will also be tested for differences between trial arms.

5. (a) Prevalence of adverse event type 1 within 3 hours of dosing
(b) Prevalence of adverse event type 2 within 3 hours of dosing
(c) Prevalence of adverse event type 3 within 3 hours of dosing
continued for all adverse event types occurring with prevalence >5%

For secondary outcomes 6 to 13 below, two null hypotheses will be tested. The first null hypothesis is that there is no difference in the morbidity outcomes between children who received six-monthly praziquantel (either 40 mg/kg or 80 mg/kg) and children who received 12-monthly praziquantel (either 40 mg/kg or 80 mg/kg). The second null hypothesis is that there is no difference in the morbidity outcomes between children who received 40 mg/kg praziquantel (regardless of dosing schedule) and children who received 80 mg/kg praziquantel (regardless of dosing schedule).

6. Mean weight-for-height z-score at 12 months
7. Proportion with weight-for-height z-score at 12 months < -2
8. Mean MUAC-for-age z-score at 12 months
9. Proportion with MUAC-for-age z-score at 12 months < -2
10. Mean height-for-age z-score at 12 months
11. Proportion with height-for-age z-score at 12 months < -2
12. Mean haemoglobin level at 12 months
13. Proportion with anaemia at 12 months
14. Exploratory: EED markers
15. Exploratory: immune responses to *S. mansoni* infection and treatment
16. Exploratory: prevalence and pattern of schistosomiasis-related morbidity by ultrasound scan.

11.2. Sample Size Considerations

The sample size calculations are based on the primary outcome of cure rate at 4 weeks. Cure rate is defined as the proportion of individuals who are uninfected at the follow-up, where infection will be assessed using parasitological methods. The null hypothesis is that cure rate at 4 weeks is the same between children who received 40 mg/kg praziquantel and children who received 80 mg/kg praziquantel. The null hypothesis will be tested using a chi-squared test statistic. The analysis population will be comprised of all participants as randomised, regardless of whether or not they received the allocated treatment (intention-to-treat).

Data from Uganda found cure rates for *S. mansoni* infected 3-9 year olds of 70% and 82% for 40 mg/kg and 60 mg/kg praziquantel, respectively. We anticipate that cure rates may be lower in younger children and that the 80 mg/kg dose will have a higher cure rate than the 60 mg/kg. However, we conservatively power the trial to detect a difference in cure rate of 70% versus 82%. Using a two-sided 5% significance level, approximately 173 children per trial arm will be required for 80% power and 232 per arm (N=464) for 90% power to detect a difference in cure rate at 4 weeks between the trial arms. Allowing for loss to follow-up of 7%, a total of approximately 500 children will be required. A sample size of 600 will allow us adequate power to examine sub-groups such as younger (12-30 months) versus older (30-47 months) children, particularly given that the effect size is likely to be larger based on a higher dose (80 mg/kg).

This sample size will give 80% power to detect differences in the secondary morbidity outcomes measures. We increase the estimated loss to follow up for these endpoints given they occur at six and 12 months following treatment. With 10% attrition, we will have 540 subjects at the 12 month follow up. As one example of the effect size we will detect for the key secondary outcome of weight-for-height z-score at 12 months, we will have 80% power to detect a difference in mean weight-for-height z-score between the six-monthly and 12-monthly dosing groups as low as 0.24 z-score, assuming a standard deviation of 1 and two-sided significance level 5% between children who received six-monthly praziquantel (either 40 mg/kg or 80 mg/kg) and children who received 12-monthly praziquantel (either 40 mg/kg or 80 mg/kg). A weight for age z-score difference of 0.23 is biologically relevant, particularly based on mitigation of only one cause of nutritional morbidity in this setting. For hemoglobin, we will be able to detect a difference of 0.29 g/dL using a standard deviation of 1.2, power of 80%, and functional sample size of 540.

For the PK study, 137 children from both sites (Uganda/Philippines) will be sampled. These are the numbers needed for 80% power to show a slope of the relationship between log CAA at 24 days and AUC is significant to $p < 0.05$. We will include 150 children to allow for loss to follow-up and enable sufficient power.

To assess immunological responses, assuming an SD of 0.9, the sub-study would require a sample size of 104 to achieve 80% power at 5% significance level for detecting difference in mean of $0.35\log_{10}$ cytokine response between the groups. We will recruit 150 children to allow for attrition.

11.3. Planned Interim Analyses

11.3.1. Interim Safety Review

Given that the study population is vulnerable the project will require rigorous independent oversight by a data safety and monitoring board (DSMB). DSMB membership will be independent of the trial with input from investigators; we anticipate that it will comprise experts on schistosomiasis and child health, and a statistician with experience of trials in LMICs. The frequency of meetings and other procedural issues will be overseen by the study sponsor.

The DSMB will regularly monitor all data to consider any potential harm to participants. Formal rules for stopping due to harm will be discussed with the DSMB at their first meeting. An interim analysis will be performed on the primary outcome when approximately 20% of children have been randomised. Only the DSMB and the trial statistician will be unblinded for this interim analysis.

The DSMB will meet once three months after study enrollment begins and then every six months during enrollment.

11.4. Analysis Plan

A trial flow chart will be constructed, showing the number of children screened, enrolled and randomised, together with reasons for exclusion at each stage. Baseline characteristics of trial participants will be summarised by trial arm. Numbers and proportions will be reported for categorical characteristics. Means, standard deviations, medians and ranges will be used for continuous characteristics.

All trial analyses will be done using the intention-to-treat population, i.e. all children will be included as randomised, regardless of whether or not they received the allocated treatment. Children will contribute to 4 week outcomes if they are assessed within 1 week of the 4 week time point. Children will contribute to 6 and 12 month outcomes if they are assessed within 2 weeks of these time points. Since loss to follow-up is expected to be low at 4 weeks, only children for whom outcome data are available will be included in analyses (complete case analysis), with no imputation of missing outcome data planned.

The primary outcome of cure rate will be compared between trial arms using a chi-squared test statistic. The difference in proportions cured and a corresponding 95% confidence interval will be calculated. The related primary outcome, egg reduction rate, is defined as the percentage decrease in egg count between baseline and follow-up. The mean egg reduction rate will be compared between trial arms using a t-test, with the difference in mean egg reduction rate and its 95% confidence interval calculated. Schistosomal (CCA and CAA) antigenic egg clearance outcomes will be analyzed using the same approach as for cure rate (based on microscopy).

Prevalence of adverse events (both any and separately for types of event that occur with overall prevalence >5%) will be compared between trial arms using chi-squared tests. Rare adverse events will be tabulated by trial arm but no formal statistical comparisons done. Severity of adverse events will also be tabulated, by trial arm.

For the secondary outcomes assessed at 6 and 12 months (anthropometry and anemia), continuous outcomes will be compared between trial arms using linear regression, including the corresponding baseline measure as a covariate. Binary outcomes assessed at 6 and 12 months will be compared between trial arms using binary/logistic regression, including the corresponding baseline measure as a covariate. This will be done in order to improve the precision of the treatment effect estimate.

Due to the large sample size, no imbalance is expected between trial arms. Therefore, no further adjustment for baseline characteristics is planned for any outcome, unless there are significant differences demonstrated at baseline for key potential confounders.

We will pre-specify three key potential effect modifiers to be examined. These include site (Uganda versus the Philippines), age (12-30 months versus 31-47 months) and baseline intensity of infection (Low versus moderate/high). We will examine whether cure rate and egg reduction rate, as well as key measures of morbidity differ by these sub-groups. Effect modification will be tested by fitting interaction terms in regression models.

Full details, including shell tables will be included in a formal statistical analysis plan, to be finalized and reviewed before database lock.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the NIH, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written accepted site quality management plan, each participating site(s) and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

Designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the PIs and DSMB as requested.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The site principal investigator (PI) will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [April 18, 1979]) and codified in 45 CFR 46, 21 CFR 50 and 21 CFR 56, as applicable. The PI will also ensure conformity with ICH E6 Good Clinical Practice, and applicable federal regulations, guidance, and guidelines for Good Clinical Practice and Clinical Trials with humans.

14.2. Institutional Review Board

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s), and send supporting documentation to the NIH before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. NIH must receive the documentation that verifies IRB/IEC approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects, and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current Federal wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

The IRB/IEC will determine that adequate provisions are made for soliciting the permission of each child's parent(s) or legal guardian, including whether permission of one parent is sufficient for research or whether permission is to be obtained from both parents.

14.3. Informed Consent Process

Informed consent is a process that is initiated prior to the parent agreeing to allow his/her child to participate in a trial and continuing throughout the child's trial participation. Before any study procedures are performed, informed consent of the parent will be obtained and documented. There will be separate consent processes and forms for participation in screening activities (limited to stool and urine collection) and main study activities since only those who have schistosomiasis based on stool examination are eligible to participate in the main study. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized, and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects face-to-face. This will occur in a private space in communities for the screening consent and in a private space at the respective research field sites for the main study. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts, any expected benefits to the subject, and alternative treatment will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject), the expected duration of the subject's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures. available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial, and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved and subjects will be asked to read and review the consent form. Subjects must sign the informed consent form prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the informed consent forms will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record. Research staff will obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all informed consent forms that they sign.

14.3.1. Informed Consent

14.4. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released

to any unauthorized third party without prior written approval of the NIH and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with encrypted and password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

14.5. Study Discontinuation

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC. If any subject's private information will continue to be collected for this study, the IRB/IEC must approve a consent form with the study procedures, any risks and discomforts, and applicable elements, and the investigator or designee will re-consent the subjects as approved by the IRB/IEC.

14.6. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the

participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject, [insert language according to overriding agreements, or insert: or by the participating site] for any injury suffered due to participation in this trial.

14.7. Future Use of Stored Specimens and Data

Subjects will be asked for permission to keep any remaining serum from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. These residual clinical samples will be stored indefinitely at a central clinical storage facility and may be shared with investigators at the participating site and with other investigators at other institutions.

It is anticipated that up to five 1.0 mL aliquots of serum from venous blood samples will be available specifically for the purpose of future research, including but not limited to non-traditional immune assay development, and assessing innate immune factors. Up to 500µL of whole blood in RNALater and 500µL of plasma will be stored for studies of immune transcriptomics and proteomics, respectively. These future use clinical samples will be stored indefinitely at a central clinical storage facility.

Residual clinical samples will be available upon the completion of the study; however, future use clinical samples may be requested from NIH and shipped from the NIH CAR at any time.

The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on the samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality.

There are no benefits to subjects in the collection, storage and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of this trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use and subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

15. DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, study staff will be required to cross out the original entry with a single line, and initial and date the change.

Copies of the electronic CRF (eCRF) will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

15.1. Data Management Responsibilities

Data collection is the responsibility of the trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

All source documents and laboratory reports will be reviewed by the clinical team for accuracy before transfer to CRFs. The data manager will review all completed forms and source documents for completeness, legibility, consistency, and accuracy. These include forms filled out in the field, laboratory, and clinical intake spaces. If there is any missing information or apparent inaccurate information, he/she will query the individual who initially completed the form. The appropriate and necessary correction will be made by drawing a line against the original entry, writing the correct information; this will be dated and initialled by the person who made the correction and deficiencies will be discussed in a regular meeting with the research staff and may be used as a basis for re-training.

However, if missing and out of range values are identified after these have been entered in the EDC system, an Automated or Manual Query Form will be generated. This is usually identified in

the process of the Project's Data Manager daily checks of the REDCap system. The query form is then generated and printed, and submitted to the Study Manager for resolution. In return, the Study Manager, verifies the missing information or out of range values, with the research staff who initially filled out the information or by going back to the source documents. Once verified or corrected, the correct or missing information is recorded on the appropriate CRFs by the research staff who originally filled out the form. One line will be drawn across the initial information recorded, such that the correct information written will not obscure the original entries; it shall be initialled and dated. The same information shall be recorded on the Query Report Forms, initialled and dated by the Study Manager. This Query Report Form is then scanned and sent to the data manager at the relevant site. The missing or correct information will then be entered by data entry personnel into the EDC system.

The Query Report Forms placed in the QM binder is the paper trail of all the queries made of data entered into the EDC. The Query Report Form contains information on the data queried, i.e, missing, inaccurate or inconsistent data, the correct information or a confirmation that the data entered into the system is correct, the person making the correction, date and signature of the person making the correction.

The Study Manager will meet with the research staff monthly to discuss deficiencies in recording of information into the source documents and to remind them of the correct procedures for recording and making amendments on recorded data.

Adverse events will be graded, assessed for severity and causality, and reviewed by the site PI or designee.

The designated Data Coordinating Center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

15.2. Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and reactogenicity will be collected on data collection forms by study personnel then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center. The study will use REDCap, which

is GCP compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

All data will be collected on paper source documents. Source documents filled out in the field (by field runners), in the laboratory (by medical technologists) and at the field laboratory (by study pediatrician) will be brought to the central laboratory offices for review, data entry and archiving. Source documents filled out in the field health centers will be brought to the central offices by the field runners. This includes screening source documents.

The Data Manager will review all the source documents for completeness, accuracy, legibility and consistency prior to its submission for data entry. Encoding of information will be done as soon as completed forms are received by the Data Entry person. Data will be entered into REDCap, a 21 CFR Part 11-Internet Data Entry System (IDES). The data system will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

15.3. Types of Data

Data for this study will include demographic data, medical history, physical exam including nutritional status (weight, height, MUAC), urinalysis, laboratory (CBC), socio-economic status, All data will be entered into the data system from source documents. Laboratory CRFs will be used to transcribe data from printouts. Timing/Reports

15.4. Timing/Reports

Data will be reviewed daily by study staff for completeness and accuracy. The Data Coordinating Center will generate on a daily basis query reports for missing, incomplete and inconsistent data. The local data manager will ensure that the reports are captured promptly and queries will be resolved as soon as possible.

Based on the halting rules of the trial, the data coordination center will also generate information which is the basis for calling a halt to study recruitment, if this is indicated. Such reports signal the need for prompt action on the part of the trial staff and sponsor.

Study outcomes will otherwise be compiled by the study biostatistician and provided to the DSMB for review. These reviews will be periodic, occurring every six months.

Before final data analysis, the data will be “frozen.” All analysis will be conducted before the study code is broken to assess differences in a blinded fashion. Final study data analysis will be completed within five months of completion of data collection and the final report will be completed within 15 months of completion of data collection.

The DSMB will meet once three months after study enrollment begins and then every six months during enrollment.

15.5. Study Records Retention

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to NIH per the DCC protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site principal investigator and personnel are responsible for knowing and adhering to their IRB requirements.

16. PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (<http://www.ncbi.nlm.nih.gov/pmc/>) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, <http://publicaccess.nih.gov/>
- NIH Office of Extramural Research (OER) Grants and Funding, <http://grants.nih.gov/grants/oer.htm>

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClinicalTrials.gov.

For this trial the responsible party is Dr. Jennifer Friedman who will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

17. LITERATURE REFERENCES

1. Stothard JR, Sousa-Figueiredo JC, Betson M, et al. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology* 2011; **138**(12): 1593-606.
2. Mutapi F. Changing policy and practice in the control of pediatric schistosomiasis. *Pediatrics* 2015; **135**(3): 536-44.
3. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. *Lancet* 2014.
4. Bustinduy AL, Stothard JR, Friedman JF. Paediatric and maternal schistosomiasis: shifting the paradigms. *Br Med Bull* 2017; **123**(1): 115-25.
5. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public health nutrition* 2009; **12**(4): 444-54.
6. WHO. Assessing the efficacy of anthelmintic drugs against schistosomiasis and soil-transmitted helminthiasis. Geneva, 2013.
7. Bustinduy AL, Waterhouse D, de Sousa-Figueiredo JC, et al. Population Pharmacokinetics and Pharmacodynamics of Praziquantel in Ugandan Children with Intestinal Schistosomiasis: Higher Dosages Are Required for Maximal Efficacy. *mBio* 2016; **7**(4).
8. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? *Br J Clin Pharmacol* 2010; **70**(4): 597-603.
9. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**(12): 1157-67.
10. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet* 2006; **45**(11): 1077-97.

-
11. Lovis L, Mak TK, Phongluxa K, et al. Efficacy of praziquantel against *Schistosoma mekongi* and *Opisthorchis viverrini*: a randomized, single-blinded dose-comparison trial. *PLoS neglected tropical diseases* 2012; **6**(7): e1726.
 12. Coulibaly J, Panic G, Yapi R, et al. Efficacy and safety of ascending doses of praziquantel against *Schistosoma haematobium* infection in preschool-aged and school-aged children: a single-blind randomised controlled trial. *BMC Med* 2018 **16**(1).
 13. Bustinduy AL, Sousa-Figueiredo JC, Adiriko M, et al. Fecal occult blood and fecal calprotectin as point-of-care markers of intestinal morbidity in Ugandan children with *Schistosoma mansoni* infection. *PLoS neglected tropical diseases* 2013; **7**(11): e2542.
 14. Leenstra T, Acosta LP, Langdon GC, et al. Schistosomiasis japonica, anemia, and iron status in children, adolescents, and young adults in Leyte, Philippines 1. *The American journal of clinical nutrition* 2006; **83**(2): 371-9.
 15. Coutinho HM, McGarvey ST, Acosta LP, et al. Nutritional status and serum cytokine profiles in children, adolescents, and young adults with *Schistosoma japonicum*-associated hepatic fibrosis, in Leyte, Philippines. *The Journal of infectious diseases* 2005; **192**(3): 528-36.
 16. FAO. Nutrition Country Profile, The Republic of Uganda, 2010.
 17. Stothard JR, Sousa-Figueiredo JC, Betson M, Bustinduy A, Reinhard-Rupp J. Schistosomiasis in African infants and preschool children: let them now be treated! *Trends in parasitology* 2013; **29**(4): 197-205.
 18. Koukounari A, Donnelly CA, Moustaki I, et al. A latent Markov modelling approach to the evaluation of circulating cathodic antigen strips for schistosomiasis diagnosis pre- and post-praziquantel treatment in Uganda. *PLoS Comput Biol* 2013; **9**(12): e1003402.
 19. van Dam GJ, Odermatt P, Acosta L, et al. Evaluation of banked urine samples for the detection of circulating anodic and cathodic antigens in *Schistosoma mekongi* and *S. japonicum* infections: a proof-of-concept study. *Acta Trop* 2015; **141**(Pt B): 198-203.

20. Clements MN, Donnelly CA, Fenwick A, et al. Interpreting ambiguous 'trace' results in *Schistosoma mansoni* CCA Tests: Estimating sensitivity and specificity of ambiguous results with no gold standard. *PLoS Negl Trop Dis* 2017; **11**(12): e0006102.
21. Verani JR, Abudho B, Montgomery SP, et al. Schistosomiasis among young children in Usoma, Kenya. *Am J Trop Med Hyg* 2011; **84**(5): 787-91.
22. World Health Organization. REPORT OF A MEETING TO REVIEW THE RESULTS OF STUDIES ON THE TREATMENT OF SCHISTOSOMIASIS IN PRESCHOOL-AGE CHILDREN. Geneva, Switzerland, 2010.
23. Mookink LB, van der Lee JH, Grootenhuys MA, et al. Defining chronic diseases and health conditions in childhood (0-18 years of age): national consensus in the Netherlands. *Eur J Pediatr* 2008; **167**(12): 1441-7.
24. Le Clec'h, W., Chevalier, F., McDew-White, M., Allan, F., Webster, B., Gouvras, A., . . . Anderson, T. (2018). Whole genome amplification and exome sequencing of archived schistosomemiracidia. *Parasitology*, 145(13), 1739-1747. doi:10.1017/S0031182018000811)

18. SUPPLEMENTS/APPENDICES

(NOTE: Since the protocol and the clinical study report are closely related, further relevant information can be found in the ICH E3: Structure and Content of Clinical Study Reports. These materials should not be included as part of the protocol.)

Supplements and Protocol Appendices

Substudies (if applicable)

Schedule of Study Procedures and Evaluations

Toxicity Grading Scales

Sample Consent Form(s)

Related Documents

Site Roster

Manual of Procedures

Repository instructions

Biosafety Precautions

Laboratory Handling

Other Documents

eCRF copies

Quality Management Plan

Data Management Plan

Clinical Monitoring Plan

APPENDIX A. SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS