# Novel methods to expedite schistosome development

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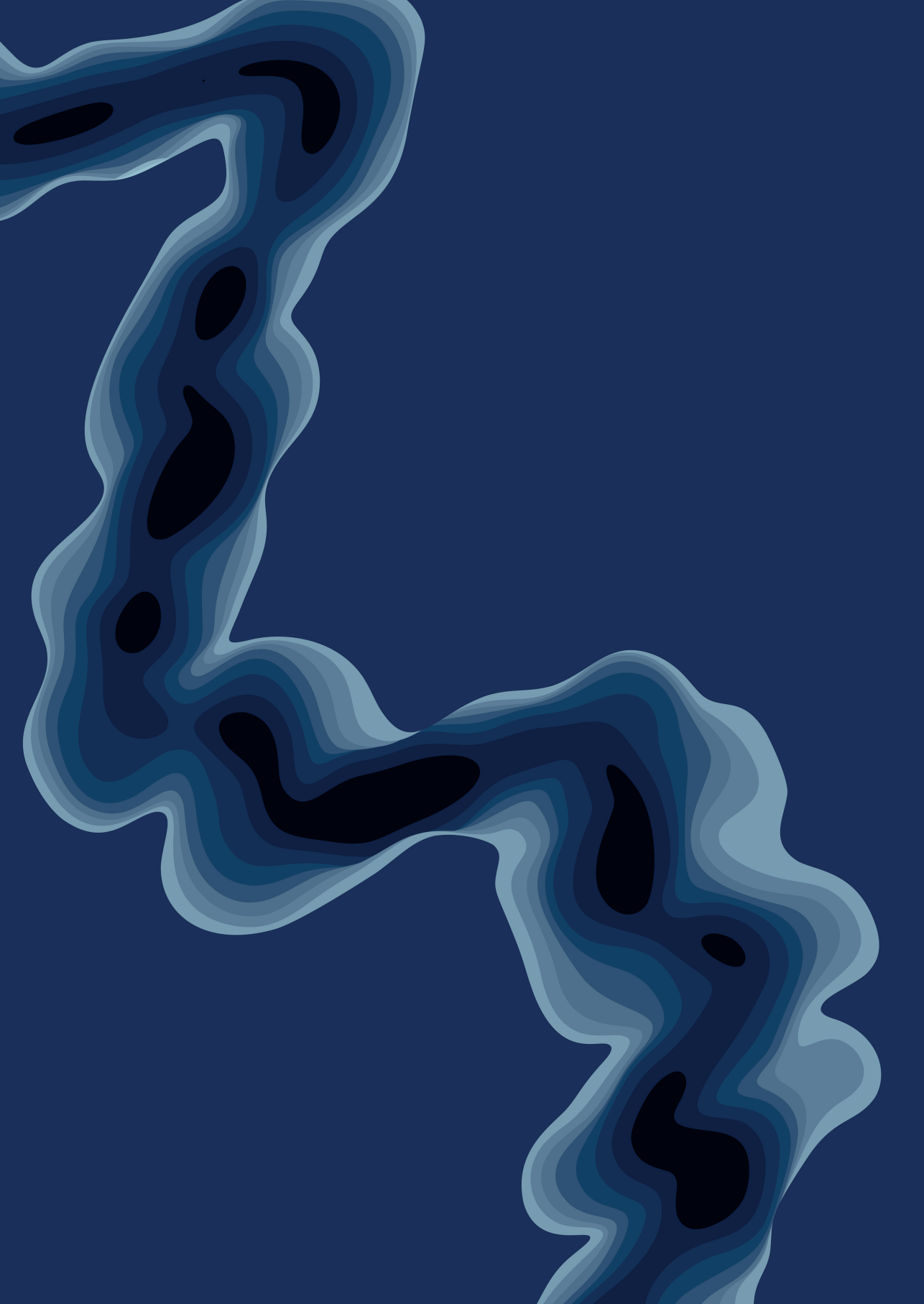

# Chapter 6

## Safety and preliminary efficacy of Sm-p80 + GLA-SE (SchistoShield®) vaccine against controlled human schistosome infection in healthy, *Schistosoma*-naïve adults: protocol for a double-blind, placebo-controlled randomised controlled human infection study

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## ABSTRACT

**Background:** Schistosomiasis continues to affect health worldwide, despite ongoing efforts to control disease through mass drug administration with praziquantel. So far, no vaccine has been licensed, but three candidates, including Sm-p80 adjuvanted with GLA-SE (SchistoShield®), are currently in clinical testing. Controlled human infection studies have the potential to speed up vaccine development as they can be used to quickly provide preliminary estimates of vaccine efficacy in a small group of participants. Recently, a controlled human infection with schistosomes (CHI-S) model has been established using single-sex cercariae that do not produce eggs and therefore prevents egg-associated morbidity in study participants. This study will evaluate the safety, immunogenicity, and preliminary vaccine efficacy of the Sm-p80 + GLA-SE vaccine candidate using CHI-S.

**Methods/design:** This is a double-blind, placebo-controlled randomised trial in which 48 *Schistosoma*-naïve participants (18-45 years old) will be enrolled and randomised in a 1:1 ratio to receive either three immunisations with 30 µg Sm-p80 + 5 µg GLA-SE or placebo (week 0,4,8). Subsequently, all participants will be challenged with 20 male *Schistosoma mansoni (Sm)* cercariae at week 12 and treated with praziquantel at week 24 to cure infection. At each visit, adverse events will be recorded and participants will undergo a blood draw by venepuncture. They will keep a diary to record adverse events for 24 weeks. The primary outcome is the protective efficacy of Sm-p80 + GLA-SE to male *Sm* cercariae measured by the difference in frequency of serum circulating anodic antigen positivity (≥1.0 pg/mL) after CHI-S between the vaccine and placebo group.

**Discussion:** The CHI-S allows for efficient evaluation of schistosomiasis candidates and can provide early efficacy data crucial for further vaccine development.

**Trial registration:** NCT05999825 (clinicaltrials.gov)


**Keywords:** Controlled human *Schistosoma* infection, Sm-p80, *Schistosoma* vaccine

## BACKGROUND

Schistosomiasis is a parasitic disease of global importance that affects around 150 million people mainly living in (sub)tropical regions (1). Control of disease relies on mass drug administration with praziquantel of at-risk populations, however sustained transmission and frequent reinfection hamper elimination efforts. So far, there is no effective licensed vaccine against schistosomiasis. Only three candidates are currently in clinical testing (2). One of these candidates is SchistoShield® consisting of Sm-p80, a recombinant *Schistosoma .mansoni (Sm)* calpain protein produced in *Escherichia coli*, and Glucopyranosyl Lipid Adjuvant (GLA) formulated in a stable emulsion (GLA-SE) as an immunological adjuvant. Preclinical studies in mice and baboons with Sm-p80 + GLA-SE show ~60% reduction in worm burdens after immunisation (3, 4). Phase 1 studies to investigate the safety and immunogenicity of Sm-p80 + GLA-SE in *Schistosoma*-naïve adults (United States, NCT05292391) have recently been completed and demonstrated excellent safety and immunogenicity (unpublished data). Subsequently, phase Ib studies in populations with prior exposure (Burkina Faso and Madagascar, NCT05762393) have recently commenced. Further studies are now required to assess the (preliminary) efficacy of this vaccine. Controlled human infection studies have the potential to speed up vaccine development as they can be used to quickly provide preliminary estimates of vaccine efficacy in a small group of participants (5). Previously, we have developed a controlled human infection with *Sm*(CHI-S) model using single-sex cercariae that do not produce eggs and preventing egg-associated morbidity in study participants. Infection with 20 male cercariae has been found to be safe and well-tolerated in previously unexposed individuals from a non-endemic setting (6). In this double-blind, placebo-controlled randomised vaccine study, we will investigate the safety, immunogenicity, and preliminary efficacy of the Sm-p80 + GLA-SE vaccine against schistosomiasis in healthy, *Schistosoma*-naïve participants.



## METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

### Participants

This study will take place at Leiden University Medical Centre (LUMC), The Netherlands. The study population will consist of healthy adults aged 18-45 years without previous exposure to *Schistosoma*. The full in- and exclusion criteria are listed in **Table 1**. Prospective participants will be recruited through (online) advertisements and social media and sent the subject information

sheet (SIS) which contains all relevant study related information prior to the screening visit. Informed consent will be obtained by the clinical investigators prior to any study procedures.

**Table 1. In- and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Subject is aged ≥ 18 and ≤ 45 years and in good health.<br>• Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby.<br>• Subject is able to communicate well with the investigator, is available to attend all study visits.<br>• Subject will not travel to *Schistosoma*-endemic countries up until treatment at week 24.<br>• Subject agrees to refrain from blood and plasma donation to blood banks or for other purposes throughout the study period.<br>• For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.<br>• Subject has signed informed consent. | • Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immune-deficient, (severe) psychiatric and other disorders, which could compromise the health of the participant during the study or interfere with the interpretation of the study results.<br>• The chronic use of any drug known to interact with praziquantel, artesunate or lumefantrine metabolism. Because lumefantrine may cause extension of QT-time, chronic use of drugs with effect on QT interval will result in exclusion from study participation.<br>• Any planned vaccination within 28 days before the start of the trial until the end of the immunisation phase (week 12), with the exception of SARS-CoV-2 vaccines or influenza vaccines.<br>• For female subjects: positive serum pregnancy test on the day before first immunisation.<br>• Any history of schistosomiasis or treatment for schistosomiasis.<br>• Positive serology for schistosomiasis or elevated serum circulating anodic antigen at screening.<br>• Known hypersensitivity to or contra-indications (including co-medication) for use of praziquantel, artesunate or lumefantrine.<br>• Being an employee or student of the department of Parasitology or Infectious Diseases of the LUMC. |

**Interventions**

Enrolled participants will be randomised to the vaccine or placebo arm. Participants in the vaccine arm will be immunised with 30 µg Sm-p80 + 5 µg GLA-SE at days 0, 28, and 56, while the placebo arm will receive mock immunisations with saline at these time points. Vaccines and placebo will be administered intramuscularly in the deltoid muscle.

At week 12 all participants will be exposed to 20 male *Sm* cercariae. *Sm* cercariae will be produced as previously described (7). In short, *Biomphalaria glabrata* snails will first exposed to a single *Sm* miracidium. After five weeks, infected

snails will start shedding cercariae that are either male or female. Cercarial sex is determined using the W1 repeat PCR and only male-shedding snails will be used for producing the challenge inoculum. The controlled human schistosome infection is achieved by pipetting 20 male cercariae in 0.5 mL of water onto the skin. After 30 minutes, the water will be removed and checked for cercarial heads and tails, or whole cercariae. After exposure, participants will regularly visit the study centre for follow-up visits and will be given treatment at week 24 with praziquantel at 60 mg/kg dose to cure infection.

**Outcomes**

The primary outcome of this study is the protective efficacy of Sm-p80 + GLA-SE to male *Sm* cercariae as measured using the difference in frequency of serum circulating anodic antigen (CAA) positivity (≥1.0 pg/mL) at any time between 2-12 weeks after CHI-S as compared between the vaccine and placebo group. The secondary outcomes include safety and immunogenicity, measured by the frequency and severity of adverse events and anti-Sm-p80 IgG antibody titres after (repeated) immunisation with Sm-p80 + GLA-SE. In addition, exploratory outcomes include the comparison of time to positive serum CAA, peak serum CAA concentrations, and peak eosinophil counts after CHI-S, as well as comparisons of antibody and cellular responses against *Sm* antigens between the two study arms and CAA positive and CAA negative participants.



## STUDY PROCEDURES

**Recruitment of participants:** Advertisements will be placed in prominent places in public spaces as well as on social media, on the intranet, on the website of the LUMC department of parasitology and infectious diseases and www.vaccinonderzoek.nl. When a potential participant shows interest in participating in the study, detailed information in a subject information sheet will be e-mailed to them. There will be at least 48 hours between this e-mail and the screening visit to make sure the potential participant has time to think about participation and discuss this with friends and relatives or with the independent expert assigned to this study.

**Screening visit:** During the screening visit, participants will first be given a summary of the study and the opportunity to address any study-related questions after which they will be asked to sign the informed consent form if they still want to participate. All participants must consent to HIV, hepatitis B, hepatitis C serological screening, urine toxicology and for females a

pregnancy test at screening. Subsequently participants are asked to complete an application form which includes a questionnaire regarding their health. The questionnaire answers will be discussed and in- and exclusion criteria will be checked. The possibility of withdrawal from the infection study, at any time and without any declaration of the reason, as well as the resulting necessary follow-up visits for safety will be pointed out to the participants. All participants will be asked to supply a phone number of a person who may be contacted in case of emergency. A physical examination will be performed and vital signs (tympanic temperature, blood pressure, and pulse) will be measured.

**Immunisation with Sm-p80 + GLA-SE or placebo (weeks 0, 4, and 8):** One day before immunisation, participants will visit the clinical trial centre for a final check of in- and exclusion criteria, a focussed physical exam and vital signs may be performed if indicated. Whether participants are subsequently immunised with vaccine or placebo depends on which group they are randomised to. Blood will be drawn for safety checks. All female participants will undergo a pregnancy test on screening and on the day before immunisation. After immunisation, participants will be observed for 30 minutes for potential allergic reactions.

**Post-immunisation visits:** After each immunisation, participants will visit the trial centre twice for regular check-ups, 3 and 7 days after immunisation. At these visits, adverse events (AEs) will be recorded and participants will undergo a blood draw by venepuncture. At every physical visit the tympanic temperature will be checked. A focused physical examination will be performed if deemed necessary by the trial physician. Participants will be requested to note adverse events in symptom diaries that will be provided.

**Infection with male *Sm* cercariae (CHI-S week 12):** One day before exposure to male *Sm* cercariae, participants will visit the clinical trial centre for a final check of in- and exclusion criteria, a focussed physical exam and vital signs may be performed if indicated. Blood will be drawn for baseline (pre-infection) assessments and safety laboratory test results will be checked. All female participants will undergo a pregnancy test on the day before infection. Exposure to male *Sm* cercariae will be performed at the LUMC according to previously established protocols at 4 weeks after the last immunisation, i.e.. week 12 of the study. Male cercariae will be allowed to penetrate the skin of human participants by applying 0.5 mL of Bar-le-duc water containing 20 *Sm* male cercariae on the skin for 30 minutes. Participants will be observed for at least 30 minutes after the exposure.

**Post-infection follow up visits:** Starting at week 14 (2 weeks after CHI-S), participants will have weekly follow-up visits until week 24. Afterwards, the frequency of visits will decrease to once every month until week 36. At all follow up visits, AEs will be recorded and participants will undergo a blood draw by venepuncture. Tympanic temperature will be checked weekly until week 24. A focused physical examination will be performed if deemed necessary by the trial physician. Participants will be instructed to report to the clinical trial physician in case of any grade 2 (moderate) or grade 3 (severe) adverse events to ensure early detection and possible treatment of symptoms of acute schistosomiasis symptoms between week 14-24. A clinical trial physician will be available by mobile phone 24/7 during the entire study period. Additional diagnostics (including serum CAA tests) can be performed on discretion of the trial physician at any time if it is deemed necessary for the safety of the study participants. Participants will provide a stool sample at week 24 (before treatment) which will be tested with PCR to rule out egg production.

**Treatment with praziquantel:** Participants will be treated with 60 mg/kg praziquantel after exposure to cercariae at week 24 (12 weeks after CHI-S). The treatment will consist of a weight-based number of praziquantel 600 mg tablets. Treatment will be evaluated at week 28 and 32 and if CAA remains detectable (≥1.0 pg/mL) or indeterminate (between 0.5- 1.0 pg/mL) another round of treatment with praziquantel will be administered.

**Safety laboratory evaluation:** The safety blood sampling schedule is depicted in **Table 2**. Safety analyses includecomplete blood count (including automated differential count of white blood cells), erythrocyte sedimentation rate, creatinine, blood urea nitrogen, sodium, potassium, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, aspartate transaminase, and alanine transaminase ,. Biological safety parameters will be measured on plasma or serum samples at the central clinical chemistry laboratory of the LUMC. Assessment of successful schistosomiasis infection will be performed by serum CAA measurements. A PCR analysis of faecal samples to check the presence of eggs will be performed at week 24.

## SAMPLE SIZE CALCULATION

Based on the combined attack rate of around 85% (29 out of 34) after challenge with 20 male cercariae in our earlier studies (6), we calculated that we would require 19 participants in each group to detect a 50% relative reduction in CAA positivity with 80% power and (two-sided) $\alpha = 0.05$ significance level. This effect size reflects a clinically relevant vaccine efficacy estimate as per WHO Scientific Working Group on Schistosomiasis in 1999. More recently, a 70% vaccine efficacy was proposed in a consensus-based preferred product characteristics for a schistosomiasis vaccine, which we would also be able to reliably detect with this sample size (8). Moreover, in baboon vaccine studies a 43% reduction in male worms was observed in Sm-p80 + GLA-SE immunised animals (4). To account for attrition, we are including 24 people per group, bringing the total to 48 participants.

**Table 2. Overview of study procedures**

Part A: Immunisation phase

| Visit no. | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | scr | I1-1d | I1 | I1+3d | I1+7d | I2-1d | I2 | I2+3d | I2+7d | I3-1d | I3 | I3+3d | I3+7d |
| Week | NA | 0 | 0 | 0 | 1 | 4 | 4 | 4 | 5 | 8 | 8 | 8 | 9 |
| Day | NA | -1 | 0 | 3 | 7 | 27 | 28 | 31 | 35 | 55 | 56 | 59 | 63 |
| Deviation (days) | NA | 1 | 0 | 1 | 2 | 1 | 0 | 1 | 2 | 1 | 0 | 1 | 2 |
| Obtain informed (re)consent | X | X | | | | X | | | | X | | | |
| Temperature | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical evaluation | X | X | | X | X | X | | X | X | X | | X | X |
| Immunisation | | | X[3] | | | | X[3] | | | | X[3] | | |
| Safety tests | X[1,2] | X[2] | | | | X[2] | | | | X[2] | | | |
| Serum pregnancy test for female participants | | X | | | | X | | | | X | | | |
| UCP CAA (serum) | X | | | | | | | | | | | | |
| Schistosomiasis serology: worm IFA, egg ELISA | X | | | | | | | | | | | | |
| Immunological assays: antibodies | | X | | X | X | X | | X | X | X | | X | X |
| Immunological assays: cellular | | X | | X[5] | X[5] | | | | | X | | X[5] | X[5] |
| Transcriptomics | | X | | X | X | X | | X | X | X | | X | X |

1: HIV, HBV, HCV, urine cocaine and amphetamines
2: automated CBC, ESR, creatinine, BUN, sodium, potassium, bilirubin, APT, γGT, AST, ALT, glucose
3: vaccination with Sm-p80/GLA-SE or water for injection depending on randomisation group
4: APT, γGT, AST, ALT
5: including leukocyte differentiation to normalise PBMCs

Part B: Challenge phase

| Visit no. | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | C-1d | C | C+2w | C+3w | C+4w | C+5w | C+6w | C+7w | C+8w | C+9w | C+10w | C+11w | C+12w | C+16w | C+20w | C+24w | C+40w |
| Week | 12 | 12 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 28 | 32 | 36 | 52 |
| Day | 83 | 84 | 98 | 105 | 112 | 119 | 126 | 133 | 140 | 147 | 154 | 161 | 168 | 196 | 224 | 252 | 364 |
| Deviation (days) | 1 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 7 | 7 | 7 | 14 |
| Obtain reconsent | X | | | | | | | | | | | | | | | | |
| Temperature | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Clinical evaluation | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Exposure to cercariae | | X | | | | | | | | | | | | | | | |
| Praziquantel (60 mg/kg) | | | | | | | | | | | | | X | | | | |
| Eosinophils | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Safety tests | X[2] | | | | | | | | X[4] | | | | | | | | |
| Serum pregnancy test for female participants | X | | | | | | | | | | | | | | | | |
| UCP CAA (serum) | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Schistosomiasis serology: worm IFA, egg ELISA, *in vitro* killing | X | | | | X | | | | X | | | | | | X | | X |
| Schistosomiasis PCR eggs (faeces) | | | | | | | | | | | | | X | | | | |
| Immunological assays (antibody and cellular) | X | | X[5] | | X[5] | | | | X[5] | | | | X[5] | | | | X[5] |
| Transcriptomics | X | | X | | X | | | | X | | | | X | | | | X |

2: automated CBC, ESR, creatinine, BUN, sodium, potassium, bilirubin, APT, γGT, AST, ALT, glucose
3: vaccination with Sm-p80/GLA-SE or water for injection depending on randomisation group
4: AF, γGT, AST, ALT
5: including leukocyte differentiation to normalise PBMCs

## ASSIGNMENT OF INTERVENTIONS: ALLOCATION AND BLINDING

### Group allocation

Participants will be allocated to the intervention group (vaccine) or placebo group (infection control) at random according to an independently prepared randomisation list with a 1:1 ratio, stratified per cohort. Group allocation will be defined by the randomisation number which will be linked to the subject identification code at the first immunisation. Based on this randomisation number, the pharmacist will prepare a syringe with vaccine or placebo for administration according to the list and provide this to the clinical team without disclosing contents of the syringe. The clinical team will check randomisation number and subject identification code before administering the product, unaware of its contents, therefore blinding is secured throughout the process.

### Blinding

Participants, trial investigators and primary outcome assessors will be blinded to the identity of the study groups for the whole duration of the trial (until week 24). Earlier unblinding will only occur in case of emergencies, by one of the investigators after discussion with the data safety monitoring committee (DSMB), or by the DSMB itself in case of an adverse event requiring emergency treatment.



## DATA COLLECTION AND MANAGEMENT

All data collected by the investigator will be reported in real time using electronic case report forms (eCRFs, Castoredc). At the inclusion visit participants will be issued a paper diary for symptoms. They will be asked to record signs, symptoms and medication use. These participant diaries are a tool to capture symptoms accurately. The diaries will be reviewed at every visit and used as a starting point to discuss possible AEs and/or medication use. Given the two distinct phases of this study (immunisation and CHI-S) characterised by specific signs and symptoms, we separately defined solicited AEs (**Table 3**).

**Table 3. Overview of solicited AE during immunisation and CHI-S phase**

| **Immunisation phase (week 0-12)** | | **CHI-S phase (week 12-24)** | |
|---|---|---|---|
| Local AEs: | Systemic AEs: | Local AEs: | Systemic AEs: |
| • Pruritis | • Fever | • Pruritis | • Fever |
| • Erythema | • Chills | • Rash | • Urticaria |
| • Induration/swelling | • Fatigue | | • Headache |
| • Pain | • Malaise | | • Fatigue |
| • Tenderness | • Myalgia | | • Malaise |
| | • Arthralgia | | • Arthralgia |
| | • Headache | | • Night sweats |
| | • Nausea | | • Back pain |
| | • Vomiting | | • Anorexia |
| | | | • Nausea |
| | | | • Vomiting |
| | | | • Abdominal pain |
| | | | • Diarrhoea |

Symptoms, signs, and lab abnormalities will generally be ranked as (1) mild, (2) moderate, (3) severe, or serious (4) depending on their intensity according to the following scale:

- Mild (grade 1): awareness of symptoms that are easily tolerated and do not interfere with usual daily activity;
- Moderate (grade 2): discomfort that interferes with or limits usual daily activity;
- Severe (grade 3): disabling, with subsequent inability to perform usual daily activity, resulting in absence or required bed rest;
- Serious (grade 4): requiring emergency treatment, life threatening.

For each AE its relationship to study procedures will be assessed. The investigators will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the trial intervention will be considered and investigated.

All clinical trial data, blood samples, or other participant material will be labelled with the participant study identification number. This is a unique code for each participant which does not contain any personal identifiers. When processing the data only the unique code will be used. Samples will be stored in a designated -80°C freezers and liquid nitrogen tank. Access to the rooms is restricted and door movements and temperature will be logged. Samples will be stored for at least 25 years.

## STATISTICAL METHODS

The protective efficacy of three times immunisation with Sm-p80 + GLA-SE against *Schistosoma mansoni* infection will be assessed using probabilities of CAA positivity 2-12 weeks after CHI-S for both groups, and will be calculated by [(% subjects with *Sm* in placebo group) – (% subjects with *Sm* in vaccine group)] / (% subjects with *Sm* in placebo group). The probability of CAA detectable *Sm* infection after exposure is also called attack rate (AR). As such the formula can be rewritten as 1- ($AR_{vaccine}$ / $AR_{placebo}$) or 1-[risk ratio]. We will calculate a 95% confidence interval (CI) around the risk ratio (RR) using exact methods, and use these to derive a 95%CI around the VE estimate. Next, we will use the CI for the risk ratio to calculate a p-value to test if RR ≠ 1. These efficacy parameters will be evaluated in a per protocol analysis, which only includes participants who underwent all three immunisations, were subsequently exposed to 20 male *Sm* cercariae, and have available serum CAA data following challenge (weeks 14-24).

All participants with at least one immunisation will be included in the modified intention-to-treat analysis. The safety and reactogenicity of Sm-p80 + GLA/SE is evaluated by tabulating all adverse events for each participant in an intention to treat analysis. Adverse events will be analysed by calculating the proportion of participants in each group who reported mild, moderate or severe adverse events. Statistical testing of these proportions will be performed using chi-square tests or Fisher's exact tests. Adverse events analysis will be performed on the modified intention-to-treat population.

Immunogenicity (Sm-p80 IgG antibodies) will be assessed in the modified intention-to-treat group. We will calculate the percentage of participants achieving seroconversion (fourfold increase from baseline), approximately four weeks after each immunisation. In addition, we will calculate the geometric mean titres (with 95% CI) one and four weeks after immunisation and estimate the geometric mean fold rise.

No interim analysis will be performed except for safety data review by the DSMB. We will try to limit missing data by carefully collecting the data and if data of a certain subject is missing, extensive effort will be undertaken (i.e. documented phone calls and certified mail), to still collect the data. If this is not possible and data is still missing, we will explore the pattern and reason for missingness. If we believe the data is missing completely at random, we will proceed with a complete case analysis.

## OVERSIGHT AND MONITORING

The study will be conducted in compliance with the protocol, EU Clinical Trial Regulation No 536/2014, and with the principles of good clinical practice. The study team will submit and obtain approval for substantial modifications to the original approved documents from the regulators before implementation. Data monitoring will be performed by internal monitors of the LUMC according to the monitor plan. During and after completion of the study, the data monitors will check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice. A DSMB will be appointed which will be independent of the investigators and sponsor and has no conflict of interest with the sponsor of the study. This DSMB will consist of four experienced researchers/clinicians and a statistician qualified to evaluate safety data from clinical studies with schistosome infections. Their main responsibility will be assessing safety reports or serious adverse events and advising the sponsor/investigator on trial continuation. Upon completion of the study, the results of this trial will be published in an open-access, peer-reviewed journal, regardless of the study outcome. Authorship arrangements will be made based on contribution to the trial and its report.

## DISCUSSION

This protocol aims to assess the safety, immunogenicity, and preliminary vaccine efficacy of the Sm-p80 + GLA-SE schistosomiasis vaccine in a CHI-S model among healthy, *Schistosoma*-naïve adults.

The development of a vaccine for schistosomiasis has been an important public health target for many years and several candidates are now in clinical testing. Controlled human infections can accelerate vaccine development through preliminary assessment of vaccine efficacy in a small group of participants (5). Previously, a controlled human infection model with schistosomes was successfully established that uses male-only infections to avoid egg-associated morbidity in study participants. A female-only CHI-S model was established with similar infectivity and tolerability, however the unexpectedly decreased susceptibility of female-only infections to praziquantel treatment limits its further use. This study compliments ongoing phase I studies of Sm-p80: in addition to preliminary efficacy data, this well-defined longitudinal sample set allows for in-depth exploration of host-pathogen interactions in vaccinated participants.

Risks for participants are related to potential side effects of the vaccine and exposure to cercariae. Based on the phase I study results, the vaccine is well-tolerated and did not result in any serious adverse events (data not published). After exposure to cercariae, nearly all develop cercarial dermatitis at the site of infection, that is expected to resolve without intervention and generally does not require symptomatic treatment. In case of severe itching, triamcinolone cream can be applied. Symptoms related to acute schistosomiasis infection are likely to occur in a subgroup of participants, starting four weeks after exposure. Previously, 6 out of 35 participants developed severe AEs suggestive of acute schistosomiasis after exposure to 20 male cercariae, which responded well to treatment with paracetamol, NSAIDs, and/or prednisolone (6). To ensure early detection and treatment, participants will be under intense follow-up. To avoid chronic infection, all participants in the study will be treated with praziquantel, which may be repeated if needed. Prior CHI-S with male schistosomes have shown that all participants can be cured using praziquantel.

It is important to note that this study will be conducted in *Schistosoma-naïve* participants from a non-endemic setting. However *Schistosoma* vaccine responses might be different in endemic settings, as seen with Ebola, BCG, and malaria, among others (9). In light of vaccine development, it is therefore especially informative to perform CHI-S studies in an endemic population, who are ultimately the target population for the vaccine. This protocol is part of a larger programme that seeks to establish a CHI-S in Uganda (10, 11) and as such study procedures are harmonised to allow comparisons between study populations in the future.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AEs | Adverse events |
| AR | Attack rate |
| CAA | Circulating anodic antigen |
| CHI-S | Controlled human infection with schistosomes |
| CI | Confidence interval |
| DSMB | Data safety monitoring board |
| eCRF | Electronic case report forms |
| GLA-SE | Glucopyranosyl Lipid Adjuvant in stable emulsion |
| LUMC | Leiden University Medical Center |
| RR | Risk ratio |
| SIS | Subject information sheet |
| *Sm* | *Schistsosoma mansoni* |
| Sm-p80 | *S. mansoni* calpain protein [of ~80 kDa] |
| VE | Vaccine efficacy |

## DECLARATIONS

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**Authors' contributions**

MR, AE, AS conceived the study. JK, EH, ED, ME, JJ, EW, AS, AE, MR contributed to study design and JS, GD, PC, LvL, DC, SG, MY, AvD, CH, AA helped with implementation. JK and MR drafted the manuscript.

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**Availability of data and materials**

After publication, all data will undergo FAIRification and will be made available anonymised through a LUMC-based fair data point which will be made accessible through data visiting.



**Ethics approval and consent to participate**

The study will be conducted in accordance with the ICH guidelines for Good Clinical Practice and Declaration of Helsinki. Ethics approval is under review at the Central Committee on Research Involving Human Subjects (no. 2023-509816-27-00).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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