TITLE: FOOD AND DRUGS AUTHORITY PUBLIC ASSESSMENT REPORT

PART 1: Administrative Details	
Full Study Title	Severe Malaria A Research and Trials consortium - Multisite Adaptive Platform trial: Renal function domain
Protocol/ Document Number	1. Master Protocol version 1.3 dated 5th June 2024 2. SMART-MAP Renal Function Domain Protocol version 1.4 dated 25th November 2024
Date of Receipt of the Application	25th March 2024
Phase of Study	Phase II
Study Registration Details	PACTR202312551082722 Clinical trial approval certificate no. FDA/CT/2417c
Name and Address of Applicant(s)	Prof. Daniel Ansong Department of Child Health Komfo Anokye Teaching Hospital P.O Box 1934 Kumasi Tel: +233 20 816 8767 E-mail: ansongd@yahoo.com
Name and Address of Sponsor(s)	Imperial College of London Room 1030 Level 10 St Mary's Campus Norfolk Palace London W2 IPG Telephone Number: 02075941872 Email: r.nicholson@imperial.ac.uk
Name and Address of Principal Investigator(s)	Prof. Daniel Ansong Department of Child Health Komfo Anokye Teaching Hospital P.O Box 1934 Kumasi Tel: +233 20 816 8767 E-mail: ansongd@yahoo.com
Study Sites	1. Komfo Anokye Teaching Hospital 2. Maternal and Child Health Clinic, Asokwa Children Hospital
Study Duration	24 Months
FAPAR Number	FDA/CT/PAR/CTA/254

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	Para-Denk 125 (Paracetamol) High dose paracetamol (15mg/kg every 6 hours for 66 hours (last dose), given rectally, orally or via a nasogastric tube) compared to no or minimal paracetamol for fever reduction only (10mg/kg no more frequently than every 8 hours) (control)
Justification of Investigational Product(s) including comparators	Children with severe malaria and poor kidney function are at higher risk of worse outcomes (including death and prolonged stay in hospital). There has been some initial research showing that paracetamol may have some benefits for treating poor kidney function and it is a safe and low-cost pill. Two small studies are looking at its use in severe malaria at individual hospitals but this study plans to include children from across several hospitals and countries. Children will be given regular doses of paracetamol (which is currently used to control fever) at a slightly higher dose than usual for three days to see if their kidney function improves.

PART 3: Study Summary

Study Objectives

The objective of the SMAART-MAP trial is to identify promising adjunctive therapies to take forward into a large Phase III trial in severe malaria with a mortality endpoint. The adaptive platform design enables additional domains to be added so a range of adjunctive therapies can be tested, across multiple clinical presentations of severe malaria, in a timely manner.

The objectives for the renal function domain are as follows:

Primary Objectives

The primary objective of the study is to test whether regularly dosed paracetamol given over 66 hours (corresponding to 72 hours exposure) will reduce levels of creatinine in children at high risk of renal impairment compared to standard of care; thus determining if paracetamol can reduce the evolution of kidney injury in severe malaria.

Secondary Objectives

The secondary objectives are to assess the impact of regularly dosed paracetamol during admission in children with elevated creatinine and severe malaria on:

- mortality and readmission by 90 days
- markers of liver function (AST and ALT)

PART 3: Study Summary

- on Grade 3 or 4 adverse events, and adverse events of any grade related to paracetamol

An additional objective is, where it is possible, to store urine in order to assess other markers of kidney function, such as the urine albumin creatinine ratio at 72 hours.

Study Design

This study is a parallel arm multi-site, open-label Phase II trial. Eligible participants will be randomized into either the high dose paracetamol arm or the no/minimal paracetamol arm. For the renal domain, eligible participants will undergo 1:1 randomisation using randomised permuted blocks, stratified by site and presence of blackwater fever. 150 children are planned to be recruited, with 75 children per arm.

All trial patients will receive standard of care including antibiotics (IV or oral) and anti-malarial drugs following national guidelines, based on WHO syndromic patient management (World Health Organisation 2013). All children enrolled in the trial should remain admitted to the ward until after the 72 hour clinical assessment and tests have been conducted wherever possible.

Children randomised to the high dose paracetamol arm willreceive 15mg/kg paracetamol every 6 hours for 66 hours (i.e. giving 72 hours exposure) given orally or via nasogastric tube. If this is difficult due to the clinical status of the child and/or local practice, then sites can give rectal doses where this formulation is available.

Children randomised to no/minimal paracetamol arm will not receive regularly dosed paracetamol. Paracetamol may be given to children at standard doses for fever control.

For assessments & follow-up, Children will be intensively monitored on the day of admission by the clinical team, and then reviewed daily by the study team until discharge. All participants will be seen at 4 weeks (28 days) and 3 months (90 days) from the date of randomisation, at outpatient clinics attached to each centre for evaluation of morbidity, and toxicity. During the 90 day study period, if a child does not attend a scheduled visit, then attempts would be made to contact the parents or guardians via phone (if available) and to follow-up with home visits, if at all possible.

Eligibility Criteria

The Inclusion criteria for the renal domain are as follows;

1. Aged >3 months and <12 years
2. Admitted to the paediatric ward in the last 24 hours at screening
3. Current or recent evidence of malaria (slide or RDT positive in this admission)
4. Guardian willing to provide consent
5. Creatinine > 1.5 x ULN on a point-of-care assay (or laboratory test) at screening
6. Meet one of the current WHO severity criteria (clinical or laboratory (where these tests are done routinely)) (Group 1 and 2 from the recent reclassification of severe malaria)

PART 3: Study Summary

The Exclusion criteria for the renal domain are as follows.

1. Enrolment into the SMAART-MAP trial on a previous admission
2. Received paracetamol within 6 hours of screening or between screening and randomisation.
3. Known allergy to paracetamol.
4. Severe malnutrition (MUAC<11.5cm or weight-for-length score <-3 for children <6 months old).
5. Known history of hepatic or renal impairment

Date of Commencement (Expected or Actual)

13th January 2025 (Expected)

Status of Study

The Authority is yet to be informed of the official commencement of the study.

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The quality of the Investigational product was assessed by the FDA. The applicant submitted the following documents which were reviewed and found satisfactory to fulfil the quality requirements for the trial:

- Ghana FDA Certificate of Registration of Para-Denk 125 suppository
- Package leaflet for Para-Denk 125 suppository
- Certificate of GMP Compliance of the manufacturer of the Investigational Product, RubiePharm Arzneimittel GmbH

Safety

With respect to safety in the renal domain, Liver function will be assessed at 72 hours using AST and ALT. The paediatric RIFLE score will also be calculated from information recorded at 24, 48 and 72 hours. AEs judged by the investigator as being related to paracetamol (any grade) would be recorded on the appropriate CRF, in addition to safety reporting applicable to all domains (grade 3/4 AEs and SAEs, see Master protocol).

The following documents were reviewed and found satisfactory to fulfil the safety requirement of the trial:

- Ghana FDA Certificate of Registration of Para-Denk 125 suppository
- Package leaflet for Para-Denk 125 suppository

Efficacy

With regards to efficacy, paracetamol is potentially a promising treatment, which attenuates nephrotoxicity of haemoproteins, red-cell free haemoglobin and myoglobin in sepsis

PART 4: Scientific Discussion

(Boutaud, Moore et al. 2010). Pilot and dose finding Phase I studies are being undertaken in Mbale, eastern Uganda (ISRCTN 84974248) in children with haemoglobinurea and elevated creatinine, and in Kinshasa, Democratic Republic of Congo (DRC) (NCT04251351) in children with fever and elevated creatinine. However, there is the need to evaluate paracetamol in the wider population with severe malaria to understand further the potential for early benefit of paracetamol (a widely available and cheap intervention) in children with elevated creatinine indicating possible renal impairment.

In assessing efficacy in this study; Creatinine will be assayed retrospectively on stored plasma samples taken at baseline, 24, 48 and 72 hours from randomisation. These measures will be used to calculate the area under the curve for creatinine levels.

Overall comments

After the initial review, the application was deferred, pending responses to specific queries raised. Once the queries were addressed, the study received approval, and a clinical trial certificate was issued.

An assessment of the medical and ethical principles indicates that the anticipated benefits to participants justify the potential risks and inconveniences associated with the study's conduct.

PART 5: Application Review Process

The application was submitted through the African Vaccine Regulatory Forum (AVAREF) platform. The application was reviewed within 8 working days.

PART 6: Status after Review

The application was approved on 27th December 2024. The PI is yet to communicate to the FDA the official date of commencement of the study.

References

1. SMAART-MAP Master Protocol version 1.3 dated 5th June 2024
2. SMAART-MAP Renal function Domain Protocol version 1.4 dated 25th November 2024
3. Completed FDA Application Form for Conducting Clinical Trials Application – SMAART MAP trial
4. Completed FDA Application form for Clinical Trial Application signed on 27th August 2024
5. Pan African Clinical Trials Registry, PACTR202312551082722– SMAART MAP Trial
6. ICH E6(R2) guideline for good clinical practice dated 9 November 2016.
7. ICH E2A guideline for clinical safety data management: definitions and standards for expedited reporting dated 27 October 1994.
8. ICH E8 general considerations for clinical trials dated 17 July 1997
9. ICH E9 statistical principles for clinical trials dated 05 February 1998
10. ICH E10 choice of control and related issues in clinical trials dated 20 July 2000
11. ICH E17 general principles for planning and design of multi-regional clinical trials