

Phase I safety and dose-finding trial of sevuparin in children with severe malaria

Submission date 13/07/2021	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 28/07/2021	Overall study status Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 10/03/2025	Condition category Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

Malaria is a serious tropical disease caused by parasites spread by mosquitoes. Even on the best antimalarial treatments (injectable artesunate) many African children with severe malaria have poor outcomes with most deaths occurring early in the course of hospital admission. In severe malaria the red blood cells that are infected with malaria parasites stick to the very deep parts of the blood vessels. This occurs throughout the body and the blood flow to tissues is poor, which leads to a build-up of body acids (called lactate). Up to the present there have been no treatments available to prevent or reverse stop red cells sticking to the blood vessels when they have malaria parasites in them.

A new drug candidate called sevuparin has been identified and safely tested in adults with malaria in Thailand. Sevuparin acts by preventing malaria parasites from getting into red cells in the first place (this means that the malaria parasite cannot survive). It also prevents red cells infected with malaria parasites from sticking to the blood vessels, and is also able to 'unstick' red cells with infected with malaria parasites that are already sticking to the blood vessel and causing poor blood flow.

Given its potential, a large group of specialist doctors in severe malaria research and clinical trials have suggested that sevuparin should be tested in children with severe malaria. They have all helped to design this study, which will be conducted in the high-dependency ward in Kilifi, Kenya.

The aim of this study is to find the best dose of sevuparin to give as a supportive treatment alongside the usual antimalarial treatments in children hospitalised with severe malaria.

Who can participate?

Children aged 3 months to 12 years presenting to Kilifi County Hospital with severe malaria

What does the study involve?

Sevuparin will be given on the first day of admission as three infusions at study enrolment (0 hours), and 8 and 16 hours after this. All other treatments for severe malaria will follow the usual guidelines. The first participants will receive a dose of 1.5 mg/kg/dose with a plan to escalate to higher doses of 3 mg/kg/dose and 6.0 mg/kg/dose. All children will have regular monitoring during the period of admission to the high dependency ward and twice daily thereafter until discharge and will be followed up to day 28. Routine blood tests will be done at

admission, 8 and 24 hours and at follow up. Additional samples will be taken to check clotting at 0 hours, 1 hour after sevuparin infusion (i.e. 1, 9 and 17 hours) and lactate (the body acid that builds up in severe malaria) will be checked regularly at admission, 4, 8, 16 and 24 hours.

What are the possible benefits and risks of participating?

Participants may benefit from close monitoring during admission and follow up to day 28 after discharge. The hospital bills for participants older than 5 years will be covered by the study (covering the costs for standard treatment for severe malaria and related complications). The study aims to improve the outcome from severe malaria. It will generate data to support a future larger phase II trial with the aim of improving the treatment of a vulnerable population of children and improving outcomes.

One potential risk of sevuparin, as it is a heparin-like drug, is that it increases one of the blood clotting markers. This was seen in the study in Thailand but was short-lived (i.e. only happened for a few hours) and did not cause any side effects. The researchers are carefully monitoring this blood clotting marker and this will help them to make decisions about whether the child receives the next dose, and as they are using a continuous reassessment method to monitor toxicity this will inform the dosages for the children enrolled in the trial.

Where is the study run from?

KEMRI Wellcome Trust Programme, Kilifi (Kenya)

When is the study starting and how long is it expected to run for?

February 2019 to June 2025

Who is funding the study?

Wellcome Trust (UK)

Who is the main contact?

Kathryn Maitland

k.maitland@imperial.ac.uk

Contact information

Type(s)

Public

Contact name

Mr Emmanuel Oguda

Contact details

KEMRI Wellcome Trust Research Programme

PO Box 230

Kilifi

Kenya

-

+254 (0)731289430

EOguda@kemri-wellcome.org

Type(s)

Scientific

Contact name

Prof Kathryn Maitland

ORCID ID

<http://orcid.org/0000-0002-0007-0645>

Contact details

Wellcome Centre for Clinical Tropical Medicine
London
United Kingdom
W2 1PG
+44 (0)7543721710
k.maitland@imperial.ac.uk

Additional identifiers**EudraCT/CTIS number**

Nil known

IRAS number**ClinicalTrials.gov number**

Nil known

Secondary identifying numbers

PACTR 02007890194806, 18IC4513, KEMRI/SERU/CGMR-C/127/3744, P71159, 209265/Z/17/Z

Study information**Scientific Title**

Sevuparin as a potential adjunctive therapy in children with severe malaria: Phase I safety and dose-finding trial

Acronym

SEVUSMART

Study objectives

Sevuparin given in addition to antimalarial treatment early in the course of admission (<24 hours) blocks merozoite invasion, prevents cytoadherence and transiently de-sequesters infected erythrocytes (which cause microcirculatory impairment) and could thus result in improvements in outcomes from severe malaria for the subgroups at greatest risk and during the period of greatest risk (first day of hospitalisation).

Ethics approval required

Old ethics approval format

Ethics approval(s)

1. Approved 18/02/2019, KEMRI Scientific and Ethics Review Unit (KEMRI PO Box 54840-00200, Nairobi, Kenya +254 (0)72220590; director@kemri.org), ref C/127/3744
2. Approved 13/07/2021, Imperial College Research Ethics Committee (Room 221, Medical

School Building, St Mary's Campus, Norfolk Place, London, W2 1PG, UK; +44 (0)2075941872; researchethicscommittee@imperial.ac.uk), ref: 18IC4513

3. Approved 24/07/2023, National Health Research Ethics Board (Paediatric Centre of Excellence, University Teaching Hospital, P.O. Box 30075, Lusaka, Zambia; no telephone; no email), ref NHREB001/24/07/2023

Study design

Phase I safety and dose-finding trial

Primary study design

Interventional

Secondary study design

Non randomised study

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

See study outputs table

Health condition(s) or problem(s) studied

Severe malaria

Interventions

Sevuparin is given as three infusions at 0, 8 and 16 hours after enrolment. Initially two cohorts of two participants will receive a dose of 1.5 mg/kg/dose with the plan to escalate to a cohort of two participants receiving 3 mg/kg/dose and a cohort of two participants receiving a 6.0 mg/kg /dose. Using the CRM each subsequent patient would then be assigned the largest dose between 1.5 and 6.0 mg/kg/dose (maximum) with an estimated risk of toxicity below the target toxicity level, designated as the maximum tolerated dose (MTD).

Intervention Type

Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)

Sevuparin

Primary outcome measure

Activated partial thromboplastin time (APTT) >2.5x upper limit of normal (ULN) (Common Toxicity Criteria grade 3), measured by the Sysmex semi-automated blood coagulation analyzer (CA-104), at 1 hour post any sevuparin dose

Secondary outcome measures

Efficacy:

1. Change in lactate measured by Stat Strip Xpress Hospital meter from 0 to 8 hours
2. Macroscopic presence of mature infected erythrocytes on the blood films at 8 and 24 hours
3. Parasite clearance time measured by microscopy during hospital admission
4. Change in sublingual microcirculation measured using Braedius cytocam for microcirculation at 0, 9 and 17 hours

Safety:

1. APTT (absolute level and grade) measured using the Sysmex semi-automated blood coagulation analyzer (CA-104) at 24 hours post enrolment
2. Development of abnormalities of coagulation indices of grade 2 and above measured using the Sysmex semi-automated blood coagulation analyzer (CA-104) at 0,1, 9, 17 and 24 hours
3. Neurological sequelae assessed by the Kilifi Developmental Index until day 28
4. Mortality measured using clinical assessment until day 28
5. Serious adverse events (mortality, readmissions and prolongation of admission) measured by clinical observation recorded on the case report forms until day 28
6. Grade 3/4 adverse events measured by clinical observation recorded on the case report forms until day 28

Overall study start date

18/02/2019

Completion date

30/06/2025

Eligibility

Key inclusion criteria

1. Aged between 3 months and 12 years admitted to the paediatric wards within the last 24 hours
2. Current or recent evidence of *P. falciparum* malaria (slide or rapid diagnostic test (RDT) positive)
3. Clinical evidence of severe malaria: impaired consciousness: coma (inability to localize painful stimulus) or prostration (inability to sit unsupported for those above 6 months) or deep breathing
4. Lactate >2 mmol/l
5. Guardian or parent willing and able to provide consent

Participant type(s)

Patient

Age group

Child

Lower age limit

3 Months

Upper age limit

12 Years

Sex

Both

Target number of participants

20

Total final enrolment

20

Key exclusion criteria

1. Clinical evidence or a history of a bleeding/coagulation disorder
2. A comorbidity which clinician believes has a significant risk of poor outcome e.g. malignancy, end-stage renal failure, major cardiac condition
3. Thrombocytopenia (platelet count $<25 \times 10^9/l$)

Date of first enrolment

01/10/2021

Date of final enrolment

07/03/2025

Locations

Countries of recruitment

Kenya

Zambia

Study participating centre

Kilifi County Hospital

Hospital Road

Kilifi

Kenya

PO Box 230

Study participating centre

Nchelenge Hospital

PO Box 71769

Nchelenge

Zambia

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Sponsor information

Organisation

Imperial College London

Sponsor details

Joint Research Office

Room 221

Medical School Building

St Mary's Campus

Norfolk Place

London

England

United Kingdom

W2 1PG

+44 (0)20 7594 1872

researchethicscommittee@imperial.ac.uk

Sponsor type

University/education

Website

<http://www.imperial.ac.uk/>

ROR

<https://ror.org/041kmwe10>

Funder(s)**Funder type**

Research organisation

Funder Name

Wellcome Trust

Alternative Name(s)

Wellcome, WT

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal

Intention to publish date

01/12/2025

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date. The key contact person regarding data requests is Elizabeth C George, MRC Clinical Trials Unit at University College, London (elizabeth.george@ucl.ac.uk).

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.1	03/10/2018	28/07/2021	No	Yes
Protocol file	version v1.3	02/09/2020	28/07/2021	No	No
Statistical Analysis Plan	version v0.2		28/07/2021	No	No
Protocol file	version 2.1	28/02/2023	03/08/2023	No	No
Protocol article		12/08/2024	02/09/2024	Yes	No