ISRCTN32271864 https://doi.org/10.1186/ISRCTN32271864

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

Submission date
13/07/2021

Recruitment status
No longer recruiting

Registration date
28/07/2021

Overall study status
Completed

Last Edited
10/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] 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?
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Contact information

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Public

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Additional identifiers

Protocol serial number
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

Primary study design
Interventional

Study design
Phase I safety and dose-finding trial

Study type(s)
Treatment

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(s)
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

Key secondary outcome(s)
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

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

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 Months

Upper age limit
12 Years

Sex
All

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 x10(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

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

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?
Protocol article		12/08/2024	02/09/2024	Yes	No
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
Protocol file	version 2.1	28/02/2023	03/08/2023	No	No
Statistical Analysis Plan	version v0.2		28/07/2021	No	No