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A study to test the safety of a new melatonin treatment for babies with brain injury receiving cooling therapy

Submission date
07/02/2025

Recruitment status
Recruiting

Registration date
14/04/2025

Overall study status
Ongoing

Last Edited
27/08/2025

Condition category
Neonatal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The ACUMEN trial is a research study aimed at improving treatments for newborn babies with a condition called hypoxic-ischemic encephalopathy (HIE). HIE is a type of brain injury that occurs when a baby does not receive enough oxygen and blood flow around the time of birth. While cooling therapy (therapeutic hypothermia) is currently the standard treatment, many babies still experience long-term challenges, including developmental delays and learning difficulties. This study will test the safety and potential benefits of a drug called melatonin. Melatonin, a naturally occurring hormone, has shown promise in protecting brain cells in preclinical studies. The drug will be tested in its intravenous (IV) form to see if it can reach effective levels in the blood safely and tolerably for newborns.

Who can participate?
Babies with HIE who have been admitted to NICU

What does the study involve?
Participants will receive the drug alongside standard cooling therapy. The study drug will be given as an IV infusion over six doses (one loading and five maintenance doses) over a 72-hour period. Babies will be closely monitored during their hospital stay to ensure their safety and evaluate the drug's effects. Blood samples (for melatonin, ethanol and biomarker analysis), MRI /MRS brain imaging, and brain activity monitoring will help researchers understand how the drug works and its impact.

What are the possible benefits and risks of participating?
Results from this trial will inform whether this formulation of melatonin could be used in future trials to improve outcomes for babies with HIE. By taking part in the ACUMEN study, participants will receive a potential new therapy (melatonin) to help protect their brain. The lowest dose we give has been shown to have some benefit in a small group of babies. Babies will be cared for with the highest level of neonatal care, including continuous brain wave monitoring and expert analysis of any seizures that occur. Additionally, they will be closely monitored for brain oxygen levels and blood flow, which will help improve their breathing support. This level of monitoring

may not yet be the standard of care in all hospitals. Babies in the ACUMEN study may receive more detailed monitoring, which can help identify health problems earlier than in some other units.
The IMP, melatonin in ethanol excipient, has demonstrated safety in preclinical studies.
Potential risks and mitigations include:
1. Allergic or Immune Reactions: Preclinical data suggest these are unlikely. Participants will remain under close observation in the neonatal intensive care unit (NICU) during dosing, and medical staff will provide immediate treatment if required.
2.; Blood Alcohol Concentration (BAC): Monitoring BAC at six time intervals will mitigate risks of ethanol being above the EMA recommendations from the ethanol excipient, particularly during the initial loading dose.
3. Hypotension: monitored using invasive blood pressure measurements. Inotropic support will be available if needed.
4. Extravasation Injury: Central venous catheters will be used when possible. For peripheral cannulas, infusion sites will be monitored, and Visual Infusion Phlebitis (VIP) scores will be recorded.
Study Procedures:
1. Blood Sampling: Necessary for pharmacokinetic (PK) and exploratory biomarker analysis, these will remain within EMA-recommended limits. Sampling for exploratory biomarker analysis will cease if haemoglobin levels fall below the transfusion threshold.
2. aEEG/EEG Monitoring: Procedures will be performed by highly trained staff using non-invasive gel probes to maximise comfort.
3. MRI/MRS Imaging: Non-invasive scans may cause mild discomfort due to noise. MRI-compatible incubators and standardised protocols will reduce potential stress.
4. Modified Sarnat Neurological Assessments: Conducted to evaluate the severity of hypoxic-ischaemic encephalopathy (HIE). Staff are trained using standardised pathways to minimise distress.
Sample Stability and Loss:
1. Blood samples may be lost, unstable, or delayed during shipment. Mitigations include:
2. A laboratory management plan with explicit instructions on sample handling.
3. Stability testing to confirm melatonin and ethanol remain stable during transit.
4. Clear shipping protocols to maintain sample integrity.
5. Site training during initiation visits to ensure standardised sample handling.
Standard of Care (SoC):
The study will not replace or withhold standard care treatments. Monitoring (e.g., aEEG/EEG, NIRS) will complement existing protocols for cooling therapy and provide local teams with enhanced tools to manage critically unwell infants effectively.

Where is the study run from?
The Comprehensive Clinical Trials Unit at University College London (UK)

When is the study starting and how long is it expected to run for?
February 2025 to March 2027

Who is funding the study?
Medical Research Council (MRC) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1011409

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CTU/2020/348, CPMS 68402

Study information

Scientific Title
Phase I dose escalation and cohort expansion study to affirm the safety of pharmacological doses of a novel formulation of intravenous melatonin in babies with hypoxic-ischaemic encephalopathy (HIE) to augment therapeutic hypothermia (HT) treatment; to reduce the incidence and severity of disability in babies with moderate-severe HIE

Acronym
ACUMEN

Study objectives
Primary objectives:
1. Safety profile assessment: to assess the safety profile of melatonin across all dose levels being studied based on the occurrence of dose-limiting events (DLE).
2. The attainment of putative therapeutic plasma melatonin levels (in the range of 15-30 mg/L) across dose levels being studied.
3. The attainment of putative ethanol safety (BAC levels <0.25 g/L) across dose levels being studied.
4. To identify the recommended Phase II dose (RP2D).

Secondary objectives:
1. Pharmacokinetic (PK) model: to establish the pharmacokinetic (PK) profile of intravenous melatonin infusion in term infants with moderate to severe hypoxic-ischemic encephalopathy (HIE) undergoing therapeutic hypothermia (HT).
2. Feasibility of neonatal neuroprotection trial network: to assess the feasibility of developing a neonatal neuroprotection trial network for future Phase II randomised controlled trials (RCTs) that will evaluate efficacy.
3. Recruitment feasibility: to assess the feasibility of recruiting participants within 6 hours of birth.

Ethics approval required
Ethics approval required

Ethics approval(s)
notYetSubmitted, ref: 25/LO/0170

Study design
Open-label non-randomized study

Primary study design
Interventional

Study type(s)
Safety

Health condition(s) or problem(s) studied
Moderate to severe hypoxic-ischaemic encephalopathy (HIE) in newborn infants

Interventions
The intervention is a novel formulation of melatonin in ethanol 50 mg/ml solution for infusion administered to newborn babies with moderate-severe HIE to augment therapeutic hypothermia (HT). HT will be started in eligible babies according to local guidelines as soon as possible after birth. Administration of IMP will be provided over 6 infusions:
A loading dose administered over 2 hours within 6 hours of birth
5 x maintenance doses every 12h from 24h after initiation of loading dose (administered over 2 hours)

ACUMEN is an open-label, non-randomized study, meaning all enrolled participants receive IMP in addition to standard therapeutic hypothermia.

The dose levels to be considered as part of this trial are outlined in the table below. Dose Level 1 and Dose Level 2 will be investigated as fixed starting points of the dose-escalation phase. From Dose Level 3 onwards, dose levels may be skipped based on accumulating safety data and population pharmacokinetic (POP-PK) modelling. In total, it is anticipated that 4 dose levels will be explored during the dose-escalation part of the study.
Loading doses:
Dose Level 1: 5 mg/kg
Dose Level 2: 10 mg/kg
Dose Level 3: 15 mg/kg
Dose Level 4: 20 mg/kg
Dose Level 5: 25 mg/kg
Dose Level 6: 30 mg/kg
Dose Level 7: 35 mg/kg
Dose Level 8: 40 mg/kg

The ACUMEN study consists of two phases:

Dose Escalation Phase:
Multiple cohorts of neonates will receive different dose levels of IMP. There are eight predefined dose levels, but only four will be investigated based on accumulating safety data and pharmacokinetic (PK) modelling.

Cohort Expansion Phase:
Once an optimal dose level is identified, a larger cohort will receive this dose to determine the recommended Phase II dose (RP2D).

Participants will be followed up for 3 months as part of the ACUMEN trial.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Melatonin

Primary outcome(s)
The overall aim of the study is to identify the Recommended Phase II Dose (RP2D) based on the totality of data and outcomes are listed below.

The primary outcomes are:
1. Safety: the safety profile of melatonin across dose levels being studied assessed based on the occurrence of dose-limiting events (DLE): DLEs will be evaluated continuously from the time of first administration of the IMP (T0) until 96 hours post-T0 (T+96 hours). T0 is defined as the time of the first loading dose administration, which must occur within the first six hours of birth.
2. The attainment of putative therapeutic plasma melatonin levels (in the range of 15-30 mg/L) across dose levels being studied: plasma melatonin levels will be evaluated at predefined

timepoints during the dosing period up to T+96 hours, with T0 as the starting point.
3. The attainment of putative ethanol safety (BAC levels <0.25 g/L across dose levels being studied: blood alcohol concentration will be monitored and evaluated at predefined intervals during the dosing period, up to T+96 hours from the initial loading dose (T0).

Key secondary outcome(s))
1. Pharmacokinetic Model (PK):
1.1. Estimation of population PK parameters of melatonin in the target population.
1.2. Estimation of population PK parameters of ethanol in the target population.
PK parameters for melatonin and ethanol will be evaluated using blood samples collected at predefined intervals up to the 96-hour time point (T+96 hours, with T0 being the first dose administered within 6 hours of birth)
2. Establishing a Neonatal Neuroprotection Trial Network in anticipation of a Phase II RCT:
2.1. Successful harmonisation of 3T MRI scanners and acquisition of magnetic resonance spectroscopy (MRS) at days 4 to 10:
2.1.1. Evaluation of pattern and severity of injury using T1/T2 MRI and diffusion-weighted imaging (DWI).
2.1.2. Assessment of HIE severity through baseline lactate/N-acetylaspartate (NAA) statistics to inform the sample size calculation of the Phase II trial.
2.2. Successful (in >90% of enrolled babies) integration and standardising of amplitude-integrated electroencephalography aEEG/EEG monitoring throughout the cooling and rewarming periods at all centres, using recovery of background activity as a proxy for outcome (a more rapid recovery of background voltage is associated with a favourable outcome). aEEG/EEG monitoring will be continuous throughout cooling (0–72 hours) and rewarming (72–96 hours).
2.3. Successful (>90% of enrolled babies) integration of continuous cerebral near-infrared spectroscopy (NIRS) as part of the neurocritical care management for infants with HIE. NIRS data will be collected continuously throughout the same timeframe.
2.4. Successful collection (>90% of enrolled babies) of early surrogate measures of neurodevelopmental outcomes (Hammersmith Infant Neurological Examination (HINE) at 3 months, Hammersmith Neonatal Neurological Examinations (HNNE) at hospital discharge, General Movement Assessment (GMA) at 3 months and ASQ-3).
3. Recruitment:
3.1. Metrics on the acceptability of the study among potential participants' parent/legal guardian (s)
3.2. Rates of informed consent obtained within the 6-hour timeframe
3.3. Timelines and initiation of the first dose administration within the specified 6-hour window
Recruitment and consent metrics will be assessed throughout the recruitment phase (from start to completion of participant enrolment)

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Baby admitted to the Neonatal Intensive Care Unit (NICU) with moderate-severe hypoxic-ischaemic encephalopathy (HIE) meeting eligibility criteria for therapeutic hypothermia (HT) (in accordance with local guidelines) and:
1.1. Born at ≥36 completed weeks gestation
1.2. Clinically stable* at the time of IMP administration
1.3. Invasive blood pressure monitoring in situ prior the administration of the IMP loading dose

2. All participants will undergo a further assessment of HIE grade as determined by amplitude-integrated EEG (aEEG)/EEG and/or a Modified Sarnat neurological examination prior to IMP administration
2.1. Sentinel Participant Criteria Only: must not meet the criteria for severe HIE
3. Informed consent from parents/guardians/person with legal responsibility

*Definition of Clinical Stability:
Eligibility of the participant must be rechecked prior to administration of the IMP given the varying clinical status of these infants. Stability will take the following into consideration:
1. Well placed central venous catheter or patent peripheral cannula in situ
2. Mean blood pressure (with or without inotropic support) must be greater than the 5th centile for gestation (see BP centile charts in Appendix 3) within 30 mins prior to IMP administration
3. Clinical or electrical seizures, if present, controlled with anti-seizure medications
4. Clinical observations within acceptable range for an infant undergoing therapeutic hypothermia
5. No clinical stability concerns from the attending neonatologist

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Sex
All

Key exclusion criteria
1. Baby would be >6 hours of age when IMP administered
2. Initiation of IMP unlikely to be administered within 6 hours of birth
3. Infants born in very poor condition or judged too sick to be included (high risk of mortality) in an experimental first in human study, for example infants that are requiring maximal intensive care therapy or in a condition considered to be life-limiting.
4. Postnatal hypoxic insult without any evidence of HIE at birth.
5. Birth weight less than 2nd centile for gestation on UK-WHO growth charts#
6. Congenital anomalies i.e. any major antenatal diagnosed congenital abnormalities such as congenital heart disease, suspected or known chromosomal abnormalities
7. Head circumference less than 2nd centile adjusted to sex of the baby on UK-WHO growth charts#
8. Infant is participating or intends to participate in another interventional study during the birth hospitalisation (note: does not include observational studies)
9. Parents/legal guardians unable to give consent due to learning or other difficulties

Please note that in the event of multiple births:
1. If one baby has HIE, participation in the trial will be offered
2. If both/multiple babies have HIE, participation in the trial will not be offered

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https://www.rcpch.ac.uk/sites/default/files

/Boys_neonatal_and_infant_close_monitoring_growth_chart.pdf
https://www.rcpch.ac.uk/sites/default/files
/Girls_neonatal_and_infant_close_monitoring_growth_chart.pdf

Date of first enrolment
30/04/2025

Date of final enrolment
30/11/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Australia

Ireland

Study participating centre
Uclh
250 Euston Road
London
United Kingdom
NW1 2PQ

Study participating centre
The Royal London Hospital
The Royal London Hospital
Alexandra House
London
United Kingdom
E1 1BB

Study participating centre
St Mary's Hospital
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
Liverpool Womens Hospital
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Cork Maternity Hospital
Wilton Road
Wilton
Cork
Ireland
T12 YE02

Study participating centre
Coombe Hospital
Cork St
Saint James
Dublin
Ireland
D08 XW7X

Study participating centre
Rotunda Hospital
Parnell Square E
Rotunda
Dublin
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D01 P5W9

Study participating centre
Flinders Medical Centre
Flinders Dr
Bedford Park
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SA 5042

Study participating centre
Monash Children's Hospital
246 Clayton Rd
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Australia
VIC 3168

Sponsor information

Organisation
The Comprehensive Clinical Trials Unit at University College London

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council Developmental Pathway Funding Scheme (UKRI MRC DPFS)

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

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		22/08/2025	27/08/2025	Yes	No
	Participant information sheet				

Participant information sheet	11/11/2025	11/11/2025	No	Yes