ACUMEN: Acute High Dose Melatonin for Encephalopathy of the Newborn

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Study Design

ACUMEN is a 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.

ACUMEN is not a randomised controlled trial. Every baby recruited will receive the study drug at varying dose levels.

The study drug in a Phase I study is called an IMP (Investigational Medicinal Product). In this case it is a formulation of melatonin and ethanol. While melatonin and ethanol have both been used previously in adults and children, this is the first time these have been given in combination in newborn babies. As such this study is classified as a 'First In Humans (FIH) study.

A total of 60 patients will be recruited across the UK, Ireland and Australia

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:

- Born at ≥36 completed weeks gestation
- Clinically stable* at the time of IMP administration
- Invasive blood pressure monitoring in situ prior to 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 (at least 10 minutes pre-recruitment and 30mins pre-administration of IMP)
  and/or
- Modified Sarnat neurological examination** prior to IMP administration

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:

- Well placed central venous catheter or patent peripheral cannula in situ
- Mean blood pressure (with or without inotropic support) must be greater than the 5th centile for gestation within 30 mins prior to IMP administration

Blood Pressure Values by Gestational Age (at birth) for Day One of Age (Zubrow et al., 1995).

Age	Mean (Calculated)		
weeks	95th CI	mean	5th CI
36	55	44	33
37	56	45	34
38	57	46	35
39	58	47	36
40	60	49	37
41	61	50	39
42	62	51	40

- Clinical or electrical seizures, if present, controlled with anti-seizure medications
- Clinical observations within acceptable range for an infant undergoing therapeutic hypothermia
- No clinical stability concerns from the attending neonatologist

** Modified Sarnat Examination

- The modified Sarnat neurological examination will be scored and classified during and after the examination. As some of the assessments are subjective, a video of the examination will be stored on the aEEG/EEG video server which will allow subsequent central review and ratification of the scores.

Exclusion criteria

- Baby would be >6 hours of age when IMP administered
- Initiation of IMP unlikely to be administered within 6 hours of birth
- 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.
- Postnatal hypoxic insult without any evidence of HIE at birth.
- Birth weight less than 2nd centile for gestation on UK-WHO growth charts
- Congenital anomalies i.e. any major antenatal diagnosed congenital abnormalities such as congenital heart disease, suspected or known chromosomal abnormalities.
- Head circumference less than 2nd centile adjusted to sex of the baby on UK-WHO growth charts
- Infant is participating or intends to participate in another interventional study during the birth hospitalisation (note: does not include observational studies)
- Parents/legal guardians unable to give consent due to learning or other difficulties

Please note that in the event of multiple births:

- If one baby has HIE, participation in the trial will be offered
- If both/multiple babies have HIE, participation in the trial will not be offered

Intervention

Following recruitment, each baby will be assigned a dose level as below. Administration of the IMP will occur as an intravenous infusion given over 2 hours, occurring over a 74-hour dosing period (covering the period of HT and rewarming).

Refer to the Melatonin in Ethanol monograph for details about preparation and administration. The dose will be prescribed and administered by a member of the local study team with a two additional checkers who are not required to be on the delegation log. The melatonin infusion will be given through its own individual lumen on central venous catheters. If a peripheral cannula is used, only 0.9% sodium chloride, 5% or 10% glucose may be infused together in the same cannula.

Each dose level consists of a single loading dose within 6h of birth followed by 5 maintenance doses 24h after the loading dose, given every 12h. The maintenance doses are ½ the loading dose. Dose escalation involves the study of increasing dose levels

throughout the study. After review of safety data at one dose level then the study sponsor will notify each site if dose escalation can occur for subsequent participants.

Dose level	Loading dose		Maintenance dose	
	Melatonin	Volume (over 2h)	Melatonin	Volume (over 2h)
Dose level 1	5mg/kg	2.5mL/kg	2.5mg/kg	1.25mL/kg
Dose level 2	10mg/kg	5mL/kg	5mg/kg	2.5mL/kg
Dose level 3	15mg/kg	7.5mL/kg	7.5mg/kg	3.75mL/kg
Dose level 4	20mg/kg	10mL/kg	10mg/kg	5mL/kg
Dose level 5	25mg/kg	12.5 mL/kg	12.5 mg/kg	6.25 mL/kg
Dose level 6	30mg/kg	15 mL/kg	15 mg/kg	7.5 mL/kg

Active cooling will occur in parallel as part of the baby's clinical care and is likely to have started before the consent is obtained for the ACUMEN study and administration of the melatonin.

Only one participant should be recruited at a time. An additional baby can be recruited once IMP administration and aEEG monitoring has finished.

What clinicians should know about patient monitoring and management

Monitoring

- Multiparameter monitoring and monitoring by 12 lead EEG, and NIRS will occur throughout the entirety of the drug administration period.
- Invasive blood pressure monitoring is mandatory for enrolment and should continue throughout the study period. As per protocol if arterial access is lost after 48h then provided baby is clinically stable (not requiring inotropes, no dose limiting events), melatonin may be continued with non-invasive BP monitoring.
- Bloods for pharmacokinetics (melatonin and ethanol), routine haematology and biochemistry and exploratory biomarkers (cytokine, renal panel, Neuro-specific proteins, Metabolomics and future research) will be sampled at five timepoints every 24 hours. These will be taken by a member of the study team.
- MRI/MRS will be performed in the first week and following discharge there will be further blood samples at 3 months at the time of neurodevelopmental follow up.
- Standardised neurodevelopmental examination on discharge and at follow up at 3 months

Management

As per the Scottish Neuroprotection Pathway

Potential adverse events

1. Effects on blood pressure
   Based on preclinical data from one study, there is a small but not clinically significant increase in inotropic requirement with melatonin doses of 20mg/kg (dose increase of dopamine 5mcg/kg/min) during the loading dose only. This is why it is essential that babies recruited to the study will have invasive intraarterial blood pressure monitoring. Four other studies have shown no evidence of hypotension.
   If required, volume expansion or inotropes will be given.

2. Sedation
   Melatonin may cause drowsiness

Adverse events which should be reported to the Sponsor are listed in section 6 of the ACUMEN protocol.

If there are any concerns about participant stability or safety between T0 to 100-hours after the last IMP administration, it is at the discretion of the site investigator/attending neonatologist responsible for the participant's care whether the next administration(s) of IMP due are administered or not.

The next administration of the IMP (where due) will only be given to the participant if the site/clinical investigator and attending neonatologist agree it is safe to do so. IMP treatment must be discontinued in an individual participant in the following cases:

- Serious AEs or severe AEs considered related to the IMP.
- PK exposure cap for melatonin (<45 mg/L) or ethanol (<0.25g/L) is exceeded

Where there are interruptions to the IMP treatment schedule due to clinical stability which later resolves and where the site investigator is happy for IMP treatment to continue, IMP must be administered as per the treatment schedule i.e., at the specified timepoints.

In the event of an interruption during the administration of the IMP infusion (e.g., due to clinical instability), the infusion may be paused and restarted once the clinical issue is resolved. The full dose of the IMP must be administered within a maximum of four hours from the initial start time of the infusion. If the interruption prevents the completion of the dose within this four-hour timeframe, the remaining dose must not be administered, and the interruption must be documented.

If any errors are made in the administration of IMP (i.e., wrong dose provided) the trial team must report this to the Sponsor immediately who will inform the DSMB accordingly.

Trial diagram

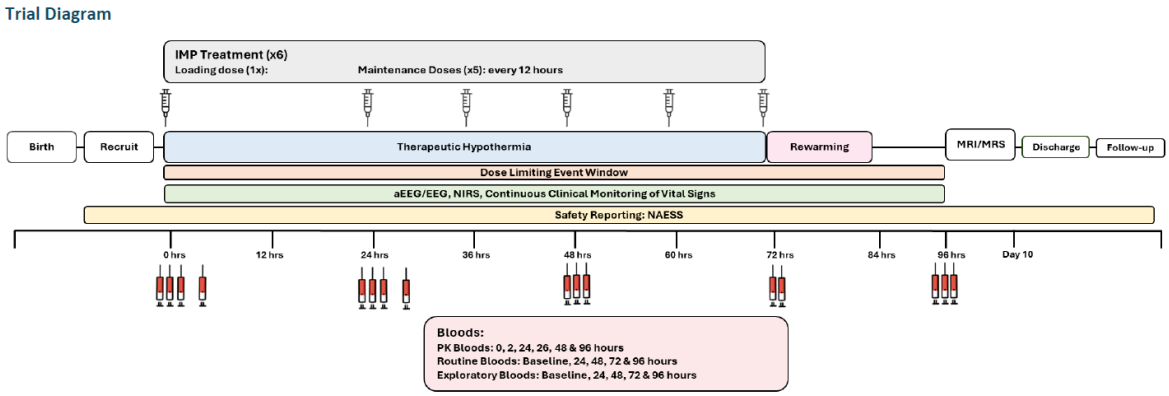

Figure 1: Trial Diagram for ACUMEN Participants in the Dose Escalation and Cohort Expansion Phases.

Background: What is melatonin?

Melatonin is a natural hormone the body makes to help regulate sleep. It is safe and is used in children to treat sleep problems when taken by mouth. However, since babies with HIE might not absorb melatonin well if taken by mouth, melatonin will be given directly into the bloodstream intravenously.

Melatonin is a potential new treatment for HIE. Multiple research studies in animals have demonstrated that high doses of melatonin alongside cooling can provide better brain protection compared to cooling alone. Results from these studies show that, for melatonin to work well, high levels of melatonin in the blood (15-30mg/L) are needed within 6-8h of baby being born. These levels are much higher than the natural levels of melatonin the body makes (about 10,000 times higher). However, its effectiveness in babies is not yet known, and this study aims to find out whether melatonin can be safely given to newborns and whether it reaches the levels in the blood that were found to be beneficial in multiple animal studies.

To make melatonin into a liquid form, a chemical has been added that helps melatonin dissolve (called an excipient). In this melatonin preparation, a small amount of ethanol (alcohol) is used. This is already found in other common medicines used in newborn care

(e.g., furosemide, iron, phenobarbital). Preclinical research shows that ethanol can also help protect the brain, which is why it is included as an “adjuvant” (helpful) excipient. After each dose of the study drug, the baby’s blood alcohol levels will be checked alongside melatonin levels to ensure they stay below a limit deemed to be safe (below 0.25 g/L).

Outcomes

Primary outcomes:

The primary outcomes are:

1. Safety: to assess the safety profile of melatonin across 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 15-30mg/L) across dose levels being studied.

3. The attainment of putative ethanol safety (BAC levels < 0.25g/L across dose levels being studied.

How to recruit and start trial protocol

It is intended that Laura Dunn and Julie-Clare Becher will carry out the majority of tasks below apart from routine bloods. Other staff on the delegation list may have to undertake tasks if Laura and JC are not immediately available to ensure compliance with protocol.

Items in red are ***only*** to be undertaken by research staff (Laura Dunn and Julie-Clare Becher)

1. **Confirm eligibility as soon as possible** and ensure no exclusion criteria (as above):
   - moderate-severe hypoxic-ischaemic encephalopathy (HIE) meeting cooling criteria (can use local Brainz CFM machine)
   - born at ≥36 completed weeks gestation
   - clinically stable*(see above) at the time of IMP administration
   - invasive blood pressure monitoring in situ prior to the administration of the IMP loading dose
   - IMP administration likely to be given within 6h
   - 2nd centile or more on WHO growth charts
   - not a SUPC
   - not requiring maximal intensive care therapy or in a condition considered to be life-limiting

2. **Check Sealed Envelope** site that recruitment is currently open: Sealed Envelope | Access

3. If trial open, **phone Laura Dunn and Julie-Clare Becher**

4. **Obtain parental consent for trial** (documents in locked drawer in Duty Room)
   1) Explain the study to the parents
   2) Provide parents with the ACUMEN study parent information sheets (short and long version in the ACUMEN box as well as maternal info sheet. If no packs made up these are in section 3 of the site file)
   3) Show parents the ACUMEN introductory video using phone, laptop or tablet (https://www.acumen-trial.co.uk/about-acumen)
   4) Obtain written parental informed consent for *both* their baby's participation in the trial *and* maternal participation in the trial

      Or

      Where the parent/legal guardian(s) are willing for their baby to be screened for trial participation and trial intervention started, verbal consent may be obtained in the first instance. Verbal consent must be witnessed by an independent member of clinical team and those taking verbal consent must

document this in the participant's medical notes and complete the verbal consent document for filing in the ISF. Informed consent, both verbal and written can only be obtained after explanation of the aims, methods, benefits, and potential hazards of the trial.

5. Access and **register participant** on Sealed Envelope website to:
    1) obtain the participant ID

confirm the dose level allocation

6. Replace CFM with **full EEG** and start EEG with trial participant ID (use demo dolls to inform correct electrode placement)

7. Record video of **Sarnat examination** on EEG machine and score on worksheet.

8. **Prescribe IMP** (ensure ACUMEN monograph is followed- see Badger), and use amber syringe *and* tubing)

9. **Take pre-IMP bloods**:
    1) PK, biomarkers bloods (fridge and then spin and freeze within 4h)
    2) gas, biochemistry, U/Es, LFTs, CRP, troponin, CK, LDH, FBC, coagulation, VBC (if not done previously)

10. Record physiological parameters, **ensure still fulfills criteria for clinical stability**

11. T0: **Administer IMP** (loading dose) and complete the IMP administration sheet

12. **Cranial US** with RI (if not already done), ensure NIRS in situ

13. T1h:
    1) Glucose and lactate

14. T2h Take post-IMP bloods:
    1) PK (fridge and then spin and freeze within 4h)
    2) Put blood spot biomarkers into tubes and freeze
    3) Glucose and lactate

15. T24h
    1) PK, biomarkers bloods (fridge and then spin and freeze within 4h)
    2) Gas, biochemistry, U/Es, LFTs, CRP, troponin, CK, LDH, FBC
    3) **Administer IMP (maintenance dose 1)** and complete the IMP administration sheet
    4) **Cranial USS with RI**
    5) **Modified Sarnat examination**

16. T25
    1) Glucose and lactate

17. T26h Take post-IMP bloods:
    1) PK (fridge and then spin and freeze within 4h)
    2) Put blood spot biomarkers into tubes and freeze
    3) Glucose and lactate

18. T36h +/-1h
    1) **Administer IMP (maintenance dose 2)** and complete the IMP administration sheet

19. T37h
    1) Glucose and lactate

20. T38h
    1) Glucose and lactate

21. T48h+/-1h
    1) PK, biomarkers bloods (fridge and then spin and freeze within 4h)
    2) Gas, biochemistry, U/Es, LFTs, CRP, troponin, CK, LDH, FBC
    3) **Administer IMP (maintenance dose 3)** and complete the IMP administration sheet
    4) **Cranial USS with RI**
    5) **Modified Sarnat examination**

22. T49h
    1) Glucose and lactate

23. T50h
    1) Glucose and lactate
    2) Put blood spot biomarkers into tubes and freeze

24. T60+/-1h
    1) **Administer IMP (maintenance dose 4)** and complete the IMP administration sheet

25. T61h
    1) Glucose and lactate

26. T62h
    1) Glucose and lactate

27. T72h+/-1h
    1) Biomarkers bloods (fridge and then spin and freeze within 4h)
    2) Gas, biochemistry, U/Es, LFTs, CRP, troponin, CK, LDH, FBC
    3) **Administer IMP (maintenance dose 5)** and complete the IMP administration sheet

4) **Cranial USS with RI**
5) **Modified Sarnat examination**

28. T73h
    1) Glucose and lactate

29. T74h
    1) Glucose and lactate
    2) Put blood spot biomarkers into tubes and freeze

30. T96h +/-1h
    1) PK (priority), biomarkers bloods (fridge and then spin and freeze within 4h)
    2) Gas, biochemistry, U/Es, LFTs, CRP, troponin, CK, LDH, FBC
    3) **Cranial USS with RI**
    4) **Modified Sarnat examination**

31. T98h
    1) Put blood spot biomarkers into tubes and freeze