Clinical trial results:
Melatonin As A Novel Neuroprotectant in Preterm Infants- Dosage study

Summary

EudraCT number	2007-007156-33
Trial protocol	GB
Global end of trial date	22 February 2011

Results information

Result version number	v1 (current)
This version publication date	06 February 2020
First version publication date	06 February 2020

Trial information

Trial identification

Sponsor protocol code	CRO970 (MIND)

Additional study identifiers

ISRCTN number	ISRCTN01115788
ClinicalTrials.gov id (NCT number)	NCT00649961
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Dr Nazakat Merchant, Imperial College London, +44 07825881907, nazakat.merchant@kcl.ac.uk
Scientific contact	Dr Nazakat Merchant, Imperial College London, +44 07825881907, nazakat.merchant@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2011
Global end of trial reached?	Yes
Global end of trial date	22 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall purpose is to investigate whether melatonin, on achieving adult maternal peak blood levels in preterm infants, will reduce cerebral white matter disease as defined by specialised magnetic resonance imaging (MRI) at term. Before testing this hypothesis in a clinical trial, the dose of melatonin required to achieve the desired concentration in preterm infants needs to be determined. This data will be used in the clinical double blinded randomised trial for which a separate application will be made to the ethics committee.

The principal research objective in this study is to determine the dose required to achieve physiological melatonin blood levels in the preterm infants similar to that of the mother.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	18
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The investigators conducted an open-label dose-ranging study between May 2010 and December 2010 in three neonatal intensive care units in the UK. Infants born less than 31 weeks gestation and less than 7 days old were eligible for the study.

Pre-assignment

Screening details:

Eighteen preterm infants (nine male, nine female) born before 31 weeks gestation and less than 7 days of postnatal age were enrolled into the study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Melatonin Open Label Single Arm - all participants

Arm description:

A single intravenous infusion of melatonin was given to each infant over 6 hours.

Arm type	Experimental
Investigational medicinal product name	Melatonin injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravesical use

Dosage and administration details:

The first dose administered was 0.1 mg kg-1 h-1 for 6 h. Successive groups received varying doses depending on the melatonin blood concentrations until mean adult physiological concentrations were achieved (approximately 46–58 pg ml-1). The dose regimens given were 0.1 mg kg-1 h-1 intravenously for 6 h, 0.1 mg kg-1 h-1 for 2 h, 0.02 mg kg-1 h-1 for 2 h, 0.01 mg kg-1 h-1 for 2 h and 0.04 mg kg-1 over 30 min.

Number of subjects in period 1	Melatonin Open Label Single Arm - all participants
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
Newborns (0-27 days)	18	18	
Age continuous			
Gestation at birth			
Units: weeks arithmetic mean full range (min-max)	 26.63 24.71 to 30.28	 -	
Gender categorical Units: Subjects			
Female Male	9 9	9 9	
Postnatal age Units: day arithmetic mean full range (min-max)	 2 1 to 6	 -	
Birth weight Units: gram(s) arithmetic mean full range (min-max)	 867.5 610 to 1430	 -	

End points

End points reporting groups

Reporting group title	Melatonin Open Label Single Arm - all participants
Reporting group description: A single intravenous infusion of melatonin was given to each infant over 6 hours.	
Subject analysis set title	0.1 mg kg-1 h-1 for 2 h
Subject analysis set type	Sub-group analysis
Subject analysis set description: 0.1 mg kg-1 h-1 for 6 h	
Subject analysis set title	0.02 mg kg-1 h-1 for 2 h
Subject analysis set type	Sub-group analysis
Subject analysis set description: 0.02 mg kg-1 h-1 for 2 h	
Subject analysis set title	0.01 mg kg-1 h-1 for 2 h
Subject analysis set type	Sub-group analysis
Subject analysis set description: 0.01 mg kg-1 h-1 for 2 h	

Primary: Dose of Melatonin Required to Achieve Physiological Blood Levels in the Preterm Infants Similar to That of the Mother

End point title	Dose of Melatonin Required to Achieve Physiological Blood Levels in the Preterm Infants Similar to That of the Mother[1]
End point description: Blood results at 2h, a dose of melatonin required to achieve physiological blood levels in the preterm infants similar to that of the mother is 160-220 pg/ml	
End point type	Primary
End point timeframe: 6 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a pharmacokinetic study with a mathematical basis and that the reporting format doesn't lend itself to this type of study.

End point values	0.1 mg kg-1 h-1 for 2 h	0.02 mg kg-1 h-1 for 2 h	0.01 mg kg-1 h-1 for 2 h	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	2	
Units: pg/ml				
median (full range (min-max))	203.3 (160 to 220)	48.7 (38.8 to 71)	54.8 (43.5 to 66)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Clearance (CL)

End point title	The Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Clearance (CL)

End point description: The Melatonin clearance (l h-1/0.867 kg) in Preterm Infants	
End point type	Secondary
End point timeframe: 6 hours	

End point values	0.1 mg kg-1 h-1 for 2 h	0.02 mg kg-1 h-1 for 2 h	0.01 mg kg-1 h-1 for 2 h	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	8	8	
Units: percent	8	15	15	

Statistical analyses

No statistical analyses for this end point

Secondary: he Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Volume of Distribution (V)

End point title	he Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Volume of Distribution (V)
End point description: The volume of distribution (l/0.867 kg)	
End point type	Secondary
End point timeframe: 6 hours	

End point values	0.1 mg kg-1 h-1 for 2 h	0.02 mg kg-1 h-1 for 2 h	0.01 mg kg-1 h-1 for 2 h	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	8	8	
Units: percent	11	32	32	

Statistical analyses

No statistical analyses for this end point

Secondary: The Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Residual Variability

End point title	The Pharmacokinetic Profile of Melatonin in Preterm Infants - Percent of the Residual Variability
End point description:	
End point type	Secondary

End point timeframe:

6 hours

End point values	0.1 mg kg-1 h-1 for 2 h	0.02 mg kg-1 h-1 for 2 h	0.01 mg kg-1 h-1 for 2 h	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	8	8	
Units: percent	30	63	63	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

6 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Melatonin Open Label Single Arm - all participants

Reporting group description:

A single intravenous infusion of melatonin was given to each infant over 6 hours.

Serious adverse events	Melatonin Open Label Single Arm - all participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Melatonin Open Label Single Arm - all participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23432339