Clinical trial results:
Clinical trial of the investigational medicinal product, local anaesthetic levo-bupivacaine in infants 3 - 6 months post natal age.

Summary

EudraCT number	2015-000393-34
Trial protocol	GB
Global end of trial date	06 June 2017

Results information

Result version number	v1 (current)
This version publication date	07 November 2019
First version publication date	07 November 2019

Trial information

Trial identification

Sponsor protocol code	R03003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC: 15/NW/0240

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Cobbet House, Manchester, United Kingdom, M13 9WU
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 1612764125, lynne.webster@cmft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 161 2764125, lynne.webster@cmft.nhs.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	06 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2017
Global end of trial reached?	Yes
Global end of trial date	06 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to ratify the safety of the present standard protocol for caudal-epidural levobupivacaine in infants three to six months age.

A bolus of levo-bupivacaine will be used, followed by an infusion in the same space, after one hour of the bolus. This study will measure plasma levels of levo-bupivacaine upto 72 hours, though the infusion will stop at 48 hours, to ensure that toxic levels are not reached in plasma.

It will help to confirm the pharmacokinetic model and the information will also be used to manage other infants undergoing other major surgery and requiring this method of pain relief.

Protection of trial subjects:

At present, infants undergoing repair of a Bladder Exstrophy have a caudal-epidural where appropriate, to provide pain relief. The local anaesthetic Levo-bupivacaine is infused through a catheter.
Previous researchers have found it difficult to obtain repeated blood samples in this age group over long periods of 48 - 72 hours.
Our study population of infants with Bladder Exstrophy, all require invasive monitoring intra-operatively which is left in situ post-operatively. Blood samples can therefore be obtained without discomfort to the infants or additional injections and bruising.
WHO recommendations for safe limits of blood sampling will be adhered to for this research.
Assay of levo-bupivacaine requires specialised equipment and this will be done in Cinical Pathology laboratoy at Nottingham. The blood sample obtained in our hospital will be centrifuged and only the plasma will be transported by designated couriers at appropriate temperatures.
Each study participant will be allocated a unique study number at recruitment and all data will be linked to this number for transport.
Identifiable patient data will be collected by one investigator and stored in paper and electronic form in the trust

Background therapy:

All patients will receive Clonidine as per current hospital guidelines except those infants under 5 kg. 1.5 ug/ml will be added to the bag.

Evidence for comparator:

There is no comparator in this study as it is a single arm study.

Actual start date of recruitment	15 June 2015
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: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	8
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:

Patients were recruited from Royal Manchester Children's Hospital, part of Manchester University NHS Foundation Trust. Opened to recruitment 12/06/2015 and lasted 24 months.

Pre-assignment

Screening details:

Only those infants whose patients consent to a caudal-epidural block, as well as to this study will be included. Preoperative assessment will be carried out one week prior to surgery by the PI who will discuss the anaesthetic process and provide an information sheet. Consent will be taken on the morning of the operation.

Period 1

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

Blinding implementation details:

Single arm study

Arms

Arm title	Levo-bupivacaine

Arm description:

Single arm study. Infusion of Levo-bupivacaine 0.2 mg/kg/hr, by the caudal - epidural route, started one hour after a bolus dose of 2 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Levo-bupivacaine
Investigational medicinal product code	PL 41042/0005
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Epidural use

Dosage and administration details:

2.0 mg/kg given as a bolus over 5 minutes. Infusion of 0.2 mg/kg/hr will start at 60 minutes after the completion of the bolus and will run for 48 hours. Clonidine will be added to this caudal-epidural infusion bag. This is a single administration during surgery.

Number of subjects in period 1	Levo-bupivacaine
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	8	8	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
arithmetic mean	5.0		
standard deviation	± 0.5	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	5	
Body weight Units: kg			
arithmetic mean	6.90		
standard deviation	± 0.96	-	

End points

End points reporting groups

Reporting group title	Levo-bupivacaine

Reporting group description:

Single arm study. Infusion of Levo-bupivacaine 0.2 mg/kg/hr, by the caudal - epidural route, started one hour after a bolus dose of 2 mg/kg.

Primary: Total levobupivacaine serum concentration

End point title	Total levobupivacaine serum concentration[1]

End point description:

End point type	Primary

End point timeframe:

1 hour

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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/L				
median (full range (min-max))	0.30 (0.20 to 0.70)			

Statistical analyses

No statistical analyses for this end point

Primary: Total levobupivacaine concentration

End point title	Total levobupivacaine concentration[2]

End point description:

End point type	Primary

End point timeframe:

47 hours

Notes:

[2] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mg/L				
median (full range (min-max))	1.21 (0.07 to 1.85)			

Statistical analyses

No statistical analyses for this end point

Primary: Levobupivacaine: Average apparent unbound clearance

End point title	Levobupivacaine: Average apparent unbound clearance[3]
End point description:	
Final parameter estimate	
End point type	Primary
End point timeframe:	
1 hour to 72 hours	

Notes:

[3] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: L/h				
number (confidence interval 95%)	61.3 (48.1 to 68.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Levobupivacaine: Apparent unbound volume of distribution

End point title	Levobupivacaine: Apparent unbound volume of distribution[4]
End point description:	
Final parameter estimate	
End point type	Primary
End point timeframe:	
1 hour to 72 hours	

Notes:

[4] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: L/h				
number (confidence interval 95%)	1.05 (0.62 to 1.27)			

Statistical analyses

No statistical analyses for this end point

Primary: AAG conversion clearance

End point title	AAG conversion clearance[5]
End point description:	
Final parameter estimate	
End point type	Primary
End point timeframe:	
1 hour to 72 hours	

Notes:

[5] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: L/h				
number (confidence interval 95%)	0.136 (0.125 to 0.141)			

Statistical analyses

No statistical analyses for this end point

Primary: AAG: concentration of AAG and pre-AAG at time zero

End point title	AAG: concentration of AAG and pre-AAG at time zero[6]
End point description:	
Final parameter estimate	

End point type	Primary

End point timeframe:

Time 0

Notes:

[6] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/L				
number (confidence interval 95%)	413 (292 to 475)			

Statistical analyses

No statistical analyses for this end point

Primary: AAG: Interaction term

End point title	AAG: Interaction term[7]

End point description:

Final parameter estimates

End point type	Primary

End point timeframe:

1 hour to 72 hours

Notes:

[7] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: scale				
number (confidence interval 95%)	4.58 (3.50 to 5.13)			

Statistical analyses

No statistical analyses for this end point

Primary: AAG: Proportion residual variability

End point title	AAG: Proportion residual variability[8]

End point description:

Final parameter estimate

End point type	Primary

End point timeframe:

1 hour to 72 hours

Notes:

[8] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage				
number (confidence interval 95%)	7.81 (4.25 to 14.34)			

Statistical analyses

No statistical analyses for this end point

Primary: Levobupivacaine: first-order absorption rate

End point title	Levobupivacaine: first-order absorption rate[9]

End point description:

Final parameter estimates

End point type	Primary

End point timeframe:

1 hour to 72 hours

Notes:

[9] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: L/h				
number (confidence interval 95%)	0.15 (0.138 to 0.156)			

Statistical analyses

No statistical analyses for this end point

Primary: Levobupivacaine: Proportional residual variability

End point title	Levobupivacaine: Proportional residual variability[10]

End point description:

Final parameter estimates

End point type	Primary

End point timeframe:

1 hour to 72 hours

Notes:

[10] - 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 study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

End point values	Levo-bupivacaine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage				
number (confidence interval 95%)	33 (12.15 to 89.72)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events will be collected for the time the patient is in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3

Reporting groups

Reporting group title	Whole cohort

Reporting group description: -

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: As this study is only small, using a drug which is already protocol, there were no non-serious adverse events noted.

Serious adverse events	Whole cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Tachypnoea	Additional description: Additional symptoms included Tachycardia and Rhinitis		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Whole cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2015	Change to the trial protocol as requested by the MHRA following their initial review of the clinical trial application. The changes related to additional exclusion criteria and additional rationale for drug dosing for the bolus and infusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported