Clinical trial results:
NIRTURE - A Randomised Trial of Early Insulin Therapy in Very Low Birth Weight Infants

Summary

EudraCT number	2004-002170-34
Trial protocol	ES
Global end of trial date	15 February 2010

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	31 July 2015
Summary attachment (see zip file)	SAE and AE Listing (NIRTURE_SAE and AE listing.xlsx)

Trial information

Trial identification

Sponsor protocol code	15/1/04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cambridge Univeristy Hospitals NHS foundation Trust
Sponsor organisation address	R&D office Box 146, Addenbrookes NHS Trust, Cambridge, United Kingdom, CB0 0QQ
Public contact	Diane Picton , Cambridge University Hospitals NHS Foundation Trust , 44 1223762944, dp223@medschl.cam.ac.uk
Scientific contact	Dr Kathy Bearsdall , Cambridge University Hospitals NHS Foundation Trust , 44 1223746791, kb274@medschl.cam.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	30 October 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2007
Global end of trial reached?	Yes
Global end of trial date	15 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of early fixed dose insulin on mortality in very low birth weight babies

Protection of trial subjects:

Regular reporting of SAE’s and meetings held yearly

Background therapy:

Insulin aspart with variable rate 20% dextrose support, Dose 0.05 units/kg/hour, Route of administration Continuous intravenous infusion in the first week of life

Evidence for comparator:

Standard care

Actual start date of recruitment	04 February 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	United Kingdom: 108
Country: Number of subjects enrolled	Belgium: 211
Country: Number of subjects enrolled	Netherlands: 45
Worldwide total number of subjects	389
EEA total number of subjects	389

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	389
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
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:

Very low birth weight infants (<1500g) were recruited from neonatal intensive care units and randomised to receive either a continuous infusion of insulin (0.05 u/kg/hr) from within 24 hours of birth and for the first 7 days of life, or to act as controls and receive standard neonatal care. Recuitment opened in Feb 2005 & closed June/July 2007.

Pre-assignment

Screening details:

Screening for eligibility was performed in conjunction with the clinical team

Period 1

Period 1 title	Start-end of study intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Early fixed dose insulin replacement

Arm type	Experimental
Investigational medicinal product name	Insulin Aspart
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.05u/kg/hr

Arm title	Control

Arm description:

Standard care

Arm type	Standard Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Intervention	Control
Started	195	194
Completed	194	192
Not completed	1	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description: Early fixed dose insulin replacement	

Reporting group title	Control
Reporting group description: Standard care	

Reporting group values	Intervention	Control	Total
Number of subjects	195	194	389
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	194	192	386
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Not recorded	1	2	3
Age continuous Units: weeks			
arithmetic mean	27.6	27.8	
standard deviation	± 2.2	± 2.2	-
Gender categorical Units: Subjects			
Female	101	95	196
Male	94	99	193
Receipt of Antenatal glucocorticoids Units: Subjects			
yes	178	176	354
no	16	16	32
not recorded	1	2	3
Birth Weight			
Birth Weight			
Units: kg			
arithmetic mean	1.007	1.009	
standard deviation	± 0.267	± 0.274	-
Head Circumference Units: cm			
arithmetic mean	25.3	25.4	
standard deviation	± 2.2	± 2.3	-

Crown Heel Length			
Units: cm			
arithmetic mean	35.3	35.4	
standard deviation	± 3.7	± 3.6	-
Birth Weight SDS			
Units: SDS			
arithmetic mean	-0.84	-0.91	
standard deviation	± 1.1	± 1.1	-
CRIB score			
Units: number			
arithmetic mean	3.99	4.02	
standard deviation	± 3.5	± 3.4	-

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
Early fixed dose insulin replacement	

Reporting group title	Control
Reporting group description:	
Standard care	

Primary: Death on or before expected date of delivery (taken as date considered to be the most accurate estimate of delivery date).

End point title	Death on or before expected date of delivery (taken as date considered to be the most accurate estimate of delivery date).
End point description:	

End point type	Primary
End point timeframe:	
Death on or before expected date of delivery (taken as date considered to be the most accurate estimate of delivery date).	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: subjects				
Death before expected date of delivery	28	18		
Alive at expected date of delivery	166	174		
Not Recorded	1	2		

Statistical analyses

Statistical analysis title	Death before expected delivery date
Statistical analysis description:	
Fisher's exact test applied to the frequency table cross-classifying the binary endpoint (death before expected deliver date) against treatment arm	
Comparison groups	Intervention v Control

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.15

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 24 hours	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	Protocol Based
Dictionary version	1

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

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: A listing of serious adverse events are given in an attachment

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2004	Protocol changes post original submission
25 November 2004	Change in Trial stastistician ,Secondary Endpoints and randomsiation procedure.
17 June 2005	Change of Trial Statistician and DMC Statistician to ensure independence. Revised study documentation
11 January 2006	Justification to allow recruitment to multiple trial
19 April 2006	Follow up plans - Appendix 3 (follow-up protocol). Patient information sheets and consent forms V2 (April 2006)
25 June 2006	Change of PI
03 April 2007	Plans to follow-up participants through Office of National Stastistic (ONS)
15 August 2007	Recruitment suspended
13 September 2007	Recruitment stopped on ground of futility
20 June 2008	Specifically requesting cause of death
06 September 2009	Change of Sponsor. Sent in for notification only but reviewed formally by ethic committee

Notes:

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/18971490