Clinical trial results:
Mindex: The efficacy and safety of very low dose dexamethasone used to facilitate the extubation of ventilator dependent preterm babies who are at high risk of bronchopulmonary dysplasia

Summary

EudraCT number	2015-005342-63
Trial protocol	GB
Global end of trial date	24 June 2018

Results information

Result version number	v1 (current)
This version publication date	10 May 2019
First version publication date	10 May 2019

Trial information

Trial identification

Sponsor protocol code	UoL001206

Additional study identifiers

ISRCTN number	ISRCTN81191607
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool / Liverpool Joint Research Office
Sponsor organisation address	2nd Floor Block D Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	NPEU Clinical Trials Unit, National Perinatal Epidemiology Unit, +44 01865289737, minidex@npeu.ox.ac.uk
Scientific contact	NPEU Clinical Trials Unit, National Perinatal Epidemiology Unit, +44 01865289737, minidex@npeu.ox.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	04 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2018
Global end of trial reached?	Yes
Global end of trial date	24 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if treatment with very low dose dexamethasone facilitates the extubation of ventilator dependent preterm babies of less than 30 weeks' gestation who are at high risk of developing BPD.

The main outcome measure is the time from randomisation to first extubation, when the baby remains extubated for more than 24 hours.

Protection of trial subjects:

Safety data was reviewed by the DMC which, if appropriate, make recommendations regarding continuation of the trial or modification of the trial protocol. The Trial Steering Committee (TSC) will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	22
Newborns (0-27 days)	0
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 trial recruitment took place in 11 tertiary neonatal units across the United Kingdom. Recruitment stopped on the 14th April 2018 after 22 babies had been randomised to the trial over a period of 9 months. This was a decision made by the funder due to poor recruitment.

Pre-assignment

Screening details:

330 babies were screened and 44 were eligible for the trial.
22 babies were not enrolled for the following reasons: 9 due to clinician decision, 11 due to parent(s) declining consent and 2 for unknown reasons.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Dexamethasone (Hospira, dexamethasone 3.3 mg/ml solution for injection) was supplied as a clear sterile solution at a concentration of 3.3 mg per 1 ml in 2 ml vials. Cartons containing 14 single-use vials were provided.

Placebo was supplied as a clear sterile solution of 0.9% saline solution for injection. Cartons identical to those for dexamethasone, each containing 14 identical single-use vials were provided.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone

Arm description:

very low dose dexamethasone (50 mcg/kg /day for 13 doses)

Arm type	Experimental
Investigational medicinal product name	Dexamethasone (Hospira, dexamethasone 3.3 mg/ml solution for injection)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Nasogastric use , Intravenous use, Oral use

Dosage and administration details:

Doses of 50 mcg/kg (0.015 ml/kg of 3.3 mg/ml solution) of dexamethasone will be administered daily on days 1 to 10 after randomisation (10 doses) then alternate days on days 12, 14 and 16, making a total of 13 doses.

Arm title	Placebo

Arm description:

matched placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Nasogastric use , Oral use

Dosage and administration details:

Placebo will be supplied as a clear sterile solution of 0.9% saline solution for injection.
Cartons identical to those for dexamethasone, each containing 14 identical single-use vials will be provided. Volume of IMP to be withdrawn from the vial will be calculated following the calculations for dexamethasone dosing and then diluted with dextrose or normal saline for administration.

Number of subjects in period 1	Dexamethasone	Placebo
Started	12	10
Completed	12	10

Baseline characteristics

Reporting groups	
Reporting group title	Dexamethasone
Reporting group description: very low dose dexamethasone (50 mcg/kg /day for 13 doses)	
Reporting group title	Placebo
Reporting group description: matched placebo	

Reporting group values	Dexamethasone	Placebo	Total
Number of subjects	12	10	22
Age categorical			
Gestational age at birth (completed weeks)			
Units: Subjects			
Preterm newborns (gestational age <=25 weeks)	10	7	17
Preterm newborns (gestational age 26 to 27 weeks)	2	1	3
Preterm newborns (gestational age 28 to 29 weeks)	0	2	2
Age continuous			
Gestational age at birth (completed weeks)			
Units: days			
median	25	25	
inter-quartile range (Q1-Q3)	24 to 25	23 to 26	-
Gender categorical			
Baby's sex			
Units: Subjects			
Female	4	6	10
Male	8	4	12
Mother's ethnic group			
Units: Subjects			
White	11	9	20
Asian	1	0	1
Black	0	1	1
Neonatal Unit			
Recruiting neonatal unit			
Units: Subjects			
Hull Royal Infirmary	2	3	5
Leicester Royal Infirmary	1	2	3
Liverpool Women's Hospital	3	0	3
Birmingham Women's Hospital	2	0	2
University Hospital Coventry	1	1	2
Bradford Royal Infirmary	1	1	2
Leeds General Infirmary	2	0	2
Royal Preston Hospital	0	2	2
Royal Victoria Infirmary, Newcastle	0	1	1
Antenatal steroids			
Units: Subjects			

Yes	10	7	17
No	2	3	5
Time between rupture of membranes and birth Units: Subjects			
<24 hours	6	7	13
>= 24 hours	4	3	7
Missing	2	0	2
Clinical chorioamnionitis evidence Units: Subjects			
Yes	0	1	1
No	12	9	21
Level of NNU at site of birth Units: Subjects			
Level II	2	0	2
Level III	10	10	20
Baby received diuretics for >24 hours at randomisation Units: Subjects			
Yes	3	2	5
No	9	8	17
Actual mode of delivery Units: Subjects			
Vaginal delivery	10	6	16
Caesarean section	2	4	6
Multiple pregnancy Units: Subjects			
Singleton	11	8	19
Multiple	1	2	3
Ibuprofen received before trial entry Units: Subjects			
Yes	4	2	6
No	8	8	16
Hydrocortisone received before trial entry Units: Subjects			
Yes	2	0	2
No	10	10	20
Ventilation method at trial entry Units: Subjects			
IPPV	8	10	18
HFOV	4	0	4
Most recent results at trial entry Units: Subjects			
No abnormality seen	4	7	11
IVH/ Hydrocephalus/ PVL/ Other white matter injury	7	3	10
Cranial ultrasound not performed	1	0	1
Maternal age			
Mother's age in years			
Units: years median	26	28	

inter-quartile range (Q1-Q3)	21 to 31	23 to 34	-
Birth weight			
Units: gram(s)			
arithmetic mean	730.4	756.5	
standard deviation	± 175.1	± 191.1	-
Birth weight centile			
Units: centile			
arithmetic mean	43.5	45.6	
standard deviation	± 32.5	± 20.1	-
Postnatal age at trial entry			
Units: day			
median	13	16	
inter-quartile range (Q1-Q3)	11 to 20	14 to 18	-
Temperature at admission to NNU			
(°C)			
Units: degree			
arithmetic mean	36.8	37.4	
standard deviation	± 1.1	± 1.1	-
Worst base deficit in first 24 hours after birth			
Units: milliequivalent(s)/litre			
arithmetic mean	10.9	9.6	
standard deviation	± 5.7	± 5.1	-
Apgar score at five minutes			
Units: score			
median	5	5	
inter-quartile range (Q1-Q3)	0 to 8	2 to 8	-
CRIB II Score			
Units: score			
median	15	15	
inter-quartile range (Q1-Q3)	12 to 16	9 to 16	-
Baby's actual weight at trial entry			
Units: gram(s)			
arithmetic mean	862.1	851.1	
standard deviation	± 252.7	± 227.5	-
Head circumference at trial entry			
Units: centimeter			
arithmetic mean	22.9	23.9	
standard deviation	± 1.5	± 2.6	-
FiO2 at trial entry			
Units: percent			
arithmetic mean	49.8	41.2	
standard deviation	± 12.9	± 8.0	-
Mean airway pressure at trial entry			
Units: cmHO			
arithmetic mean	8.9	11.5	
standard deviation	± 3.9	± 3.4	-

End points

End points reporting groups

Reporting group title	Dexamethasone
Reporting group description: very low dose dexamethasone (50 mcg/kg /day for 13 doses)	
Reporting group title	Placebo
Reporting group description: matched placebo	

Primary: Time to first extubation (if extubated for >24 hours) after first IMP dose

End point title	Time to first extubation (if extubated for >24 hours) after first IMP dose[1]
End point description: Time to event analysis	
End point type	Primary
End point timeframe: Up to 16 days post randomisation	

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: As the trial was stopped early, no comparative analysis was performed due to the small number of participants recruited. Only descriptive statistics are reported.

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[2]	2[3]		
Units: hour				
median (inter-quartile range (Q1-Q3))				
Not censored (extubated for >24 hours by day 16)	58.5 (47.9 to 91.5)	58.4 (47.3 to 69.5)		

Notes:

[2] - Subjects extubated for >24 hours by day 16

[3] - Subjects extubated >24 hours by day 16

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first extubation after first IMP dose

End point title	Time to first extubation after first IMP dose
End point description: Time-to-event analysis	
End point type	Secondary
End point timeframe: Up to 16 days post-randomisation	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[4]	6[5]		
Units: hour				
median (inter-quartile range (Q1-Q3))				
Not censored	65.7 (47.9 to 91.5)	58.4 (18.3 to 123.4)		

Notes:

[4] - Subjects extubated by day 16

[5] - Subjects extubated by day 16

Statistical analyses

No statistical analyses for this end point

Secondary: Extubation by day 7 (if extubated for >24 hours)

End point title	Extubation by day 7 (if extubated for >24 hours)

End point description:

End point type	Secondary

End point timeframe:

Day 7 after first IMP dose

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[6]	6[7]		
Units: subjects	5	2		

Notes:

[6] - Subjects not discontinued by Day 7

[7] - Subjects not discontinued by Day 7

Statistical analyses

No statistical analyses for this end point

Secondary: Extubation by day 7 (whether or not for more than 24 hours)

End point title	Extubation by day 7 (whether or not for more than 24 hours)

End point description:

End point type	Secondary

End point timeframe:

Day 7 after first IMP dose

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[8]	6[9]		
Units: subjects	5	4		

Notes:

[8] - Subjects not discontinued by Day 7

[9] - Subjects not discontinued by Day 7

Statistical analyses

No statistical analyses for this end point

Secondary: Alive at 36 weeks' PMA or discharge if sooner

End point title	Alive at 36 weeks' PMA or discharge if sooner

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: Subjects				
Yes	10	9		
No	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of invasive ventilation through ET

End point title	Total duration of invasive ventilation through ET

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: day				
median (inter-quartile range (Q1-Q3))	23 (20 to 27)	31 (20 to 47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of non-invasive respiratory support nasal CPAP, nasal ventilation or high flow oxygen therapy

End point title	Total duration of non-invasive respiratory support nasal CPAP, nasal ventilation or high flow oxygen therapy

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: day				
median (inter-quartile range (Q1-Q3))	40 (27 to 50)	40 (28 to 46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of supplemental oxygen

End point title	Total duration of supplemental oxygen

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: day				
median (inter-quartile range (Q1-Q3))	15 (2 to 19)	4 (0 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label treatment with corticosteroids received after randomisation (cumulative dose)

End point title	Open-label treatment with corticosteroids received after randomisation (cumulative dose)

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: subjects				
Yes	5	4		
No	7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Diuretics received for >48 hours after randomisation

End point title	Diuretics received for >48 hours after randomisation

End point description:

End point type	Secondary

End point timeframe:

36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: subjects				
Yes	8	9		
No	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: BPD assessment at 36 weeks' PMA or discharge if sooner

End point title	BPD assessment at 36 weeks' PMA or discharge if sooner

End point description:

End point type	Secondary

End point timeframe:

At 36 weeks' PMA or discharge if sooner

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: subjects				
Mild	2	0		
Moderate	2	2		
Severe	6	7		
Not assessed/died	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Until 36 weeks post menstrual age	
Assessment type	Systematic

Dictionary used	
Dictionary name	Not applicable
Dictionary version	n/a

Reporting groups	
Reporting group title	Dexamethasone
Reporting group description: very low dose dexamethasone (50 mcg/kg /day for 13 doses)	
Reporting group title	Placebo
Reporting group description: matched placebo	

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: Non-serious adverse events are not reported for this population.

Serious adverse events	Dexamethasone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Hypoglycaemia neonatal	Additional description: Severity: Mild. Causality: not related. Resolved.		
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Dexamethasone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2016	[Protocol v2.0 15/08/2016] Exclusion criteria edited for clarity: removal of the word 'concurrent' and 'previous' from exclusion criteria 1, 4 and 5. Secondary objectives updated to clarify recording at 36 weeks +/- 2 weeks or at discharge home if earlier. Typos/Removed ET abbreviation and replaced with 'endotracheal tube'/Consistency of phrasing: '36 weeks (or discharge home if sooner)' (Across the protocol). Clarification that 'existing diuretic therapy' is for the 24 hours prior to randomisation. Error in criteria for stopping trial medications – '48' hours changed to '72' hours. Clarification that the IMP can be administered orally as per the MHRA approved IMP labels (Section 5.5). All IMP stock will be stored on the neonatal unit rather than having separate stocks at pharmacy and on the neonatal unit (Section 5.5). Changed 'Trial Solution Request Form' to 'Pack Allocation Form' to reflect change in name of document. Addition of liver failure, left ventricular hypertrophy and hydrocephalus to foreseeable adverse events as recommended by the Chief Investigator and Clinical Lead. Removal of chronic lung disease as a separate foreseeable adverse event as this is considered the same as bronchopulmonary dysplasia. Changed 'focal' to 'gastro' for consistency (Section 6.4). Clarification of the process for reporting SAEs (Section 6.5). Oxygen reduction test flow diagram updated (Appendix 2). Signature section for the Chief Investigator and the Statistician have been removed. These signatures are now documented separately and stored in the Trial Master File (front page).
26 October 2017	[Protocol v4.0 04/10/2017] Change of Trial Statistician to Louise Linsell. 'Changes to the inflammatory cytokine profile' now listed as an exploratory outcome rather than secondary outcome (as requested by the Sponsor's GCP expert). Addition of text to section 4.6 to provide further detail about the storage and analysis of blood and ET secretion microsamples (as requested by the Sponsor's GCP expert). Further clarity of the circumstances in which trial medications should be stopped. Further clarity on the recording of open-label corticosteroids.

12 March 2018	[Protocol v5.0 14/02/2018] Correction of abbreviations. Clarification of outcomes: time to first extubation after first IMP dose and extubation by day 7 (this refers to 7 completed days after first IMP dose). Correction of typos and minor grammatical errors. Increase in number of sites to ≤25. Clarification of timing of completion of Diary of Care and cytokine sampling. Addition of text regarding cytokine profiling, as requested by the laboratory team responsible for this aspect of the trial. Removal of 'continuation of a treatment course of antibiotic therapy beyond 72 hours duration' for stopping trial medication. Addition of text clarifying that study medication should be stopped if treatment is required which would be contra-indicated with use of steroids in the opinion of the treating clinical team Clarification of censoring of babies and exclusions from analyses Removal of 'temporarily' discontinued, as babies will only be permanently discontinued Removal of text regarding adjustment of effect estimates and exploratory analysis Change of risk ratios from 99 to 95% CI Clarification that the '28 days' for assessing BPD and suitability for an oxygen reduction test should be considered cumulative

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported