Clinical trial results:
PROPHYLACTIC OROPHARYNGEAL SURFACTANT FOR PRETERM INFANTS: A RANDOMISED TRIAL (THE POPART TRIAL)

Summary

EudraCT number	2016-004198-41
Trial protocol	IE BE SE CZ PT NO
Global end of trial date	18 January 2021

Results information

Result version number	v1 (current)
This version publication date	28 December 2022
First version publication date	28 December 2022

Trial information

Trial identification

Sponsor protocol code	UCDCRC/16/003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Nelson Street, Dublin, Ireland, Dublin 7
Public contact	Quality & Regulatory Affairs, University College Dublin, 00353 17164593, rabia.hussain@ucd.ie
Scientific contact	Quality & Regulatory Affairs, University College Dublin, 00353 17164593, rabia.hussain@ucd.ie

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	27 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2021
Global end of trial reached?	Yes
Global end of trial date	18 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our primary objective is to investigate the efficacy of prophylactic oropharyngeal surfactant for reducing the rate of endotracheal intubation, compared to no intervention in infants at risk of RDS.

Protection of trial subjects:

Ethics approval was obtained prior to commencement of the trial. Ethical approval was obtained from each participating site before site initiation.This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki,in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. Written consent for enrolment of the infant in the study was obtained, where applicable, by both parents/guardians prior to any study-related activities, or as per local requirements and as approved by the ethics committee for the site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2017
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	Norway: 39
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Ireland: 180
Worldwide total number of subjects	252
EEA total number of subjects	252

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	252
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:

Names of potential participants' parents(s)/guardians(s) were obtained from the obstetric team, antenatal wards and clinics. They were approached by a member of the research team or other senior doctor (neonatal consultant or registrar) to inform them of the study.

Pre-assignment

Screening details:

During the screening period subjects were evaluated for eligibility. Once informed consent was obtained, where preterm delivery prior to 29 weeks gestation ensued, subjects were randomised at the time of delivery.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Oropharyngeal Surfactant

Arm description:

Note that originally 127 subjects were allocated to this arm. However, one infant was discontinued early due to meeting exclusion criteria (major congenital anomaly). This infant is excluded from the full analysis set and hence is not included in summary of baseline characteristics or efficacy analysis.

Arm type	Experimental
Investigational medicinal product name	CUROSURF (poractant alfa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Oropharyngeal use

Dosage and administration details:

Surfactant (Curosurf, Chiesi Farmeceutici, Parma, Italy) is a white suspension. Each mL of suspension contains 80mg poractant alfa (surfactant extract) that includes 76mg of phospholipids and 1mg of protein of which 0.45mg is SP-B and 0.59mg is SP-C.
There are two vials of Curosurf: 1.5ml vial (contains 120mg poracant alfa) or 3ml vial (240mg poractant alfa).
The 120mg vial was be given to infants <26weeks gestation and a full 240mg vial to infants 26-28 weeks gestation.
The surfactant will be warmed by the clinicians prior to being drawn up in a sterile syringe as per manufacturer's recommendation. This will be done by opening the mouth gently and injecting the surfactant as a single bolus into the oropharynx using a syringe without a needle attached. This will be done as soon as possible after delivery, ideally before the umbilical cord has been clamped.

Arm title	No Intervention

Arm description:

Infants randomised to the control group will not have anything injected into their oropharynx and will be stabilised on CPAP in the delivery room (DR) as per routine practice.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Oropharyngeal Surfactant	No Intervention
Started	126	125
Completed	126	125

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject was enrolled without meeting eligibility criteria and was withdrawn from the trial before any follow up data were collected. This subject is omitted from all statistical analysis, except for safety data analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Oropharyngeal Surfactant
Reporting group description:	
Note that originally 127 subjects were allocated to this arm. However, one infant was discontinued early due to meeting exclusion criteria (major congenital anomaly). This infant is excluded from the full analysis set and hence is not included in summary of baseline characteristics or efficacy analysis.	
Reporting group title	No Intervention
Reporting group description:	
Infants randomised to the control group will not have anything injected into their oropharynx and will be stabilised on CPAP in the delivery room (DR) as per routine practice.	

Reporting group values	Oropharyngeal Surfactant	No Intervention	Total
Number of subjects	126	125	251
Age categorical			
Best Estimate of Gestational Age (completed weeks). All estimates were determined by early dating ultrasound (<20 weeks), with the exception of two infants in the No Intervention arm whose Gestational Age was recorded as the best clinical estimate			
Units: Subjects			
<26 weeks	48	44	92
26-28 weeks	78	81	159
Age continuous			
Reported for the Full Analysis Set			
Units: weeks			
median	26	26	
inter-quartile range (Q1-Q3)	25 to 27	25 to 27	-
Gender categorical			
Full analysis set.			
Units: Subjects			
Female	57	62	119
Male	69	63	132
Maternal ethnicity Units: Subjects			
Caucasian	110	112	222
Asian	9	5	14
African	6	6	12
Other	1	2	3
Administration of antenatal steroids Units: Subjects			
Yes	126	125	251
No	0	0	0
Spontaneous labour Units: Subjects			
Yes	62	61	123
No	64	64	128
Evidence of preterm premature rupture of membrane? Units: Subjects			
Yes	55	51	106

No	71	74	145
Mode of delivery Units: Subjects			
Vaginal vertex	35	32	67
Vaginal breach	7	13	20
Forceps	0	2	2
Vacuum	0	0	0
Caesarean section in labour	22	15	37
Caesarean section not in labour	62	63	125
Administration of regional anaesthesia (e.g. spinal, epidural)			
In women undergoing caesarean delivery			
Units: Subjects			
Yes	70	70	140
No	13	8	21
Missing	1	0	1
N/A	42	47	89
General Anaesthesia			
In women undergoing caesarean section			
Units: Subjects			
Yes	16	8	24
No	67	66	133
Missing	1	4	5
N/A	42	47	89
Birth multiplicity Units: Subjects			
One	82	80	162
Two	34	36	70
Three	10	9	19
Maternal age Units: Years			
arithmetic mean	32.9	32	
standard deviation	± 5.5	± 5.3	-
Total number of doses of antenatal corticosteroids			
Maternal baseline characteristic			
Units: Number of doses			
median	2	2	
inter-quartile range (Q1-Q3)	2 to 2	2 to 2	-
Duration of premature membrane rupture			
This is reported only for the 106 mothers with evidence of PROM (55 in the Oropharyngeal Surfactant arm and 51 in the No Intervention arm)			
Units: Hours before birth			
median	123	62	
inter-quartile range (Q1-Q3)	48.5 to 411.5	25 to 173	-
Birth weight Units: grams			
median	857.5	829	
inter-quartile range (Q1-Q3)	671.2 to 1035	640 to 1025	-
Apgar score (1 min)			
6 infants in the Oropharyngeal Surfactant arm and 4 in the No Intervention arm were missing data Apgar score at 1 minute post birth.			

Units: points			
median	6	5	
inter-quartile range (Q1-Q3)	4 to 7	4 to 7	-
Apgar score (5 min)			
6 infants in the Oropharyngeal Surfactant arm and 4 in the No Intervention arm were missing data Apgar score at 5 minutes post birth.			
Units: points			
median	8	8	
inter-quartile range (Q1-Q3)	7 to 9	6 to 9	-
Apgar score (10 min)			
56 infants in the Oropharyngeal Surfactant arm and 51 in the No Intervention arm were missing data Apgar score at 10 minutes post birth.			
Units: Points			
median	8	8	
inter-quartile range (Q1-Q3)	8 to 9	7 to 9	-

End points

End points reporting groups

Reporting group title	Oropharyngeal Surfactant

Reporting group description:

Note that originally 127 subjects were allocated to this arm. However, one infant was discontinued early due to meeting exclusion criteria (major congenital anomaly). This infant is excluded from the full analysis set and hence is not included in summary of baseline characteristics or efficacy analysis.

Reporting group title	No Intervention

Reporting group description:

Infants randomised to the control group will not have anything injected into their oropharynx and will be stabilised on CPAP in the delivery room (DR) as per routine practice.

Primary: Intubation for respiratory failure

End point title	Intubation for respiratory failure

End point description:

The primary endpoint is endotracheal intubation for respiratory failure within 120 hours of birth. Enrolled infants were intubated for persistent apnoea and/or bradycardia in the DR, or for respiratory failure in the NICU defined as ≥ 2 of:
• Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
• Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
• O2 –FiO2 >0.4 to keep SpO2 ≥90% for >30 minutes • PCO2 > 9.0 kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
• Apnoea – recurrent apnoea treated with mask ventilation The frequency of blood gas monitoring is based on the clinical decision of the treating physician, as per routine practice.

End point type	Primary

End point timeframe:

120 hours of life

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	80	81		
No	46	44		

Statistical analyses

Statistical analysis title	Primary analysis of the primary endpoint
Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9327
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9798
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8124
upper limit	1.1811

Statistical analysis title	Sensitivity analysis adjusting for covariates

Statistical analysis description:

A generalized estimating equation (GEE) model was fitted to the primary endpoint, intubation for respiratory failure within 120 hours of birth, to estimate the effect of treatment on this endpoint while adjusting for relevant covariates, including gestational age category, center, gender, doses of antenatal steroids, mode of delivery and birth weight. Within center correlation was allowed for using an exchangable correlation structure. The model was fit with a logit link.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78614
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.651
upper limit	1.476

Statistical analysis title	Sensitivity analysis - protocol criteria

Statistical analysis description:

This sensitivity analysis assumes that infants who were intubated without strictly meeting the protocol defined criteria would not have met the primary endpoint (11 in the intervention arm and 9 in the control arm). In the intervention arm, 69 (54.8%) of subjects were intubated after meeting the protocol-defined criteria for respiratory depression within 120 hours of life, compared with 72 (57.6%) of the control arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7445
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9507

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7623
upper limit	1.1841

Statistical analysis title	Sensitivity analysis - Per protocol analysis

Statistical analysis description:

Per protocol analysis of the primary endpoint excludes two subjects who were included in the intention-to-treat set but who did not meet trial eligibility criteria - both were allocated to the standard-of-care (control) arm. Therefore 249 subjects were included in this analysis.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.933
Method	Z test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9885
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.19

Statistical analysis title	Sensitivity analysis - competing risks

Statistical analysis description:

This sensitivity analysis accounts for competing risks in estimation of treatment effect on the primary endpoint. To evaluate sensitivity of results to the reason for intubation (meeting pre- defined criteria or not), a competing risks analysis was carried out using the cmprsk package in R.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378 [1]
Method	Grey's test (Chi Square)

Notes:

[1] - Grey's test for between-group difference in CIF functions (for event of intubation meeting protocol-defined criteria for primary endpoint), in the presence of the competing risk of intubation before meeting protocol-defined criteria

Statistical analysis title	Subgroup analysis - gestational age <26w

Statistical analysis description:

Relative risk of the primary endpoint for gestational age <26 weeks for oropharyngeal surfactant vs standard-of-care (CPAP). In this age category there were 48 subjects in the oropharyngeal surfactant (intervention) arm 44 subjects in the standard-of-care (control) arm.

Comparison groups	No Intervention v Oropharyngeal Surfactant

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.0748
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.888
upper limit	1.2986

Statistical analysis title	Subgroup analysis - gestational age 26-28w

Statistical analysis description:

Relative risk of the primary endpoint for gestational age 26-28 weeks for oropharyngeal surfactant vs standard-of-care (CPAP). In this age category there were 78 subjects in the oropharyngeal surfactant (intervention) arm of whom 50% met the primary endpoint and 81 subjects in the standard-of-care (control) arm of whom 56.8% met the primary endpoint.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.179

Statistical analysis title	Subgroup analysis - center- NMH, Dublin

Statistical analysis description:

Relative risk of the primary endpoint for subjects enrolled at NMH, Dublin for oropharyngeal surfactant vs standard-of-care (CPAP). In this center there were 65 subjects in the oropharyngeal surfactant (intervention) arm and 66 subjects in the standard-of-care (control) arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.704
upper limit	1.31

Statistical analysis title	Subgroup analysis - center - Coombe, Dublin
Statistical analysis description: Relative risk of the primary endpoint for subjects enrolled at Coombe, Dublin for oropharyngeal surfactant vs standard-of-care (CPAP). In this center there were 23 subjects in the oropharyngeal surfactant (intervention) arm and 25 subjects in the standard-of-care (control) arm.	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.815
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.165

Statistical analysis title	Subgroup analysis - Norwegian centers
Statistical analysis description: Relative risk of the primary endpoint for subjects enrolled in the two Norwegian centers for oropharyngeal surfactant vs standard-of-care (CPAP). In this centre there were 21 subjects in the oropharyngeal surfactant (intervention) arm and 18 subjects in the standard-of-care (control) arm.	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.888
upper limit	1.862

Statistical analysis title	Subgroup analysis - Other centres
Statistical analysis description: Relative risk of the primary endpoint for subjects enrolled in Other centers (centers not including Ireland or Norway) for oropharyngeal surfactant vs standard-of-care (CPAP). In these centers there were 17 subjects in the oropharyngeal surfactant (intervention) arm and 16 subjects in the standard-of-care (control) arm.	
Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.941
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.429

Secondary: Death before hospital discharge

End point title	Death before hospital discharge
End point description:	

End point type	Secondary
End point timeframe:	
Randomisation to hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	23	22		
No	103	103		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.0372
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6142
upper limit	1.7528

Statistical analysis title	Cox proportional hazard regression model
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.7

Statistical analysis title	Subgroup analysis - <26 weeks gestational age
Statistical analysis description:	
Relative risk of death before hospital discharge for gestational age <26 weeks for oropharyngeal surfactant vs standard-of-care (CPAP). In this age category there were 48 subjects in the oropharyngeal surfactant (intervention) arm 44 subjects in the standard-of-care (control) arm.	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.564
upper limit	1.682

Statistical analysis title	Subgroup analysis - gestational age 26-28w
Statistical analysis description:	
Relative risk of death before hospital discharge for gestational age 26-28 weeks for oropharyngeal surfactant vs standard-of-care (CPAP). In this age category there were 78 subjects in the oropharyngeal surfactant (intervention) arm of whom 50% met the primary endpoint and 81 subjects in the standard-of-care (control) arm of whom 56.8% met the primary endpoint.	
Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3498
upper limit	3.083

Statistical analysis title	Subgroup analysis - center- NMH, Dublin

Statistical analysis description:

Relative risk of death before hospital discharge for subjects enrolled at NMH, Dublin for oropharyngeal surfactant vs standard-of-care (CPAP). In this center there were 65 subjects in the oropharyngeal surfactant (intervention) arm and 66 subjects in the standard-of-care (control) arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.624
upper limit	2.794

Statistical analysis title	Subgroup analysis - centre - Coombe, Dublin

Statistical analysis description:

Relative risk of death before hospital discharge for subjects enrolled at Coombe, Dublin for oropharyngeal surfactant vs standard-of-care (CPAP). In this center there were 23 subjects in the oropharyngeal surfactant (intervention) arm and 25 subjects in the standard-of-care (control) arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.234
upper limit	2.246

Statistical analysis title	Subgroup analysis - Norwegian centers

Statistical analysis description:

Relative risk of death before hospital discharge for subjects enrolled in the two Norwegian centers for oropharyngeal surfactant vs standard-of-care (CPAP). In this centre there were 21 subjects in the oropharyngeal surfactant (intervention) arm and 18 subjects in the standard-of-care (control) arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	2.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.471
upper limit	9.741

Statistical analysis title	Subgroup analysis - Other centres

Statistical analysis description:

Relative risk of death before hospital discharge for subjects enrolled in Other centers (centers not including Ireland or Norway) for oropharyngeal surfactant vs standard-of-care (CPAP). In these centers there were 17 subjects in the oropharyngeal surfactant (intervention) arm and 16 subjects in the standard-of-care (control) arm.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	1.888

Secondary: Intubation in the delivery room

End point title	Intubation in the delivery room

End point description:

End point type	Secondary

End point timeframe:

Randomisation to delivery room discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	28	38		
No	98	87		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1841
Method	Two-sample Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.731
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4796
upper limit	1.1079

Secondary: Number of attempts to successfully intubate in the delivery room

End point title	Number of attempts to successfully intubate in the delivery room
End point description:	
End point type	Secondary
End point timeframe:	
Randomisation to delivery room discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Analysed for infants intubated in the delivery room only (28 in the intervention arm and 38 in the control arm). There was one missing data value in the control arm and complete case analysis was performed.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3959
Method	Mann-Whitney U
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7613
upper limit	1.2429

Statistical analysis title	Best-worst case sensitivity analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.303
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.674
upper limit	1.2982

Notes:

[2] - Best-worst case analysis

Statistical analysis title	Worst-best case sensitivity analysis

Statistical analysis description:

Worst-best case imputation of missing data

Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4472
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.718
upper limit	1.1116

Secondary: Chest compressions in the delivery room

End point title	Chest compressions in the delivery room

End point description:

End point type	Secondary

End point timeframe:

Randomisation to delivery room discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	5	3		
No	121	122		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7279
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.6534

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4459
upper limit	6.1636

Secondary: Adrenaline administration in the delivery room

End point title	Adrenaline administration in the delivery room

End point description:

End point type	Secondary

End point timeframe:

Randomisation to delivery room discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	1	0		
No	125	125		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test

Secondary: Rectal temperature on admission to the NICU

End point title	Rectal temperature on admission to the NICU

End point description:

Analysed for rectal temperature on admission to NICU only with 67 in the intervention arm and 61 in the control arm. There were 59 missing data values in the intervention arm and 61 missing data value in the control arm.

End point type	Secondary

End point timeframe:

Admission to NICU

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	36.3 (35.9 to 36.7)	36.5 (35.9 to 36.9)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Frequence of missing data for this variable was greater than 40% and hence, in accordance with the statistical analysis plan, only complete case analysis is performed. Results should be interpreted with caution.

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1022
Method	Regression, Linear
Parameter estimate	Median difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.552
upper limit	0.09

Secondary: NICU intubation-first intubation occurring in the NICU

End point title	NICU intubation-first intubation occurring in the NICU

End point description:

End point type	Secondary

End point timeframe:

120 hours of life

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	55	49		
No	71	76		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5568
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.1135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8299
upper limit	1.4983

Secondary: Intra-tracheal surfactant received post-intervention

End point title	Intra-tracheal surfactant received post-intervention

End point description:

End point type	Secondary

End point timeframe:

Post intervention to death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	75	78		
No	51	47		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7357
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9539
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7804
upper limit	1.1643

Secondary: Number of doses of post-intervention surfactant

End point title	Number of doses of post-intervention surfactant

End point description:

Analysed for infants who received post-intervention intra-tracheal surfactant before death or hospital discharge only (75 in the intervention arm and 78 in the control arm).

End point type	Secondary

End point timeframe:

Post intervention to death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	2.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1902
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4446
upper limit	2.5726

Secondary: Respiratory distress syndrome

End point title	Respiratory distress syndrome
End point description:	
Clinical evidence of respiratory distress with radiological evidence (ground glass appearance on CXR)	
End point type	Secondary
End point timeframe:	
Randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	54	53		
No	72	72		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.0108
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7583
upper limit	1.3479

Secondary: Incidence of pneumothorax

End point title	Incidence of pneumothorax

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	21	8		
No	105	117		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0189
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	2.6042
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2299
upper limit	5.5874

Secondary: Incidence of pulmonary haemorrhage

End point title	Incidence of pulmonary haemorrhage

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	6	5		
No	120	120		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.1905
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3951
upper limit	3.5948

Secondary: Mechanical ventilation

End point title	Mechanical ventilation

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	78	84		
No	48	41		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4563
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9212
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7638
upper limit	1.1077

Secondary: Days of mechanical ventilation

End point title	Days of mechanical ventilation
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	1.0 (0.0 to 7.0)	2.0 (0.0 to 7.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4678
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7173
upper limit	-0.0576

Secondary: Use of postnatal corticosteroids for ventilator dependence

End point title	Use of postnatal corticosteroids for ventilator dependence

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	29	30		
No	97	95		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9721
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6152
upper limit	1.4942

Secondary: Days of duration of respiratory support

End point title	Days of duration of respiratory support

End point description:

There was no missing data value in the intervention arm and 1 missing value in the control arm. Primary analysis was by complete case analysis with sensitivity analysis with imputation of missing data

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	53 (27.2 to 73.0)	50 (25.5 to 70.2)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8274
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4718
upper limit	14.7284

Statistical analysis title	Best-worst case sensitivity analysis

Statistical analysis description:

Best-worst case imputation of missing data

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7444
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3298
upper limit	15.1468

Statistical analysis title	Worst-best case sensitivity analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.914
Method	Two-sided Z-test
Parameter estimate	Median difference (net)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7387
upper limit	14.5366

Secondary: Bronchopulmonary dysplasia-supplemental O2 at 28 days of life

End point title	Bronchopulmonary dysplasia-supplemental O2 at 28 days of life
End point description:	
Analysed for infants who were alive at 28 days of life only (105 in the intervention arm and 107 in the control arm). There were two missing data values in the intervention arm and one missing data value control arm. Primary analysis was by complete case analysis, with sensitivity analysis with missing data imputation	
End point type	Secondary
End point timeframe:	
At 28 days of life	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	108		
Units: Subjects				
Yes	73	74		
No	32	33		
Missing	2	1		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Complete case analysis	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.0053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8376
upper limit	1.206

Statistical analysis title	Best-worst case analysis
Statistical analysis description: Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9634
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9824
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8176
upper limit	1.179

Statistical analysis title	Worse-best case analysis
Statistical analysis description: Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9184
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8539
upper limit	1.2266

Secondary: Chronic lung disease of prematurity-supplemental O2 at 36 week

End point title	Chronic lung disease of prematurity-supplemental O2 at 36 week

End point description:

Analysed for infants who were alive at 36 weeks of life only (103 in the intervention arm and 102 in the control arm). There were no missing data values in the intervention arm and one missing data value control arm. Primary analysis was by complete case analysis with sensitivity analysis with imputation of missing data

End point type	Secondary

End point timeframe:

36 weeks of life

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	103		
Units: Subjects				
Yes	28	30		
No	75	72		
Missing	0	1		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Complete case analysis

Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8423
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9243
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5982
upper limit	1.4258

Statistical analysis title	Best-worst case analysis
Statistical analysis description:	
Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7579
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5868
upper limit	1.3869

Statistical analysis title	Worse-best case analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8769
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9333
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6038
upper limit	1.4403

Secondary: Medical treatment for patent ductus arteriosus

End point title	Medical treatment for patent ductus arteriosus

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	27	37		
No	99	88		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1801
Method	Two-sided Z-test
Parameter estimate	Risk difference (RD)
Point estimate	0.7239
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4707
upper limit	1.107

Secondary: Surgical treatment for patent ductus arteriosus

End point title	Surgical treatment for patent ductus arteriosus

End point description:

There were two missing data points per arm. Primary analysis is by complete case analysis, with best-worst case and worst-best case imputation for sensitivity analysis.

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	2	2		
No	122	121		
Missing	2	2		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9919
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1771
upper limit	5.5562

Statistical analysis title	Best-worst case analysis
Statistical analysis description: Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6722
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.496
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1075
upper limit	2.2747

Statistical analysis title	Worse-best case analysis
Statistical analysis description: Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6867
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.9841
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4327
upper limit	9.1559

Secondary: Proven necrotising enterocolitis

End point title	Proven necrotising enterocolitis
End point description:	
End point type	Secondary
End point timeframe: From randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	10	15		
No	116	110		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	No Intervention v Oropharyngeal Surfactant

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3875
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.6614
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3134
upper limit	1.3878

Secondary: Incidence of intraventricular haemorrhage

End point title	Incidence of intraventricular haemorrhage

End point description:

There were five missing data values in the intervention arm and one missing data value control arm. Primary analysis was by complete case analysis with best-worst case and worst-best case imputation for sensitivity analysis.

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	16	18		
No	105	106		
Missing	5	1		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Complete case analysis

Comparison groups	No Intervention v Oropharyngeal Surfactant
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9141
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9109

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4915
upper limit	1.6848

Statistical analysis title	Best-worst case analysis
Statistical analysis description:	
Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6967
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.8354
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.454
upper limit	1.5333

Statistical analysis title	Worse-best case analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7479
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.1574
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6542
upper limit	2.0528

Secondary: Incidence of severe intraventricular haemorrhage

End point title	Incidence of severe intraventricular haemorrhage

End point description:

There were five missing data values in the intervention arm and one missing data value control arm.

Primary analysis was by complete case analysis with best-worst case and worst-best case imputation for sensitivity analysis.

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	7	9		
No	114	115		
Missing	5	1		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Complete case analysis

Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8353
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.7971
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3162
upper limit	2.0018

Statistical analysis title	Best-worst case analysis

Statistical analysis description:

Best-worst case imputation of missing data

Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6035
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.6944
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.249
upper limit	1.9259

Statistical analysis title	Worst-best case analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6622
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.3228
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5917
upper limit	2.9687

Secondary: Incidence of cystic periventricular leukomalacia

End point title	Incidence of cystic periventricular leukomalacia
End point description:	
There were five missing data values in the intervention arm and one missing data value control arm. Primary analysis was by complete case analysis with best-worst case and worst-best case imputation for sensitivity analysis.	
End point type	Secondary
End point timeframe:	
From randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	4	5		
No	117	119		
Missing	5	1		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Complete case analysis	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.8198
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.243
upper limit	2.7587

Statistical analysis title	Best-worst case analysis
Statistical analysis description: Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7372
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.6614
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2043
upper limit	2.1313

Statistical analysis title	Worst-best case analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4181
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.7857
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6463
upper limit	4.9691

Secondary: Retinopathy of prematurity treated with laser photocoagulation

End point title	Retinopathy of prematurity treated with laser photocoagulation
End point description:	
There were 24 missing data values in the intervention arm and 23 missing data value in the control arm. Primary analysis used multiple imputation by chained equations to impute missing data.	
End point type	Secondary
End point timeframe:	
From randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	14	10		
No	88	92		
Missing	24	23		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Multiple imputation for this endpoint using Gestational age, Treatment group allocation, Birth weight, and Use of postnatal steroids, carried out using the mice package in R. Results shown are pooled results from logistic regression	
Comparison groups	Oropharyngeal Surfactant v No Intervention

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4642
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.605
upper limit	3.012

Secondary: Survival without BPD at hospital discharge

End point title	Survival without BPD at hospital discharge

End point description:

End point type	Secondary

End point timeframe:

From randomisation until death or hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	31	30		
No	95	95		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	1.0251

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6642
upper limit	1.5832

Secondary: Survival without CLD at hospital discharge

End point title	Survival without CLD at hospital discharge

End point description:

There was one missing data value in the control arm and complete case analysis was performed.

End point type	Secondary

End point timeframe:

From randomisation to hospital discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	71	72		
No	55	52		
Missing	0	1		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Complete case analysis

Comparison groups	No Intervention v Oropharyngeal Surfactant
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8838
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9705
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7816
upper limit	1.2043

Statistical analysis title	Best-worst case analysis
Statistical analysis description: Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8408
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9649
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7778
upper limit	1.1958

Statistical analysis title	Worst-best case analysis
Statistical analysis description: Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9421
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.9783
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7875
upper limit	1.2147

Secondary: Duration of hospitalisation	
End point title	Duration of hospitalisation
End point description:	
End point type	Secondary
End point timeframe: From randomisation until death or hospital discharge	

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
median (inter-quartile range (Q1-Q3))	74 (53.5 to 92.8)	76 (53.0 to 89.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.865
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2209
upper limit	3.6004

Secondary: Use of home oxygen therapy

End point title	Use of home oxygen therapy

End point description:

There were three missing data value in the control arm and complete case analysis was performed for the primary analysis. Sensitivity analysis carried out imputation of missing data.

End point type	Secondary

End point timeframe:

Discharged home on oxygen therapy, measured at discharge

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Subjects				
Yes	5	10		
No	21	112		
Missing	0	3		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Complete case analysis	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2584
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.4841
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1771
upper limit	1.3126

Statistical analysis title	Best-worst case analysis
Statistical analysis description:	
Best-worst case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0836
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.3816
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1449
upper limit	0.9934

Statistical analysis title	Worst-best case analysis
Statistical analysis description:	
Worst-best case imputation of missing data	
Comparison groups	Oropharyngeal Surfactant v No Intervention
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2797
Method	Two-sided Z-test
Parameter estimate	Risk ratio (RR)
Point estimate	0.496

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1814
upper limit	1.3451

Secondary: Total dose of surfactant administered

End point title	Total dose of surfactant administered

End point description:

End point type	Secondary

End point timeframe:

From randomisation to death or hospital discharge.

End point values	Oropharyngeal Surfactant	No Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: mg				
median (inter-quartile range (Q1-Q3))	240 (240 to 433.1)	120 (0 to 492)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	No Intervention v Oropharyngeal Surfactant
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	120
Confidence interval	
level	95 %
sides	2-sided
lower limit	84
upper limit	240

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were recorded from randomisation to end of study (discontinuation, completion or death) for each subject.

Adverse event reporting additional description:

Only AEs which were not directly associated with the underlying condition of extreme prematurity were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1-22

Reporting groups

Reporting group title	Oropharyngeal Surfactant

Reporting group description:

Note that one infant who was randomised into this arm was discontinued early due to meeting exclusion criteria (major congenital anomaly). This infant is excluded from the full analysis set

Reporting group title	No Intervention

Reporting group description:

Infants randomised to the control group will not have anything injected into their oropharynx and will be stabilised on CPAP in the delivery room (DR) as per routine practice.

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: The number of non-serious adverse events recorded was low (24 in total, 13 in the intervention arm and 11 in the control arm). None of these occurred with more than 5% frequency per treatment arm and so are not reported here. The most frequently occurring was sepsis, occurring in 4 cases (2 in each treatment arm).

Serious adverse events	Oropharyngeal Surfactant	No Intervention	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 127 (19.69%)	23 / 125 (18.40%)	
number of deaths (all causes)	23	22	
number of deaths resulting from adverse events	22	22	
Congenital, familial and genetic disorders			
Pulmonary hypoplasia	Additional description: 10037407 Pulmonary hypoplasia (Preferred term)		
subjects affected / exposed	2 / 127 (1.57%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest neonatal	Additional description: 10007618 Cardio-respiratory arrest neonatal		
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary valve stenosis	Additional description: 10037450 Pulmonary valve stenosis (Preferred Term)		

subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage	Additional description: 10008111 Cerebral haemorrhage (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial	Additional description: 10018985 Haemorrhage intracranial (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Periventricular leukomalacia	Additional description: 10052594 Periventricular leukomalacia (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy	Additional description: 10070511 Hypoxic-ischaemic encephalopathy (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pregnancy, puerperium and perinatal conditions			
Premature baby	Additional description: 10036590 Premature baby (Preferred Term)		
subjects affected / exposed	4 / 127 (3.15%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
General disorders and administration site conditions			
Death	Additional description: 10011906 Death (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Neonatal multi-organ failure	Additional description: 10050401 Neonatal multi-organ failure (Preferred Term)		

subjects affected / exposed	1 / 127 (0.79%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Eye disorders			
Retinopathy	Additional description: 10038923 Retinopathy (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Necrotising colitis	Additional description: 10051606 Necrotising colitis (Preferred term)		
subjects affected / exposed	1 / 127 (0.79%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Necrotising enterocolitis neonatal	Additional description: 10055667 Necrotising enterocolitis neonatal (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neonatal intestinal perforation	Additional description: 10074160 Neonatal intestinal perforation (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia	Additional description: 10006475 Bronchopulmonary dysplasia (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neonatal respiratory distress syndrome	Additional description: 10028974 Neonatal respiratory distress syndrome (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary haemorrhage	Additional description: 10037394 Pulmonary haemorrhage (Preferred Term)		

subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure	Additional description: 10038695 Respiratory failure (Preferred Term)		
subjects affected / exposed	6 / 127 (4.72%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 2	
Pulmonary haemorrhage neonatal	Additional description: 10082194 Pulmonary haemorrhage neonatal (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Pneumonia escherichia	Additional description: 10035699 Pneumonia escherichia (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis neonatal	Additional description: 10040049 Sepsis neonatal (Preferred Term)		
subjects affected / exposed	3 / 127 (2.36%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Candida sepsis	Additional description: 10053166 Candida sepsis (Preferred Term)		
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial sepsis	Additional description: 10053840 Bacterial sepsis (Preferred Term)		
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Oropharyngeal Surfactant	No Intervention	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 127 (0.00%)	0 / 125 (0.00%)	

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