Clinical trial results:
A multi-centre randomised placebo-controlled trial of prophylactic enteral lactoferrin supplementation to prevent late-onset invasive infection in very preterm infants.

Summary

EudraCT number	2012-004260-22
Trial protocol	GB
Global end of trial date	03 May 2018

Results information

Result version number	v1 (current)
This version publication date	26 August 2018
First version publication date	26 August 2018

Trial information

Trial identification

Sponsor protocol code	ELFIN01

Additional study identifiers

ISRCTN number	ISRCTN88261002
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Wellington Square, Oxford, United Kingdom,
Public contact	Ursula Bowler, National Perinatal Epidemiology Unit, 0044 01865289749, ursula.bowler@npeu.ox.ac.uk
Scientific contact	Ursula Bowler, National Perinatal Epidemiology Unit, 0044 01865289749, ursula.bowler@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	03 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2018
Global end of trial reached?	Yes
Global end of trial date	03 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the efficacy of the enteral administration of 150 mg/kg/day of bovine lactoferrin in reducing the incidence of microbiologically-confirmed or clinically suspected late-onset invasive infection (defined as more than 72 hours after birth) from trial entry until hospital discharge in a population of very preterm infants.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2013
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: 2203
Worldwide total number of subjects	2203
EEA total number of subjects	2203

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	2203
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 was conducted in 37 neonatal units in the UK between 7th May 2014 and 28th September 2017.

Pre-assignment

Screening details:

Eligible participants were very preterm infants (gestational age at birth <32 weeks) who were <72 hours old at randomisation. Exclusion criteria were presence of a severe congenital anomaly, anticipated enteral fasting for longer than 14 days, and no realistic prospect of survival.

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, Carer, Assessor

Blinding implementation details:

The lactoferrin powder had similar granularity to sucrose so that when the dry IMP was shaken within the opaque, sealed pots it was not possible to distinguish lactoferrin from sucrose by the sound generated. The opaque containers did not allow the dry IMP to be seen unless the sealed stopper was removed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lactoferrin

Arm description:

Bovine lactoferrin

Arm type	Experimental
Investigational medicinal product name	Bovine lactoferrin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Nasogastric use

Dosage and administration details:

The IMP was prescribed at a dose of 150 mg/kg body weight per day (up to a maximum of 300 mg/day). The IMP was prepared for administration by addition by syringe of sterile water (4 mL) plus expressed breast or formula (1 mL). The pot was shaken vigorously by hand for 30 seconds to generate a mixture containing 75mg/mL of IMP. The mixture was allowed to stand for 30 minutes before removal for administration using an enteral feeding syringe. The IMP was administered once daily by naso- or oro-gastric tube once the infant’s enteral feed volume was >12 mL/kg/day and continued until 34 weeks’ postmenstrual age.

Arm title	Placebo

Arm description:

Sucrose

Arm type	Placebo
Investigational medicinal product name	Sucrose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Nasogastric use

Dosage and administration details:

The IMP was prescribed at a dose of 150 mg/kg body weight per day (up to a maximum of 300

mg/day). The IMP was prepared for administration by addition by syringe of sterile water (4 mL) plus expressed breast or formula (1 mL). The pot was shaken vigorously by hand for 30 seconds to generate a mixture containing 75mg/mL of IMP. The mixture was allowed to stand for 30 minutes before removal for administration using an enteral feeding syringe. The IMP was administered once daily by naso- or oro-gastric tube once the infant's enteral feed volume was >12 mL/kg/day and continued until 34 weeks' postmenstrual age.

Number of subjects in period 1	Lactoferrin	Placebo
Started	1099	1104
Completed	1098	1101
Not completed	1	3
Consent withdrawn by subject	-	3
Consent not confirmed	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lactoferrin
Reporting group description: Bovine lactoferrin	
Reporting group title	Placebo
Reporting group description: Sucrose	

Reporting group values	Lactoferrin	Placebo	Total
Number of subjects	1099	1104	2203
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
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 65-84 years			0
85 years and over			0
Age continuous Units: days			
median	2	2	
inter-quartile range (Q1-Q3)	2 to 3	2 to 3	-
Gender categorical Units: Subjects			
Female	523	521	1044
Male	575	578	1153
Not recorded	1	5	6
Multiple pregnancy Units: Subjects			
Yes	350	346	696
No	748	755	1503
Not recorded	1	3	4
Caesarean section delivery Units: Subjects			
Yes	635	616	1251
No	463	485	948
Not recorded	1	3	4
Membranes ruptured before labour Units: Subjects			
Yes	422	428	850
No	671	669	1340
Not recorded	6	7	13

Membranes ruptured >24hrs before delivery Units: Subjects			
Yes	286	264	550
No	806	832	1638
Not recorded	7	8	15
Mother received antenatal corticosteroids Units: Subjects			
Yes	998	997	1995
No	95	102	197
Not recorded	6	5	11
Infant heart rate >100bpm at 5 mins Units: Subjects			
Yes	995	1010	2005
No	95	83	178
Not recorded	9	11	20
Infant ventilated via endotracheal tube at randomisation Units: Subjects			
Yes	338	357	695
No	760	744	1504
Not Recorded	1	3	4
Infant had absent or reverse end diastolic flow Units: Subjects			
Yes	134	130	264
No	945	951	1896
Not recorded	20	23	43
Birth weight Units: grams			
arithmetic mean	1126	1143	
standard deviation	± 356	± 367	-
Completed weeks gestation at delivery Units: weeks			
median	29	29	
inter-quartile range (Q1-Q3)	27 to 30	27 to 30	-
Mother's age at trial entry Units: years			
arithmetic mean	30.3	30.4	
standard deviation	± 6.1	± 6.0	-
Infant temperature on admission Units: degrees centigrade			
arithmetic mean	36.9	37	
standard deviation	± 0.7	± 0.7	-
Infant worst base excess within first 24 hours of birth Units: mmol/l			
arithmetic mean	-6.2	-6.3	
standard deviation	± 3.9	± 3.8	-

End points

End points reporting groups	
Reporting group title	Lactoferrin
Reporting group description:	
Bovine lactoferrin	
Reporting group title	Placebo
Reporting group description:	
Sucrose	

Primary: Microbiologically-confirmed or clinically suspected late-onset infection	
End point title	Microbiologically-confirmed or clinically suspected late-onset infection
End point description:	
End point type	Primary
End point timeframe:	
From trial entry to hospital discharge home	

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1093	1089		
Units: Number of infants				
Yes	316	334		
No	777	755		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.233
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.95
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.86
upper limit	1.04

Secondary: Microbiologically-confirmed late-onset infection

End point title	Microbiologically-confirmed late-onset infection

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1093	1089		
Units: Number of infants				
Yes	190	180		
No	903	909		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.87
upper limit	1.26

Secondary: All-cause mortality

End point title	All-cause mortality

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1076	1076		
Units: Number of infants				
Yes	71	68		
No	1005	1008		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.782
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.66
upper limit	1.68

Secondary: Necrotising enterocolitis Bell stage II and above

End point title	Necrotising enterocolitis Bell stage II and above

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1085	1084		
Units: Number of infants				
Yes	63	56		
No	1022	1028		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.538
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.67
upper limit	1.89

Secondary: Severe retinopathy of prematurity treated medically or surgically

End point title	Severe retinopathy of prematurity treated medically or surgically

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1080	1080		
Units: Number of infants				
Yes	64	72		
No	1016	1008		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo

Number of subjects included in analysis	2160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.62
upper limit	1.28

Secondary: Bronchopulmonary dysplasia at 36 week postmentrual age

End point title	Bronchopulmonary dysplasia at 36 week postmentrual age

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1023	1027		
Units: Number of infants				
Yes	358	355		
No	665	672		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.01

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.9
upper limit	1.13

Secondary: Late-onset infection, NEC, ROP, BPD or mortality

End point title	Late-onset infection, NEC, ROP, BPD or mortality

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092	1094		
Units: Number of infants				
Yes	525	521		
No	567	573		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.743
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.94
upper limit	1.08

Secondary: Administration of antimicrobials

End point title	Administration of antimicrobials

End point description:

End point type	Secondary

End point timeframe:

From commencment of IMP until 34 weeks postmenstrual age

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1059	1057		
Units: days				
median (inter-quartile range (Q1-Q3))	2 (0 to 8)	3 (0 to 8)		

Statistical analyses

Statistical analysis title	Median difference
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	Quantile regression
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1
upper limit	1

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1003	1004		
Units: days				
median (inter-quartile range (Q1-Q3))	59 (40 to 85)	58 (40 to 84)		

Statistical analyses

Statistical analysis title	Median difference
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.446
Method	Quantile regression
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1
upper limit	3

Secondary: Length of stay in intensive care

End point title	Length of stay in intensive care

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1011	1035		
Units: days				
median (inter-quartile range (Q1-Q3))	8 (4 to 16)	8 (4 to 16)		

Statistical analyses

Statistical analysis title	Median difference
Comparison groups	Lactoferrin v Placebo

Number of subjects included in analysis	2046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.963
Method	Quantile regression
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1
upper limit	1

Secondary: Length of stay in high dependency care

End point title	Length of stay in high dependency care

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1015	1041		
Units: days				
median (inter-quartile range (Q1-Q3))	10 (3 to 30)	9 (3 to 29)		

Statistical analyses

Statistical analysis title	Median difference
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2056
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Quantile regression
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1
upper limit	3

Secondary: Length of stay in special care

End point title	Length of stay in special care

End point description:

End point type	Secondary

End point timeframe:

From trial entry to hospital discharge home

End point values	Lactoferrin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1023	1046		
Units: days				
median (inter-quartile range (Q1-Q3))	29 (21 to 39)	30 (22 to 39)		

Statistical analyses

Statistical analysis title	Median difference
Comparison groups	Lactoferrin v Placebo
Number of subjects included in analysis	2069
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.216
Method	Quantile regression
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-3
upper limit	1

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From trial entry to hospital discharge home	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Not collected as there are multiple non-serious adverse events in this population of very preterm babies.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2013	Text amendments to protocol. IMP Dossier amended. Consent form amended. Parent information leaflet amended. ELFIN Statement of Responsibilities introduced.
17 January 2014	IMP Dossier amended.
27 May 2014	ELFIN/SIFT Summary Leaflet added.
21 July 2014	Notification of temporary halt to trial.
29 October 2014	Two parent posters introduced.
03 November 2014	IMP Dossier amended. Storage requirements of IMP changed.
23 April 2015	Addition of extra recruiting sites in England.
31 July 2015	Parent information leaflet and consent form amended.
10 September 2015	Some continuing care sites converted to recruiting sites.
16 December 2015	Removed requirement for temperature monitoring of IMP at continuing care sites.
31 December 2015	Amendment to text in protocol.
21 January 2016	Conversion of additional continuing care sites to recruiting sites.
04 March 2016	Amendments to text in protocol.
09 August 2016	Additional recruiting sites and change in PIs at existing sites.
21 November 2016	Added continuing care sites in Wales and adapted PIL for Wales.
06 September 2017	Change of existing PI at a a site.
15 March 2018	Amendment to text in protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

21 July 2014	Temporary halt to trial recruitment due to IMP issues.	03 November 2014

Notes:

Limitations and caveats

None reported