Clinical trial results:
Amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double blind controlled trial of Nutritional Evaluation and Optimisation in Neonates.

Summary

EudraCT number	2009-016731-34
Trial protocol	GB
Global end of trial date	23 December 2013

Results information

Result version number	v1 (current)
This version publication date	18 November 2016
First version publication date	18 November 2016
Summary attachment (see zip file)	Final report (end of study report.pdf) NIHR final report (FullReport-eme03020.pdf)

Trial information

Trial identification

Sponsor protocol code	CRO1413

Additional study identifiers

ISRCTN number	ISRCTN29665319
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Room 221, Medical School Building, Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Dr Sabita Uthaya, Chelsea and Westminster NHS Foundation Trust, London, UK Imperial College London, +44 (0)2033157975, s.uthaya@imperial.ac.uk
Scientific contact	Dr Sabita Uthaya, Chelsea and Westminster NHS Foundation Trust, London, UK Imperial College London, +44 (0)2033157975, s.uthaya@imperial.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	23 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2013
Global end of trial reached?	Yes
Global end of trial date	23 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Amino acid arm: Does immediate rather than incremental introduction of Recommended Daily Intake (RDI) of amino acids compared to current practice of incremental and low intake in extremely preterm infants result in a greater accrual of non-adipose (lean) body mass?

Lipid arm: Does 20% SMOFlipid (Soy bean, Medium chain triglycerides, Olive oil and Fish oil combination, a 3rd generation lipid with a lower ratio of n6 to n3 fatty acids and liver protective) compared to 20% Intralipid (currently used lipid formulation composed of Soy bean oil) in extremely preterm infants reduce Intrahepatocellular lipid (IHCL) at term age equivalent?

The three main components of nutrition or 'macronutrients' are carbohydrates, lipids and protein. Amino acids are the 'building blocks' of protein and important for the development of lean tissue such as muscle.

Intrahepatocellular lipid (IHCL) or fatty liver is associated with problems such as diabetes and insulin resistance. We have shown that p

Protection of trial subjects:

All infants recruited to the trial were inpatients in Neonatal Intensive Care Units (NICU) at the time of recruitment and throughout parenteral nutrition. This is in line with routine care for extreme preterm infants. Participation in the trial did not introduce any additional distress over and above routine care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2010
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: 168
Worldwide total number of subjects	168
EEA total number of subjects	168

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	168
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:

Recruitment lasted for 3 years, the first patient was recruited on 06/07/2010 and the last patient on 31/07/2013. A total of 168 infants were recruited from four UK sites; Chelsea and Westminster hospital, West Middlesex hospital, Northwick Park Hospital and Medway Maritime Hospital.

Pre-assignment

Screening details:

460 infants below 31 weeks gestational age were admitted during the trial period. Of the 382 infants meeting the eligibility criteria, 168 were randomised to the trial. Reasons for non recruitment: declined (73), recruited to another trial (3), missed/pharmacy unavailable (46), missed/not approached (33), unknown (59).

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	Investigator, Subject

Blinding implementation details:

Unblinded trial PN was delivered to the pharmacy department at each participating centre. Trained pharmacy staff were responsible for blinding the trial parenteral nutrition (PN) prior to dispensing the supply for administration to each infant.
Secure copies of the randomisation list were held by each pharmacy team in case of the need for emergency unblinding. There was no requirement for unblinding at any point over the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Inc-AA / Intralipid

Arm description:

Incremental amino acid and 20% Intralipid

Arm type	Active comparator
Investigational medicinal product name	Vaminolact (incremental)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Inc-AA arms protein content starts at 1.5 g/kg/day on Day 1, increases to 1.9 g/kg/day on day to and 2.4 g/kg/day on day 3 onwards.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Investigational medicinal product name	20% Intralipid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Inc-AA arms protein content starts at 1.5 g/kg/day on Day 1, increases to 1.9 g/kg/day on day to and 2.4 g/kg/day on day 3 onwards.

Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Arm title	Inc-AA/SMOFlipid

Arm description:

Incremental amino acid and 20% SMOF lipid

Arm type	Experimental
Investigational medicinal product name	Vaminolact (incremental)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Inc-AA arms protein content starts at 1.5 g/kg/day on Day 1, increases to 1.9 g/kg/day on day to and 2.4 g/kg/day on day 3 onwards.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Investigational medicinal product name	SMOFlipid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Inc-AA arms protein content starts at 1.5 g/kg/day on Day 1, increases to 1.9 g/kg/day on day to and 2.4 g/kg/day on day 3 onwards.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Arm title	Imm-RDI/Intralipid

Arm description:

Recommended Daily Intake of amino acids and 20% Intralipid

Arm type	Experimental
Investigational medicinal product name	Vaminolact (RDI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Imm-RDI arms protein content starts at 3.2 g/kg/day on Day 1 and continues at this dose.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Investigational medicinal product name	20% Intralipid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs

are established.
In the Imm-RDI arms protein content starts at 3.2 g/kg/day on Day 1, and continues at this dose.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Arm title	Imm-RDI/SMOFlipid

Arm description:

Recommended Daily Intake of amino acids and 20% SMOF lipid

Arm type	Experimental
Investigational medicinal product name	Vaminolact (RDI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Imm-RDI arms protein content starts at 3.2 g/kg/day on Day 1 and continues at this dose.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Investigational medicinal product name	SMOFlipid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral nutrition will be administered to an infant until milk feeds of 150ml/kg/day for at least 24 hrs are established.
In the Imm-RDI arms protein content starts at 3.2 g/kg/day on Day 1 and continues at this dose.
Lipid content is the same in all arms (2g/kg/day on day 1, increasing to 3g/kg/day on day 2 onwards), only the type of lipid varies

Number of subjects in period 1	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid
Started	42	42	41
Completed	34	28	34
Not completed	8	14	7
Adverse event, serious fatal	3	7	3
Consent withdrawn by subject	-	1	-
Physician decision	-	1	1
Parents participating in conflicting trial	-	1	-
Still inpatient at 44 weeks	1	2	1
Lost to follow-up	4	2	2

Number of subjects in period 1	Imm-RDI/SMOFlipid
Started	43
Completed	37
Not completed	6

Adverse event, serious fatal	3
Consent withdrawn by subject	1
Physician decision	-
Parents participating in conflicting trial	-
Still inpatient at 44 weeks	-
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Inc-AA / Intralipid
Reporting group description:	
Incremental amino acid and 20% Intralipid	
Reporting group title	Inc-AA/SMOFlipid
Reporting group description:	
Incremental amino acid and 20% SMOF lipid	
Reporting group title	Imm-RDI/Intralipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% Intralipid	
Reporting group title	Imm-RDI/SMOFlipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% SMOF lipid	

Reporting group values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid
Number of subjects	42	42	41
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Infant age at birth expressed as gestational age in weeks			
Units: weeks			
arithmetic mean	27.8	27.5	28.1
standard deviation	± 1.9	± 2.4	± 2.1
Gender categorical Units: Subjects			
Female	15	16	19
Male	27	26	22
Multiple births Units: Subjects			
Yes	6	6	9
No	36	36	32
Mother’s ethnicity Units: Subjects			
White	17	19	20
Asian	13	7	13
Black	6	13	6

Mixed	2	2	1
Other	3	0	1
Missing	1	1	0
Mode of delivery Units: Subjects			
Vaginal	8	18	16
Elective caesarean	7	3	4
Emergency caesarean	27	21	21
Antenatal steroids Units: Subjects			
Yes	30	34	32
No	7	6	7
Unknown	5	2	2
Birthweight Units: kilogram(s)			
arithmetic mean	1.03	1.05	1.04
standard deviation	± 0.29	± 0.34	± 0.28
Birth length Units: centimetre(s)			
arithmetic mean	35	34.6	35.3
standard deviation	± 3.6	± 4.2	± 3.8
Head circumference Units: centimetre(s)			
arithmetic mean	25.2	25	25.3
standard deviation	± 2	± 3	± 1.9
Mother's age Units: years			
arithmetic mean	32.9	31.3	32.9
standard deviation	± 5.3	± 7.7	± 6.3
Mother's weight Units: kilogram(s)			
arithmetic mean	67.3	65.9	64
standard deviation	± 13.4	± 11.4	± 12.7
Mother’s height Units: centimetre(s)			
arithmetic mean	161.9	164.9	161.3
standard deviation	± 7.8	± 7.7	± 9.2
Father’s weight Units: kilogram(s)			
arithmetic mean	80.8	82.3	85.3
standard deviation	± 10.7	± 13.2	± 16.1
Father's height Units: centimetre(s)			
arithmetic mean	178.4	179.6	175.7
standard deviation	± 6.5	± 6.8	± 10
Time from birth to starting Parenteral Nutrition Units: hour(s)			
median	18.4	19.5	20.4
inter-quartile range (Q1-Q3)	12.3 to 22.7	13.6 to 22.8	12.6 to 23.6
Birthweight (z-score) Units: z-score			

arithmetic mean	-0.2	0.1	-0.2
standard deviation	± 0.9	± 1	± 1
Birth length (z-score)			
Units: z-score			
arithmetic mean	-1	-0.9	-1.1
standard deviation	± 1	± 1.2	± 1
Head circumference (z-score)			
Units: z-score			
arithmetic mean	-0.5	-0.3	-0.7
standard deviation	± 0.9	± 1	± 0.9

Reporting group values	Imm-RDI/SMOFlipid	Total	
Number of subjects	43	168	
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			
Infant age at birth expressed as gestational age in weeks			
Units: weeks			
arithmetic mean	27.8		
standard deviation	± 2.1	-	
Gender categorical			
Units: Subjects			
Female	21	71	
Male	22	97	
Multiple births			
Units: Subjects			
Yes	15	36	
No	28	132	
Mother’s ethnicity			
Units: Subjects			
White	21	77	
Asian	12	45	
Black	6	31	
Mixed	2	7	
Other	2	6	
Missing	0	2	
Mode of delivery			
Units: Subjects			
Vaginal	17	59	
Elective caesarean	2	16	
Emergency caesarean	24	93	

Antenatal steroids Units: Subjects			
Yes	35	131	
No	4	24	
Unknown	4	13	
Birthweight Units: kilogram(s)			
arithmetic mean	1.06		
standard deviation	± 0.29	-	
Birth length Units: centimetre(s)			
arithmetic mean	35.2		
standard deviation	± 5.2	-	
Head circumference Units: centimetre(s)			
arithmetic mean	25.6		
standard deviation	± 2.9	-	
Mother's age Units: years			
arithmetic mean	32.5		
standard deviation	± 6.6	-	
Mother's weight Units: kilogram(s)			
arithmetic mean	68.5		
standard deviation	± 15.2	-	
Mother’s height Units: centimetre(s)			
arithmetic mean	164.5		
standard deviation	± 8.6	-	
Father’s weight Units: kilogram(s)			
arithmetic mean	86.3		
standard deviation	± 14.9	-	
Father's height Units: centimetre(s)			
arithmetic mean	182		
standard deviation	± 9.7	-	
Time from birth to starting Parenteral Nutrition Units: hour(s)			
median	17.7		
inter-quartile range (Q1-Q3)	13 to 22.4	-	
Birthweight (z-score) Units: z-score			
arithmetic mean	0		
standard deviation	± 0.9	-	
Birth length (z-score) Units: z-score			
arithmetic mean	-0.8		
standard deviation	± 1.5	-	
Head circumference (z-score) Units: z-score			

arithmetic mean	-0.2		
standard deviation	± 1.6	-	

End points

End points reporting groups	
Reporting group title	Inc-AA / Intralipid
Reporting group description:	
Incremental amino acid and 20% Intralipid	
Reporting group title	Inc-AA/SMOFlipid
Reporting group description:	
Incremental amino acid and 20% SMOF lipid	
Reporting group title	Imm-RDI/Intralipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% Intralipid	
Reporting group title	Imm-RDI/SMOFlipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% SMOF lipid	

Primary: Non-adipose mass	
End point title	Non-adipose mass
End point description:	
Non-adipose (lean) body mass measured by whole body magnetic resonance imaging (MRI)	
End point type	Primary
End point timeframe:	
Measured at term age equivalent, i.e. 37-44 weeks gestational age.	

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	28	34	37
Units: gram(s)				
arithmetic mean (confidence interval 95%)	2450 (2246 to 2655)	2337 (2164 to 2510)	2344 (2244 to 2444)	2485 (2327 to 2643)

Statistical analyses

Statistical analysis title	Multiple regression
Statistical analysis description:	
A multiple regression was used with non-adipose mass (g) as the dependent variable and amino acid group (Inc-AA or Imm-RDI), lipid group (Intralipid or SMOFlipid), stratifying variables (gestational age, birthweight and centre), sex and age at assessment as the independent variables. An interaction term was added to assess if the effect of amino acid regimen is influenced by lipid type.	
Comparison groups	Inc-AA / Intralipid v Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Imm-RDI/SMOFlipid

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-108
upper limit	111

Notes:

[1] - 2x2 Factorial design.
Comparison for non-adipose mass based on Inc-AA versus Imm-RDI groups.

Primary: Intrahepatocellular Lipid (IHCL)

End point title	Intrahepatocellular Lipid (IHCL)

End point description:

Intrahepatocellular lipid content (IHCL) measured by hepatic magnetic resonance spectroscopy (MRS)

End point type	Primary

End point timeframe:

Measured at term age equivalent, i.e. 37-44 weeks gestational age

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	28	34	36
Units: not applicable				
arithmetic mean (confidence interval 95%)	0.6 (0.4 to 0.9)	0.7 (0.5 to 1)	0.5 (0.4 to 0.6)	0.5 (0.3 to 0.7)

Statistical analyses

Statistical analysis title	Multiple regression

Statistical analysis description:

A multiple regression was used with IHCL content (natural logarithmic scale) as the dependent variable and amino acid group (Inc-AA or Imm-RDI), lipid group (Intralipid or SMOFlipid), stratifying variables (gestational age, birthweight and centre), sex and age at assessment as the independent variables. An interaction term was added to assess if the effect of amino acid regimen is influenced by lipid type.

Comparison groups	Inc-AA / Intralipid v Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Imm-RDI/SMOFlipid
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	geometric mean ratio
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.6

Notes:

[2] - 2 x 2 Factorial trial
IHCL based comparison of Intralipid and SMOFlipid arms

Secondary: Total cerebral volume

End point title	Total cerebral volume

End point description:

End point type	Secondary

End point timeframe:

Term age equivalent, i.e. 37-44 weeks gestational age

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	11	15
Units: cm^3				
arithmetic mean (confidence interval 95%)	468 (419 to 518)	480 (425 to 534)	468 (414 to 523)	511 (440 to 583)

Statistical analyses

Statistical analysis title	Multiple regression
Comparison groups	Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Inc-AA / Intralipid v Imm-RDI/SMOFlipid
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42
upper limit	71

Notes:

[3] - 2X2 factorial trial
Analysis based on comparison of Imm-AA and Imm-RDI arms

Secondary: Whole-brain volume

End point title	Whole-brain volume

End point description:

End point type	Secondary

End point timeframe:

Term age equivalent, i.e. 37-44 weeks gestational age

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	11	15
Units: cm^3				
arithmetic mean (confidence interval 95%)	339 (304 to 373)	352 (319 to 385)	344 (296 to 393)	365 (321 to 410)

Statistical analyses

Statistical analysis title	Multiple regression
Comparison groups	Inc-AA / Intralipid v Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Imm-RDI/SMOFlipid
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	47

Notes:

[4] - 2X2 factorial design
Analysis based on comparison of Inc-AA and Imm-RDI arms

Secondary: Posterior fossa volume

End point title	Posterior fossa volume

End point description:

End point type	Secondary

End point timeframe:

Term age equivalent, i.e. 37-44 weeks gestational age

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	11	15
Units: cm^3				
arithmetic mean (confidence interval 95%)	30 (26 to 33)	31 (28 to 34)	30 (27 to 34)	35 (29 to 38)

Statistical analyses

Statistical analysis title	Multiple regression
Comparison groups	Inc-AA / Intralipid v Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Imm-RDI/SMOFlipid
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	4.87

Notes:

[5] - 2X2 factorial design
Analysis based on comparison of Inc-AA and Imm-RDI arms

Secondary: QUICKI

End point title	QUICKI

End point description:

Metabolic index of insulin resistance at term age equivalent (Quantitative insulin-sensitivity check index: QUICKI), calculated using fasting serum glucose and insulin.

End point type	Secondary

End point timeframe:

Term age equivalent (37-44 weeks gestational age)

End point values	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid	Imm-RDI/SMOFlipid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	6	11	11
Units: not applicable				
arithmetic mean (confidence interval 95%)	0.18 (0.17 to 0.19)	0.19 (0.18 to 0.2)	0.19 (0.18 to 0.2)	0.18 (0.17 to 0.2)

Statistical analyses

Statistical analysis title	Multiple regression
Comparison groups	Inc-AA / Intralipid v Inc-AA/SMOFlipid v Imm-RDI/Intralipid v Imm-RDI/SMOFlipid
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.02

Notes:

[6] - 2 x 2 factorial design
Analysis based on comparison of Intralipid and SMOFlipid arms

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
From randomisation to term age equivalent, i.e. 37-44 weeks gestational age	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Inc-AA / Intralipid
Reporting group description:	
Incremental amino acid and 20% Intralipid	
Reporting group title	Inc-AA/SMOFlipid
Reporting group description:	
Incremental amino acid and 20% SMOF lipid	
Reporting group title	Imm-RDI/Intralipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% Intralipid	
Reporting group title	Imm-RDI/SMOFlipid
Reporting group description:	
Recommended Daily Intake of amino acids and 20% SMOF lipid	

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: This trial evaluated standard treatments used within their licensed indications so it was not necessary to report and assess non-Serious AEs.

Serious adverse events	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 42 (19.05%)	13 / 42 (30.95%)	8 / 41 (19.51%)
number of deaths (all causes)	3	7	3
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Chromosome abnormality			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular haemorrhage			

subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Convulsion neonatal			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
cot death			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Ileal perforation			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis			
subjects affected / exposed	3 / 42 (7.14%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal sepsis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 42 (4.76%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Imm-RDI/SMOFlipid		

Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 43 (25.58%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Chromosome abnormality			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intraventricular haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion neonatal			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
cot death			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileal perforation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising enterocolitis				
subjects affected / exposed	4 / 43 (9.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Respiratory, thoracic and mediastinal disorders				
Pneumothorax				
subjects affected / exposed	3 / 43 (6.98%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchiolitis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterobacter sepsis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fungal sepsis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Sepsis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Inc-AA / Intralipid	Inc-AA/SMOFlipid	Imm-RDI/Intralipid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)

Non-serious adverse events	Imm-RDI/SMOFlipid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2010	Protocol version 2 Clarifications implemented following review by the Trial Steering Committee (TSC): a) clarification that randomisation would be performed by minimisation with 25% chance of random allocation b) randomisation to be stratified by birthweight in addition to existing factors (centre and gestational age at birth) c) addition of a monthly evaluation to assess trace elements for infants on PN for > 28 days d) Addition of a metabonomic substudy e) Administrative corrections
28 October 2010	a) Additional blood samples on days 1 and 5 of life to assess inflammatory markers and lipid profile: The intention was to conduct a substudy to collect these samples at the lead site but it was never implemented. b) Clarification of randomisation time window. The protocol previously stated that infants must be randomised within 12 hours of birth. The purpose of this time window was to allow adequate time for preparation and dispensing of trial PN. The time window was revised for this version of the protocol so that infants needed to be randomised in enough time to allow administration of PN within 24 hours. c) Administrative corrections.
16 October 2012	The protocol was amended to include a follow-up visit for neurodevelopmental outcomes at 2 years corrected age using the Bayley Scale of Infant Development, the Hammersmith Optimality Score as well as parental questionnaires (Social-Emotional scale of the Bayley Scales and the Quantitative Checklist for Autism in Toddlers). A funding application for this additional visit was not successful, so the additional visit was not implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27099248

http://www.ncbi.nlm.nih.gov/pubmed/27030860