Clinical trial results:
A randomised controlled trial of iodide supplementation in preterm infants with follow-up at 2 years

Summary

EudraCT number	2008-001024-31
Trial protocol	GB
Global end of trial date	22 April 2015

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	08/S0501/31

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00638092
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTRG, Joint Research Office, Block 60, Churchill Hospital, Old Road, Headington,, Oxford , United Kingdom, OX3 7LE
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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 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2015
Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does iodide supplementation of extreme preterm infants improve neurodevelopmental outcome at 2 years corrected age?

Protection of trial subjects:

The trial solutions were given as part of routine nutrition - no pain or inconvenience was associated. Blood for trial measurements was coincided with routine clinical blood samples - so no additional pain or inconvenience was associated with trial participation.

Background therapy:

All infants in I2S2 trial were recruited while in neonatal intensive care units and they remained in the units for the duration of the intervention phase of the trial. As such all infants were very likely in receipt of a range of drug and clinical therapies.

Evidence for comparator:

The comparator was sodium chloride at chloride content of 75mcg/ml. The daily chloride allowance for preterm neonates is 2 mmol/kg/day and the additional chloride content derived from the trial solutions was miniscule. The placebo was given in the same dose and volume as the intervention and the solutions were visually indistinguishable.

Actual start date of recruitment	10 March 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: 1259
Worldwide total number of subjects	1259
EEA total number of subjects	1259

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	1259
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:

Infants were eligible if they were <42 hours old, born <31 weeks' gestation in one of the 21 trial recruiting hospitals and had a realistic prospect of survival.

Pre-assignment

Screening details:

The only exclusion criterion was maternal exposure to iodine during pregnancy or delivery.

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, Monitor, Data analyst, Carer, Subject, Assessor

Blinding implementation details:

The packaging and visual appearance of trial solutions was identical; the dose for both was 30 mcg/kg/day, given daily from randomisation until the equivalent of 34 weeks' gestational age (had the fetus remained in utero), referred to hereafter as equivalent gestational age. The trial solutions could be given parenterally or enterally. Masking ensured that the research team, parents of I2S2 participants, neonatal staff and pharmacy were blind to the content of the trial solutions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium Chloride

Arm description:

This is the placebo arm

Arm type	Placebo
Investigational medicinal product name	Sodium Chloride
Investigational medicinal product code	sodium chloride
Other name	NaCl
Pharmaceutical forms	Solution for infusion
Routes of administration	Enteral use , Parenteral use

Dosage and administration details:

30 mcg/kg/day.
Enteral or parenteral use.

Arm title	Sodium Iodide

Arm description:

This is the intervention arm

Arm type	Experimental
Investigational medicinal product name	Sodium Iodide
Investigational medicinal product code	
Other name	sodium iodide injection BP 2004
Pharmaceutical forms	Solution for infusion
Routes of administration	Enteral use , Parenteral use

Dosage and administration details:

30 mcg/kg/day
Enteral or parenteral route

Number of subjects in period 1	Sodium Chloride	Sodium Iodide
Started	628	631
Completed	628	631

Baseline characteristics

Reporting groups	
Reporting group title	Sodium Chloride
Reporting group description:	
This is the placebo arm	
Reporting group title	Sodium Iodide
Reporting group description:	
This is the intervention arm	

Reporting group values	Sodium Chloride	Sodium Iodide	Total
Number of subjects	628	631	1259
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			
gestational age at birth			
Units: weeks			
arithmetic mean	27.4	27.4	
standard deviation	± 2	± 2	-
Gender categorical			
Units: Subjects			
Female	281	282	563
Male	347	349	696
Main causes of preterm birth			
Main causes of preterm birth			
Units: Subjects			
pre-labour rupture of membranes	183	173	356
preterm labour without PROM	201	215	416
Antepartum haemorrhage	60	66	126
Pregnancy induced hypertension with or without APH	68	54	122
Other maternal illness	58	55	113
Poor fetal growth	56	67	123
Other	2	1	3
missing data	0	0	0
Infant ancestry			
Units: Subjects			
Black	23	16	39
Asian	43	48	91

White	516	531	1047
Other	45	35	80
missing data	1	1	2
Region of birth Units: Subjects			
Scotland	135	140	275
North East England	183	183	366
remainder England	264	263	527
Northern Ireland	46	45	91
Analgesia given during labour Units: Subjects			
none	52	54	106
entonox	136	132	268
general anaesthesia	62	70	132
epidural/spinal	205	219	424
opiod	20	15	35
other	10	8	18
More than one form of pain relief given	132	125	257
missing data	11	8	19
Smoking status (maternal) Units: Subjects			
current	139	150	289
ex	86	68	154
non	401	410	811
missing data	2	3	5
maternal steroids given (other than for RDS)			
RDS= respiratory distress syndrome			
Units: Subjects			
yes	34	40	74
no	594	591	1185
maternal steroids given for prevention of RDS			
RDS= Respiratory distress syndrome			
Units: Subjects			
yes	569	586	1155
no	59	45	104
maternal thyroid disease			
concurrent with pregnancy			
Units: Subjects			
yes	19	22	41
no	609	609	1218
Mode of delivery Units: Subjects			
spontaneous cephalic vaginal	237	221	458
vaginal breech	69	74	143
instrumental cephalic vaginal	14	11	25
elective caesarean	33	41	74
emergency caesarean	275	284	559

Agar Score at 5 mins			
Apgar Score at 5 minutes of age			
Units: Apgar points			
arithmetic mean	7.8	7.8	
standard deviation	± 1.8	± 1.8	-
Age at receipt of first trial solution			
Age at receipt of first trial solution			
Units: hr:min			
arithmetic mean	39.03	39.3	
standard deviation	± 13.77	± 15.15	-
Birth weight			
Units: grams			
arithmetic mean	1053	1055	
standard deviation	± 309	± 308	-
maternal age at delivery			
Units: years			
arithmetic mean	29.4	29.3	
standard deviation	± 6.5	± 6.4	-

End points

End points reporting groups	
Reporting group title	Sodium Chloride
Reporting group description: This is the placebo arm	
Reporting group title	Sodium Iodide
Reporting group description: This is the intervention arm	

Primary: Bayley-III Cognitive Score	
End point title	Bayley-III Cognitive Score
End point description: Cognitive score is a Bayley-III main domain. The data included in this table are the intention-to-treat population and includes deaths and severely disabled infants who were coded 55; missing outcomes for losses to follow up were imputed using multiple imputation.	
End point type	Primary
End point timeframe: Bayley-III neurodevelopment assessment was measured in all infants at 2 years of age corrected for prematurity	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	89.2 (± 19.5)	88.9 (± 19.2)		

Statistical analyses

Statistical analysis title	95% CI
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	1.89

Variability estimate	Standard error of the mean
Dispersion value	1.136

Primary: Bayley-III Motor Composite Score

End point title	Bayley-III Motor Composite Score

End point description:

The Bayley-III motor composite scale is a main domain of the Bayley-III
The data included in this table are the intention-to-treat population and includes deaths and severely disabled infants who were coded 46; missing outcomes for losses to follow up were imputed using multiple imputation.

End point type	Primary

End point timeframe:

2 years corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	88 (± 21.6)	88.2 (± 21)		

Statistical analyses

Statistical analysis title	95% Confidence Interval

Statistical analysis description:

Comparison was sodium iodide v sodium chloride

Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	2.65
Variability estimate	Standard error of the mean
Dispersion value	1.243

Primary: Bayley-III Language composite score

End point title	Bayley-III Language composite score

End point description:

The Bayley-III language composite scale is a main domain of the Bayley-III
The data included in this table are the intention-to-treat population and includes deaths and severely disabled infants who were coded 47; missing outcomes for losses to follow up were imputed using multiple imputation.

End point type	Primary

End point timeframe:

at two years of age corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley-III units				
arithmetic mean (standard deviation)	85.2 (± 21.8)	85.1 (± 21.7)		

Statistical analyses

Statistical analysis title	95% CI

Statistical analysis description:

95% Confidence Interval

Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	2.39
Variability estimate	Standard error of the mean
Dispersion value	1.24

Primary: Bayley-III cognitive score (including death and severe disability)

End point title	Bayley-III cognitive score (including death and severe disability)

End point description:

Single imputation was used for deaths and severe disability, which were coded 55
(These data exclude infants lost to follow up)

End point type	Primary

End point timeframe:

2 years corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	572		
Units: bayley				
arithmetic mean (standard deviation)	88.7 (± 19.8)	88.2 (± 19.4)		

Statistical analyses

Statistical analysis title	95% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1148
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.69
upper limit	1.85
Variability estimate	Standard error of the mean
Dispersion value	1.16

Primary: Bayley-III motor composite score (including death and severe disability)

End point title	Bayley-III motor composite score (including death and severe disability)

End point description:

Single imputation was used for deaths and severe disability, which were coded 46
(These data exclude infants lost to follow up)

End point type	Primary

End point timeframe:

measured at 2 years corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Bayley units				
arithmetic mean (standard deviation)	87.5 (± 22)	87.6 (± 21.4)		

Statistical analyses

Statistical analysis title	95% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	2.59
Variability estimate	Standard error of the mean
Dispersion value	1.28

Primary: Bayley-III Language composite score (including death and severe disability)

End point title	Bayley-III Language composite score (including death and severe disability)

End point description:

Single imputation was used for deaths and severe disability, which were coded 47
(These data exclude infants lost to follow up)

End point type	Primary

End point timeframe:

measured at 2 years of age corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	574	572		
Units: Bayley-III units				
arithmetic mean (standard deviation)	84.7 (± 22.1)	84.6 (± 22)		

Statistical analyses

Statistical analysis title	95% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1146
Analysis specification	Pre-specified
Analysis type	superiority
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.3

Secondary: Bayley-III Subset score: Receptive Language

End point title	Bayley-III Subset score: Receptive Language

End point description:

The data included in this table are the intention-to-treat population and includes deaths and severely disabled who were coded at the lowest achievable score; missing outcomes for losses were imputed using multiple imputation

End point type	Secondary

End point timeframe:

measured at two years of age, corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	7.46 (± 3.77)	7.51 (± 3.8)		

Statistical analyses

Statistical analysis title	99% Confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride

Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.51
upper limit	0.61

Secondary: Bayley-III Subset score: Expressive Language

End point title	Bayley-III Subset score: Expressive Language

End point description:

The data included in this table are the intention-to-treat population and includes deaths and severely disabled who were coded at the lowest achievable score; missing outcomes for losses were imputed using multiple imputation

End point type	Secondary

End point timeframe:

measured at 2 years of age corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	7.34 (± 4.06)	7.31 (± 4.06)		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.62
upper limit	0.57

Secondary: Bayley-III Subset score: Fine Motor

End point title	Bayley-III Subset score: Fine Motor

End point description:

The data included in this table are the intention-to-treat population and includes deaths and severely disabled who were coded at the lowest achievable score; missing outcomes for losses were imputed using multiple imputation

End point type	Secondary

End point timeframe:

measured at 2 years of age corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	8.72 (± 4.13)	8.86 (± 3.99)		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.47
upper limit	0.76

Secondary: Bayley-III subset score: Gross Motor

End point title	Bayley-III subset score: Gross Motor

End point description:

The data included in this table are the intention-to-treat population and includes deaths and severely disabled who were coded at the lowest achievable score; missing outcomes for losses were imputed using multiple imputation

End point type	Secondary

End point timeframe:

Measured at 2 years corrected for prematurity

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: Bayley units				
arithmetic mean (standard deviation)	7.16 (± 3.68)	7.07 (± 3.61)		

Statistical analyses

Statistical analysis title	99% confidnece intervals
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.63
upper limit	0.45

Secondary: Composite outcome

End point title	Composite outcome
End point description:	
Low Bayley-III score (or death) in any of the main Bayley-III domains (i.e. cognitive, motor composite or language composite) in the intention-to-treat population	
End point type	Secondary
End point timeframe:	
counted at two years of age	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
Bayley-III equal to or over 85	320	306		
Bayley-III under 85 (or death)	308	325		

Statistical analyses

Statistical analysis title	Odds Ratio
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.82
upper limit	1.49

Secondary: postnatal conditions-chronic lung disease	
End point title	postnatal conditions-chronic lung disease
End point description:	

End point type	Secondary
End point timeframe:	
counted at the equivalent of 36 week's gestation	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	235	262		
no	393	367		
missing data	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride

Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.19
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.89
upper limit	1.61

Secondary: Postnatal conditions- respiratory distress syndrome

End point title	Postnatal conditions- respiratory distress syndrome
End point description:	

End point type	Secondary
End point timeframe:	
counted at the equivalent of 36 week's gestation	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	581	591		
no	47	38		
data missing	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.7
upper limit	2.25

Secondary: Postnatal conditions - persistent ductus arteriosus

End point title	Postnatal conditions - persistent ductus arteriosus

End point description:

End point type	Secondary

End point timeframe:

counted at the equivalent of 36 week's gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	195	192		
no	433	437		
data missing	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.71
upper limit	1.34

Secondary: Postnatal conditions - necrotising enterocolitis

End point title	Postnatal conditions - necrotising enterocolitis

End point description:

End point type	Secondary

End point timeframe:

counted at the equivalent of 36 week's gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	103	128		
no	525	501		
missing data	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.89
upper limit	1.9

Secondary: Postnatal illnesses - hyperbilirubinaemia

End point title	Postnatal illnesses - hyperbilirubinaemia

End point description:

End point type	Secondary

End point timeframe:

collected at the equivalent of 36 week's gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	519	522		
no	109	107		
missing data	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.7
upper limit	1.51

Secondary: Postnatal conditions - infants with more than one acquired infection

End point title	Postnatal conditions - infants with more than one acquired infection

End point description:

End point type	Secondary

End point timeframe:

collected at the equivalent of 36 week's gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	258	283		
no	370	346		
missing data	0	2		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride

Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.92
upper limit	1.16

Secondary: Postnatal conditions- cerebral pathology

End point title	Postnatal conditions- cerebral pathology

End point description:

End point type	Secondary

End point timeframe:

measured closest to the equivalent of 34 week's gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	89	93		
no	392	385		
missing data	147	153		

Statistical analyses

Statistical analysis title	99% confidence interval

Statistical analysis description:

summary statistic

Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.62
upper limit	1.44

Secondary: Hearing impairment	
End point title	Hearing impairment
End point description: Hearing impairment = deaf or requires hearing aids	
End point type	Secondary
End point timeframe: counted at 2 years of age	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	14	15		
no	528	536		
missing data	86	80		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.4
upper limit	2.79

Secondary: vision impairment	
End point title	vision impairment
End point description: vision impairment = blind or difficulty seeing even with glasses	
End point type	Secondary
End point timeframe: counted at 2 years of age	

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
yes	14	9		
no	527	542		
missing data	87	80		

Statistical analyses

Statistical analysis title	99% confidence interval
Comparison groups	Sodium Iodide v Sodium Chloride
Number of subjects included in analysis	1259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.21
upper limit	1.9

Secondary: Level of Nursing Care Day 7

End point title	Level of Nursing Care Day 7

End point description:

End point type	Secondary

End point timeframe:
counted at day 7 postnatal

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
Level 1	321	323		
Level 2	212	206		
Level 3	82	84		
missing data	13	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Nursing Care day 14

End point title	Level of Nursing Care day 14

End point description:

End point type	Secondary

End point timeframe:
day 14 postnatal

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
Level1	219	230		
Level 2	230	200		
Level 3	147	168		
missing data	32	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Nursing Care day 28

End point title	Level of Nursing Care day 28

End point description:

End point type	Secondary

End point timeframe:
day 28 postnatal

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
Level 1	131	137		
Level 2	228	216		
Level 3	218	230		
missing data	51	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Nursing Care at the equivalent of 34 weeks gestation

End point title	Level of Nursing Care at the equivalent of 34 weeks gestation

End point description:

End point type	Secondary

End point timeframe:

the equivalent of 34 weeks gestation

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	631		
Units: infants				
Level 1	33	39		
Level 2	181	188		
Level 3	355	337		
missing data	59	67		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Score by Hypothyroxinaemic status

End point title	Cognitive Score by Hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	498	498		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
hypothyroxinaemic	89 (± 17)	92 (± 15)		
euthyroid	95 (± 15)	94 (± 16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Motor Composite Score by Hypothyroxinaemic status

End point title	Motor Composite Score by Hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	498	497		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	91 (± 18)	92 (± 14)		
Euthyroid	95 (± 15)	94 (± 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Language Composite Score by Hypothyroxinaemic status

End point title	Language Composite Score by Hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	496	498		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	85 (± 19)	89 (± 18)		
Euthyroid	92 (± 17)	91 (± 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Receptive language by hypothyroxinaemic status

End point title	Receptive language by hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	496	498		
Units: Bayley-III				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	7.3 (± 3)	8.1 (± 3)		
Euthyroid	8.7 (± 3)	8.4 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Expressive language by hypothyroxinaemic status

End point title	Expressive language by hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	498		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	7.4 (± 3)	8.1 (± 4)		
Euthyroid	8.6 (± 3)	8.3 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fine motor score by hypothyroxinaemic status

End point title	Fine motor score by hypothyroxinaemic status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	497		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	9.3 (± 4)	9.7 (± 3)		
Euthyroid	9.9 (± 3)	10 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Gross Motor Score by Hypothyroxinaemic Status

End point title	Gross Motor Score by Hypothyroxinaemic Status

End point description:

Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder.

End point type	Secondary

End point timeframe:

Hypothyroxinaemic status classified during first 28 days of life, neurodevelopment outcome assessed at 2 years of age.

End point values	Sodium Chloride	Sodium Iodide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	498		
Units: Bayley-III units				
arithmetic mean (standard deviation)				
Hypothyroxinaemic	7.7 (± 3)	7.7 (± 3)		
Euthyroid	8.3 (± 3)	8.1 (± 3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SUSARS and AEs were reported for each infant for the period of the trial solutions supplementation plus two weeks or discharge from hospital (which ever was first).

Adverse event reporting additional description:

The infants were all in neonatal intensive care units during the trial. Many adverse events were anticipated as all infants were extremely preterm. A guidance sheet listed the anticipated events that did not require specific recording for the purposes of the I2S2 trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	we did not use one
Dictionary version	0

Reporting groups

Reporting group title	Placebo arm

Reporting group description:

These infants were all extremely preterm and have an anticipated death rate of 10-11% . Anticipated adverse events were recorded in the clinical notes and on the case report form. Some screening laboratories instigate follow-up tests at TSH levels ≥6 mU/l, so we classified this level as an adverse event to ensure that these infants were quickly investigated by local units; such mildly raised TSHs were not considered clinically as an adverse events although they were recorded as such for trial monitoring purposes.

Reporting group title	Intervention arm

Reporting group description:

These infants were all extremely preterm and have an anticipated death rate of 10-11% . Anticipated adverse events were recorded in the clinical notes and on the case report form. Some screening laboratories instigate follow-up tests at TSH levels ≥6 mU/l, so we classified this level as an adverse event to ensure that these infants were quickly investigated by local units; such mildly raised TSHs were not considered clinically as an adverse events although they were recorded as such for trial monitoring purposes.

Serious adverse events	Placebo arm	Intervention arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 628 (0.80%)	13 / 631 (2.06%)	
number of deaths (all causes)	66	65	
number of deaths resulting from adverse events	0	0	
Investigations			
miscellaneous	Additional description: persistent metabolic acidosis, fluctuating sodium levels, intrahepatic calcification, hypernatraemia, fulminating NEC, GI obstruction, abdominal mass, pleural effusion, clot in aorta, aortic sleeve thrombus, hypoglycaemia		
subjects affected / exposed	5 / 628 (0.80%)	13 / 631 (2.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo arm	Intervention arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 628 (3.66%)	45 / 631 (7.13%)	
Endocrine disorders			
TSH levels =>6mU/L	Additional description: All infants who has a TSH level=>6 mU/L were recorded as an adverse event solely to ensure that such infants were quickly monitored locally; they were NOTconsidered an adverse event from a clinical perspective.		
alternative assessment type: Systematic			
subjects affected / exposed	23 / 628 (3.66%)	45 / 631 (7.13%)	
occurrences (all)	23	45	

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