# 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 |
| Public contact | Fiona Williams, Population Health Sciences, Medical Research Institute, University of Dundee, DD2 4B, Fiona Williams, Population Health Sciences, Medical Research Institute, University of Dundee, DD2 4B, 01382 383726, f.l.r.williams@dundee.ac.uk |
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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<br>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<br>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)<br>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<br>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:<br>This is the placebo arm | |
| Reporting group title | Sodium Iodide |
| Reporting group description:<br>This is the intervention arm | |

| Primary: Bayley-III Cognitive Score | |
|---|---|
| End point title | Bayley-III Cognitive Score |
| End point description:<br>Cognitive score is a Bayley-III main domain.<br>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:<br>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:<br>Hearing impairment = deaf or requires hearing aids | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>vision impairment = blind or difficulty seeing even with glasses | |
| End point type | Secondary |
| End point timeframe:<br>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