



Clinical trial results: International Collaborative Infantile Spasms Study (ICISS) Summary

EudraCT number	2006-000788-27
Trial protocol	GB DE
Global end of trial date	31 December 2017

Results information

Result version number	v1
This version publication date	16 July 2018
First version publication date	16 July 2018

Trial information

Trial identification

Sponsor protocol code	RD01273
-----------------------	---------

Additional study identifiers

ISRCTN number	ISRCTN54363174
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal United Hospitals Bath NHS Foundation Trust
Sponsor organisation address	Combe Park, Bath, United Kingdom, BA1 3NG
Public contact	The ICISS Trial Office, The Childrens Centre, Royal United Hospital, Combe Park, Bath, BA1 3NG, United Kingdom, iciss@ruh-bath.swest.nhs.uk
Scientific contact	The ICISS Trial Office, The Childrens Centre, Royal United Hospital, Combe Park, Bath, BA1 3NG, United Kingdom, iciss@ruh-bath.swest.nhs.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	21 June 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to examine if combining hormonal treatment and vigabatrin is better at early control of infantile spasms (day 14-42 of treatment) and at helping development at 18 months of age than taking a hormonal treatment alone.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol and adhered to the principles of good clinical practice as stated in European Commission Directive 2005/28/EC and data protection regulations. A clinical trial risk assessment was undertaken by the Sponsor prior to commencement of recruitment and a Data Monitoring and Ethics Committee (DMEC) was appointed who met once a year to review study recruitment, serious adverse reactions (SARs) and approve the annual safety reports. A Trial Steering Committee (TSC) met approximately every 3 months to oversee the progress of the trial. The TSC and the Sponsor could both request the DMEC to assess the progress of the trial, including safety and drop out. The DMEC could recommend to the TSC and/or Sponsor whether to continue, modify or stop the trial. Any SAR or Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported to the relevant authorities within the required time-frames. Informed signed consent was obtained for each child and the parents or guardians were informed they were free to withdraw their child from the trial at any time without giving a reason and without affecting the care they receive. Central monitoring of data was undertaken by the Trial Centre.

Background therapy: -

Evidence for comparator:

Vigabatrin and hormonal therapies are the two most commonly used and investigated treatments for the treatment of infantile spasms (see Hancock EC, Osborne JP, Edwards SW. Treatment of Infantile Spasms. Cochrane Database Syst Rev. 2013 Jun 5;6:CD001770. DOI: 10.1002/14651858.CD001770.pub3. PubMed ID: 23740534). Our previous study demonstrated that hormonal therapy was superior to vigabatrin at stopping spasms (see Lux AL et al., Lancet 2004; 364: 1773-1778. PubMed ID: 15541450). However, it was also evident from the UKISS study that some patients who failed on their initially randomised therapy (either hormonal therapy or vigabatrin) responded to the other therapy when they were crossed over. Consequently we formed the hypothesis that combining hormonal therapy with vigabatrin may be more effective than hormonal therapy alone at stopping spasms and may therefore also be associated with better developmental outcomes.

Actual start date of recruitment	07 March 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 285
Country: Number of subjects enrolled	Germany: 31

Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	Switzerland: 20
Worldwide total number of subjects	377
EEA total number of subjects	316

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	377
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:

Between March 7 2007 and May 22 2014, 766 infants were assessed for eligibility, of whom 377 met the inclusion criteria and were randomly assigned. Recruitment took place in Australia, Germany, New Zealand, Switzerland and the United Kingdom.

Pre-assignment

Screening details:

Incl: Clinical features of Infantile Spasms confirmed by clinician, EEG hypsarrhythmic or similar compatible with diagnosis. Signed informed consent

Excl: Age < 2mths or > 14mths, > 7 days since diagnosis, TS, prev treatment for IS, prev hormonal or vgb treatment, potentially lethal condition, can't follow-up @ 18mths, language difficulty, in concurrent trial

Pre-assignment period milestones

Number of subjects started	377
Number of subjects completed	377

Period 1

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

Blinding implementation details:

Blinding of outcome measures: The pre-treatment and post-treatment EEGs were assessed by investigators masked to treatment and to clinical outcome: a majority view of three of four assessors was accepted for determination of the resolution of EEG features supporting the diagnosis. Aetiology was determined masked to treatment through clinical history, examination, and investigation. A study radiologist masked to treatment reviewed MRI scans done after the primary clinical outcome was determined

Arms

Are arms mutually exclusive?	Yes
Arm title	Hormonal therapy and Vigabatrin (Combination therapy)

Arm description:

Combination therapy is hormonal therapy (prednisolone OR tetracosactide depot) with vigabatrin

Arm type	Experimental
Investigational medicinal product name	Vigabatrin
Investigational medicinal product code	
Other name	Sabril Sachets
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Vigabatrin was given orally in two doses per day: 50 mg/kg per day for the first two doses; increasing to 100 mg/kg per day after 24 h and, if spasms continued after a further 72 h, to 150 mg/kg per day. Vigabatrin was given at the same dose on a bodyweight basis until 3 months from the start of treatment, and then the dose was reduced over 4 weeks.

Investigational medicinal product name	Tetracosactide Depot
Investigational medicinal product code	
Other name	Synacthen Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tetracosactide depot was given intramuscularly (0.5 mg [40 IU] on alternate days) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 0.75 mg on alternate days. After 2 weeks of treatment, hormonal therapy was tapered: all children received a reduced dose of prednisolone, with reductions of 10 mg every 5 days or, if on the higher dose of treatment, 40 mg daily, then 20 mg, then 10 mg. Hormonal therapy ceased after day 29.

Investigational medicinal product name	Prednisolone (Soluble tablets)
Investigational medicinal product code	
Other name	Soluble Prednisolone Tablets
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone was given orally (10 mg four times a day) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 20 mg three times a day. After 2 weeks of treatment, hormonal therapy was tapered: all children received a reduced dose of prednisolone, with reductions of 10 mg every 5 days or, if on the higher dose of treatment, 40 mg daily, then 20 mg, then 10 mg. Hormonal therapy ceased after day 29.

Arm title	Hormonal therapy alone
------------------	------------------------

Arm description:

Hormonal therapy alone is either prednisolone OR tetracosactide depot

Arm type	Active comparator
Investigational medicinal product name	Tetracosactide Depot
Investigational medicinal product code	
Other name	Synacthen Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tetracosactide depot was given intramuscularly (0.5 mg [40 IU] on alternate days) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 0.75 mg on alternate days. After 2 weeks of treatment, hormonal therapy was tapered: all children received a reduced dose of prednisolone, with reductions of 10 mg every 5 days or, if on the higher dose of treatment, 40 mg daily, then 20 mg, then 10 mg. Hormonal therapy ceased after day 29.

Investigational medicinal product name	Prednisolone (Soluble tablets)
Investigational medicinal product code	
Other name	Soluble Prednisolone Tablets
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone was given orally (10 mg four times a day) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 20 mg three times a day. After 2 weeks of treatment, hormonal therapy was tapered: all children received a reduced dose of prednisolone, with reductions of 10 mg every 5 days or, if on the higher dose of treatment, 40 mg daily, then 20 mg, then 10 mg. Hormonal therapy ceased after day 29.

Number of subjects in period 1	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone
Started	186	191
Completed	186	191

Baseline characteristics

Reporting groups

Reporting group title	Hormonal therapy and Vigabatrin (Combination therapy)
Reporting group description:	
Combination therapy is hormonal therapy (prednisolone OR tetracosactide depot) with vigabatrin	
Reporting group title	Hormonal therapy alone
Reporting group description:	
Hormonal therapy alone is either prednisolone OR tetracosactide depot	

Reporting group values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone	Total
Number of subjects	186	191	377
Age categorical			
Units: Subjects			
60-119 days	17	8	25
120-179 days	42	57	99
180-239 days	70	63	133
>=240 days	57	63	120
Gender categorical			
Units: Subjects			
Female	87	80	167
Male	99	111	210
Lead time to treatment			
Units: Subjects			
Up to 7 days	54	56	110
8-14 days	36	36	72
15-28 days	37	42	79
29 days to 2 months	33	27	60
More than 2 months	24	29	53
Not known	2	1	3
Risk of developmental impairment			
Units: Subjects			
Yes	103	104	207
No	83	87	170
Antiepileptic drugs for other seizure types			
Units: Subjects			
None	156	166	322
One	19	20	39
Two or more	11	5	16
Pyridoxine given to exclude dependent seizures			
Units: Subjects			
Yes	20	12	32
No	166	179	345

End points

End points reporting groups

Reporting group title	Hormonal therapy and Vigabatrin (Combination therapy)
Reporting group description: Combination therapy is hormonal therapy (prednisolone OR tetracosactide depot) with vigabatrin	
Reporting group title	Hormonal therapy alone
Reporting group description: Hormonal therapy alone is either prednisolone OR tetracosactide depot	

Primary: Cessation of spasms

End point title	Cessation of spasms
End point description: The primary early outcome was cessation of spasms which was defined as no witnessed spasms on and between Days 14 and Day 42 from trial entry.	
End point type	Primary
End point timeframe: Between Day 14 and Day 42 after enrolment	

End point values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	191		
Units: number				
Responder	133	108		
Non-responder	53	83		

Statistical analyses

Statistical analysis title	Early primary outcome - Chi-squared
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Chi-squared
Parameter estimate	Percentage difference in response
Point estimate	15

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	24.9

Statistical analysis title	Early primary outcome - logistic regression
-----------------------------------	---------------------------------------------

Statistical analysis description:

Sensitivity analysis using logistic regression to control for stratification variables and potential confounders

Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	3.2

Secondary: Time to response

End point title	Time to response
-----------------	------------------

End point description:

Defined as the first day after initiation of trial treatment on which spasms were not seen and after which response was maintained until Day 42 of treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 0 to Day 42

End point values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	191		
Units: day				
median (inter-quartile range (Q1-Q3))	2 (2 to 4)	4 (3 to 6)		

Statistical analyses

Statistical analysis title	Secondary outcome - time to response analysis
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.6

Secondary: Electro-clinical response

End point title	Electro-clinical response
End point description: Defined as cessation of spasms and resolution of the EEG features supporting the diagnosis (i.e. hysarrythmia or similar, compatible with the diagnosis of infantile spasms).	
End point type	Secondary
End point timeframe: Between Day 14 and Day 42 after enrolment	

End point values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185 ^[1]	189 ^[2]		
Units: Number				
Responder	123	104		
Non-responder	62	85		

Notes:

[1] - 1 missing value from total of 186

[2] - 2 missing values from total of 191

Statistical analyses

Statistical analysis title	Electro-clinical response analysis
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Chi-squared
Parameter estimate	Percentage difference in response
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	21.6

Statistical analysis title	Electro-clinical response logistic regression
Statistical analysis description:	
Sensitivity analysis controlling for stratification variables and potential confounders	
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.8

Secondary: Absence of spasms on Days 13 and 14

End point title	Absence of spasms on Days 13 and 14
End point description:	
Absence of spasms on Days 13 and 14	
End point type	Secondary
End point timeframe:	
Day 13 to Day 14 inclusive	

End point values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	191		
Units: Number				
Responder	166	132		
Non responders	20	59		

Statistical analyses

Statistical analysis title	Cessation at Days 13 and 14 analysis
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Percentage difference in response
Point estimate	20.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.8
upper limit	28.6

Secondary: Number of responders if single spasms are allowed in responders from Day 14 to Day 42 inclusive

End point title	Number of responders if single spasms are allowed in responders from Day 14 to Day 42 inclusive
End point description:	Number of responders if single spasms are allowed in responders from Day 14 to Day 42 inclusive
End point type	Secondary
End point timeframe:	Day 0 to Day 42

End point values	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	191		
Units: Number				

Responder	141	121		
Non responder	45	70		

Statistical analyses

Statistical analysis title	Responders if single spasms allowed analysis
Comparison groups	Hormonal therapy and Vigabatrin (Combination therapy) v Hormonal therapy alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Chi-squared
Parameter estimate	Percentage difference in response
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	21.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 0 to Day 42 inclusive from trial entry

Adverse event reporting additional description:

****PLEASE NOTE:** All adverse events were assessed by the local investigator to determine whether in their view they were adverse reactions. Only adverse reactions were reported to the trial centre using the classification stated in the ICISS protocol. Therefore ADVERSE REACTIONS ONLY are presented in this report.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	ICISS Protocol
-----------------	----------------

Dictionary version	1.3
--------------------	-----

Reporting groups

Reporting group title	Hormonal therapy and Vigabatrin (Combination therapy)
-----------------------	-------------------------------------------------------

Reporting group description:

Combination therapy is hormonal therapy (prednisolone OR tetracosactide depot) with vigabatrin

Reporting group title	Hormonal therapy alone
-----------------------	------------------------

Reporting group description:

Hormonal therapy alone is either prednisolone OR tetracosactide depot

Serious adverse events	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 186 (9.14%)	16 / 191 (8.38%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Obstructive cardiac hypertrophy **	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Drowsiness			
subjects affected / exposed	4 / 186 (2.15%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertonia			

subjects affected / exposed	1 / 186 (0.54%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritability			
subjects affected / exposed	2 / 186 (1.08%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric (disturbed sleep)			
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder **	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed	3 / 186 (1.61%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immunosuppression			
subjects affected / exposed	2 / 186 (1.08%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal upset			
subjects affected / exposed	2 / 186 (1.08%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Fluid or electrolyte disturbance			
subjects affected / exposed	1 / 186 (0.54%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 186 (2.15%) 5 / 5 0 / 0	5 / 191 (2.62%) 5 / 5 0 / 0	
Varicella zoster (chicken pox)* subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: *Required treatment to prevent infection or was infected 1 / 186 (0.54%) 1 / 1 0 / 0	1 / 191 (0.52%) 1 / 1 0 / 0	

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

Non-serious adverse events	Hormonal therapy and Vigabatrin (Combination therapy)	Hormonal therapy alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 186 (62.90%)	111 / 191 (58.12%)	
Vascular disorders			
Pallor**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences (all)	0	1	
Immune system disorders			
Allergic rash or anaphylaxis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences (all)	0	2	
Immunosuppression			
subjects affected / exposed	3 / 186 (1.61%)	3 / 191 (1.57%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Abnormal breathing pattern**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences (all)	0	1	
Hypoxia**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed	0 / 186 (0.00%)	1 / 191 (0.52%)	
occurrences (all)	0	1	
Tachypnoea**	Additional description: ** Unexpected adverse reaction		

subjects affected / exposed occurrences (all)	0 / 186 (0.00%) 0	1 / 191 (0.52%) 1	
Cardiac disorders			
Bardycardia**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed occurrences (all)	1 / 186 (0.54%) 1	0 / 191 (0.00%) 0	
Obstructive cardiac hypertrophy**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed occurrences (all)	0 / 186 (0.00%) 0	1 / 191 (0.52%) 1	
Nervous system disorders			
Drowsiness			
subjects affected / exposed occurrences (all)	45 / 186 (24.19%) 51	3 / 191 (1.57%) 3	
Hypertonia			
subjects affected / exposed occurrences (all)	3 / 186 (1.61%) 4	9 / 191 (4.71%) 10	
Hypotonia			
subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 10	8 / 191 (4.19%) 9	
Irritability			
subjects affected / exposed occurrences (all)	61 / 186 (32.80%) 71	75 / 191 (39.27%) 90	
Neuropsychiatric (disturbed sleep)			
subjects affected / exposed occurrences (all)	29 / 186 (15.59%) 37	35 / 191 (18.32%) 44	
High MRI signal in basal ganglia**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed occurrences (all)	2 / 186 (1.08%) 2	1 / 191 (0.52%) 1	
Movement disorder**	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed occurrences (all)	14 / 186 (7.53%) 15	2 / 191 (1.05%) 2	
Blood and lymphatic system disorders			
Blood disorder (high platelet count) **	Additional description: ** Unexpected adverse reaction		
subjects affected / exposed occurrences (all)	1 / 186 (0.54%) 1	0 / 191 (0.00%) 0	
Eye disorders			

Abnormal eye movements** subjects affected / exposed occurrences (all)	Additional description: **Unexpected adverse reaction		
	1 / 186 (0.54%) 1	0 / 191 (0.00%) 0	
Not focusing (vision)** subjects affected / exposed occurrences (all)	Additional description: ** Unexpected adverse reaction		
	1 / 186 (0.54%) 1	0 / 191 (0.00%) 0	
Squinting** subjects affected / exposed occurrences (all)	Additional description: ** Unexpected adverse reaction		
	0 / 186 (0.00%) 0	1 / 191 (0.52%) 1	
Gastrointestinal disorders Gastrointestinal upset subjects affected / exposed occurrences (all)	23 / 186 (12.37%) 26	26 / 191 (13.61%) 30	
Skin and subcutaneous tissue disorders Sweating** subjects affected / exposed occurrences (all)	Additional description: ** Unexpected adverse reaction		
	1 / 186 (0.54%) 1	1 / 191 (0.52%) 1	
Renal and urinary disorders Fluid or electrolyte disturbance subjects affected / exposed occurrences (all)	12 / 186 (6.45%) 13	23 / 191 (12.04%) 28	
Endocrine disorders Endocrine or metabolic disturbance subjects affected / exposed occurrences (all)	1 / 186 (0.54%) 2	2 / 191 (1.05%) 2	
Infections and infestations Infection subjects affected / exposed occurrences (all) Varicella zoster (chicken pox)* subjects affected / exposed occurrences (all)	Additional description: *Required treatment to prevent infection or was infected		
	14 / 186 (7.53%) 16	19 / 191 (9.95%) 20	
	2 / 186 (1.08%) 2	4 / 191 (2.09%) 4	
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all) Weight gain	35 / 186 (18.82%) 42	51 / 191 (26.70%) 61	

subjects affected / exposed	24 / 186 (12.90%)	34 / 191 (17.80%)	
occurrences (all)	31	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2005	Protocol updated from version 1.0 to version 1.1. This occurred between the original ethics submission in the UK and obtaining final approval. Please see Appendix 1 Section A1 of Protocol Version 1.3 for a description and explanation of all the amendments made to the protocol as part of this amendment. ICISS Protocol Version 1.3 can be downloaded from the trial website at www.iciss.org.uk
20 December 2006	Protocol updated from version 1.1 to version 1.2. This occurred before the start date of recruitment. Please see Appendix 1 Section A2 of Protocol Version 1.3 for a description and explanation of all the amendments made to the protocol as part of this amendment. ICISS Protocol Version 1.3 can be downloaded from the trial website at www.iciss.org.uk
05 January 2011	Protocol updated from version 1.2 to version 1.3. Please see Appendix 1 Section A3 of Protocol Version 1.3 for a description and explanation of all the amendments made to the protocol as part of this amendment. ICISS Protocol Version 1.3 can be downloaded from the trial website at www.iciss.org.uk

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results Version 1 presents the early outcome measures. Version 2 will include the late outcome measures at 18 months of age (currently in press). Version 3 will include the late outcome measures at 42 months of age.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27838190>