Clinical trial results:
A multi-centre (UK) double-blind randomised parallel group placebo controlled trial to evaluate the efficacy, safety, and tolerability of Intravenous Immunoglobulin (IVIg) 0.5g/kg plus standard treatment, versus matched placebo plus standard treatment in patients with longstanding Complex Regional Pain Syndrome.

Summary

EudraCT number	2012-000058-73
Trial protocol	GB
Global end of trial date	19 March 2016

Results information

Result version number	v1 (current)
This version publication date	21 August 2018
First version publication date	21 August 2018
Summary attachment (see zip file)	Summary Trial Results (LIPS Results.pdf)

Trial information

Trial identification

Sponsor protocol code	LIPS

Additional study identifiers

ISRCTN number	ISRCTN42179756
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	University of Liverpool: UOL000773, REC Reference:: 12/EE/0164

Notes:

Sponsors

Sponsor organisation name	The Walton Centre NHS Foundation Trust
Sponsor organisation address	Lower Lane, Fazakerley, United Kingdom,
Public contact	Dr Andreas Goebel, The Walton Centre NHS Foundation Trust, 0151 5295666, rdi@thewaltoncentre.nhs.uk
Scientific contact	Dr Andreas Goebel, The Walton Centre NHS Foundation Trust, 0151 5295666, rdi@thewaltoncentre.nhs.uk
Sponsor organisation name	The University of Liverpool
Sponsor organisation address	Research Support Office, Waterhouse Building, 3 Brownlow Street, Liverpool, Liverpool, United Kingdom, L69 3GL
Public contact	Ms Karen Wilding, Research Support Office, 0151 7948385,
Scientific contact	Dr Andreas Goebel, The Walton Centre NHS Foundation Trust, 0151 5295666, rdi@thewaltoncentre.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	22 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2016
Global end of trial reached?	Yes
Global end of trial date	19 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To gain, within 44 months, both definite proof of the clinical efficacy, and a more confident estimate of the effect size of low-dose IVIg treatment to reduce pain in patients with msCRPS.

Protection of trial subjects:

Throughout the project measures were put in place to minimise any risk, pain or distress to trial participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	111
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 15 Aug 2013 - 8 Oct 2015, 111 were randomised to one of two trial arms. 56 were randomised to Placebo and 55 were randomised to IVIg.
8 participants were excluded from the primary analysis. The primary analysis was performed on 103 patients, with 53 in Placebo and 50 in IVIg.

Pre-assignment

Screening details:

Between 15 Aug 2013 - 8 Oct 2015, 121 patients were screened for eligibility into the trial. 10 participants did not meet the inclusion/exclusion criteria as follows; 4 no longer consenting, 1 not contactable, 1 ineligible pain scores, 2 ineligible blood results, 1 ineligible disease duration and 1 ineligible Budapest Criteria.

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, Carer, Assessor, Subject

Blinding implementation details:

Patients, Providers, Researchers and Outcome Assessors were blinded to treatment assignment (ISRCTN42179756)

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Visually indistinguishable placebo of 0.1% albumin in saline

Arm type	Placebo
Investigational medicinal product name	visually indistinguishable placebo of 0.1% albumin in saline
Investigational medicinal product code	visually indistinguishable placebo of 0.1% albumin
Other name	visually indistinguishable placebo of 0.1% albumin in saline
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

visually indistinguishable placebo of 0.1% albumin

Arm title	Study Drug

Arm description:

0.5g/kg of body weight Human normal immunoglobulin for intravenous use (IVIg)

Arm type	Experimental
Investigational medicinal product name	Human normal immunoglobulin for intravenous use (IVIg)
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Two blinded infusions 3 weeks apart (day 1 and day 22 post-randomisation) followed by two optional open label infusions 3 weeks apart (day 43 and day 64 post randomisation
maximum dosage allowed - 80g (2.5ml/kg/hour)

Number of subjects in period 1	Placebo	Study Drug
Started	56	55
Completed	56	55

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description:

Between 27th August 2013 and 28th October 2015, 111 patients were randomised to one of the two trial arms. 56 were randomised to Placebo and 55 were randomised to IVIg. Two of these patients did not receive their first infusion and supplied no outcome pain data. Three further patients did receive their first infusion but also did not supply any outcome pain data. All 5 of these patients are excluded from the primary analysis.

In addition, three patients were randomised in error. Two of these had an average baseline pain score (over the first 7 days) below 5 and one patient had a disease duration of less than 12 months. These 3 patients (all randomised to IVIg) are excluded from the primary analysis.

The primary analysis was performed on 103 patients, with 53 in Placebo and 50 in IVIg.

Reporting group values	overall trial	Total	
Number of subjects	111	111	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	111	111	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
male	34	34	
Female	77	77	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Visually indistinguishable placebo of 0.1% albumin in saline	
Reporting group title	Study Drug
Reporting group description:	
0.5g/kg of body weight Human normal immunoglobulin for intravenous use (IVIg)	

Primary: The primary outcome is the average 24h pain intensity over 15 days, recorded in pain diaries entries for the previous 24 hours collected on days 28 to 42 (day 1=day of first infusion).

End point title	The primary outcome is the average 24h pain intensity over 15 days, recorded in pain diaries entries for the previous 24 hours collected on days 28 to 42 (day 1=day of first infusion).[1]
End point description:	
The primary outcome is the average 24h pain intensity over 15 days, recorded in pain diaries entries for the previous 24 hours collected on days 28 to 42 (day 1=day of first infusion).	
End point type	Primary
End point timeframe:	
The primary outcome is the average 24h pain intensity over 15 days, recorded in pain diaries entries for the previous 24 hours collected on days 28 to 42 (day 1=day of first infusion).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary outcome is the average 24h pain intensity over 15 days, recorded in pain diaries entries for the previous 24 hours collected on days 28 to 42 (day 1=day of first infusion). Summary Analysis has been uploaded as an additional PDF with the dataset

End point values	Placebo	Study Drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: Pain Inference/Quality of Life, worst 24				
arithmetic mean (full range (min-max))	6.9 (0 to 10)	7.2 (1 to 10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reporting on an ongoing basis throughout the life of the project.

Adverse event reporting additional description:

A total of 6 Serious Adverse Events were reported across the blinded and open label phases of the trial. 2 patients in the blinded phase (1 in the placebo and 1 in the IVIG group) and 4 in the open IVIg phase. 0 SUSARS were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	Not Applicable
Dictionary version	NA

Reporting groups

Reporting group title	Placebo

Reporting group description:

Visually indistinguishable placebo of 0.1% albumin in saline

Reporting group title	Study Drug

Reporting group description:

0.5g/kg of body weight Human normal immunoglobulin for intravenous use (IVIg)

Serious adverse events	Placebo	Study Drug	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)	5 / 104 (4.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aseptic Meningitis			
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased heart rate			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

DVT			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Study Drug	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 56 (69.64%)	78 / 104 (75.00%)	
Vascular disorders			
Heart Flutter			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	4	
Exhaustion	Additional description: Exhaustion		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Headache	Additional description: Headache		
subjects affected / exposed	18 / 56 (32.14%)	48 / 104 (46.15%)	
occurrences (all)	22	74	
Dizziness	Additional description: DIzziness		
subjects affected / exposed	5 / 56 (8.93%)	8 / 104 (7.69%)	
occurrences (all)	5	10	
Myoclonic jerks	Additional description: Myoclonic jerks		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	3	
FIts (non-epileptic)	Additional description: FIts (non-epileptic)		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	2	
Shaking/tremors	Additional description: Shaking/tremors		

subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	3	
Paresthesia	Additional description: Paresthesia		
subjects affected / exposed	3 / 56 (5.36%)	5 / 104 (4.81%)	
occurrences (all)	4	5	
Lack of Concentration	Additional description: Lack of Concentration		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Word finding difficulties	Additional description: Word finding difficulties		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
Burning pain all over	Additional description: Burning pain all over		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Feeling in scar returned	Additional description: Feeling in scar returned		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
excruciating scar pain	Additional description: excruciating scar pain		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Left Hand Pain (2x fingers)	Additional description: Left Hand Pain (2x fingers)		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Burning left hand (2x fingers)	Additional description: Burning left hand (2x fingers)		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Lethargy/Tiredness	Additional description: Lethargy/Tiredness		
subjects affected / exposed	5 / 56 (8.93%)	3 / 104 (2.88%)	
occurrences (all)	6	4	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Trembling Spasm (left arm)	Additional description: Trembling Spasm (left arm)		

subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Forgetfulness	Additional description: Forgetfulness		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Nightmares	Additional description: Nightmares		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Tingling (right hand)	Additional description: Tingling (right hand)		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Blocked nose	Additional description: Blocked nose		
subjects affected / exposed	2 / 56 (3.57%)	2 / 104 (1.92%)	
occurrences (all)	2	3	
Blisters (sole of left foot)	Additional description: Blisters (sole of left foot)		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
sore/bleeding gums	Additional description: bleeding gums		
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Nose bleed			
subjects affected / exposed	2 / 56 (3.57%)	2 / 104 (1.92%)	
occurrences (all)	4	2	
Tonsillitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
aversion to light			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Taste of blood in mouth			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
sensitive to noise			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Increased/exacerbation pain			

subjects affected / exposed	2 / 56 (3.57%)	12 / 104 (11.54%)	
occurrences (all)	2	12	
Increased sensitivity			
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
swollen arms			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
aching arms			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
intermittent pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left knee pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left foot pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left thigh pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
exacerbation of allodynia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Pain on soles of feet			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
intermittent burning/sweating and cold sensations	Additional description: intermittent burning/sweating and cold sensations		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
worsening intermittent burning/sweating and cold sensations			

subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
right foot pain				
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
right leg pain				
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
increased limb swelling				
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
spreading of CRPS to other limb				
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
skin rash (ISR)				
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	2		
Pain in left hand				
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Hot flush				
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)		
occurrences (all)	0	2		
right facial swelling with trigeminal neuralgia				
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Vitamin D deficiency				
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Chills/sweating				
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
weightloss (unintentional)				
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)		
occurrences (all)	1	1		

Infected cyst			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
taste of metal			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Post menopausal bleeding			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
muscle pain			
subjects affected / exposed	0 / 56 (0.00%)	3 / 104 (2.88%)	
occurrences (all)	0	6	
stiffness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	2	
chest pain			
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	3	
back pain			
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
shaking			
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
burning pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
cramping			
subjects affected / exposed	2 / 56 (3.57%)	1 / 104 (0.96%)	
occurrences (all)	2	2	
pain (localised)			
subjects affected / exposed	1 / 56 (1.79%)	6 / 104 (5.77%)	
occurrences (all)	1	20	

stiffness (localised)			
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
fatigability			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	2	
trapped nerve in right (unaffected) foot			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
bilateral knee swelling			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left hand weakness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
worsening pain of the anterior aspect of left foot			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
cold, white, numb middle finger left hand			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left leg pain flared up			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
left side jaw pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
cold left foot			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Falls			
subjects affected / exposed	2 / 56 (3.57%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Immune system disorders			

Flu Symptoms	Additional description: Flu Symptoms		
subjects affected / exposed	9 / 56 (16.07%)	4 / 104 (3.85%)	
occurrences (all)	10	4	
Cold symptoms	Additional description: Cold symptoms		
subjects affected / exposed	5 / 56 (8.93%)	6 / 104 (5.77%)	
occurrences (all)	5	6	
Raised temperature	Additional description: Raised temperature		
subjects affected / exposed	1 / 56 (1.79%)	3 / 104 (2.88%)	
occurrences (all)	1	3	
Sore Throat	Additional description: Sore Throat		
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Sore sinuses	Additional description: sore sinuses		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Cough	Additional description: Cough		
subjects affected / exposed	1 / 56 (1.79%)	2 / 104 (1.92%)	
occurrences (all)	1	2	
Bleeding blisters on both legs	Additional description: Bleeding blisters on both legs		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Infected involution of nail on right halux	Additional description: Infected involution of nail on right halux		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
ear ache			
subjects affected / exposed	2 / 56 (3.57%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Eye disorders			
Eye pain	Additional description: eye pain		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
watering eyes			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Intermittent left eye blurred vision			

subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 56 (26.79%)	28 / 104 (26.92%)	
occurrences (all)	18	35	
Diarrhoea			
subjects affected / exposed	3 / 56 (5.36%)	7 / 104 (6.73%)	
occurrences (all)	4	9	
sickness/vomiting			
subjects affected / exposed	6 / 56 (10.71%)	15 / 104 (14.42%)	
occurrences (all)	7	17	
Irritable bowel syndrome			
subjects affected / exposed	2 / 56 (3.57%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
worsening gastric reflux			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Intermittent stomach pain			
subjects affected / exposed	0 / 56 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
weightloss			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Pain in chest due to vomiting			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Gallstones			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Loss of appetite			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	

abdominal pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Sugar sensitivity			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chest infection			
subjects affected / exposed	1 / 56 (1.79%)	3 / 104 (2.88%)	
occurrences (all)	1	3	
consolidation in the lower left pulmonary lobe			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Retching after coughing			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Shortness of breath			
subjects affected / exposed	2 / 56 (3.57%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Localised rash	Additional description: Localised rash		
subjects affected / exposed	4 / 56 (7.14%)	13 / 104 (12.50%)	
occurrences (all)	5	16	
Itchy Skin	Additional description: Itchy Skin		
subjects affected / exposed	2 / 56 (3.57%)	3 / 104 (2.88%)	
occurrences (all)	3	4	
Bilateral swollen feet/legs	Additional description: Bilateral swollen feet/legs		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	3	
Hair loss/thinning	Additional description: Hair loss/thinning		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Dry skin patch	Additional description: Dry skin patch		
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
skin tender left inner thumb area	Additional description: skin tender left inner thumb area		

subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Skin infection	Additional description: skin infection (cellulitis)		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Foot ulcer	Additional description: foot ulcer		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Naval Discharge	Additional description: Naval Discharge		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
lumps on toes	Additional description: lumps on toes		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
abrasion left big toe	Additional description: abrasion left big toe		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
hot bilateral knees	Additional description: hot bilateral knees		
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Small weeping area at end of stump	Additional description: Small weeping area at end of stump		
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Kidney pain			
subjects affected / exposed	1 / 56 (1.79%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			

aches			
subjects affected / exposed	2 / 56 (3.57%)	1 / 104 (0.96%)	
occurrences (all)	3	1	
locking (localised)			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	3	0	
ulcer (right leg)			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Tremors			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
ligament damage (left ankle)			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
swollen left hand			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
wrist strain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
muscle twitching			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
left leg trembling (spasm)			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
weak ankle (left)			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
jerking leg			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
feeling cold			
subjects affected / exposed	1 / 56 (1.79%)	0 / 104 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2012	SA 1 (Protocol 2.0 19.10.12) Primary Outcome Measure - extended period for 24 hour diary from 15 to 37 days Secondary Outcome Measure -EQ-SD used as a measure of quality of life Exclusion Criteria - IgA levels redefined Screening Recruitment and consent - text added for clarification selection and timing of dose for each participant - text added to clarify inclusion packaging and labelling of IMP - study name and Eudract now included on label Concomitant Medications - additional information provided Biochemistry - Additional tests included Implementation Procedures - clarification of the implementation procedures Efficacy safety - treatment stopping rules agreed and included Sample size calculation Withdrawal of patients - clarification of discontinuation of participants in the study Monitoring Quality Control and Assurance Safety - changes made to representatives in the TSC and DMC Addition of PI video
11 April 2013	SA2 - Protocol V3.0 dated 11/04/2013 REC - updated REC address Secondary and exploratory outcome measures - removal of time trade off scale Inclusion criteria - rewording of inclusion criteria 4 Study medication - clarification of drug/placebo availability pregnancy - addition of urine pregnancy test PI video - addition of slides
01 July 2013	SA3 - Protocol V4.0 dated 14/06/2013 Secondary outcome measures - CRPS Questionnaire and Neglect-like symptoms added Statistical Considerations - allergy status and low baseline IgG plasma level added
04 October 2013	SA4 - PIS V3.0 dated 02/09/2013 Protocol - additional site (Leicester) PIS - amendment to common, occasional and rare side effect of IVIG
28 March 2014	SA5 - Interim Report for RLBUHT dated 20/02/2014 Selection and timing of dose for each participant

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported