



## 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     |
| <b>Arm title</b>             | 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

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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)

| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>Visually indistinguishable placebo of 0.1% albumin in saline                  |            |
| Reporting group title                                                                                         | Study Drug |
| Reporting group description:<br>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). <sup>[1]</sup> |
| End point description:<br>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:<br>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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| Burning sensation                                | Additional description: Burning sensation                  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1                                        | 1 / 104 (0.96%)<br>1 |  |
| Skin infection                                   | Additional description: skin infection (cellulitis)        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1                                        | 0 / 104 (0.00%)<br>0 |  |
| Foot ulcer                                       | Additional description: foot ulcer                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1                                        | 0 / 104 (0.00%)<br>0 |  |
| Naval Discharge                                  | Additional description: Naval Discharge                    |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| lumps on toes                                    | Additional description: lumps on toes                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| abrasion left big toe                            | Additional description: abrasion left big toe              |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| hot bilateral knees                              | Additional description: hot bilateral knees                |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1                                        | 0 / 104 (0.00%)<br>0 |  |
| Small weeping area at end of stump               | Additional description: Small weeping area at end of stump |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| Renal and urinary disorders                      |                                                            |                      |  |
| Urinary tract infection                          |                                                            |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0                                        | 1 / 104 (0.96%)<br>1 |  |
| Kidney pain                                      |                                                            |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1                                        | 1 / 104 (0.96%)<br>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)<br><br>Primary Outcome Measure - extended period for 24 hour diary from 15 to 37 days<br><br>Secondary Outcome Measure -EQ-SD used as a measure of quality of life<br><br>Exclusion Criteria - IgA levels redefined<br><br>Screening Recruitment and consent - text added for clarification<br><br>selection and timing of dose for each participant - text added to clarify inclusion<br><br>packaging and labelling of IMP - study name and Eudract now included on label<br><br>Concomitant Medications - additional information provided<br><br>Biochemistry - Additional tests included<br><br>Implementation Procedures - clarification of the implementation procedures<br><br>Efficacy safety - treatment stopping rules agreed and included<br><br>Sample size calculation<br><br>Withdrawal of patients - clarification of discontinuation of participants in the study<br><br>Monitoring Quality Control and Assurance Safety - changes made to representatives in the TSC and DMC<br><br>Addition of PI video |
| 11 April 2013    | SA2 - Protocol V3.0 dated 11/04/2013<br><br>REC - updated REC address<br>Secondary and exploratory outcome measures - removal of time trade off scale<br>Inclusion criteria - rewording of inclusion criteria 4<br>Study medication - clarification of drug/placebo availability<br>pregnancy - addition of urine pregnancy test<br>PI video - addition of slides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 01 July 2013     | SA3 - Protocol V4.0 dated 14/06/2013<br>Secondary outcome measures - CRPS Questionnaire and Neglect-like symptoms added<br>Statistical Considerations - allergy status and low baseline IgG plasma level added                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 04 October 2013  | SA4 - PIS V3.0 dated 02/09/2013<br>Protocol - additional site (Leicester)<br>PIS - amendment to common, occasional and rare side effect of IVIG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 28 March 2014    | SA5 - Interim Report for RLBUHT dated 20/02/2014<br>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