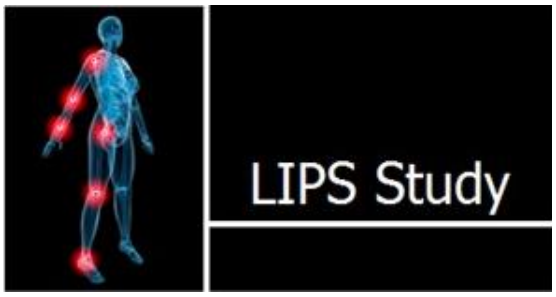

Low-dose Intravenous Immunoglobulin Treatment for Complex Regional Pain Syndrome

STUDY PROTOCOL

Version 5.1 (07.07.2014)

Co-sponsors:	**University of Liverpool and the Walton Centre NHS Trust**
Funder:	**NIHR Efficacy and Mechanism Evaluation (EME)**
Funder ref:	**11/14/33**
REC	**Committee name and address** East of England Hatfield REC (Formally known as: NRES Committee East of England – Welwyn) Room 002 TEDCO Business Centre, Rolling Mill Road Jarrow, NE32 3DT
EUDRACT:	**2012-000058-73**

Study protocol version authorised by:

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Candida McCabe	Site Principal Investigator	_____	
Nicholas Shenker	Site Principal Investigator	_____	
Mick Serpell	Site Principal Investigator	_____	
Nick Padfield	Site Principal Investigator	_____	
Mark Sanders	Site Principal Investigator	_____	
Karim Shoukrey	Site Principal Investigator		
Gareth Ambler	Trial Statistician	_____	
Caroline Murphy	KCTU Operational Director	_____	

Richard Hughes	TSC Chair	_____

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Dr. Phil Wiffen (independent)
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Trial Statistician
KCTU Manager
Trial Manager
Data Manager
Sponsor Representative

DATA MONITORING AND ETHICS COMMITTEE

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Dr Siraj Misbah MSc (Medical Immunology) FRCP FRCPath Consultant Clinical Immunologist Oxford Radcliffe Hospitals NHS Trust Oxford	Prof. Solomon Tesfaye, Sheffield; Zoe Hoare, Statistician, Bangor Clinical Trials Unit, ,

SERIOUS ADVERSE EVENTS

SAE REPORTING

Where the adverse event meets one of the serious categories an SAE form should be completed by the co-investigator at the clinical recruitment centre and scanned/emailed or faxed to the co-ordinating centre within 24 hours upon becoming aware of the event. Note, an acknowledgement of receipt will be sent back to site. If this is not received, please contact the KCTU.

(See Section 19 for detailed instruction)

Email: CTU@kcl.ac.uk

Fax Number: (0207) 848 5229

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APPROVALS

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1 CONTENTS PAGE

2 GLOSSARY

Abbreviation	Definition
AE	Adverse Event
AR	Adverse Reaction
CRPS	Complex Regional Pain Syndrome
CTU	(King's) Clinical Trials Unit, King's College London (also KCTU)
DMC	Data Monitoring Committee
EME	Efficacy and Mechanism Evaluation
GCP	Good Clinical Practice
IVIg	Intravenous immunoglobulin
IMP	Investigational Medicinal Product
ISRCTN	International Standardised Randomised Controlled Trial Number
MHRA	Medicines & Healthcare products Regulatory Agency
msCRPS	Those patients with CRPS of moderate to severe pain intensity
MRIS	Medical Research Information Service
MRC	Medical Research Council
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
NRS	Numeric Rating Scale
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC / SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRN	UK Clinical Research Network

3 RESPONSIBILITIES

Refer to co-sponsorship agreement, subcontracts and to site contracts for clarification and delegation of responsibilities.

4 PROTOCOL SUMMARY

Short title:	LIPS
Protocol version:	5.1
Protocol date:	07/07/2014
Chief Investigator:	Dr Andreas Goebel
Sponsor:	University of Liverpool / The Walton NHS Trust
Funder:	NIHR Efficacy and Mechanisms Evaluation
Study design & intervention:	A multi-centre (UK) double-blind randomised parallel group placebo controlled trial to evaluate the efficacy, safety, and tolerability of Intravenous Immunoglobulin (IVIg) 0.5 g/kg plus standard treatment, versus matched placebo plus standard treatment in patients with longstanding Complex Regional Pain Syndrome. Participants will be randomly allocated to receive IVIg 0.5 g/kg (Intratect™ 50g/l solution for infusion) or matching placebo administered day 1 and day 22 after randomisation, followed by two optional doses of open label medication on day 43 after randomisation and on day 64 after randomisation.
Primary objective:	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 moderate or severe Complex Regional Pain Syndrome.
Secondary objectives:	To achieve better understanding of this technology, including: 1. stability of effect with repeat administration 2. factors predicting a beneficial response 3. effects on additional outcome parameters including stimulus evoked pain, pain interference, quality of life, and short-term risk profile 4. health economics evaluation 5. creation of a bank of biological samples for future Complex Regional Pain Syndrome research
Primary outcome:	Average 24h pain intensity over 37 days (to be completed on day 6 to day 42 after randomisation to record pain intensity during the previous 24 hours).
Number of study sites:	Seven UK based specialist pain clinics in secondary care (Liverpool, London, Bath, Glasgow, Norfolk & Norwich, Cambridge, Leicester)
Study population/size:	108 (54 in each study arm)
Study duration:	44 months (from study set-up to analysis)

5 BACKGROUND

Complex Regional Pain Syndrome (CRPS) is a posttraumatic pain in a limb, associated with sensory, motor, autonomic, skin and bone changes (1;2). Complex Regional Pain Syndrome can resolve spontaneously, but if spontaneous resolution does not occur early, it is less likely to occur later. Many patients with CRPS have no effective method to relieve their ongoing pain (3). Those patients with CRPS of moderate to severe pain intensity, the target group for this study, report on average a very poor quality of life, and they usually cannot work (4). Immunoglobulin treatment for chronic pain is a novel technology (5). In a first, open trial we found that low dose intravenous immunoglobulin (IVIg) may be effective in some patients with CRPS (11 participants: 3 had >70% pain relief, 2 had >25%<70%, and 6 had 0-25% relief, following a variable number of low-dose infusion repeats) (6). We later showed that in one patient repeat treatments provided reproducible effects (7). Recently we confirmed in a UK single-centre crossover randomised placebo-controlled trial (RCT) (8), that a single, low dose (0.5 g/kg) infusion of IVIg significantly reduced pain in patients with CRPS (n=13, pain intensity on an validated 11-point Numeric Rating Scale higher than 4 (Numeric Rating Scale NRS 0=no pain, 10=pain as bad as you can imagine (9)); these patients had a disease duration of 0.5-2.5 years. The treatment difference was 1.55 NRS points (95% CI: 1.29-1.82, $p<0.001$). In a responder analysis (12 patients had received treatment), three patients had ≥ 50% less pain (4.5, 5 and 5 NRS points) after IVIg when compared with after saline treatment, and two patients had 2 and 2.5 NRS points less pain (29% and 31% less pain). One patient had 2 NRS points less pain (25% less pain) after saline compared with after IVIg treatment. The average effect duration was 5 weeks. There was also a significant overall reduction of CRPS related, non-painful symptoms and, in responders, improved sleep and global improvement, with few adverse events (headaches and pain increases for <3 days). Post-infusion questionnaires showed successful blinding of patients and study doctors.

Very recently we commenced a trial to explore whether subcutaneous immunoglobulin, in weekly self-administration at home over one year would provide sustained pain relief in initial responders to 0.5g/kg IVIg (ISRCTN63226217). We invited all five patients with at least 2 NRS points less pain after IVIg in the earlier RCT. Of these patients one declined participation, and a second patient unfortunately developed metastasizing colon cancer. Three patients participated. By August 2011 two patients, with disease durations of 6 and 5 years at study entry, and baseline pain intensities of NRS 7 and 6 had experienced sustained pain reduction of >70%, for 12 and 3.5 months respectively. The third patient, who had had 31% relief in the RCT, showed no benefit. The two responding patients reported major improvement in their quality of life. EQ5D scores (10) improved from 0.26 and 0.30 at baseline to 0.66 and 0.65 at twelve/three months, and reduced interference of their pain with daily functioning (Brief Pain Inventory (11) interference scores (pain interference = the impact of pain on activities of daily life) improved from 7.7 and 6.1 at baseline to 1.4 and 0 at twelve/three months).

The implication of the existing research for this trial is that the above evidence provides proof of concept for the efficacy of low dose immunoglobulin treatment for msCRPS in reducing pain, with an advantageous side-effect profile. These data also suggest that this treatment may improve quality of life and pain interference. Because the numbers of treated patients have been small, and most research was conducted in a single centre, it is now important to confirm these findings in a larger group of patients, and across several centres, to gain confidence about both efficacy and effect size of this novel technology, and to demonstrate its generalizability.

6 OBJECTIVES

6.1 Primary Objective:

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 moderate or severe Complex Regional Pain Syndrome.

6.2 Secondary Objectives:

To achieve better understanding of this technology, including:

1. stability of effect with repeat administration
2. factors predicting a beneficial response
3. effects on additional outcome parameters including stimulus evoked pain, pain interference, quality of life, and short-term risk profile
4. health economics evaluation
5. creation of a bank of biological samples for future CRPS research

7 STUDY DESIGN

LIPS is a multicentre, randomised, double-blind, placebo-controlled, parallel group trial with an open extension. The parallel group design is an established research technique; the open extension is included to take account of service users' preferences.

Blinding will be achieved by preparing both study drug and placebo (0.1% albumin in Normal Saline) solution into identical bottles. The albumin is added to achieve indistinguishable foaming and colour to the IVIg. Batch numbers and expiry dates for both active and placebo drug will be indistinguishable.

In those who decide to receive the open infusion on day 43 and day 64, pain diaries will be completed daily from day 43 to day 85 and then weekly for 9 weeks further to explore the duration of combined drug- and unspecific treatment effects.

An interim analysis will be performed for futility and safety, after half of patients have completed the trial. It will be suggested that the trial is stopped if there is a statistically significant difference between the groups in the "wrong" direction at the 5% level (i.e. one-sided test at the 2.5% level). This stopping rule will have a negligible effect on the type I error and power of the trial. There will no statistical stopping rule for efficacy although the DMC may suggest stopping the trial on the grounds of safety if there is an overwhelming positive effect of IVIg.

Clinical stopping rules will relate to unexpectedly poor recruitment and excessive withdrawals.

7.1 Primary outcome measure:

- The primary outcome is the average 24h pain intensity over 37 days, recorded in pain diary entries for the previous 24 hours collected on days 6 to 42 (day 1=day of first infusion). Consenting patients providing a mobile phone number will be prompted automatically by SMS daily from day 2-42 to enter their pain intensity into their diary. In addition return SMSs from the patient, with the daily NRS pain value will be automatically saved as backup for the paper diary. The paper diary score will override the texted diary score, however every effort will be made to resolve any discrepancies. In

participating patients unexplained lack of a response over two or three days will prompt a phone call from the study nurse to confirm that there are no issues.

7.2 Secondary and exploratory outcome measures:

- Secondary outcomes will be pain interference measured using the interference subscale of the Brief Pain Inventory(11),and quality of life measured using the Euroqol EQ-5D-5L(12).
- All other outcomes are exploratory

List of measures to be used (measurement times see Table 2):

- Screening pain diaries (average 24h pain intensity numeric rating scale (NRS) only)
- Detailed daily- (three items: pain unpleasantness(13), average 24h NRS pain intensity, last 24h sleep quality (14)), and simplified weekly (weekly NRS pain intensity) pain diaries
- Adverse events
- Brief Pain Inventory- (diagram, worst pain intensity, and interference scales only) (11)
- Concomitant medications
- Concomitant therapies
- Patient weight
- Skin temperature measured with a surface thermometer
- Limb volume measured with a water-bath technique
- EQ-5D (5 Item)(12)
- Expectations from treatment (15)
- Functional items and fatigue suggested by-, and developed together with patient group (5 scales)
- Patient Global Impression of change (16)
- Hospital Anxiety and Depression Scale (17)
- Health and Social care utilisation
- Limb Exam recording Budapest CRPS signs, and any additional abnormalities on inspection, and sensory (cotton wool, pinprick, cold-fork) and motor (observation of active range) examination
- McGill(18)
- Quantitative Sensory Testing in 40 patients with stimulus evoked pain, excepting thermosensitivities (only in three trial centres)
- Sullivan's Pain Catastrophising Scale (19)
- Work interference (Stanford Presenteeism Scale) (21)
- Neglect-Like Symptoms in CRPS (30)

7.3 Definition of end of study:

The end of the study will be the last participant's final study contact, at day 148 (for those who elect to receive open label infusions) or at day 64 (for those who elect not to receive open label infusion).

SAEs will be monitored for 21 days after final dose of IVIg, or until resolution.

8 SUBJECT POPULATION

8.1 Inclusion criteria

1. Diagnosis of Complex Regional Pain Syndrome I or II according to Budapest research criteria (appendix 5) (22)).
2. Disease duration of 1-5 years and a mean pain intensity on an 11-point (0-10) Numeric Rating Scale (NRS) over the first seven daily entries after screening within a pre-defined range (see section 9 for details of pain thresholds for eligibility)

3. Failure to respond (poor efficacy or unacceptable side effects) to drugs recommended for the treatment of neuropathic pain (23), including pregabalin or gabapentin, a tricyclic antidepressant, and mild and strong opioids (where not contraindicated or refused by the patient).
4. Previous specialised pain physiotherapy (24) (where not contraindicated or refused by the patient)
5. Willingness to confirm the use of adequate birth control while on the trial will be required in pre menopausal women without evidence for an inability to become pregnant.
6. Willingness to not start any other treatment for CRPS during the parallel part of the trial
7. Age 18 years and above

8.2 Exclusion criteria

Any individuals meeting any of the following will be excluded from the study:

1. Other significant chronic pains, which in the view of the study doctor may make assessment of the pain arising from CRPS difficult,
2. If the patient recently started a new therapy for CRPS which in the view of the study doctor may change the patient's pain level during the time of participation in the trial.
3. Unstable medical conditions
4. Litigation. Patients in litigation will be excluded only if conclusion of that litigation is imminent during the course of the study.
5. Pregnant or breastfeeding patients.
6. Complete IgA deficiency
7. Rare contraindications to IVIg therapy as per summary of product characteristics (SmPC)
8. Receiving IVIg for other reasons,
9. Patients previously enrolled in CRPS IVIg/SCIG trials
10. Ongoing drug or alcohol abuse
11. Psychiatric or mental health disorder which could in the judgement of the site investigator interfere with successful study participation
12. Unwillingness or inability to complete daily diaries, or inability to understand the questionnaires being used.
13. Cancer other than basal cell carcinoma within the last 5 years. However those patients who have received definitive treatment, such as curative surgery more than 6 months ago, with no known recurrence can be included.
14. A history of hypercoagulable or thrombophilic clotting abnormalities.
15. A history of thrombembolic events: ischaemic stroke, confirmed myocardial infarction, pulmonary embolism; deep venous thrombosis except where immobility related (e.g. after injury or operation).
16. Unstable angina
17. Renal failure, or serum creatinine greater than 1.5 times the upper limit of normal at screening
18. Any medical condition which in the opinion of the investigator would make it unsafe for the patient to participate or which would interfere with assessment of the outcome measures.
19. Participation in another interventional trial within 3 months of randomisation. Participation in non-interventional studies is not a reason for exclusion.

9 SCREENING, RECRUITMENT AND CONSENT

Patients will be identified through clinics at each of the 7centres, which are all specialist pain/ Complex Regional Pain Syndrome clinics in secondary care. Strategies will be implemented to maximise awareness of the trial in the patient population and increase referrals to the recruiting centres (see details of strategies to be employed in appendix 2). Patients will be given the patient information sheet to read at least 24 hours before the screening visit, where they will give informed consent. At the screening visit, there will be an opportunity for the participants to ask questions of a member of staff trained in all trial procedures, as delegated by the PI. The Principal Investigator or a co-investigator at each site will ensure that the participants meet the inclusion and exclusion criteria at the point of screening

Patients will be telephoned at least 8 days, and maximally 14 days after screening to check pain diary scores and confirm eligibility to participate.

A mean pain intensity of five or higher on a 11-point (0-10) Numeric Rating Scale (NRS) over the first seven daily entries after screening (the first entry is the day after the screening visit), and whose recorded pain intensity during this period never drops below four, is required for eligibility. At least 6 of 7 entries are required.

The above information is not listed in the inclusion criteria list as that will be public information when the trial is registered and bias may be introduced if patients are aware of the threshold being used. Site staff must not inform patients of the above details. This pain intensity, which determines eligibility is also the 'baseline pain intensity' for the secondary analysis of the primary outcome (described in section 14.1.1.).

Visit 2 will be scheduled no earlier than 10 days, and no later than three weeks after visit 1.

Screen failures may be rescreened ONLY where there is a short term reason for ineligibility, such as non-availability for study visits due to planned holidays or an ongoing acute illness. Pain diary scores which make the patient ineligible cannot be considered a reason for rescreening.

A screening log will be kept at site to document details of patients invited to be screened for participation in the study. For patients who decline or are ineligible, this will document any reasons available for non-participation (where provided). The log will ensure potential participants are only approached once.

The original signed consent form will be retained in the Investigator Site File, with a copy in the participant's hospital medical notes, and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study.

The right to refuse to participate without giving reasons will be respected.

10 STUDY MEDICATION

10.1 Description of Randomised Treatments

10.1.1 Placebo

Matching placebo infusions will be manufactured for the 5g/100ml & 10 g/200ml Intratect™ IVIg infusion. These will be identical in appearance to the active infusions — they will be indistinguishable by colour and foaming of the infusion.

10.1.2 Intratect™ IVIg infusion

The experimental intervention is 0.5 g/kg Intratect™ IVIg infusion, in combination with ongoing normal standard treatment for Complex Regional Pain Syndrome.

For reported side effects of Intratect™ IVIg infusion please refer to section 17.2 and the summary of product characteristics (appendix 4)

Contraindications include:

1) hypersensitivity to any of the components
2) hypersensitivity to homologous immunoglobulin, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

10.2 Selection of Doses for the Trial

The study medication is being used within normal clinical doses.

10.3 Selection & Timing of Dose for Each Participant

Interventions will be available in 5g/100ml & 10 g/200ml bottles Intratect™ IVIg infusion or matching placebo.

Each participant will be scheduled to receive infusions of active Intratect™ (0.5 g/kg) or matching placebo day 1 post randomisation and day 22 post randomisation. In exceptional circumstances, where a randomized patient does not attend for the first infusion on day 1, delay of the first infusion up to 5 working days is acceptable. Data collection timelines remain the same, regardless of when infusions are received. Any patient who has not received their trial infusion by the 5th working day will be withdrawn and not given trial medication. All patients receiving any amount of trial infusion on days 1 and up to the 5th working day will be included in the intention to treat analysis. All patients who receive = or >80% of the target dose on day 1 will be included in the per protocol analysis. All patients will be offered open label infusions of Intratect™ on day 43 and day 64 post randomization. Intratect™ or placebo will be infused intravenously at an initial rate of not more than 1.4 ml/kg/hr for 30 minutes. If well tolerated, the rate of administration may be increased to a maximum of 2.5 ml/kg/hr for the remainder of the infusion. This is higher than the usual recommended rate of 1.9 ml/kg/hr in order to ensure the entire infusion can be completed in a single day and in view of the experience of clinicians that higher rates of infusion are generally well tolerated.

Infusion rate adjustments can be made if patients experience mild adverse clinical effects, reducing to 1.9ml/kg/hr in the first instance and further if required, while aiming that there is sufficient time to complete the entire infusion in a single day.

10.4 Blinding of Investigational Medicinal Product

Active study medication (Intratect™ IVIg infusion 5g/100ml & 10 g/200ml) and placebo will be identical.

10.5 Identity & Supply of Investigational Medicinal Product

Intratect™ IVIg infusion 10g/200ml – Biotest UK
IntratectTM IVIg infusion 5g/100ml – Biotest UK

The trial medication is supplied as 100ml & 200ml bottles containing 5g & 10g IVIg. The volume prescribed per patient is weight determined, with a target of 0.5 g/kg.

10.6 Packaging & Labelling of Investigational Medicinal Product

Investigational medicinal product will be supplied in individual 100ml & 200ml bottles, containing 5g & 10g IVIg, or 0.1% albumin in normal saline as a control. For the day 1 and day 22 infusions, each bottle will be blinded during dispensing by the study site pharmacy. Day 43 and Day 64 infusions will use unblinded bottles of Intratect™ 5g/100ml or 10 g/200ml.

Packaging and labelling will be completed in accordance with Good Manufacturing Practice (GMP) Annex 13 requirements and GCP, by the Aseptic Manufacturing Pharmacy Unit (AMPU) at Royal Liverpool & Broadgreen Hospital, Liverpool

Label design for primary and secondary packaging:

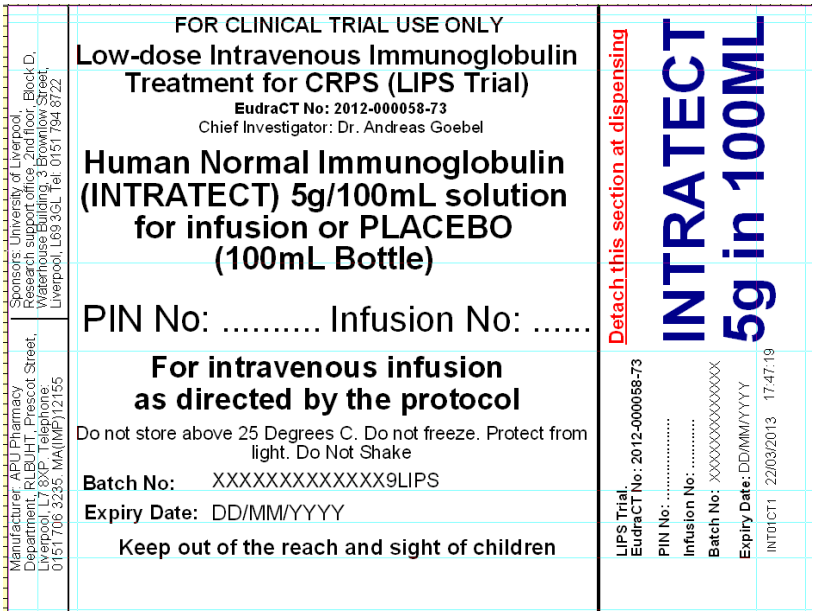
Label designs will incorporate a structure that allows the IMP or placebo to remain blinded to clinical staff and participants. Both the primary container (bottle) & the secondary packing of IMP and placebo will be labelled in an identical manner.

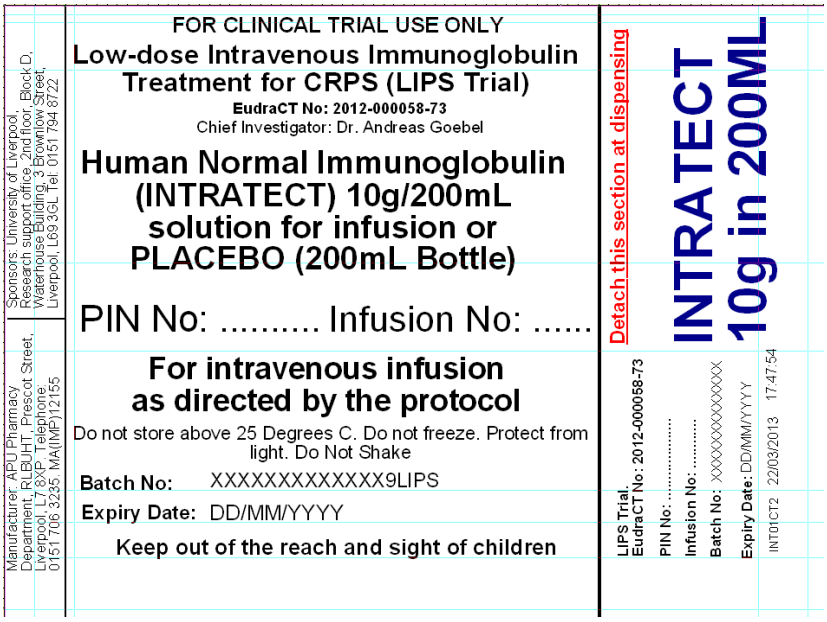
All labels will carry a tear off section that will be removed by the Pharmacy Departments at participating sites at the point of blinding and dispensing..

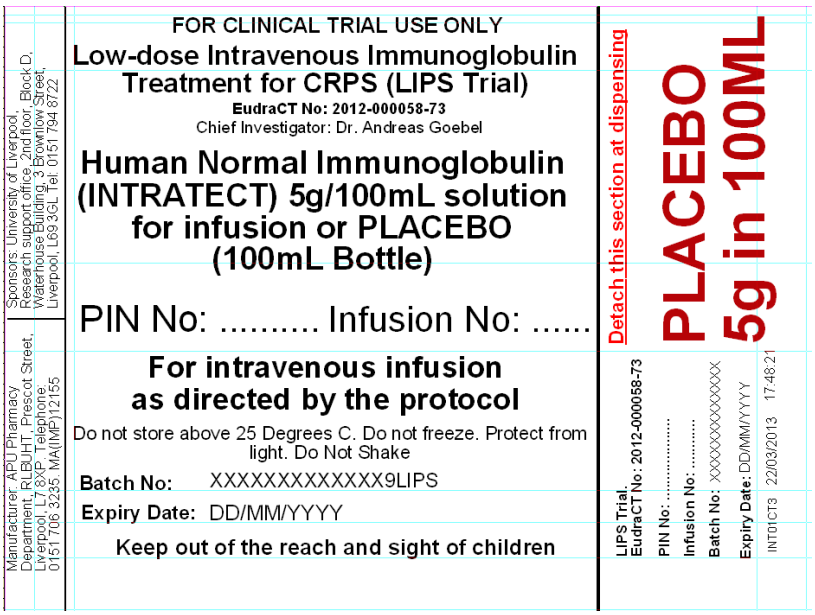
The 6 tear off sections of labels which will be detached by the study site pharmacy department during dispensing are:

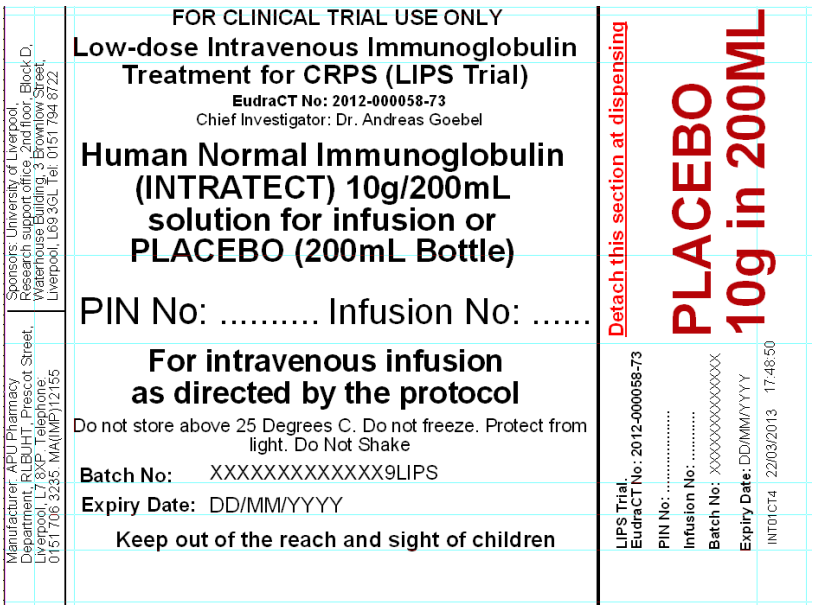
- INTRATECT 5g/100ml
- INTRATECT 10g/200ml
- PLACEBO 5g/100ml
- PLACEBO 10g/200ml
- OPEN LABEL INTRATECT 5g/100ml
- OPEN LABEL INTRATECT 10g/200ml

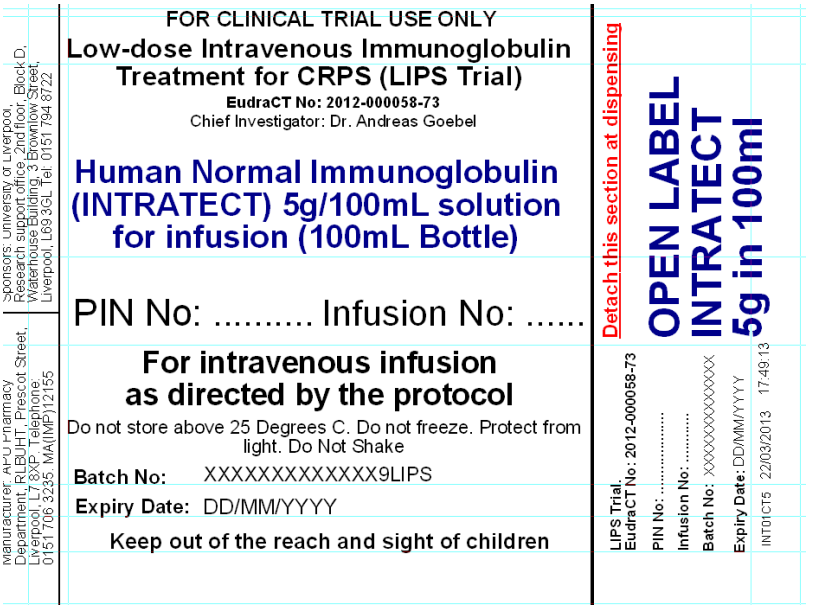
Example labels of the primary container (bottle) & the secondary packing of IMP and placebo are shown below:

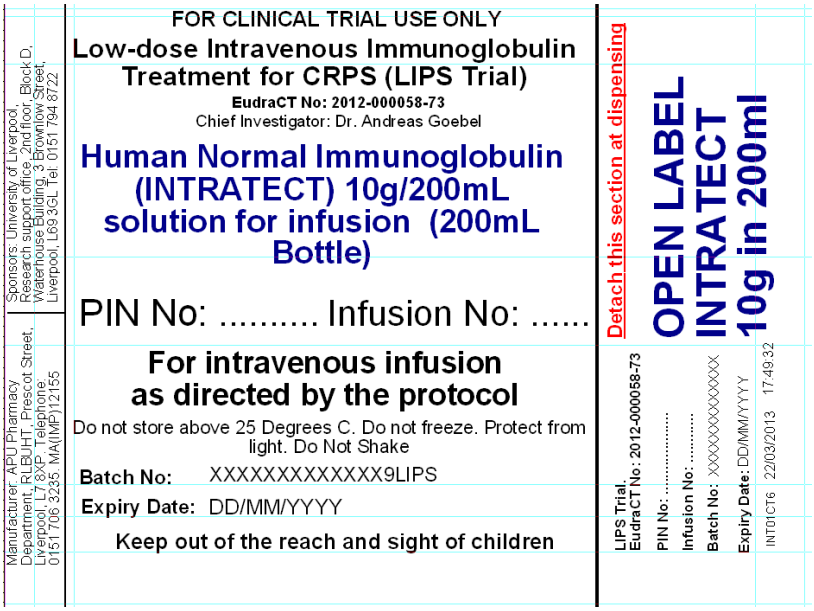





FOR CLINICAL TRIAL USE ONLY
Low-dose Intravenous Immunoglobulin Treatment for CRPS (LIPS Trial)
EudraCT No: 2012-000058-73
Chief Investigator: Dr. Andreas Goebel
Human Normal Immunoglobulin (INTRATECT) 5g/100mL solution for infusion or PLACEBO (100mL Bottle)
PIN No: ..... Infusion No: .....
For intravenous infusion as directed by the protocol
Do not store above 25 Degrees C. Do not freeze. Protect from light. Do Not Shake
Batch No: XXXXXXXXXXXXX9LIPS
Expiry Date: DD/MM/YYYY
Keep out of the reach and sight of children
Manufacturer: APU Pharmacy Department, RLBUHT, Prescot Street, Liverpool, L7 8XP Telephone: 0151 706 3235 MA(IMP)12155
Sponsors: University of Liverpool, Research support office, 2nd floor, Block D, Waterhouse Building, 3 Brownlow Street, Liverpool, L69 3GL Tel: 0151 794 8722
Detach this section at dispensing
LIPS Trial.
EudraCT No: 2012-000058-73
PIN No: .....
Infusion No: .....
Batch No: XXXXXXXXXXXXX
Expiry Date: DD/MM/YYYY
INT01CT3 22/03/2013 17:48:21
PLACEBO
5g in 100ML


FOR CLINICAL TRIAL USE ONLY
Low-dose Intravenous Immunoglobulin Treatment for CRPS (LIPS Trial)
EudraCT No: 2012-000058-73
Chief Investigator: Dr. Andreas Goebel
Human Normal Immunoglobulin (INTRATECT) 10g/200mL solution for infusion or PLACEBO (200mL Bottle)
PIN No: ..... Infusion No: .....
For intravenous infusion as directed by the protocol
Do not store above 25 Degrees C. Do not freeze. Protect from light. Do Not Shake
Batch No: XXXXXXXXXXXXX9LIPS
Expiry Date: DD/MM/YYYY
Keep out of the reach and sight of children
Manufacturer: APU Pharmacy Department, RLBUHT, Prescot Street, Liverpool, L7 8XP Telephone: 0151 706 3235 MA(IMP)12155
Sponsors: University of Liverpool, Research support office, 2nd floor, Block D, Waterhouse Building, 3 Brownlow Street, Liverpool, L69 3GL Tel: 0151 794 8722
Detach this section at dispensing
LIPS Trial.
EudraCT No: 2012-000058-73
PIN No: .....
Infusion No: .....
Batch No: XXXXXXXXXXXXX
Expiry Date: DD/MM/YYYY
INT01CT4 22/03/2013 17:48:50
PLACEBO
10g in 200ML


FOR CLINICAL TRIAL USE ONLY
Low-dose Intravenous Immunoglobulin Treatment for CRPS (LIPS Trial)
EudraCT No: 2012-000058-73
Chief Investigator: Dr. Andreas Goebel
Human Normal Immunoglobulin (INTRATECT) 5g/100mL solution for infusion (100mL Bottle)
PIN No: ..... Infusion No: .....
For intravenous infusion as directed by the protocol
Do not store above 25 Degrees C. Do not freeze. Protect from light. Do Not Shake
Batch No: XXXXXXXXXXXXX9LIPS
Expiry Date: DD/MM/YYYY
Keep out of the reach and sight of children
Manufacturer: APU Pharmacy Department, RLBUHT, Prescot Street, Liverpool, L7 8XP Telephone: 0151 706 3235 MA(IMP)12155
Sponsors: University of Liverpool, Research support office, 2nd floor, Block D, Waterhouse Building, 3 Brownlow Street, Liverpool, L69 3GL Tel: 0151 794 8722
Detach this section at dispensing
LIPS Trial.
EudraCT No: 2012-000058-73
PIN No: .....
Infusion No: .....
Batch No: XXXXXXXXXXXXX
Expiry Date: DD/MM/YYYY
INT01CT5 22/03/2013 17:49:13
OPEN LABEL
INTRATECT
5g in 100ml



10.7 Prescription of Investigational Medicinal Product

Study medication will be prescribed by an authorised study physician according to the protocol, using a trial specific prescription. The volume to be dispensed per patient will be calculated according to patient weight and the site pharmacist will dispense the required number of bottles. Medication will be dispensed according to local pharmacy practice. Bottles will contain 100mls or 200mls of IVIg or placebo. Participants will be informed of potential adverse reactions and advised to seek medical help and contact the research team, if required. Patients will carry cards with an emergency 24 hour code break number (Guy's Medical Toxicology Unit, 020 7188 0300. Documentation of prescribing, dispensing and return of study medication shall be maintained for study records in the pharmacy file and reconciled with the investigator site file at end of study. A study specific prescription must be submitted to pharmacy the day prior to the patient's infusion. The pharmacy will have received an email from the randomisation service at the time of randomisation, which must be printed and filed with the dispensing records and which will be referred to by the dispensing pharmacist to decide whether to dispense active or placebo medication for the blinded infusions.

See table below.

Weight (kg) range	Dose (g) to be administered	Kits (100mls) to be dispensed	Kits (200mls) to be dispensed	Volume to be administered (mls)	Maximum hourly infusion rate
35.5 – 45.4 kg	20g	-	2	400mls	88-113 ml/hr
45.5 – 55.4 kg	25g	1	2	500mls	113-138ml/hr
55.5 – 65.4 kg	30g	-	3	600mls	138 -163 ml/hr
65.5 – 75.4 kg	35g	1	3	700mls	163 – 188 ml/hr
75.5 – 85.4 kg	40g	-	4	800mls	188 – 213 ml/hr
85.5 – 95.4 kg	45g	1	4	900mls	213 – 238 ml/hr
95.5 – 105.4 kg	50g	-	5	1000mls	238 – 263 ml/hr
105.5 – 115.4 kg	55g	1	5	1100mls	263 – 288 ml/hr
115.5 – 125.4 kg	60g	-	6	1200mls	288 – 313 ml/hr
125.5 -135.4 kg	65g	1	6	1300mls	313 – 338 ml/hr
135.5 -145.4 kg	70g	-	7	1400mls	338 – 363 ml/hr
145.5 -155.4 kg	75g	1	7	1500mls	363 – 388 ml/hr
155.5 -165.4 kg	80g	-	8	1600mls	388 – 413 ml/hr

If the event that a 200ml bottle is not available, it is permitted to dispense two 100ml bottles, but where possible the preferred options are above. Where two 100ml bottles are dispensed, the trial manager must be informed as the next shipment of drug to site may need to be adjusted as a result. The exception is where the IMP expiry is coming close and in the judgment of the site pharmacist, it makes sense to use up some expiring 100ml bottles in preference to using 200ml bottles with a later expiry. Ideally this should be discussed with the trial manager in advance.

10.8 Dispensing & Distribution of Investigational Medicinal Product

Study drug will be stored in a secure area with limited access within each local pharmacy according to the storage requirements documented on the clinical trial label, prior to dispensing for each participant's infusion visit. A temperature log will be maintained as per local pharmacy procedures.

Study medication will be distributed to the 7 study site pharmacies by and from the Aseptic Manufacturing Pharmacy Unit (AMPU) at Royal Liverpool & Broadgreen Hospital, Liverpool. Study medication receipt will be recorded in the study pharmacy file. A study medication dispensing and return log will be maintained by the site pharmacies. Research staff will be instructed not to dispose of empty medication bottles, but to return these to pharmacy post-infusion.

Supplies of study medications dispensed on Day 1 and Day 22 post randomization will be blinded by the study site pharmacy department by detaching the tear off section from both the primary container (bottle) & the secondary packing. Dispensing records will be retained by the study site pharmacy department. For those who wish to receive open label medication, either a single additional open label dose will be given on Day 43 post randomization, or additional open label doses will be given on both Day 43, and Day 64 post randomization, if patients wish to receive two open label doses).

10.9 Administration of Investigational Medicinal Product

The infusion speed is calculated and titrated for both types of infusions. We recommend beginning the infusion at 1.4ml/kg/hr for 30 minutes and then infusing at a higher maximum rate than recommended in

the SmPC, with a maximum infusion rate of 2.5ml/kg/hr. The purpose of this is to reduce the visit duration. If centres prefer to run a slower infusion, this will not be considered a protocol violation.

Where a patient reports bothersome side effects developing during the infusion (such as headaches or dizziness or pain increase), the infusion rate is reduced from 2.5 ml/kg/hr to 1.9ml/kg/hr. The infusion rate can be further decreased if necessary to the minimal speed which would allow completion of the infusion during the study day. Patients may be offered paracetamol 1g orally during the infusion, where clinically indicated. Patients are under continuous nurse observation during the infusion; in cases where no reduction of the infusion rate is required the infusion duration for a participant of 75-85 kg body weight is about 4.5 hours.

In the event that patients do not receive their entire first infusion, either due to having to stop early because of time constraints arising from a long infusion duration with a low rate, or because side effects are intolerable even with the lowest infusion rate, they should still be offered the second infusion, as patients often tolerate second infusions better. Details of the amount infused should be recorded in the medical notes and eCRF.

Where the infusion cannot be tolerated, and the patient wishes to not receive additional infusion, this patient is withdrawn from further infusion, but follow up data will be collected until the end of the study.

10.10 Unused Trial Study Medication & Study Medication Accountability

Research staff will be asked to return any surplus study drug and empty bottles to the site pharmacy, who will verify and document returns. In the event that an infusion is not given as scheduled, reasons must be documented in the patients' notes and eCRF. The study monitor will check the pharmacy records against the eCRF before arranging destruction at site.

10.11 Concomitant Medications

All concomitant drug therapies received will be recorded at baseline and follow-up assessments.

Interactions include:

1) Live attenuated virus vaccines: Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.
2) Interference with serological testing: After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B D may interfere with some serological tests including the antiglobulin test (Coomb's test).

Details of all other agents that might interact with Intratect™ can be found in the British National Formulary (BNF) (http://www.bnf.org/bnf/).

Study site investigators and patients will be provided with an emergency 24 hr unblinding contact number (Guy's Medical Toxicology Unit, 020 7188 0300).

Participants should not receive any other investigational drugs or agents during their participation in the study.

Should patients experience a flare-up of their CRPS pain, or a trial-intervention-induced *reduced* pain level, they may in discussion with their PI (or a delegated experienced Pain Specialist) increase or reduce the dose of their current medications.

10.12 Safety Monitoring

The following blood tests will be done at baseline only. Additional blood monitoring is only required for the protocol in response to adverse events.

10.12.1 Routine Haematology

- White Blood Cell and differential count (eosinophils, basophils, neutrophils, lymphocytes and monocytes)
- Red Blood Cell and indices (PCV, MCV, MCH , MCHC)
- Haemoglobin
- Platelets
- Serum IgA
- Serum IgM
- Serum IgG

10.12.2 Biochemistry

- Sodium
- Potassium
- Urea
- Serum Creatinine
- ALT, AST, GGT, bilirubin

10.12.3 Pregnancy

- Blood pregnancy testing at baseline for female patients of childbearing potential, and urine pregnancy testing at visit 4 if receiving open label Intratect™

11 RANDOMISATION

11.1 Method of Identification of Patients

Patient identification number will be allocated by registering the patient on the MACRO eCRF system, after consent has been signed. The system will generate a unique identifier to be used throughout the study.

The PIN will be a five digit number; the initial two digits indicate the centre
(Bath = 01; Cambridge = 02; Glasgow = 03; Liverpool = 04; London= 05; Norwich = 06; Leicester = 07 and then a three-digit number indicating the number within the centre.

11.2 Method of Randomisation

Patients will be allocated (on study day 0) to placebo or IVIg (ratio 1:1) by sites via an online system based at the King's Clinical Trials Unit (King's CTU) based at the Institute of Psychiatry. The randomisation website

address can be accessed at www.ctu.co.uk by clicking 'randomisation – advanced' on the lower right hand side of the page.

Allocation will be at the level of the individual patient, using block randomisation with randomly varying block sizes, stratified by centre.

Only site staff authorised to request randomisation will receive passwords for the randomisation system. Requests for passwords are via the trial manager to the King's CTU.

11.3 Implementation Procedures

Sites will be responsible for maintaining a baseline of 'in date' stock on shelf of both Active & placebo IMPs.

Unblinded bottles for the open label phase of the study will also be available and supplied to participating sites.

Once an eligible patient has provided written informed consent and completed the baseline assessments, he/she will be asked to complete pain diaries daily after the screening visit until the infusion visit. The study site investigator will contact the patient by telephone at an agreed time between 8 and 14 days after the screening visit and collect screening pain diary scores. If the patient is eligible on pain diary and blood results, an infusion visit will be scheduled.

Online randomisation will be requested by site one day prior to the infusion. Patients can only be randomised after the allocated study site nurse has confirmed by telephone a) that the patient is well, b) that the patient is willing and able to come to the infusion unit the next day, c) the details of the arranged transport, d) any anticipated problems from the patient's perspective, e) that the pharmacy will be able to dispense in good time.

The randomisation system will automatically generate two emails at the point of randomisation. The first will be sent to appropriate members of the study team who are blinded to treatment allocation and will just confirm that the patient has been randomised. The second will be sent to the dispensing pharmacy, to inform them of the treatment allocation, and will be copied to the eSMS emergency code break service, so they have the unblinding information available in the event of the need to unblind. . A study specific prescription will be completed and sent to pharmacy for dispensing. The dispensing pharmacist will refer to the randomisation email when the prescription is received. Any bottle of IMP in the appropriate trial arm can be selected for dispensing but if IMP is available with an earlier expiry this should be used in preference to IMP with a later expiry.

Any problems with the online randomisation system should be reported to the trial manager or to the King's CTU at the email address below:

Contact details for Randomisation: CTU@kcl.ac.uk / 0207 848 0532

12 BLINDING

The trial will be double blinded. Blinding will be achieved by preparing both study drug and placebo (0.1% albumin in Normal Saline) solution into identical looking bottles. Batch numbers and expiry dates for both active and placebo drug will be indistinguishable.

IMP will be supplied directly to designated pharmacy contacts at participating sites. The tear off section on the primary container (bottle) & the secondary packing will inform the dispensing site pharmacy of the true nature of contents (Active or Placebo). At dispensing, this section of label is removed to maintain blinding.

In the event of an urgent need to unblind treatment, the 24 hour emergency code break service must be contacted This should be the preferred route to code break, even in office hours when the site pharmacist is available, as there is then a full audit trail of the code break event. The site pharmacy will also be aware of the patients treatment allocation.
Unblinding should only occur where knowledge of the randomised treatment is needed for immediate patient care and this cannot be delayed until the next working day when the study team can be contacted. Code breaks will not be routinely opened for participants who complete study treatment.

If a request for code break is received from a physician (e.g. the patient's general practitioner) outside the research team, Guy's Medical Toxicology Unit (eSMS) will attempt to contact the research team to verify the request before the code is broken.

If the code is broken, details including patient study number, the date code break was performed, the person who broke the code, and reason for code break shall be recorded by the emergency code break service and retained. The trial manager will be informed of the unblinding event. If clinically indicated, the participant will be withdrawn from study medication.

Accidental unblindings will be dealt with on a case by case basis, if and when they arise. The patient's data should continue to be collected according to the visit schedule, even if the event of unblinding or withdrawal from study medication, unless the patient refuses.

13 STUDY DATA

13.1 Trial Database

An electronic Case Report Forms (eCRF) will be created using the InferMed Macro system. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). The eCRF will be created in collaboration with the trial statisticians and the investigators and maintained by the King's Clinical Trials Unit. It will be hosted on a dedicated secure server within KCL.

Source data will be entered by authorised staff onto the eCRF with a full audit trail.

13.2 Trial Database Website Address:

Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

13.3 Database passwords

Database access will be strictly restricted through passwords to the authorised research team. The trial manager will request usernames and passwords from the KCTU administrator. It is a legal requirement that passwords to the eCRF are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a personalised username and password should be requested via the Trial Manager.

13.4 Data Handling & Confidentiality/Format of Records

Data will be handled, computerised and stored in accordance with the Data Protection Act, 1998. Participants will be identified on the study database using a unique code and initials. The investigator will maintain accurate patient records/results detailing observations on each patient enrolled.

13.4.1 Identifiable Data

All participant contact/screening and recruitment data will be will be stored on spreadsheets within the recruiting NHS sites, which will have restricted access from password protected computers. Accrual data uploaded to the UKCRN portfolio database will be anonymised and collated by the Trial Manager to CLRN. No identifiable data will be entered on the eCRF or transferred to the co-ordinating CTU.

13.4.2 Main Database

SAE data will be collected on paper SAE report forms and scanned, and then e-mailed to the King's CTU at CTU@kcl.ac.uk. If scanning is not possible, SAE reports will instead be faxed to the King's CTU at 0207 848 5229. An acknowledgement of receipt will be sent back to site and should be filed with the SAE report. Failure to receive an acknowledgement indicates that the SAE has not been received and is not considered to have been reported. Therefore sites must alert the trial manager or KCTU if an acknowledgement is not received. SAEs will be transcribed to eCRF. For all other data, collected source data worksheets (see Appendix 1) will be provided to recruiting sites, and data will be entered onto the main eCRF database. Source data worksheets will be reconciled at the end of the trial with the patients NHS medical notes in the recruiting centre. Trial related clinical letters will be copied to the medical notes during the trial. The Principal Investigator will provide an electronic signature for each patient Case Record Form once all queries are resolved and immediately prior to database lock, when instructed to do so by the Trial Manager.

At the end of the study, essential documentation will be archived in accordance with sponsor and local requirements. The retention of study data will be the responsibility of the Chief Investigator.

13.5 On-Site/Central Monitoring

The Trial Manager will conduct on-site/central monitoring. The Data Manager/Statistician may identify data fields that should be checked against the source data during site monitoring visits, the specifics will be outlined in a Data Management SOP. Where there are data queries the research nurses will be responsible for resolving the queries. The Trial Manager will review responses before closing the query.

13.6 Assessments/Data Collection

Written informed consent must be obtained prior to screening and any other study specific procedures taking place.

13.6.1. Visit Schedule

See table below.

Table 2: Table of events - summary of study procedures

LIPS - Summary of study procedures

			Day 0	**Day 1**	**Day 2** (+ up to 3 day)	**Day 5** (+/- 2 days)	**Day 22** (+/- 1 day)	**Day 23** (+ up to 3 days)	**Day 26** (+/- 2 days)	**Day 43** (+/- 1 day)	**Day 64** (+/- 1 day)	**Day 85** (+ up to 3 days)	**Day 148** (+/- 1 day)	
Study Week/month	**Visit 1** Screen (Day -21 to Day -	Telephone to confirm eligibility (Day -11 to Day -1)	**Randomisation**	**Visit 2** (1st blinded infusion)	**Telephone**	**Telephone**	**Visit 3** (2nd blinded infusion)	**Telephone**	**Telephone**	**Visit 4** (Obligatory, with optional 1st open infusion)	**Visit 5** (This visit is only for 2nd open infusion)	**Telephone**	**Telephone** **End of Trial**	**Withdrawal**
Registration/Demographics	X													
Informed Consent	X													
Eligibility form	X													
Randomisation form			X											
Medical History	X													
CRPS History	X													
Limb Exam	X			X			X			X				
Limb temperature, limb volume	X									X				
Safety bloods (U&E,FBC,serum-Ig,LFT)	X													
Pregnancy test (beta HCG)	X													
Pregnancy test (urine)										X				
Screening pain diaries (Average 24h pain intensity only) ^=day of collection back from patient, *=day issued to patient)	*	X (over phone)		^										
Detailed (blind) diary, weeks 1,2,3 (average pain intensity, pain unpleasantness, sleep quality) (^=day of collection back from patient, *=day issued to patient) (patients who consent will receive daily prompting texting reminders during days 2-42)				*			^							
Detailed (blind) diary, weeks 4,5,6 (average pain intensity, pain unpleasantness, sleep quality) (^=day of collection back from patient, *=day issued to patient) (patients who consent will receive daily prompting texting reminders during days 2-							*			^				

				Day 0	Day 1	Day 2 (+ up to 3 day)	Day 5 (+/- 2 days)	Day 22 (+/- 1 day)	Day 23 (+ up to 3 days)	Day 26 (+/- 2 days)	Day 43 (+/- 1 day)	Day 64 (+/- 1 day)	Day 85 (+ up to 3 days)	Day 148 (+/- 1 day)	
Study Week/month		**Visit 1** Screen (Day -21 to Day -	Telephone to confirm eligibility (Day -11 to Day -1)	**Randomisation**	**Visit 2** (1st blinded infusion)	**Telephone**	**Telephone**	**Visit 3** (2nd blinded infusion)	**Telephone**	**Telephone**	**Visit 4** (Obligatory, with optional 1st open infusion)	**Visit 5** (This visit is only for 2nd open infusion)	**Telephone**	**Telephone End of Trial**	**Withdrawal**
Detailed (open) diary, weeks 7,8,9 (average pain intensity, pain unpleasantness, sleep quality) (^=day of collection back from patient, *=day issued to patient) **For patients who receive open label infusion only.**											*	^			
LIPS detailed (open) dairy, weeks 10, 11, 12 (average pain intensity, pain unpleasantness, sleep quality) (^=day of collection back from patient, *=day issued to patient, ^1 diary returned using pre-paid envelope) **For patients who receive open label infusion only**												*	^1		
Simplified Pain Diaries (weekly pain intensity scores only) (^ = day diaries collected back from patient, *=day diaries issued to patient,^1 dairy returned using pre-paid envelope)											* (patients who do not receive open label infusion)	^1 (patients who do not receive open infusion)	* (patients who do receive open infusions)	^1 (patients who do receive open infusions)	*
Questionnaires:	1. Expectation from treatment				X										
	2. EQ-5D-5L	x						x			x				
	3. Mc Gill	x						x			x				
	4. BPI	x						x			x				
	5. HADs	x						x			x				
	6. Pain Catastrophising	x						x			x				
	7. Global impression of change							X			x	X		X	
	8. Health/Social care utilisation	X													
	9.Patient-developed measures	X						X			X				
	10. Stanford Presenteeism	X									X				
	11. Neglect-Like Symptoms	X									X				
Vital signs (pulse, blood pressure, before and after infusion)					X			X			X	X			
Treatment Infusion Administration					X			X			X	X			
Research Bloods (30ml)		x									X				

			Day 0	**Day 1**	**Day 2** (+ up to 3 day)	**Day 5** (+/- 2 days)	**Day 22** (+/- 1 day)	**Day 23** (+ up to 3 days)	**Day 26** (+/- 2 days)	**Day 43** (+/- 1 day)	**Day 64** (+/- 1 day)	**Day 85** (+ up to 3 days)	**Day 148** (+/- 1 day)	
Study Week/month	**Visit 1** Screen (Day -21 to Day -	Telephone to confirm eligibility (Day -11 to Day -1)	**Randomisation**	**Visit 2** (1st blinded infusion)	**Telephone**	**Telephone**	**Visit 3** (2nd blinded infusion)	**Telephone**	**Telephone**	**Visit 4** (Obligatory, with optional 1st open infusion)	**Visit 5** (This visit is only for 2nd open infusion)	**Telephone**	**Telephone** **End of Trial**	**Withdrawal**
Quantitative Sensory Testing (QST) (Subset of 40 patients only)	x			X (if not done on visit 1)						X				
Concomitant & CRPS Pain Treatments Medications	x	x		X	x		x			x	X		x	x
Concomitant Therapies	x	x		X	x		x			x	X		x	x
Adverse Events Form				X	x		x			x	X		x	x
Patient Medication Guess				X	x		x							x
Physician Medication Guess				X			x							x
Research Nurse Medication Guess				X			x							x
Withdrawal Form														x

Table Legend: McGill = McGill Pain Questionnaire (Short Form) pain descriptors; BPI = Brief Pain Inventory interference scores; HADS= Hospital Anxiety and Depression Scale; Catastrophising= Sullivan's catastrophising scale; Global Impression = Patient Global Impression of Change Scale; Stanford Presenteeism Scale = Work interference ; LFT = Liver function test; FBC = Full blood count; Beta HCG = Beta Human chorionic gonadotropin

14 STATISTICAL CONSIDERATIONS

Data analysis will be performed by the study statistician at University College London, using a password-protected computer in a private office.

14.1 Statistical Analysis

A comprehensive statistical analysis plan will be developed and agreed with the trial's oversight committees. Descriptive analysis (e.g. summary statistics and plots) will be performed to investigate the distribution of the primary outcome, pain score, across participants.

14.1.1 Efficacy

Primary analysis:

The primary outcome will be analysed using a mixed model to establish any difference between pain scores after IVIg and placebo. The stratification factor (centres) will be a fixed effect. The model will efficiently model the repeated measurements data. Modelling assumptions will be checked (e.g. residuals). All analyses will be performed on an intention to treat basis. Every effort will be made to reduce loss to follow up (using phone calls etc.). Participants who do not contribute any outcome measurements for the primary outcome will be omitted from the analysis. Participants who provide any outcome data will be included. No imputation will be performed.

Secondary analysis:

As a secondary analysis, we will calculate the proportion of patients in each arm that achieve 50% or 30% pain relief (based on the average pain level entered on day 6-42), compared to their baseline level of pain (the average pain level recorded during the first seven days of the screening period). Using these proportions we will calculate the number needed to treat (NNT) with IVIg so that one additional patient will achieve 50% pain relief.

Possible changes in treatment effect over time and association between disease duration, psychological baseline measurements, allergy status/, low baseline IgG plasma level, IgG increase, and treatment response, and any association between psychological measurements with the primary outcome will be investigated using exploratory plots and regression models with interaction terms. Change in McGill Pain Questionnaire (Short Form) descriptor terms(28) limb temperature and QST changes before-after IVIg/placebo treatments on affected/contra lateral sides, pain interference and QoL outcomes will be investigated using either standard regression models or mixed models. In those who decide to receive both open infusions, and who have at least 30% or 2 NRS points average pain relief from six to twenty days after their last open infusion as compared with baseline, the time between the last open infusion, and the first period with average weekly pain equalling or exceeding baseline -1NRS point) is calculated as the IVIg effect duration. As the study ends on day 148 (12 weeks after the second open infusion), later effects will not be recorded

Safety:
An interim analysis will be performed for futility and safety, after half of patients have completed the trial. The trial may be stopped if there is a statistically significant difference between the groups at the 5% level (2-sided test), and if with the statistician remaining blinded the unblinded DMC recognizes that the effect is into the 'wrong' direction. This stopping rule will only have a minor effect on the type I error and power of the trial.

There will no statistical stopping rule for efficacy although the DMC may suggest stopping the trial on the grounds of safety if there is an overwhelming positive effect of IVIg.
All cause withdrawal from randomised treatment will be reported at days 22 and 43 post randomisation. The prevalence of adverse events and reactions will be reported descriptively at 22 and 43 days post randomisation. If given open label infusion, AE's reported from 43 to 85 days post randomisation, will be tabulated separately for reports rather than being reported with blinded AE's.

14.2 Sample Size Calculation

The sample size was calculated as follows: 122 participants are required to detect a difference in pain score of 1.2 using a two-sample t-test assuming 5% statistical significance, 85% power and a common standard deviation of 2.2 (as in our previous study (8)). Assuming 10% loss to follow-up and 5% non-compliance increases this number to 152 participants. We actually intend to collect 37 measurements of pain intensity (the primary outcome) per participant and analyse the outcome using a mixed effects regression model. Thus we can reduce this sample size based on these extra measurements. The correlation between a patient's measures is assumed to be 0.7 (from our previous study) and hence the multiplying factor is (1+(37-1)x0.7)/ 37 =0.71 Therefore the total required sample size is 152 x 0.71 = 108 participants (29).

15 COMPLIANCE AND WITHDRAWAL

15.1 Subject Compliance

Compliance will be measured by attendance at infusion visits on day 1 and day 22 and tolerance of entire prescribed infusion.

15.2 Treatment Cessation

Patients who develop an unexpected new condition precluding further participation will be withdrawn from receiving further infusions, but will continue to complete daily pain diaries and asked to attend for collection of other outcome data (intention to treat). If patients do not tolerate blinded infusion 1, they may still be administered blinded infusion 2, if both the patient and clinician are agreeable.

15.3 Withdrawal of Participants

Study drug must be discontinued if:

- the participant decides they no longer wish to continue;
- recommended by the Investigator or another clinician (e.g. intercurrent illness during course of study, side effects from study drug); or
- the trial is terminated at the request of the DMC.

Patients also discontinue if:

- they are randomized, but never receive any drug (i.e. the first infusion is never started – this is also termed 'non-compliance')
- they do not provide any values for the day 6-43 outcome pain diary data (this is also termed 'missing data')

Participants have the right to withdraw from the study at any time and for any reason, without providing a reason. The investigator also has the right to withdraw participants from the study if they consider that it is in the best interests of the participant. Should a participant decide to withdraw from the study, he/she will be asked to volunteer a reason for withdrawal but are at liberty not to state a reason.

Should a participant withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient. Subjects who withdraw from treatment early will be encouraged to return to the study site to have follow-up until day 43, providing that consent is not withdrawn.

16 DATA MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Discontinuation rules

The trial may be prematurely discontinued on the basis of predefined stopping criteria, or for other reasons given by the independent Data Monitoring & Ethics Committee, study sponsor, regulatory authority or ethics committee concerned.

16.2 Monitoring, Quality Control and Assurance

The LIPS protocol has been developed with extensive review by clinicians, statisticians, and patient groups.

The LIPS Trial Coordination Centre will be based in the King's Clinical Trials Unit in the Department of Biostatistics at the Institute of Psychiatry, King's College London (IoP/KCL). Day to day management of LIPS will be the responsibility of the Chief Investigator and the Trial Manager. The Coordinating Centre will arrange meetings of the Trial Management Group (TMG) and Trial Steering Committee (TSC) and will coordinate independent Data Monitoring Committee (DMC) meetings.

The TMG will comprise Dr Andreas Goebel (Chair), the Trial Manager, the Data Manager, the Trial Statistician, and the manager of King's Clinical Trials Unit. The TMG will arrange telephone conferences and provide monthly recruitment email updates during recruitment and status reports 6-monthly thereafter. The TMG will organise a meeting for all PIs (and for key staff working on the study) to sign the protocol, and to agree the content and undergo training on SOPs, before the start of recruitment. A second investigators meeting will be held at the end of the study to review the results. The TMG will also meet face-to-face every 6 months in Liverpool or London. The TMG will report to the Trial Steering Committee (TSC). All PIs will be kept informed of TSC and DMC advice and consulted by e-mail or teleconference as required.

The TSC will consist of: an independent chair; two independent members; a site investigator; a patient representative; a non-voting member, the Chief Investigator; the names are detailed on page 4 of this protocol. The TSC will be responsible for approving the trial protocol, and overseeing the conduct of the study, including advising on continuing or stopping the study in the light of advice from the DMEC. Meetings of the TSC will be at least annually.

Membership of the DMEC will comprise: an Independent Chair; an independent specialist with interest in neuropathic pain analgesic trials; and an independent statistician. The DMC will have access to the unblinded data and will monitor the progress of the trial in terms of safety and ethical issues. The DMC may advise the TSC to continue or to stop the trial according to pre-agreed stopping rules.

The Principal Investigators will be responsible for the day-to-day study conduct at site. This includes: establishing and carrying out the trial at his/her centre, in accordance with international, national and local law and regulations and GCP; ensuring that all site specific documentation is complete and correct, and that all staff involved in the trial are compliant with Trust, GMC and other relevant regulations, are appropriately trained in those aspects of GCP relevant to their role in the study and are familiar with the trial protocol; managing recruitment on target and collecting and submitting accrual and outcome data in a timely manner; responding in timely fashion to requests from the Trial Coordinating Centre for information; providing and responding promptly to SAEs and SUSAR reports; agreeing to monitoring and audit visits as required.

Quality control will be maintained through adherence to relevant King's CTU SOPs, study protocol, the principles of GCP, research governance and regulatory requirements.

Data management will be supervised by the study statistician, the study data manager, the Senior Data Manager at the King's CTU, and by the Unit Manager at the King's CTU using the KCTU's InferMed MACRO web based data entry system.

Statistical analysis will be carried out by the study statistician at University College London.

Central and site monitoring of study conduct and data collected will be performed by the Trial Manager at the KCTU on behalf of the Sponsor. Full details will be documented in a monitoring plan, agreed with the study sponsor. The main areas of focus will include consent, serious adverse events, essential documents, and drug accountability & management. All monitoring findings will be reported and followed up with appropriate persons in a timely manner.

The study may also be subject to audit or inspection by the University of Liverpool or the Walton NHS Trust under their remit as co-sponsors, or by MHRA or other regulatory bodies to ensure adherence to GCP and regulatory requirements.

Direct access to source data and documents
The investigators agree to provide full access to all source data, study data and materials to the trust research governance department, ethics committee, regulatory authority and trial manager for purposes of monitoring, audit or inspection.

17 PHARMACOVIGILENCE

17.1 Definitions:

Adverse event (AE): Any untoward medical occurrence which does not necessarily have a causal relationship with the treatment. "Treatment" includes all investigational and non-investigational agents administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse Reaction (AR): Any untoward or unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered - *All AEs judged by either the reporting investigator or the sponsor as having a reasonable suspected causal relationship to a medicinal product (i.e. definitely, probably or possibly related) qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.*

Causality:
The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. If any doubt about the causality exists, the investigator should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	Description
None	There is no evidence of any causal relationship to study treatment.
Remote	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable*	There is evidence to suggest a causal relationship and the influence of other factors

	is unlikely.
Definite*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*Reportable to MHRA

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR):** any untoward medical occurrence or effect that at any dose

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected, Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction that is both unexpected and serious. An adverse reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information (See appendix 4).

17.2 Expected adverse reactions:

Most adverse drug reactions that occur in this study, whether serious or not, will be expected treatment-related side effects as IVIg has a well-established side effect profile.

Intratect™ can cause adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild back pain, which may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

Details of further spontaneously reported adverse reactions:

- Cardiac disorders: Angina pectoris (very rare)
- General disorders and administrations site conditions: Rigors (very rare)
- Immune system disorders: Anaphylactoid shock (very rare), hypersensitivity (very rare)
- Investigations: Blood pressure decreased (very rare)
- Musculoskeletal and connective tissue disorders: Back pain (very rare)
- Respiratory, thoracic and mediastinal disorders: Dyspnoe NOS (very rare)
- Vascular disorders: Shock (very rare)

The adverse events reported above are expected, in the sense that they are possible known side-effects of the study medication, but all reported instances of both serious and non-serious adverse events will be reported in this study.

During the trial, investigators will be made aware of any updates to the SPC but the protocol need not be amended every time there is a change unless it directly affects the study conduct. The source of accurate information regarding the active medication must always be the SPC and not the study protocol and the above information is provided to reflect the situation at study start only.

17.3 Protocol Specifications

For purposes of this protocol

- Any serious adverse events will be recorded throughout the duration of the trial until 21 days after cessation of study drug, or until resolution.
- Non-serious adverse events will be recorded throughout duration of trial until 21 days after cessation of study drug.
- Serious adverse events exclude any pre-planned hospitalisations not associated with clinical deterioration.

17.4. Recording & Reporting Serious Adverse Events or Reactions

All adverse events and all serious adverse events should be recorded. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event recording/reporting should be directed to the Trial Manager in the first instance.

Non-serious Adverse Events: All non-serious adverse events will be recorded on the study CRF. Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):

Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

Relation of an AE to treatment should be assessed by the investigator/delegate (must be a clinician) at site. Investigators will be responsible for managing all adverse events according to local protocols as the study drug is already licensed for use in other indications.

Serious Adverse Event / Reaction (SAE/SAR, including SUSARs): All SAEs, SARs & SUSARs shall be recorded and reported on the serious adverse event form to the Chief Investigator / delegate within 24 hours of learning of its occurrence. The initial report can be made by completing the serious adverse event form, and faxingor emailing to the King's CTU (Fax: 020 7848 5229, email: KCTU@kcl.ac.uk). A record of this notification (including date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available.

Relationship of the SAE to the treatment should be assessed by the investigator/delegate (must be a clinician) at site, as should the expected or unexpected nature of any serious adverse reactions. As this is a blinded trial involving a placebo and active drug, seriousness, causality and expectedness should be evaluated as though the patient was on active drug.

All SUSAR - reporting responsibilites to MHRA will be that of the Sponsor, with the support of the Kings CTU. The Sponsor will report SUSARs (Suspected Unexpected Serious Adverse Reactions) and other SARs to the regulatory authority (MHRA).

The Chief Investigator will report to the relevant ethics committees, with the support of the Kings CTU. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.

- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator will provide an annual report of all SARs (expected and unexpected), and SAEs which will be distributed to the Sponsor, MHRA and the REC.

As this is a blinded study, cases that are considered SUSARs would have to be unblinded to the King's CTU manager prior to reporting to the Sponsor and main REC. Only those events occurring among patients on the active drug (unless thought to be due to the excipient in the placebo) should be considered SUSARs.

All investigators will be informed of all SAE's assessed as fulfilling criteria as a SUSAR (ie, possibly, probably or definitely related to the study intervention and unexpected per the SPC) on a case-by-case basis. This will be regardless of medication administered in order to avoid the risk of inadvertently unblinding investigators, unless this information is needed for medical management of patients. Therefore, occasions may arise where a potential SUSAR is unblinded and where the patient is taking placebo, the MHRA would not need to be informed but the investigators will not be made aware of this information. All reports to PI's will refer to events fulfilling criteria as a 'potential SUSAR' and only the KCTU and Sponsor will be aware of the events reported onward to the MHRA in an expedited manner.

The Chief Investigator will ensure University of Liverpool as lead sponsor is notified of anypotential SUSARs.

* The Trial coordinating centre MUST be informed of all SAEs or SUSARs within 24 hours of learning of its occurrence. A record of this notification (including date of notification and acknowledgement of receipt from the KCTU) must be clearly documented to provide an audit trail.

Contact details for reporting SAEs and SUSARs:
Trial Manager, King's CTU: email CTU@kcl.ac.uk, Fax 020 7848 5229

The KCTU will onward report to the CI and Sponsor in compliance with regulatory requirements

17.5 Pregnancy

Should a trial participant become pregnant during the trial, she will be immediately withdrawn from study treatment, and the pregnancy followed up until outcome. The need to unblind will be considered on a case by case basis. Pregnancy will be reported as a serious adverse event. Data collection at the planned scheduled follow up timeline must continue, unless the patient is unwilling to provide further data.

18 RESEARCH BLOOD SAMPLES

Research blood samples will be requested at baseline and day 43. Patients not consenting to provide research blood samples may still be randomised into the study. Patients only willing to provide research blood samples on a single occasion should have sample collection accordingly.

On consenting patients, 30mls of blood will be collected in a gel tube and centrifuged at 2000G for 10 minutes according to local policy (no specific centrifuge protocol is required). Serum must then be pipetted or poured into 10ml aliquots and stored frozen in a -20 or -80 freezer. Each aliquot must be labelled with the patients study PIN, initials, date of birth and date of sample collection. Details of sample collection must be entered on the eCRF system.

The blood samples will be used to examine serum-antibodies, mediators or substances in patients with Complex Regional Pain Syndrome. Samples will be stored and examined for 30 years.

On a periodic basis, the study monitor will arrange for a shipment of dry ice to be delivered to the study site and for samples to be shipped via courier to the University of Liverpool on the same day. Shipment forms will be provided to sites by the study monitor.

19 ETHICS AND REGULATORY ISSUES

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures. Participants will be provided with a copy of the completed consent form for their records.

Favourable ethical opinion and MHRA Clinical Trial Authorisation will be sought prior to commencement of the study. Local approvals will also be sought, including site specific assessment and trust R&D approval. The participating site must also sign a Clinical Trial Agreement (CTAg) with the study sponsor. The Trial Coordination Centre at the King's Clinical Trials Unit will require a written copy of local approval documentation and a copy of the signed CTAg before initiating each centre and accepting participants into the study.

20 FINANCE AND INSURANCE

NIHR EME is the main funder of this study. Biotest UK Ltd will provide active study medication free of charge and some funds. The Pain Relief Foundation, Liverpool has provided additional support funding to the study.

The participating NHS Trusts have liability for clinical negligence that harms individuals towards whom they have a duty of care. NHS indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial. University insurance covers research staff, that have their substantive contract with the University for potential liability arising from negligence in study design. There are no arrangements for non-negligent compensation.

21 PUBLICATION POLICY

The data will be the property of the co-sponsors. Publication will be the responsibility of the Chief Investigator. Results from the study will be submitted for publication by the investigators only, in international medical journals. All manuscripts, abstracts or other modes of presentation will be reviewed by the TSC and DMC prior to submission. No reference will be made to any particular study subject. Results of the study will also be reported to the Sponsor and Funder in the required format.

Participants will be informed about their treatment allocation at the end of the study, along with a summary of the results, once the primary paper has been accepted for publication.

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APPENDIX 1

CRF Pack (To be added prior to recruitment)

APPENDIX 2

Recruitment Strategy

	Method of approach	Ways in which patients can respond, in order to request for more info, or arrange screening, or decline	Where there is no patient response to the approach after 14 days, contact with
Approach through infusing centre	In clinic with Patient Information Sheet (PIS)	By phone	Reminder letter
	Through invitation letter with PIS	Using a response slip or by phone	If no response within 14 days of the reminder letter: phone call
Approach through named Patient Identification Centre (PIC)	In clinic with PIS	By phone or by response slip directly to the infusion centre (with notification to own doctor), or to the PIC, with request to forward contact details to the infusion centre	Reminder letter sent by (PIC)
	Through invitation letter with PIS		If no response within 14 days of the reminder letter: phone call (by PIC doctor)
Approach through any UK doctor	Generally in clinic without PIS	Generally patients will directly confirm their interest to be contacted by one of the infusing centres, so that the doctor can then forward contact details to the infusion centre.	N/A

Table legend. PIS=Patient Information sheet; N/A= Not applicable; PIC=Patient identification centres

Note: patients or doctors contacting one centre will be made aware of the closest centre to the patient's home address.
Patients registered on the Complex Regional Pain Syndrome national registry will be approached by their nearest infusion centre through an invitation letter, as described in the first row

APPENDIX 3

Summary of substantial amendments

Substantial amendment number	Summary of changes
Substantial amendment 1, Protocol version 2.0, (19.10.12)	**Sponsor contact** The new details reflect a change to the legal representative for one of the sponsors **7.1 Primary outcome measure** The new text describes an extended period for 24 hour pain diary from 15 to 37 days. An additional description of the text prompting system is described to improve compliance. This change reverts back to the original design agreed by the funders as the TSC felt it more robust. **7.2 Secondary outcome measures** The EQ-5D will now be used as a measure of quality of life. The rewording clarifies the two parts to the secondary outcomes. The secondary outcomes and the Exploratory outcomes. There were additionally missing references for the assessments to be used that have now been included. The standard gamble was removed on the advice of a health economist. **8.2 Exclusion criteria** Serum IgA levels previously defined as an exclusion criteria, have now been redefined. An additional exclusion criterion has been included to prevent the inclusion of individuals that have participated in an intervention trial within the last 3 months. **9 Screening Recruitment and consent** Additional text has been included for clarification. **10.3 Selection & Timing of Dose for each participant** Additional details included to clarify the inclusion of participants that are non-compliant for the infusion visit. **10.6 Packaging and Labelling of Investigational medicinal product** Study name and Eudract number now included on label **10.11 Concomitant Medications** Additional information is provided on how to proceed if there is a change in a participant's condition with regards to CRPS and trial intervention. **10.12.2 Biochemistry** Additional tests have been included for biochemistry. **11.3 Implementation Procedures** Clarification of the implementation procedures, including a checklist for the site nurses to go through before a participant can be randomised. **14.1.1 Efficacy Safety** Treatment stopping rules agreed and included. The reporting of AE's has also been clarified. **14.2 Sample size calculation** The sample size calculation was adjusted to account for the increased number of days included for the measurement of the primary outcome. This change reverts back to the original design agreed by the funders as the TSC felt it more robust. **15.3 Withdrawal of participants** The following points were included to clarify discontinuation of participants in the study. **16.2 Monitoring Quality Control and Assurance Safety** Changes have been made to the representatives in the TSC and the DMEC

	Addition of PI video The video is intended to standardise the explanation of the trial across sites. As the outcome is subjective this is felt to be of importance
Substantial amendment 2, Protocol version 3.0, (11.04.13)	**REC** Updated REC address **7.2 Secondary and exploratory outcome measures** Removal of time trade off scale. **8.1 Inclusion criteria** Rewording of inclusion criteria 4: Previous specialised pain physiotherapy (24) (where not contraindicated or refused by the patient). **10 STUDY MEDICATION** Clarification of drug/placebo availability, drug/placebo labelling and packaging. Changes to the blinding procedure. **10.12.3 pregnancy** Addition of urine pregnancy test at visit 4 for females wanting open lebel drug **Summary of study procedures** Clarification to study procedures **PI video** Addition of slides
Substantial amendment 3, Protocol version 4.0, (01.07.13)	**7.2 Secondary outcome measures** Neglect-Like Symptoms in CRPS questionnaire has been added to the list of measures to be used within the secondary and exploratory outcome measures **14 STATISTICAL CONSIDERATIONS** Allergy status & low baseline IgG plasma level have been added to secondary analysis
Substantial amendment 4, Protocol version 5.0, (04.10.2013)	**Protocol (throughout)** Additional site, Leicester Minor corrective changes **Participant Information Sheet** Amendment to common, occasional and rare side effect of IVIG

APPENDIX 4

Intratect Summary of Product Characteristics

http://www.medicines.org.uk/emc/medicine/23175/SPC/intratect/

APPENDIX 5

Research Diagnostic Criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome

General definition of the syndrome:
Complex Regional Pain Syndrome describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom in all four following categories:
   - Sensory: Reports of hyperesthesia and/or allodynia
   - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - Vasomotor: Evidence of temperature asymmetry (>1 °C) and/or skin color changes and/or asymmetry
   - Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms