



Clinical trial results:

Is it clinically effective to treat arm flexor spasticity, with Botulinum toxin – type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed?

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-021257-39 |
| Trial protocol | GB |
| Global end of trial date | 28 May 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 02 April 2016 |
| First version publication date | 02 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | PB-PG-0808-16319 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | ISRCTN57435427 |
| ClinicalTrials.gov id (NCT number) | NCT01882556 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Research Ethics Committee Reference: 10/H1003/111 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sandwell and West Birmingham Hospitals NHS Trust |
| Sponsor organisation address | City Hospital, Dudley Road, Birmingham, United Kingdom, B18 7QH |
| Public contact | Dr Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, 0121 507 4811 , jocelyn.bell@nhs.net |
| Scientific contact | Dr Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, 0121 507 4811 , jocelyn.bell@nhs.net |
| Sponsor organisation name | Keele University |
| Sponsor organisation address | Keele University, Keele, United Kingdom, ST5 5BG |
| Public contact | Professor Anand Pandyan, Keele University, 01782 734252, a.d.pandyan@keele.ac.uk |
| Scientific contact | Professor Anand Pandyan, Keele University, 01782 734252, a.d.pandyan@keele.ac.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 | 28 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 May 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to establish whether treating spasticity using a combination of BoNTA and standardised physiotherapy, as soon as signs of abnormal muscle activity are observed is more effective in facilitating the recovery of arm function following stroke than standardised physiotherapy alone by evaluating the clinical effects of BOTOX® and Physiotherapy when compared against placebo and Physiotherapy, in patients with focal spasticity post-stroke, identified on clinical and neurophysiological grounds, in facilitating the recovery of arm function (measured using the Action Research Arm Test). NB: The scores range from 0 (no arm function) to 57 (good arm function) and an improvement of 6 in this scale is considered a clinically important.

Protection of trial subjects:

Patients who have had a stroke are often clinically unwell and may also have communication problems making obtaining informed consent difficult. The approach used was to obtain consent from the patient directly whenever possible. However, where they were deemed unable to provide informed consent, their legal representative or next of kin was asked to provide consent and the patient's cooperation with the procedures taken as assent to participation in the trial. Where third party consent was not available or the patient actively resisted the procedure then the intervention did not proceed and the patient did not participate in the study.

It was vital to optimise the selection of patients with high tone who might benefit from treatment. We were concerned that reliance on clinical detection of high tone is very unreliable. We therefore utilised an additional method (surface EMG) , to identify patients with early spasticity who might benefit from treatment if there was a positive effect.

Botulinum toxin is a powerful agent but enjoys a relatively low side-effect profile. Risks of side effects were minimised by use of the smallest known effective dose in the setting of upper limb spasticity and injections were given only by clinicians highly experienced in botulinum injection technique.

Background therapy:

To prevent secondary complications the treatment ensured that the joint was not held in a shortened position for prolonged periods of time. Joints were also mobilised through full range as often as possible using electrical stimulation as this was the easiest to apply and most cost effective to use. Treatment could be carried out independently by the patients themselves and/or their carers and the devices could be used at home. A secondary benefit of electrical stimulation was its potential to prevent atrophy and hence reduce the rate at which secondary complications set in. The exercise protocol involved cyclical stimulation to the wrist and elbow. Although unlikely, treatment with electrical stimulation may contribute to a transient reduction in spasticity but this was accounted for in the study design. Recovery of function is associated with the return of strength and is normally facilitated by functionally relevant therapy. In current practice rehabilitation therapy incorporates functionally relevant exercises when a patient has sufficient strength to participate. In order to reflect this progression in a systematic way for the purpose of this study all patients who achieved an MRC grade of 2 (i.e. movement through full range with mass of limb supported) carried out functionally relevant tasks (e.g. pick and place objects of varying sizes).

Evidence for comparator:

In this trial half the participants receive the active agent botulinum and half received saline injections instead. The use of a placebo with neither the patient or the injecting clinician knowing whether active drug or saline is being administered was justified because there is a state of clinical equipoise with

respect to our knowledge of this treatment. We know that botulinum has powerful effects on muscle tone and can be useful in established spasticity but we do not know if it is clinically useful or not when given early on in the course of rehabilitation. There are good theoretical reasons to believe that it may be helpful when given in this way.

The only ethical course of action was to seek to scientifically answer the question "Is the use of botulinum toxin in this way genuinely helpful to patients." Since no one knows the answer to that question, patients who do not receive the active agent are not being deprived of treatment they would benefit from. Likewise patients receiving the agent were not being given something that would be harmful. Advice was taken from a patient group formed to specifically advise us on these issues. This approach has also been used in previous protocols of trials with botulinum and other agents in the management of stroke.

| | |
|---|-----------------|
| Actual start date of recruitment | 30 January 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 93 |
| Worldwide total number of subjects | 93 |
| EEA total number of subjects | 93 |

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) | 32 |
| From 65 to 84 years | 47 |
| 85 years and over | 14 |

Subject disposition

Recruitment

Recruitment details:

The trial recruited between January 2012 and December 2013 in the UK only. Subjects were recruited from clinical case loads. Subjects were consented, enrolled and screened in the first instance and then monitored until confirmed as eligible for randomisation. Eligible patients were then randomised.

Pre-assignment

Screening details:

1143 patients were admitted during the trial period, 345 patients fulfilled the criteria of no arm function. 120 consented in to the trial and subsequently screened for eligibility. Of the subsequent 100 patients found to be eligible, 97 progressed from screening to randomisation and 93 patients received treatment and were included in analysis.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 120 ^[1] |
| Number of subjects completed | 93 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Adverse event, non-fatal: 3 |
| Reason: Number of subjects | Adverse event, serious fatal: 1 |
| Reason: Number of subjects | Protocol deviation: 1 |
| Reason: Number of subjects | Recovered function, developed spasticity: 16 |
| Reason: Number of subjects | Refused injection: 3 |
| Reason: Number of subjects | Developed no spasticity, recovered no arm function: 3 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 120 patients consented in to the trial and subsequently screened for eligibility. Of the subsequent 100 patients found to be eligible, 93 patients progressed to treatment and were considered enrolled in the trial.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

The Research Pharmacist was responsible for randomisation using sealed envelopes held securely in Pharmacy. The dispensed drug was taken to the ward in a sealed opaque bag where an independent clinician filled the syringes according to the randomisation. Separate sharps bins were used for preparation/reconstitution and injecting. Placebo and active injection appeared indistinguishable in the syringe and the injecting clinician and patient remained blind to treatment.

Arms

| | |
|--|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | IMP (treatment) |
| Arm description: | |
| OnabotulinumtoxinA + CDP (Clearly Defined Physiotherapy) | |
| Arm type | Experimental |

| | |
|--|--|
| Investigational medicinal product name | Onabotulinumtoxin |
| Investigational medicinal product code | PR1 |
| Other name | Botox purified neurotoxin complex, BoNTA, botulinum toxin, Botox |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

Maximum dose allowed was 200 Botox units in total, as follows; Biceps 50units, Brachialis 50units; Flexor Digitorum Profundus 30units; Flexor Digitorum Superficialis 30units; Flexor Carpi Radialis 20units; Flexor Carpi Ulnaris 20units. Patients received between 4 and 6 injections, with the exact dosage and number of injection sites tailored to the individual based on: size, number and location of muscles involved; severity of spasticity; presence of local muscle weakness. Reconstituted BOTOX® and placebo was injected using a sterile 25-, 27-, or 30-gauge needle for superficial muscles. Localisation of the involved muscles was determined clinically by superficial anatomical landmarks and using electrical stimulation techniques. Where localisation of the muscles proved to be difficult using surface anatomy and EMG, ultrasound was used to guide the injection procedure and check accuracy of placement of the needle.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo + CDP (Clearly Defined Physiotherapy)

| | |
|--|-----------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL1 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

0.9% Sodium Chloride Solution for injection. Patients received between 4 and 6 injections, with the exact dosage and number of injection sites tailored to the individual based on: size, number and location of muscles involved; severity of spasticity; presence of local muscle weakness. Maximum dose allowed was 200 Botox units in total, as follows; Biceps 50units, Brachialis 50units; Flexor Digitorum Profundus 30units; Flexor Digitorum Superficialis 30units; Flexor Carpi Radialis 20units; Flexor Carpi Ulnaris 20units. Reconstituted BOTOX® and placebo was injected using a sterile 25-, 27-, or 30-gauge needle for superficial muscles. Localisation of the involved muscles was determined clinically by superficial anatomical landmarks and using electrical stimulation techniques. Where localisation of the muscles proved to be difficult using surface anatomy and EMG, ultrasound was used to guide the injection procedure and check accuracy of needle placement.

| Number of subjects in period 1 | IMP (treatment) | Placebo |
|---------------------------------------|-----------------|---------|
| Started | 45 | 48 |
| Completed | 45 | 48 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |

| | |
|---------------|---|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
|---------------|---|

Blinding implementation details:

All individuals remained blind during the follow-up period

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | IMP (treatment) |

Arm description:

OnabotulinumtoxinA + CDP (Clearly Defined Physiotherapy)

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Onabotulinumtoxin |
| Investigational medicinal product code | PR1 |
| Other name | Botox purified neurotoxin complex, BoNTA, botulinum toxin, Botox |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

Maximum dose allowed was 200 Botox units in total, as follows; Biceps 50units, Brachialis 50units; Flexor Digitorum Profundus 30units; Flexor Digitorum Superficialis 30units; Flexor Carpi Radialis 20units; Flexor Carpi Ulnaris 20units. Patients received between 4 and 6 injections, with the exact dosage and number of injection sites tailored to the individual based on: size, number and location of muscles involved; severity of spasticity; presence of local muscle weakness. Reconstituted BOTOX® and placebo was injected using a sterile 25-, 27-, or 30-gauge needle for superficial muscles. Localisation of the involved muscles was determined clinically by superficial anatomical landmarks and using electrical stimulation techniques. Where localisation of the muscles proved to be difficult using surface anatomy and EMG, ultrasound was used to guide the injection procedure and check accuracy of placement of the needle.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo + CDP (Clearly Defined Physiotherapy)

| | |
|--|-----------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL1 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

0.9% Solution for injection. Patients received between 4 and 6 injections, with the exact dosage and number of injection sites tailored to the individual based on: size, number and location of muscles involved; severity of spasticity; presence of local muscle weakness. Maximum dose allowed was 200 Botox units in total, as follows; Biceps 50units, Brachialis 50units; Flexor Digitorum Profundus 30units; Flexor Digitorum Superficialis 30units; Flexor Carpi Radialis 20units; Flexor Carpi Ulnaris 20units. Reconstituted BOTOX® and placebo was injected using a sterile 25-, 27-, or 30-gauge needle for superficial muscles. Localisation of the involved muscles was determined clinically by superficial anatomical landmarks and using electrical stimulation techniques. Where localisation of the muscles proved to be difficult using surface anatomy and EMG, ultrasound was used to guide the injection procedure and check accuracy of needle placement.

| Number of subjects in period 2 | IMP (treatment) | Placebo |
|---------------------------------------|-----------------|---------|
| Started | 45 | 48 |
| Completed | 40 | 43 |
| Not completed | 5 | 5 |
| Adverse event, serious fatal | 4 | 5 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|-----------------|
| Reporting group title | IMP (treatment) |
| Reporting group description: OnabotulinumtoxinA + CDP (Clearly Defined Physiotherapy) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo + CDP (Clearly Defined Physiotherapy) | |

| Reporting group values | IMP (treatment) | Placebo | Total |
|---|-----------------|---------|-------|
| Number of subjects | 45 | 48 | 93 |
| Age categorical | | | |
| All subjects were aged 18 years and over. | | | |
| Units: Subjects | | | |
| Adults (18 years and over) | 45 | 48 | 93 |
| Age continuous | | | |
| Mean age of treatment group | | | |
| Units: years | | | |
| arithmetic mean | 67 | 68.1 | |
| standard deviation | ± 17.1 | ± 14.8 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 24 | 45 |
| Male | 24 | 24 | 48 |
| Stroke Classification | | | |
| Following stroke classification was used: Total Anterior Circulation Stroke (TACS), Partial Anterior Circulation Syndrome (PACS), Lacunar Syndrome (LACS) | | | |
| Units: Subjects | | | |
| LACS | 2 | 7 | 9 |
| PACS | 15 | 4 | 19 |
| TACS | 28 | 37 | 65 |
| NIHSS | | | |
| The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. Now, the scale is also widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome | | | |
| Units: score | | | |
| arithmetic mean | 16 | 16.4 | |
| standard deviation | ± 6.2 | ± 6.2 | - |
| Barthel | | | |
| The Barthel scale or Barthel ADL index is an ordinal scale used to measure performance in activities of daily living (ADL). | | | |
| Units: score | | | |
| arithmetic mean | 1.9 | 1.5 | |
| standard deviation | ± 2.9 | ± 3.1 | - |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | IMP (treatment) |
| Reporting group description: OnabotulinumtoxinA + CDP (Clearly Defined Physiotherapy) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo + CDP (Clearly Defined Physiotherapy) | |
| Reporting group title | IMP (treatment) |
| Reporting group description: OnabotulinumtoxinA + CDP (Clearly Defined Physiotherapy) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo + CDP (Clearly Defined Physiotherapy) | |

Primary: Change in Action Research Arm Test (ARAT) between baseline and 3 months

| | |
|--|---|
| End point title | Change in Action Research Arm Test (ARAT) between baseline and 3 months |
| End point description: The Action Research Arm Test consists of 20 questions categorised relating to as Grasp, Grip, Pinch, Gross Movement. Scores range from 0 (no function) to 57 (good arm function) and an improvement of 6 in this scale is considered to be clinically important. | |
| End point type | Primary |
| End point timeframe: Primary endpoint measured at 3 months | |

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 10.9 (\pm 17.3) | 9.1 (\pm 17.2) | | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | ARAT change during treatment phase |
| Statistical analysis description: Independent sample T-test | |
| Comparison groups | Placebo v IMP (treatment) |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.61 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.3 |
| upper limit | 9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Primary: Change in Action Research Arm Test (ARAT) between 3 months and 6 months

| | |
|---|---|
| End point title | Change in Action Research Arm Test (ARAT) between 3 months and 6 months |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Mean change to ARAT between 3months (end of treatment) and 6months (end of follow-up) | |

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 3.4 (± 7.6) | 2.9 (± 6.7) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Mean change during follow-up |
| Comparison groups | Placebo v IMP (treatment) |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.52 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.52 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.42 |
| upper limit | 3.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Secondary: Change in elbow spasticity-EMG between baseline and 3months

| | |
|------------------------|---|
| End point title | Change in elbow spasticity-EMG between baseline and 3months |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to 3 months | |

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: microV | | | | |
| arithmetic mean (standard deviation) | 6 (± 5) | 14 (± 28) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | INdependent sample T-test |
| Comparison groups | IMP (treatment) v Placebo |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.045 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Secondary: Change in elbow spasticity-EMG between 3 months and 6 months

| | |
|-----------------|--|
| End point title | Change in elbow spasticity-EMG between 3 months and 6 months |
|-----------------|--|

End point description:

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

End point timeframe:

Change between 3months and 6months

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: microV | | | | |
| arithmetic mean (standard deviation) | 2 (\pm 7) | -3 (\pm 15) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Independent sample t-test |
| Comparison groups | IMP (treatment) v Placebo |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.051 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 10 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Secondary: Change in wrist spasticity-EMG between baseline and 3 months

| | |
|-----------------|--|
| End point title | Change in wrist spasticity-EMG between baseline and 3 months |
|-----------------|--|

End point description:

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

End point timeframe:

between baseline and 3 months

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: microV | | | | |
| arithmetic mean (standard deviation) | 3 (\pm 8) | 3 (\pm 7) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Independent sample t-test |
| Comparison groups | IMP (treatment) v Placebo |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.82 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Secondary: Change in wrist spasticity-EMG between 3 months and 6 months

| | |
|------------------------|--|
| End point title | Change in wrist spasticity-EMG between 3 months and 6 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 3 months to 6 months | |

| End point values | IMP (treatment) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 48 | | |
| Units: microV | | | | |
| arithmetic mean (standard deviation) | 2 (± 5) | 2 (± 6) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Independent 2 sided t-test |
| Comparison groups | IMP (treatment) v Placebo |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.9 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.96 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Serious adverse events occurring between Informed Consent and the participant's last visit are reported here for those who were randomised.

Adverse event reporting additional description:

Investigators recorded all SAEs and assessed for classification of seriousness. SAEs required immediate notification to the CI and Sponsor (SWBHT). Causality and expectedness were assessed by the CI and Sponsor. All SAEs were reviewed by the independent Trial Steering Committee.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | IMP (treatment) |
|-----------------------|-----------------|

Reporting group description:

IMP group includes 2 participants who were randomised to IMP but did not receive the injection due to SAEs. 3 SAEs were experienced by these 2 patients, both of whom died.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|----------------|
| Reporting group title | Not randomised |
|-----------------------|----------------|

Reporting group description:

Patients consented to be screened but did not reach enrollment.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only serious adverse events were recorded for this low risk study.

| Serious adverse events | IMP (treatment) | Placebo | Not randomised |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 45 (44.44%) | 25 / 48 (52.08%) | 18 / 27 (66.67%) |
| number of deaths (all causes) | 4 | 5 | 7 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stroke | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 48 (4.17%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Aorto-Iliac Thrombotic Occlusion | | | |

| | | | |
|---|--|----------------|----------------|
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ischaemic collitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | Additional description: Multiple emboli | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Blood disorder | Additional description: Low Hb | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | Additional description: Leg Oedema | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac disorder | Additional description: Chest pain, cardiac event, end stage cardiac failure | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 48 (2.08%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Surgical and medical procedures | | | |
| Elective surgery | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 2 / 48 (4.17%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgery | Additional description: Treatment for Cancer of the larynx | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|--|--|----------------|----------------|
| Seizure | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 2 / 48 (4.17%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| dural venous sinus thrombosis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Confusional state | Additional description: Acute delirium | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Parotiditis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 48 (4.17%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| anorexia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | Additional description: GI pain plus Enteritis | | |

| | | | |
|---|---|----------------|-----------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GI Bleed | Additional description: GI bleed plus Dropped GCS | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia | Additional description: Combination of aspiration pneumonia and hospital acquired pneumonia | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 3 / 48 (6.25%) | 3 / 27 (11.11%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| Chronic obstructive pulmonary disease | Additional description: Exacerbation of COPD | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 48 (2.08%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 48 (4.17%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 48 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | IMP (treatment) | Placebo | Not randomised |
|--|-----------------|----------------|----------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 0 / 45 (0.00%) | 0 / 48 (0.00%) | 0 / 27 (0.00%) |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 24 August 2011 | Amendment to go to V3.0 of protocol, dated 04/07/2011 <ul style="list-style-type: none">• Explicit that IMP only given after assessment and prescription by medic• Amendment to Inclusion Criteria to clarify patients must be within 1-42 days of symptom onset• Addition of modified rankin scale to endpoint measures |
| 11 October 2011 | Amendment to go to V4.0 of protocol, dated 11/10/2011 <ul style="list-style-type: none">• Introduction of ultrasound guidance for injection |
| 12 January 2013 | Amendment to go to V5.0 of protocol, dated 12/01/2013 <ul style="list-style-type: none">• Clarification of AE and AR reporting process• Addition of advice for nurses caring for patients after IMP received• Modification of method of data collection• Personnel changes, including contact details of CI and change of PI at Sandwell and West Birmingham Hospitals Trust• Addition of new participating site |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Treatment with electrical stimulation is not considered routine treatment. However, in local practice this was therapeutic stimulation was routinely applied. Although treatment was given to both control and treatment groups this could be confounding.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24401159>