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

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 be determined clinically by superficialanatomical 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 be determined clinically by superficialanatomical 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 be determined clinically by superficialanatomical 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 be determined clinically by superficialanatomical 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 (± 17.3)	9.1 (± 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 (± 7)	-3 (± 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 (± 8)	3 (± 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-Illiac 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 delerium		
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 • 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 • Introduction of ultrasound guidance for injection
12 January 2013	Amendment to go to V5.0 of protocol, dated 12/01/2013 • 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