Clinical trial results:
A phase III, multicentre, prospective, double blind, randomised, placebo controlled study, assessing the efficacy and safety of Dysport intramuscular injections used for the treatment of upper limb spasticity in adult subjects with spastic hemiparesis due to stroke or traumatic brain injury.

Summary

EudraCT number	2010-019069-28
Trial protocol	BE CZ SK PL IT HU
Global end of trial date	04 September 2013

Results information

Result version number	v1 (current)
This version publication date	25 March 2016
First version publication date	25 March 2016

Trial information

Trial identification

Sponsor protocol code	Y-52-52120-145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Innovation
Sponsor organisation address	5 Avenue du Canada, Les Ulis, France, 91940
Public contact	Medical Director, Neurology, Ipsen Innovation, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology., Ipsen Innovation, clinical.trials@ipsen.com

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	17 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2013
Global end of trial reached?	Yes
Global end of trial date	04 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective is to assess the efficacy of Dysport compared to placebo in reducing upper limb muscle tone in hemiparetic subjects with upper limb spasticity due to stroke or traumatic brain injury. The primary study objective will be assessed by comparing between treatment groups at Week 4 the change from baseline in muscle tone (using the Modified Ashworth Scale (MAS)) in the primary targeted muscle group

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 August 2011
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	Russian Federation: 22
Country: Number of subjects enrolled	United States: 95
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	243
EEA total number of subjects	126

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)	193
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multi-center study was conducted in 34 investigation sites. Subjects screened were 281 and randomized and treated were 243.

Pre-assignment

Screening details:

A total of 281 subjects were screened and 243 were randomised and treated into study.

Period 1

Period 1 title	Randomized population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo intramuscular injection single treatment cycle on day 1

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo intramuscular injection single treatment cycle on day 1

Arm title	Dysport 500 U

Arm description:

Botulinum type A toxin (Dysport) 500 U intramuscular injection single treatment cycle on day 1

Arm type	Active comparator
Investigational medicinal product name	Dysport 500 U
Investigational medicinal product code	
Other name	Botulinum type A toxin
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Botulinum type A toxin (Dysport) 500 U intramuscular injection single treatment cycle on day 1

Arm title	Dysport 1000 U

Arm description:

Botulinum type A toxin (Dysport) 1000 U intramuscular injection single treatment cycle on day 1

Arm type	Active comparator
Investigational medicinal product name	Dysport 1000 U
Investigational medicinal product code	
Other name	Botulinum type A toxin
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
Botulinum type A toxin (Dysport) 1000 U intramuscular injection single treatment cycle on day 1

Number of subjects in period 1	Placebo	Dysport 500 U	Dysport 1000 U
Started	81	81	81
Completed	74	78	77
Not completed	7	3	4
lack of subject compliance	-	-	1
Protocol violation	2	-	-
Family reason and moved out of state	-	2	-
Adverse event	3	1	1
Withdrawal by Subject	1	-	2
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 500 U
Reporting group description:	
Botulinum type A toxin (Dysport) 500 U intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 1000 U
Reporting group description:	
Botulinum type A toxin (Dysport) 1000 U intramuscular injection single treatment cycle on day 1	

Reporting group values	Placebo	Dysport 500 U	Dysport 1000 U
Number of subjects	81	81	81
Age categorical Units: Subjects			
<65 years	66	66	61
>=65 years	15	15	20
Age continuous Units: years			
arithmetic mean	52.9	52.8	53.2
standard deviation	± 13.8	± 12.8	± 13.8
Gender categorical Units: Subjects			
Female	31	28	28
Male	50	53	53
Race/Ethnicity, Customized Units: Subjects			
Asian	1	3	2
Black/African American	9	7	11
Caucasian/White	71	70	67
Multiple	0	1	1
Ethnicity Units: Subjects			
Hispanic/Latino	5	3	10
Not Hispanic/Latino	76	78	71
BMI			
Aggregate analysis for BMI is 27.33(5.17) for participants Placebo: N=78, Dysport 500 U: N=80, and Dysport 1000 U: N=80.			
Units: kg/m2			
arithmetic mean	26.78	27.63	27.58
standard deviation	± 5.38	± 4.61	± 5.51
Modified Ashworth Scale Score			
Aggregate analysis for MAS at baseline is 3.9(0.4) for participants Placebo:N=79, Dysport500U:N=80 & Dysport1000U:N=79. MAS scale is used to assess MT using a 6-point scale where:0=No increase in MT, 1=Slight increase in MT,1±=Slight increase in MT manifested by a catch followed by minimal resistance throughout remainder of ROM,2=Marked increase in MT through most of ROM but affected part easily moved,3=Considerable increase in MT passive movement difficult or 4=Affected part(s) rigid in flexion			

extension. The MAS has been derived for analyses as follows:0=0 ; 1=1; 1+=2; 2=3; 3=4; 4=5.			
Units: units on a scale			
arithmetic mean	3.9	3.9	3.9
standard deviation	± 0.4	± 0.5	± 0.4
Disability Assessment Scale Score			
Aggregate analysis for DAS at baseline is 2.6(0.5) for participants Placebo:N=79 Dysport500U:N=80 Dysport1000U:N=78 DAS is a 4-point scale used to determine the extent of functional impairment in 4 functional domains(dressing, hygiene, limb position and pain). DAS scale rating: 0=No disability,1=Mild disability (noticeable but does not interfere significantly with normal activities),2=Moderate disability (normal activities require increased effort and/or assistance),3=Severe disability (normal activities limited). If the subject chose Hygiene as PTT the score collected will be between 0 & 3			
Units: units on a scale			
arithmetic mean	2.6	2.6	2.5
standard deviation	± 0.5	± 0.5	± 0.5

Reporting group values	Total		
Number of subjects	243		
Age categorical Units: Subjects			
<65 years	193		
>=65 years	50		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	87		
Male	156		
Race/Ethnicity, Customized Units: Subjects			
Asian	6		
Black/African American	27		
Caucasian/White	208		
Multiple	2		
Ethnicity Units: Subjects			
Hispanic/Latino	18		
Not Hispanic/Latino	225		
BMI			
Aggregate analysis for BMI is 27.33(5.17) for participants Placebo: N=78, Dysport 500 U: N=80, and Dysport 1000 U: N=80.			
Units: kg/m2 arithmetic mean standard deviation	- -		
Modified Ashworth Scale Score			
Aggregate analysis for MAS at baseline is 3.9(0.4) for participants Placebo:N=79, Dysport500U:N=80 & Dysport1000U:N=79. MAS scale is used to assess MT using a 6-point scale where:0=No increase in MT, 1=Slight increase in MT,1±=Slight increase in MT manifested by a catch followed by minimal resistance throughout remainder of ROM,2=Marked increase in MT through most of ROM but affected part easily moved,3=Considerable increase in MT passive movement difficult or 4=Affected part(s) rigid in flexion or			

extension. The MAS has been derived for analyses as follows:0=0 ; 1=1; 1+=2; 2=3; 3=4; 4=5.			
Units: units on a scale arithmetic mean standard deviation	- 		
Disability Assessment Scale Score			
Aggregate analysis for DAS at baseline is 2.6(0.5) for participants Placebo:N=79 Dysport500U:N=80 Dysport1000U:N=78 DAS is a 4-point scale used to determine the extent of functional impairment in 4 functional domains(dressing, hygiene, limb position and pain). DAS scale rating: 0=No disability,1=Mild disability (noticeable but does not interfere significantly with normal activities),2=Moderate disability (normal activities require increased effort and/or assistance),3=Severe disability (normal activities limited). If the subject chose Hygiene as PTT the score collected will be between 0 & 3			
Units: units on a scale arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 500 U
Reporting group description:	
Botulinum type A toxin (Dysport) 500 U intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 1000 U
Reporting group description:	
Botulinum type A toxin (Dysport) 1000 U intramuscular injection single treatment cycle on day 1	

Primary: Change From Baseline in MAS Score in the Primary Targeted Muscle Group (PTMG)

End point title	Change From Baseline in MAS Score in the Primary Targeted Muscle Group (PTMG)[1]

End point description:

MAS scale is used to assess muscle tone (MT) using a 6-point scale where: 0=No increase in muscle tone, 1=Slight increase in muscle tone manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the part is flexed or extended, 1±Slight increase in muscle tone manifested by a catch followed by minimal resistance throughout the remainder of the ROM, 2=Marked increase in muscle tone through most of the ROM but affected part easily moved, 3=Considerable increase in muscle tone passive movement difficult or 4=Affected part(s) rigid in flexion or extension. The MAS has been derived for analyses as follows: 0=0 ; 1=1; 1+=2; 2=3; 3=4 and 4=5.

Intention to treat (ITT) population included all randomized subjects who received at least one injection of study drug and had a MAS score at baseline (pretreatment) and at week 4. Total 5 subjects were excluded from ITT population as they did not have MAS score at baseline or/and at week 4.

End point type	Primary

End point timeframe:

From Baseline (Day 1) to Week 4.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this endpoint.

End point values	Placebo	Dysport 500 U	Dysport 1000 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	80	79	
Units: units on a scale				
arithmetic mean (standard deviation)				
Change From Baseline in MAS Score in the PTMG	-0.3 (± 0.6)	-1.2 (± 1)	-1.4 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment (PGA) of Treatment Response

End point title	Physician's Global Assessment (PGA) of Treatment Response

End point description:

PGA is a 9-point scale used to assess global overall treatment response by the investigator (-4: markedly worse, -3: much worse, -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved and +4: markedly improved).

ITT population. Two subjects each from Placebo and Dysport 1000 U had missed PGA assessment at week 4

End point type	Secondary

End point timeframe:

At week 4

End point values	Placebo	Dysport 500 U	Dysport 1000 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	80	78	
Units: units on a scale				
arithmetic mean (standard deviation)				
PGA of Treatment Response	0.6 (± 1)	1.4 (± 1.1)	1.8 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS Score for the Principal Target of Treatment (PTT)

End point title	Change From Baseline in DAS Score for the Principal Target of Treatment (PTT)

End point description:

DAS is a 4-point scale used to determine the extent of functional impairment in 4 functional domains (dressing, hygiene, limb position and pain). DAS scale rating: 0=No disability, 1=Mild disability (noticeable but does not interfere significantly with normal activities), 2=Moderate disability (normal activities require increased effort and/or assistance) and 3=Severe disability (normal activities limited).

If subject chose 'Hygiene' as PTT the score collected will be between 0 and 3.

ITT population. Two subjects from Placebo and one subject from Dysport 1000 U had missed DAS assessment at baseline and week 4.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) to Week 4

End point values	Placebo	Dysport 500 U	Dysport 1000 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	80	78	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.5 (± 0.7)	-0.7 (± 0.8)	-0.7 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24±2 weeks	
Adverse event reporting additional description:	
Non-serious adverse event affecting >2% of total subjects are reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 500 U
Reporting group description:	
Botulinum type A toxin (Dysport) 500 U intramuscular injection single treatment cycle on day 1	
Reporting group title	Dysport 1000 U
Reporting group description:	
Botulinum type A toxin (Dysport) 1000 U intramuscular injection single treatment cycle on day 1	

Serious adverse events	Placebo	Dysport 500 U	Dysport 1000 U
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 81 (3.70%)	3 / 81 (3.70%)	3 / 81 (3.70%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 81 (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
Ligament sprain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Behcet's syndrome			

subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 81 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 81 (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
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			

subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 81 (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
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 81 (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
Muscular weakness			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 81 (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			
Sepsis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 81 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Dysport 500 U	Dysport 1000 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 81 (12.35%)	25 / 81 (30.86%)	18 / 81 (22.22%)
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Blood pressure increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Blood triglycerides increased			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	1 / 81 (1.23%)
occurrences (all)	0	3	1
Gamma glutamyl transferase increased			

subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	2 / 81 (2.47%)
occurrences (all)	0	2	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	1	2	0
Injection site bruising			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	1 / 81 (1.23%)
occurrences (all)	2	1	1
Injection site erythema			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	0	2
Injection site pain			
subjects affected / exposed	3 / 81 (3.70%)	1 / 81 (1.23%)	0 / 81 (0.00%)
occurrences (all)	3	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Nausea			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	0 / 81 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	0	3	1
Epistaxis			

subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	1	4	1
Back pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	2 / 81 (2.47%)
occurrences (all)	1	0	2
Muscular Weakness			
subjects affected / exposed	1 / 81 (1.23%)	2 / 81 (2.47%)	4 / 81 (4.94%)
occurrences (all)	1	2	4
Musculoskeletal pain			
subjects affected / exposed	1 / 81 (1.23%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	1	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 81 (1.23%)	7 / 81 (8.64%)	1 / 81 (1.23%)
occurrences (all)	1	7	1
Sinusitis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Urinary tract infections			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2011	Protocol amendment 1: Made the following changes: • The primary efficacy analysis was changed from a Hochberg procedure to a hierarchical testing procedure following feedback from the Food and Drug Administration. • The procedure for breaking the blind was clarified. • The definition of treatment naïve was harmonised to that used in similar protocols. • Minor formatting and typographical issues were corrected.
17 February 2012	Protocol amendment 2: Made the following changes: •In inclusion criterion 2, it was clarified that subjects had to have a diagnosis of hemiparesis. • In inclusion criterion 5, the definition of naïve/non-naïve subjects was clarified. Naive subjects were defined as those who had never previously received BTX in the injected upper limb. • In exclusion criterion 6, the text for exclusion due to surgery was clarified and made more specific. • Exclusion criterion 20 was added to exclude the use of intrathecal baclofen during or for the 4 weeks prior to the study. • For the PTMG for elbow flexors, a clarification was added regarding the choice of 'brachialis' or 'brachialis and brachioradialis'. • For the assessments of upper limb muscle groups, assessments for elbow pronators were removed owing to the number of evaluations to be performed. • Minor formatting and typographical issues were corrected. • The time for which subjects were required to be supine before ECG was recorded was corrected. • Text was added to item 9 in the Modified Frenchay Scale to clarify that the affected hand holds the fork during the assessment. In light of the amendment, the CRF, database and RAP required updating.
12 July 2012	Protocol amendment 3, dated 12 July 2012, made the following changes: • The pharmacovigilance/emergency contact details for the USA were updated. • Inclusion criterion 3 was altered to allow entry into the study of subjects with a non-evolutive lesion diagnosed before the stroke and in the same cerebral hemisphere. • Inclusion criterion 7 was altered to include subjects with a spasticity angle of 10°. • The wording of Section 9.5 was amended to clarify the meaning and take into account all possibilities regarding used and unused treatments and empty boxes for destruction. • References to Sponsor's CDDS Department were amended to Statistics Department. • Instructions for disposal of used vials were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported