Clinical trial results:
A phase III, prospective, multicentre, open label, extension study, to assess the long term safety and efficacy of repeated treatment of Dysport intramuscular injection in the treatment of lower limb spasticity in adult subjects with spastic hemiparesis due to stroke or traumatic brain injury.

Summary

EudraCT number	2009-017723-26
Trial protocol	BE CZ SK IT PT HU
Global end of trial date	14 April 2015

Results information

Result version number	v1 (current)
This version publication date	31 March 2017
First version publication date	31 March 2017

Trial information

Trial identification

Sponsor protocol code	Y-55-52120-142

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01251367
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Neurology, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen Pharma, 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	14 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2015
Global end of trial reached?	Yes
Global end of trial date	14 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to assess the long-term safety of Dysport in hemiparetic subjects with lower limb spasticity due to stroke or traumatic brain injury over repeated treatment cycles.

Protection of trial subjects:

The clinical study was conducted in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, under the ethical principles laid down in the Declaration of Helsinki. In addition, this clinical study adhered to all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 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	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Poland: 83
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Portugal: 12
Worldwide total number of subjects	352
EEA total number of subjects	230

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	286
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was designed as a multicentre study and included 51 sites in Australia, Belgium, the Czech Republic, France, Hungary, Italy, Poland, Portugal, Russia, Slovakia and the United States of America that included at least one subject. The current study (Study 142) was an open label extension to the double blind Study 140 (Y-55-52120-140).

Pre-assignment

Screening details:

A total of 366 subjects completed Study 140, of which 352 subjects were enrolled in Study 142. Of these, 7 subjects entered an observational phase and never received open label treatment with Dysport in Study 142 and the remaining 345 subjects started treatment and received at least one open label injection of Dysport in Study 142.

Pre-assignment period milestones

Number of subjects started	352
Number of subjects completed	345

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Entered Observational Phase: 7

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Total Dysport

Arm description:

Subjects who had completed Study 140 were offered to continue to receive open label treatment with Dysport in Study 142 for a maximum of 4 additional treatment cycles, with a minimum interval of 12 weeks between treatment cycles. All subjects were administered an appropriate dosage of Dysport (1500 Units [U] or 1000 U) by intramuscular (i.m.) injection in the lower limb on Day 1 of treatment Cycle 1. In all cases, the administration of the Dysport injections was limited to a maximum dose of 1500 U every 12 weeks. Follow up visits were timed to assess the onset and progression of treatment response. From treatment Cycle 3 onwards, subjects with co-existing upper limb spasticity were able to receive concomitant injections of Dysport into at least one upper limb muscle at a dose not exceeding 500 U.

Arm type	Experimental
Investigational medicinal product name	Dysport
Investigational medicinal product code	
Other name	Botulinum toxin type A haemagglutinin complex
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vials containing 500 U of botulinum toxin type A haemagglutinin complex (Dysport) were reconstituted with 2.5 millilitre (mL) sodium chloride for injection (0.9 %). A total volume of 7.5 mL of the reconstituted product for any Dysport dose was injected.

Number of subjects in period 1[1]	Total Dysport
Started	345
Cycle 1	345
Cycle 2	297
Cycle 3	224 [2]
Cycle 4	139 [3]
Completed	269
Not completed	76
Consent withdrawn by subject	36
Adverse event, non-fatal	19
Other	13
Lost to follow-up	5
Protocol deviation	1
Lack of efficacy	2

Notes:

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

Justification: Worldwide data is reported for safety population of 352 subjects (including all enrolled subjects who provided informed consent to participate in this open label extension study). Baseline data is reported for 345 subjects for intention to treat population (including all enrolled subjects who had received at least one injection of Dysport in this open label extension study).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 275 Subjects completed Cycle 2. 51 subjects completed the study at this point and 224 subjects progressed to Cycle 3.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 211 Subjects completed Cycle 3. 72 subjects completed the study at this point and 139 subjects progressed to Cycle 4.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

The summary of baseline characteristics presented are from subjects completing Study 140 who were selected by the investigator for entry into Study 142 and received at least one injection of study treatment in this open label extension study.

Reporting group values	Overall Trial	Total	
Number of subjects	345	345	
Age categorical Units: Subjects			
<65 years	280	280	
>=65 years	65	65	
Age Continuous Units: years			
arithmetic mean	53.1		
standard deviation	± 12.8	-	
Gender Categorical Units: Subjects			
Male	235	235	
Female	110	110	
Race Units: Subjects			
Asian	7	7	
Black / African American	21	21	
Caucasian / White	313	313	
Native Hawaiian/Other Pacific Islander	1	1	
American Indian /Alaska Native	0	0	
Multiple	3	3	
Ethnicity Units: Subjects			
Hispanic or Latino	34	34	
Not Hispanic or Latino	311	311	

End points

End points reporting groups

Reporting group title	Total Dysport

Reporting group description:

Subjects who had completed Study 140 were offered to continue to receive open label treatment with Dysport in Study 142 for a maximum of 4 additional treatment cycles, with a minimum interval of 12 weeks between treatment cycles. All subjects were administered an appropriate dosage of Dysport (1500 Units [U] or 1000 U) by intramuscular (i.m.) injection in the lower limb on Day 1 of treatment Cycle 1. In all cases, the administration of the Dysport injections was limited to a maximum dose of 1500 U every 12 weeks. Follow up visits were timed to assess the onset and progression of treatment response. From treatment Cycle 3 onwards, subjects with co-existing upper limb spasticity were able to receive concomitant injections of Dysport into at least one upper limb muscle at a dose not exceeding 500 U.

Primary: Assessment of the Long-Term Safety of Dysport Through the Collection of Treatment Emergent Adverse Events (TEAEs)

End point title	Assessment of the Long-Term Safety of Dysport Through the Collection of Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

Adverse events (AEs) were monitored from the time that the subject gave informed consent to the end of the study/early withdrawal (EOS/EW).
An AE was reported as a TEAE if it was not present prior to study treatment administration in Study 140, or if it was present prior to study treatment in Study 140 but the intensity increased during the treatment phase of this study. Adverse events of special interest (AESIs) were identified as those assessed as being due to remote spread of effect of Dysport, or any AE that was assessed as a hypersensitivity reaction. TEAEs, treatment related TEAEs, severe TEAEs, TEAEs leading to death, TEAEs leading to withdrawal, treatment emergent AESIs, and serious adverse events (SAEs) are summarised by treatment cycle (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

Up to Week 24

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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Participants				
TEAE - Cycle 1 (n=345)	140			
TEAE - Cycle 2 (n=297)	97			
TEAE - Cycle 3 (n=224)	47			
TEAE - Cycle 4 (n=139)	21			
Treatment Related TEAE - Cycle 1 (n=345)	43			
Treatment Related TEAE - Cycle 2 (n=297)	23			
Treatment Related TEAE - Cycle 3 (n=224)	7			
Treatment Related TEAE - Cycle 4 (n=139)	5			
Severe TEAE - Cycle 1 (n=345)	13			
Severe TEAE - Cycle 2 (n=297)	9			

Severe TEAE - Cycle 3 (n=224)	4			
Severe TEAE - Cycle 4 (n=139)	2			
TEAE leading to death - Cycle 1 (n=345)	0			
TEAE leading to death - Cycle 2 (n=297)	1			
TEAE leading to death - Cycle 3 (n=224)	1			
TEAE leading to death - Cycle 4 (n=139)	0			
TEAE leading to withdrawal - Cycle 1 (n=345)	8			
TEAE leading to withdrawal - Cycle 2 (n=297)	10			
TEAE leading to withdrawal - Cycle 3 (n=224)	1			
TEAE leading to withdrawal - Cycle 4 (n=139)	0			
AESI - Cycle 1 (n=345)	31			
AESI - Cycle 2 (n=297)	24			
AESI - Cycle 3 (n=224)	10			
AESI - Cycle 4 (n=139)	5			
SAE - Cycle 1 (n=345)	23			
SAE - Cycle 2 (n=297)	14			
SAE - Cycle 3 (n=224)	7			
SAE - Cycle 4 (n=139)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Systolic and Diastolic Blood Pressure (BP)

End point title	Mean Change from Baseline to Week 4 in Systolic and Diastolic Blood Pressure (BP)[2]

End point description:

Systolic and diastolic BP were recorded at baseline and at each subsequent study visit. BP was measured with the subject in a sitting position after resting for 3 minutes. Mean change in BP from baseline at Week 4 is reported per cycle (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[2] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Millimetres Mercury (mmHg)				
arithmetic mean (full range (min-max))				
Systolic BP - Cycle 1 (n=331)	-0.7 (-67 to 37)			
Systolic BP - Cycle 2 (n=281)	-1.9 (-69 to 37)			

Systolic BP - Cycle 3 (n=200)	-2.4 (-58 to 79)			
Systolic BP - Cycle 4 (n=92)	-5.1 (-73 to 25)			
Diastolic BP - Cycle 1 (n=331)	0.3 (-34 to 37)			
Diastolic BP - Cycle 2 (n=281)	-0.2 (-38 to 30)			
Diastolic BP - Cycle 3 (n=200)	-0.3 (-32 to 28)			
Diastolic BP - Cycle 4 (n=92)	-1.1 (-35 to 32)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Heart Rate (HR)

End point title	Mean Change from Baseline to Week 4 in Heart Rate (HR)[3]

End point description:

HR was recorded at baseline and at each subsequent study visit. HR was measured with the subject in a sitting position after resting for 3 minutes. Mean change in HR from baseline at Week 4 is reported per cycle (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[3] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Beats per minute (bpm)				
arithmetic mean (full range (min-max))				
Cycle 1 (n=331)	3.7 (-28 to 39)			
Cycle 2 (n=281)	4.9 (-27 to 41)			
Cycle 3 (n=200)	3.9 (-25 to 52)			
Cycle 4 (n=92)	4.5 (-16 to 33)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Red Blood Cell (RBC) Count

End point title	Mean Change from Baseline to Week 4 in Red Blood Cell (RBC) Count[4]

End point description:

Blood samples for RBC count were taken at baseline, at Week 4, and at EOS/EW. Outcome measure is

reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[4] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Tera/Litre (L)				
arithmetic mean (full range (min-max))				
Cycle 1 (n=305)	0.049 (-0.51 to 0.66)			
Cycle 2 (n=260)	0.074 (-0.59 to 0.68)			
Cycle 3 (n=180)	0.046 (-0.59 to 0.66)			
Cycle 4 (n=78)	0.028 (-1.24 to 0.61)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Haemoglobin and Mean Corpuscular Haemoglobin Concentration (MCHC)

End point title	Mean Change from Baseline to Week 4 in Haemoglobin and Mean Corpuscular Haemoglobin Concentration (MCHC)[5]

End point description:

Blood samples for haemoglobin and MCHC were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[5] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: grams (g)/L				
arithmetic mean (full range (min-max))				
Haemoglobin - Cycle 1 (n=305)	1.2 (-17 to 32)			
Haemoglobin - Cycle 2 (n=260)	1.5 (-46 to 25)			
Haemoglobin - Cycle 3 (n=180)	1.5 (-22 to 26)			

Haemoglobin - Cycle 4 (n=78)	1.2 (-39 to 17)			
MCHC - Cycle 1 (n=305)	1.9 (-29 to 34)			
MCHC - Cycle 2 (n=260)	1.3 (-33 to 41)			
MCHC - Cycle 3 (n=180)	3.4 (-23 to 33)			
MCHC - Cycle 4 (n=78)	8.9 (-14 to 37)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Haematocrit

End point title	Mean Change from Baseline to Week 4 in Haematocrit[6]

End point description:

Blood samples for haematocrit were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[6] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Percentage of RBC in Blood				
arithmetic mean (full range (min-max))				
Cycle 1 (n=305)	0.001 (-0.057 to 0.081)			
Cycle 2 (n=260)	0.003 (-0.107 to 0.098)			
Cycle 3 (n=180)	-0.001 (-0.066 to 0.086)			
Cycle 4 (n=78)	-0.009 (-0.12 to 0.047)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Mean Corpuscular Haemoglobin (MCH)

End point title	Mean Change from Baseline to Week 4 in Mean Corpuscular Haemoglobin (MCH)[7]

End point description:

Blood samples for MCH were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[7] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: picograms (pg)				
arithmetic mean (full range (min-max))				
Cycle 1 (n=305)	-0.06 (-4.7 to 6.3)			
Cycle 2 (n=260)	-0.17 (-9.3 to 4.6)			
Cycle 3 (n=180)	0 (-2.8 to 5.3)			
Cycle 4 (n=78)	0.05 (-1.8 to 2)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Mean Corpuscular Volume (MCV)

End point title	Mean Change from Baseline to Week 4 in Mean Corpuscular Volume (MCV)[8]

End point description:

Blood samples for MCV were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[8] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Femtolitres (fL)				
arithmetic mean (full range (min-max))				
Cycle 1 (n=305)	-0.74 (-10.3 to 14.8)			
Cycle 2 (n=260)	-0.9 (-21.2 to 12.5)			
Cycle 3 (n=180)	-1.02 (-8.5 to 13.7)			

Cycle 4 (n=78)	-2.44 (-9.1 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in White Blood Cell (WBC) Count, Neutrophils, Lymphocytes and Platelets

End point title	Mean Change from Baseline to Week 4 in White Blood Cell (WBC) Count, Neutrophils, Lymphocytes and Platelets[9]

End point description:

Blood samples for WBC count with differentials (neutrophils, lymphocytes) and platelet count were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[9] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Giga/L				
arithmetic mean (full range (min-max))				
WBC count - Cycle 1 (n=305)	-0.21 (-8.7 to 5.3)			
WBC count - Cycle 2 (n=260)	-0.32 (-5.7 to 4.9)			
WBC count - Cycle 3 (n=180)	-0.26 (-5.2 to 5.1)			
WBC count - Cycle 4 (n=78)	-0.02 (-4.3 to 5.2)			
Neutrophils - Cycle 1 (n=304)	-0.17 (-7.5 to 4.5)			
Neutrophils - Cycle 2 (n=259)	-0.27 (-5.3 to 4.2)			
Neutrophils - Cycle 3 (n=179)	-0.28 (-5.6 to 4.8)			
Neutrophils - Cycle 4 (n=78)	-0.06 (-4.4 to 5.5)			
Lymphocytes - Cycle 1 (n=303)	-0.05 (-1.3 to 1.3)			
Lymphocytes - Cycle 2 (n=258)	-0.05 (-1.3 to 1.4)			
Lymphocytes - Cycle 3 (n=179)	0.03 (-1.2 to 2.5)			
Lymphocytes - Cycle 4 (n=78)	-0.01 (-0.9 to 2)			

Platelets - Cycle 1 (n=300)	-0.1 (-193 to 192)			
Platelets - Cycle 2 (n=257)	0 (-133 to 276)			
Platelets - Cycle 3 (n=178)	0.1 (-139 to 152)			
Platelets - Cycle 4 (n=77)	4.6 (-67 to 167)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Alkaline Phosphatase (ALP), Gamma Glutamyl Transferase (GGT), Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT)

End point title	Mean Change from Baseline to Week 4 in Alkaline Phosphatase (ALP), Gamma Glutamyl Transferase (GGT), Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT)[10]

End point description:

Blood samples were taken at baseline, at Week 4, and at the EOS/EW for analysis of the following clinical chemistry parameters: ALP, GGT, SGOT and SGPT. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[10] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: IU/L				
arithmetic mean (full range (min-max))				
ALP - Cycle 1 (n=319)	-1.2 (-60 to 110)			
ALP - Cycle 2 (n=268)	-2.9 (-141 to 57)			
ALP - Cycle 3 (n=188)	-5.2 (-238 to 33)			
ALP - Cycle 4 (n=85)	-3.2 (-45 to 39)			
SGOT - Cycle 1 (n=319)	2.7 (-47 to 35)			
SGOT - Cycle 2 (n=268)	3 (-27 to 144)			
SGOT - Cycle 3 (n=188)	1.3 (-109 to 34)			
SGOT - Cycle 4 (n=85)	1.8 (-12 to 19)			
SGPT - Cycle 1 (n=319)	1.2 (-60 to 45)			
SGPT - Cycle 2 (n=268)	2.4 (-53 to 302)			
SGPT - Cycle 3 (n=188)	1.7 (-444 to 69)			

SGPT - Cycle 4 (n=85)	0.8 (-28 to 25)			
GGT - Cycle 1 (n=320)	1 (-122 to 614)			
GGT - Cycle 2 (n=268)	-1.9 (-145 to 121)			
GGT - Cycle 3 (n=188)	-3 (-254 to 107)			
GGT - Cycle 4 (n=85)	-0.4 (-61 to 70)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in Total Bilirubin and Creatinine

End point title	Mean Change from Baseline to Week 4 in Total Bilirubin and Creatinine[11]

End point description:

Blood samples for clinical chemistry analysis of total bilirubin and creatinine were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[11] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Micromole/L (µmol/L)				
arithmetic mean (full range (min-max))				
Total bilirubin - Cycle 1 (n=319)	0.13 (-13.7 to 12.8)			
Total bilirubin - Cycle 2 (n=268)	0.14 (-10.6 to 15.2)			
Total bilirubin - Cycle 3 (n=188)	0.03 (-10.4 to 7)			
Total bilirubin - Cycle 4 (n=85)	-0.05 (-9.1 to 16.1)			
Creatinine - Cycle 1 (n=320)	-2 (-36 to 27)			
Creatinine - Cycle 2 (n=268)	-5.3 (-36 to 35)			
Creatinine - Cycle 3 (n=188)	-7.9 (-53 to 35)			
Creatinine - Cycle 4 (n=85)	-14.2 (-62 to 9)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline to Week 4 in Blood Urea Nitrogen (BUN) and Fasting Blood Glucose

End point title	Mean Change From Baseline to Week 4 in Blood Urea Nitrogen (BUN) and Fasting Blood Glucose[12]

End point description:

Blood samples for analysis of BUN and fasting blood glucose levels were taken at baseline, at Week 4, and at the EOS/EW. Outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[12] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: millimole/L (mmol/L)				
arithmetic mean (full range (min-max))				
BUN - Cycle 1 (n=320)	0.14 (-3.93 to 5)			
BUN - Cycle 2 (n=268)	-0.05 (-3.57 to 5.72)			
BUN - Cycle 3 (n=188)	-0.19 (-11.06 to 4.29)			
BUN - Cycle 4 (n=85)	-0.37 (-4.64 to 3.57)			
Fasting blood glucose - Cycle 1 (n=169)	-0.046 (-6.16 to 6.38)			
Fasting blood glucose - Cycle 2 (n=143)	0.009 (-4.17 to 9.44)			
Fasting blood glucose - Cycle 3 (n=101)	0.015 (-5.66 to 7)			
Fasting blood glucose - Cycle 4 (n=55)	0.231 (-3.44 to 8.61)			

Statistical analyses

No statistical analyses for this end point

Primary: Presence of Botulinum Toxin Type A (BTX-A) Neutralising Putative Antibodies (NAbs) following Injection of Dysport

End point title	Presence of Botulinum Toxin Type A (BTX-A) Neutralising Putative Antibodies (NAbs) following Injection of Dysport[13]

End point description:

Blood samples were collected at baseline, Week 4 and at EOS/EW to test for the presence of BTX-A antibodies. The number of subjects who were either NAb positive at baseline or negative at baseline but then positive following injection of Dysport were reported. Outcome measure is reported for subjects with data available for analysis.

End point type	Primary

End point timeframe:

Up to Week 24

Notes:

[13] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	343			
Units: Subjects				
Positive at baseline	3			
Negative at baseline & positive post baseline	0			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to Week 4 in 12-Lead Electrocardiogram (ECG)

End point title	Mean Change from Baseline to Week 4 in 12-Lead Electrocardiogram (ECG)[14]

End point description:

12-lead ECG tracing was performed at baseline, at Week 4 of each cycle and at EOS/EW. The 12-lead ECG recordings were performed at a paper speed of 25 millimetres/second (mm/s), recorded with the subject in a supine position after 5 minutes rest. The ECG parameters; QT Duration, QT interval corrected with Fridericia's method (QTcF), QT interval corrected with Bazett's method (QTcB), QRS duration and PR duration were recorded and outcome measure is reported per cycle as change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Primary

End point timeframe:

At Week 4

Notes:

[14] - 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: Only descriptive analysis was planned and performed for this primary end point.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	342			
Units: Milliseconds (ms)				
arithmetic mean (standard deviation)				
QT Duration – Cycle 1 (n=301)	-10.1 (± 24.9)			
QT Duration – Cycle 2 (n=260)	-12.2 (± 22.9)			
QT Duration – Cycle 3 (n=181)	-13.6 (± 26.5)			
QT Duration – Cycle 4 (n=83)	-16.5 (± 23.5)			
QTcF – Cycle 1 (n=301)	-0.6 (± 16.9)			
QTcF – Cycle 2 (n=260)	-1.9 (± 14.8)			
QTcF – Cycle 3 (n=181)	-3.8 (± 16.2)			
QTcF – Cycle 4 (n=83)	-1.8 (± 16.1)			
QTcB – Cycle 1 (n=301)	4.5 (± 20.2)			

QTcB – Cycle 2 (n=260)	3.5 (± 18.4)			
QTcB – Cycle 3 (n=181)	1.5 (± 19.5)			
QTcB – Cycle 4 (n=83)	6.1 (± 21.3)			
QRS Duration – Cycle 1 (n=301)	-0.6 (± 6.3)			
QRS Duration – Cycle 2 (n=260)	-0.7 (± 5.8)			
QRS Duration – Cycle 3 (n=181)	-0.8 (± 6.2)			
QRS Duration – Cycle 4 (n=83)	-0.9 (± 6.7)			
PR Duration – Cycle 1 (n=300)	-2.2 (± 14.5)			
PR Duration – Cycle 2 (n=259)	-1.7 (± 15.2)			
PR Duration – Cycle 3 (n=181)	-0.5 (± 14.4)			
PR Duration – Cycle 4 (n=83)	-0.6 (± 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in the Modified Ashworth Scale (MAS) Score measured in the Gastrocnemius-soleus Complex (GSC) (Knee Extended)

End point title	Mean Change from Baseline to Week 4 in the Modified Ashworth Scale (MAS) Score measured in the Gastrocnemius-soleus Complex (GSC) (Knee Extended)

End point description:

Muscle tone in the treated limb was assessed by MAS in the GSC (with the knee extended) at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. The MAS consists of six grades: 0, 1, 1+, 2, 3, or 4 and can be applied to muscles of both the upper and lower limbs. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4.

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=341)	-0.8 (± 0.9)			
Cycle 2 (n=290)	-0.9 (± 1)			
Cycle 3 (n=218)	-1 (± 1)			
Cycle 4 (n=135)	-1 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in the MAS measured in the Soleus Muscle (Knee Flexed)

End point title	Mean Change from Baseline to Week 4 in the MAS measured in the Soleus Muscle (Knee Flexed)

End point description:

Muscle tone in the treated limb was assessed by MAS in the soleus muscle (with the knee flexed) at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. The MAS consists of six grades: 0, 1, 1+, 2, 3, or 4 and can be applied to muscles of both the upper and lower limbs. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=340)	-1 (± 1.2)			
Cycle 2 (n=290)	-1.1 (± 1)			
Cycle 3 (n=218)	-1.2 (± 1)			
Cycle 4 (n=135)	-1.1 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with At Least a 1 or 2 Grade Reduction in the MAS Measured in the GSC (Knee Extended) at Week 4

End point title	Proportion of Subjects with At Least a 1 or 2 Grade Reduction in the MAS Measured in the GSC (Knee Extended) at Week 4

End point description:

Muscle tone in the treated limb was assessed by MAS in the GSC (with the knee extended) at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. The MAS consists of six grades: 0, 1, 1+, 2, 3, or 4 and can be applied to muscles of both the upper and lower limbs. Outcome measure is reported per cycle as the percentage of subjects with at least a 1 grade or 2 grades reduction in MAS score at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Percentage of Subjects				
number (not applicable)				
At least 1 grade reduction - Cycle 1 (n=345)	56.2			
At least 1 grade reduction - Cycle 2 (n=297)	57.6			
At least 1 grade reduction - Cycle 3 (n=224)	60.7			
At least 1 grade reduction - Cycle 4 (n=139)	66.9			
At least 2 grades reduction - Cycle 1 (n=345)	18.3			
At least 2 grades reduction - Cycle 2 (n=297)	23.2			
At least 2 grades reduction - Cycle 3 (n=224)	23.2			
At least 2 grades reduction - Cycle 4 (n=139)	22.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with At Least a 1 or 2 Grade Reduction in the MAS Measured in the Soleus Muscle (Knee Flexed) at Week 4

End point title	Proportion of Subjects with At Least a 1 or 2 Grade Reduction in the MAS Measured in the Soleus Muscle (Knee Flexed) at Week 4

End point description:

Muscle tone in the treated limb was assessed by MAS in the soleus muscle (with the knee flexed) at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. The MAS consists of six grades: 0, 1, 1+, 2, 3, or 4 and can be applied to muscles of both the upper and lower limbs. Outcome measure is reported per cycle as the percentage of subjects with at least a 1 grade or 2 grades reduction in MAS score at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Percentage of Subjects				
number (not applicable)				
At least 1 grade reduction - Cycle 1 (n=345)	61.4			
At least 1 grade reduction - Cycle 2 (n=297)	68.4			

At least 1 grade reduction - Cycle 3 (n=224)	72.3			
At least 1 grade reduction - Cycle 4 (n=139)	71.9			
At least 2 grades reduction - Cycle 1 (n=345)	28.4			
At least 2 grades reduction - Cycle 2 (n=297)	30.6			
At least 2 grades reduction - Cycle 3 (n=224)	30.4			
At least 2 grades reduction - Cycle 4 (n=139)	28.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment (PGA) of Treatment Response at Week 4

End point title	Physician's Global Assessment (PGA) of Treatment Response at Week 4

End point description:

An assessment of overall treatment response was conducted by the investigator at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. The investigator rated the response to treatment in the subject's lower limb after injection of Dysport relative to the status at the baseline. Answers were made on a nine-point rating scale: -4=markedly worse, -3=much worse, -2=worse, -1=slightly worse, 0=no change, +1=slightly improved, +2=improved, +3=much improved, +4=markedly improved. The mean PGA scores per cycle at Week 4 were reported (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=340)	1.4 (± 1.1)			
Cycle 2 (n=288)	1.6 (± 1)			
Cycle 3 (n=216)	1.8 (± 1)			
Cycle 4 (n=134)	1.9 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with a score of at least +1 on the PGA scale at Week 4

End point title	Proportion of subjects with a score of at least +1 on the PGA scale at Week 4

End point description:

An assessment of overall treatment response was conducted by the investigator at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. The investigator rated the response to treatment in the subject's lower limb after injection of Dysport relative to the status at the baseline. Answers were made on a nine-point rating scale: -4=markedly worse, -3=much worse, -2=worse, -1=slightly worse, 0=no change, +1=slightly improved, +2=improved, +3=much improved, +4=markedly improved. The percentage of responders with a PGA score of +1 or greater are reported at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Percentage of Subjects				
number (not applicable)				
Cycle 1 (n=345)	83.8			
Cycle 2 (n=297)	86.2			
Cycle 3 (n=224)	89.3			
Cycle 4 (n=139)	89.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in the Range of Active Ankle Dorsiflexion both with the Knee Flexed and with the Knee Extended

End point title	Mean Change from Baseline to Week 4 in the Range of Active Ankle Dorsiflexion both with the Knee Flexed and with the Knee Extended

End point description:

Range of active dorsiflexion of the ankle joint of the treated limb, measured using a goniometre, both with the knee flexed (90°) and extended, was used to assess treatment response. The measurements were obtained at the end of baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Degrees				
arithmetic mean (standard deviation)				
Knee Extended - Cycle 1 (n=340)	4.1 (± 10.6)			
Knee Extended - Cycle 2 (n=290)	4.4 (± 10.6)			
Knee Extended - Cycle 3 (n=218)	6 (± 11.4)			
Knee Extended - Cycle 4 (n=135)	6.5 (± 10.9)			
Knee Flexed - Cycle 1 (n=341)	4.1 (± 10.7)			
Knee Flexed - Cycle 2 (n=290)	5 (± 10.3)			
Knee Flexed - Cycle 3 (n=218)	5.2 (± 10.9)			
Knee Flexed - Cycle 4 (n=135)	3.8 (± 9.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Lower Limb Pain

End point title	Mean Change from Baseline to Week 4 in Lower Limb Pain

End point description:

The intensity of lower limb pain in the treated limb was evaluated by the subject using the Scale of Pain Intensity (SPIN) which provided a pictorial representation of pain in a 6-point graphic scale with the degree of red shading representing the intensity of pain. The SPIN assessments were obtained at baseline, Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at the EOS/EW. The mean changes from baseline in subjects with a baseline SPIN Score >0 at Week 4 was reported per cycle (n =number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=189)	-0.7 (± 1.2)			
Cycle 2 (n=160)	-0.8 (± 1.2)			
Cycle 3 (n=118)	-0.9 (± 1.2)			
Cycle 4 (n=75)	-0.9 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Short Form (36) Health Survey (SF-36) Quality of Life (QoL)

End point title	Mean Change from Baseline to Week 4 in Short Form (36) Health Survey (SF-36) Quality of Life (QoL)

End point description:

Subjects were asked to complete the SF-36 health surveys prior to the study treatment at baseline, at Week 4 and at the EOS/EW visit. The SF-36 is a generic non preference based health status measure. This instrument assessed subject health across 8 dimensions, which are specific health domains such as physical functioning, social functioning and vitality. The mean change in the Physical Component Summary (PCS) and Mental Component Summary (MCS) from baseline to Week 4 are reported (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
PCS - Cycle 1 (n = 330)	1.05 (± 7.5)			
PCS - Cycle 2 (n = 287)	1.43 (± 7.67)			
PCS - Cycle 3 (n = 213)	1.85 (± 7.01)			
PCS - Cycle 4 (n = 134)	2.8 (± 6.65)			
MCS - Cycle 1 (n =330)	-1.13 (± 11.27)			
MCS - Cycle 2 (n = 287)	-0.82 (± 12.7)			
MCS - Cycle 3 (n = 213)	0.56 (± 12.24)			
MCS - Cycle 4 (n = 134)	0.14 (± 13.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in European Quality of Life - 5 Dimensions (EQ-5D) QoL

End point title	Mean Change from Baseline in European Quality of Life - 5 Dimensions (EQ-5D) QoL

End point description:

Subjects were asked to complete the EQ-5D QoL questionnaire prior to the study treatment at baseline, at Week 4 and at EOS/EW visit. The EQ-5D index is a generic preference based measure of health related QoL producing utility scores that represent subject preferences for particular health states. This instrument rated subject health state looking at 5 specific dimensions such as mobility, self-care, usual activity, pain/discomfort and anxiety/ depression and scored their general health state. The mean change in pain and discomfort and Visual Analogue Scale (VAS) scores from baseline to Week 4 are reported (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Pain/discomfort - Cycle 1 (n=337)	-0.1 (± 1)			
Pain/discomfort - Cycle 2 (n=288)	-0.2 (± 1)			
Pain/discomfort - Cycle 3 (n=215)	-0.2 (± 1)			
Pain/discomfort - Cycle 4 (n=133)	-0.4 (± 1.2)			
VAS - Cycle 1 (n=336)	2.8 (± 18.3)			
VAS - Cycle 2 (n=286)	3.8 (± 17.7)			
VAS - Cycle 3 (n=215)	4.4 (± 19.9)			
VAS - Cycle 4 (n=133)	5.5 (± 21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Walking Speed (WS)

End point title	Mean Change from Baseline to Week 4 in Walking Speed (WS)

End point description:

All WS tests were conducted without walking aids over a distance of 10 metres at both a comfortable WS and at maximal WS. Evaluations of WS were made barefoot and with shoes on, at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: metres/second (m/s)				
arithmetic mean (standard deviation)				
Comfortable WS, barefoot - Cycle 1 (n=335)	0.07 (± 0.12)			
Comfortable WS, barefoot - Cycle 2 (n=285)	0.08 (± 0.13)			
Comfortable WS, barefoot - Cycle 3 (n=215)	0.08 (± 0.13)			
Comfortable WS, barefoot - Cycle 4 (n=134)	0.09 (± 0.14)			
Comfortable WS, with shoes - Cycle 1 (n=336)	0.06 (± 0.13)			

Comfortable WS, with shoes - Cycle 2 (n=289)	0.07 (± 0.14)			
Comfortable WS, with shoes - Cycle 3 (n=217)	0.08 (± 0.13)			
Comfortable WS, with shoes - Cycle 4 (n=134)	0.08 (± 0.14)			
Maximal WS, barefoot - Cycle 1 (n=336)	0.07 (± 0.169)			
Maximal WS, barefoot - Cycle 2 (n=286)	0.08 (± 0.18)			
Maximal WS, barefoot - Cycle 3 (n=215)	0.09 (± 0.18)			
Maximal WS, barefoot - Cycle 4 (n=134)	0.1 (± 0.18)			
Maximal WS, with shoes - Cycle 1 (n=335)	0.07 (± 0.17)			
Maximal WS, with shoes - Cycle 2 (n=286)	0.09 (± 0.19)			
Maximal WS, with shoes - Cycle 3 (n=217)	0.09 (± 0.19)			
Maximal WS, with shoes - Cycle 4 (n=134)	0.1 (± 0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Step Length

End point title	Mean Change from Baseline to Week 4 in Step Length

End point description:

All WS tests were conducted without walking aids over a distance of 10 metres at both a comfortable WS and at maximal WS. Evaluations of step length were made barefoot and with shoes on, at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: m/step				
arithmetic mean (standard deviation)				
Comfortable WS, barefoot - Cycle 1 (n=335)	0.03 (± 0.06)			
Comfortable WS, barefoot - Cycle 2 (n=285)	0.03 (± 0.09)			
Comfortable WS, barefoot - Cycle 3 (n=215)	0.03 (± 0.08)			
Comfortable WS, barefoot - Cycle 4 (n=134)	0.5 (± 0.09)			
Comfortable WS, with shoes - Cycle 1 (n=336)	0.03 (± 0.07)			

Comfortable WS, with shoes - Cycle 2 (n=289)	0.03 (± 0.08)			
Comfortable WS, with shoes - Cycle 3 (n=217)	0.03 (± 0.08)			
Comfortable WS with shoes - Cycle 4 (n=134)	0.04 (± 0.09)			
Maximal WS, barefoot - Cycle 1 (n=336)	0.03 (± 0.08)			
Maximal WS, barefoot - Cycle 2 (n=286)	0.03 (± 0.09)			
Maximal WS, barefoot - Cycle 3 (n=215)	0.03 (± 0.09)			
Maximal WS, barefoot - Cycle 4 (n=134)	0.04 (± 0.09)			
Maximal WS, with shoes - Cycle 1 (n=335)	0.02 (± 0.08)			
Maximal WS, with shoes - Cycle 2 (n=286)	0.03 (± 0.09)			
Maximal WS, with shoes - Cycle 3 (n=217)	0.03 (± 0.09)			
Maximal WS, with shoes - Cycle 4 (n=134)	0.04 (± 0.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Cadence

End point title	Mean Change from Baseline to Week 4 in Cadence

End point description:

All WS tests were conducted without walking aids over a distance of 10 metres at both a comfortable WS and at maximal WS. Evaluations of cadence were made barefoot and with shoes on, at baseline, at Weeks 4 and 12, at discretionary visits at Weeks 16, 20 and 24 of each cycle, and at EOS/EW. Outcome measure is reported per cycle as mean change from baseline at Week 4 (n = number of subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: steps/s				
arithmetic mean (standard deviation)				
Comfortable WS, barefoot - Cycle 1 (n=335)	0.08 (± 0.21)			
Comfortable WS, barefoot - Cycle 2 (n=285)	0.08 (± 0.23)			
Comfortable WS, barefoot - Cycle 3 (n=215)	0.08 (± 0.21)			
Comfortable WS, barefoot - Cycle 4 (n=134)	0.07 (± 0.21)			
Comfortable WS, with shoes - Cycle 1 (n=336)	0.07 (± 0.21)			

Comfortable WS, with shoes - Cycle 2 (n=289)	0.08 (± 0.22)			
Comfortable WS, with shoes - Cycle 3 (n=217)	0.08 (± 0.22)			
Comfortable WS with shoes - Cycle 4 (n=134)	0.07 (± 0.21)			
Maximal WS, barefoot - Cycle 1 (n=336)	0.07 (± 0.26)			
Maximal WS, barefoot - Cycle 2 (n=286)	0.08 (± 0.28)			
Maximal WS, barefoot - Cycle 3 (n=215)	0.09 (± 0.26)			
Maximal WS, barefoot - Cycle 4 (n=134)	0.11 (± 0.25)			
Maximal WS, with shoes - Cycle 1 (n=335)	0.07 (± 0.23)			
Maximal WS, with shoes - Cycle 2 (n=286)	0.09 (± 0.27)			
Maximal WS, with shoes - Cycle 3 (n=217)	0.09 (± 0.27)			
Maximal WS, with shoes - Cycle 4 (n=134)	0.09 (± 0.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Angle of Arrest (XV1), Angle of Catch (XV3) and Spasticity Angle (X) in the GSC (Knee Extended)

End point title	Mean Change from Baseline to Week 4 in Angle of Arrest (XV1), Angle of Catch (XV3) and Spasticity Angle (X) in the GSC (Knee Extended)

End point description:

Spasticity in the treated limb was assessed using the Tardieu Scale (TS) for the GSC (knee extended). The TS is administered by applying passive stretch to a muscle group at two velocities. Slow speed of muscle stretch measures the range of passive motion. During a slow stretching movement, the examiner determines the angle of movement arrest, either due to subject discomfort or a mechanical resistance. The same movement is repeated at high velocity (as fast as possible) to determine the angle of catch and release. The angle of movement arrest at slow velocity (XV1) and the angle of catch at fast speed (XV3) were recorded at baseline, at Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. The spasticity angle (X) was calculated as the difference between XV1 and XV3. Mean changes in Angles XV1, XV3 and X from baseline to Week 4 are reported per cycle (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Degrees				
arithmetic mean (standard deviation)				
Angle of arrest (XV1) – Cycle 1 (n=341)	2.7 (± 7.9)			
Angle of arrest (XV1) – Cycle 2 (n=290)	2.4 (± 7.8)			
Angle of arrest (XV1) – Cycle 3 (n=218)	2.6 (± 8.9)			
Angle of arrest (XV1) – Cycle 4 (n=135)	2.7 (± 8.4)			

Angle of catch (XV3) – Cycle 1 (n=341)	7.1 (± 10.6)			
Angle of catch (XV3) – Cycle 2 (n=289)	7.3 (± 11.1)			
Angle of catch (XV3) – Cycle 3 (n=218)	7.9 (± 12.2)			
Angle of catch (XV3) – Cycle 4 (n=135)	9.5 (± 12.4)			
Spasticity angle (X) – Cycle 1 (n=341)	-4.4 (± 8.6)			
Spasticity angle (X) – Cycle 2 (n=289)	-4.9 (± 9.2)			
Spasticity angle (X) – Cycle 3 (n=218)	-5.4 (± 9.3)			
Spasticity angle (X) – Cycle 4 (n=135)	-6.8 (± 9.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Spasticity Grade (Y) in the GSC (Knee Extended)

End point title	Mean Change from Baseline to Week 4 in Spasticity Grade (Y) in the GSC (Knee Extended)

End point description:

Spasticity in the treated limb was assessed using the TS for the GSC (knee extended). The TS is administered by applying passive stretch to a muscle group. The spasticity grade (Y) assesses quality of muscle reaction on a 5-point scale (measured at fast speed): 0=No resistance throughout passive movement, 1=slight resistance throughout passive movement, 2=clear catch at precise angle, interrupting passive movement, followed by release, 3=fatigable clonus (less than 10 seconds when maintaining pressure) occurring at a precise angle, followed by release. 4=unfatigable clonus (more than 10 seconds when maintaining pressure) occurring at precise angle. Spasticity grade (Y) was recorded at baseline, at Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. Mean changes in spasticity grade (Y) from baseline to Week 4 are reported per cycle (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=341)	-0.5 (± 0.8)			
Cycle 2 (n=290)	-0.5 (± 0.7)			
Cycle 3 (n=218)	-0.5 (± 0.7)			
Cycle 4 (n=135)	-0.5 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Angle of Arrest (XV1), Angle of Catch (XV3) and Spasticity Angle (X) in the Soleus Muscle (Knee Flexed)

End point title	Mean Change from Baseline to Week 4 in Angle of Arrest (XV1), Angle of Catch (XV3) and Spasticity Angle (X) in the Soleus Muscle (Knee Flexed)

End point description:

Spasticity in the treated limb was assessed using the TS for the soleus muscle (knee flexed). The TS is administered by applying passive stretch to a muscle group at two velocities. Slow speed of muscle stretch measures the range of passive motion. During a slow stretching movement, the examiner determines the angle of movement arrest, either due to subject discomfort or a mechanical resistance. The same movement is repeated at high velocity (as fast as possible) to determine the angle of catch and release. The angle of movement arrest at slow velocity (XV1) and the angle of catch at fast speed (XV3) were recorded at baseline, at Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. The spasticity angle (X) was calculated as the difference between XV1 and XV3. Mean changes in Angles XV1, XV3 and X from baseline to Week 4 are reported per cycle (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Degrees				
arithmetic mean (standard deviation)				
Angle of arrest (XV1) – Cycle 1 (n=341)	1.9 (± 8)			
Angle of arrest (XV1) – Cycle 2 (n=290)	2.8 (± 8.1)			
Angle of arrest (XV1) – Cycle 3 (n=218)	2.6 (± 8.5)			
Angle of arrest (XV1) – Cycle 4 (n=135)	2.4 (± 8.6)			
Angle of catch (XV3) – Cycle 1 (n=341)	6.9 (± 10.3)			
Angle of catch (XV3) – Cycle 2 (n=289)	7.5 (± 10.8)			
Angle of catch (XV3) – Cycle 3 (n=218)	7.8 (± 11.2)			
Angle of catch (XV3) – Cycle 4 (n=135)	8.8 (± 11.4)			
Spasticity angle (X) – Cycle 1 (n=341)	-5 (± 10)			
Spasticity angle (X) – Cycle 2 (n=289)	-4.7 (± 9.8)			
Spasticity angle (X) – Cycle 3 (n=218)	-5.2 (± 9.6)			
Spasticity angle (X) – Cycle 4 (n=135)	-6.4 (± 11.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 4 in Spasticity Grade (Y) in the Soleus Muscle (Knee Flexed)

End point title	Mean Change from Baseline to Week 4 in Spasticity Grade (Y) in the Soleus Muscle (Knee Flexed)

End point description:

Spasticity in the treated limb was assessed using the TS for the soleus muscle (knee flexed). The TS is administered by applying passive stretch to a muscle group. The spasticity grade (Y) assesses quality of muscle reaction on a 5-point scale (measured at fast speed): 0=No resistance throughout passive

movement, 1=slight resistance throughout passive movement, 2=clear catch at precise angle, interrupting passive movement, followed by release, 3=fatigable clonus (less than 10 seconds when maintaining pressure) occurring at a precise angle, followed by release. 4=unfatigable clonus (more than 10 seconds when maintaining pressure) occurring at precise angle. Spasticity grade (Y) was recorded at baseline, at Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at EOS/EW. Mean changes in spasticity grade (Y) from baseline to Week 4 are reported per cycle (n=subjects with data available for analysis).

End point type	Secondary

End point timeframe:

At Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 (n=341)	-0.6 (± 0.8)			
Cycle 2 (n=290)	-0.6 (± 0.7)			
Cycle 3 (n=218)	-0.7 (± 0.8)			
Cycle 4 (n=135)	-0.7 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Walking Aids/Orthoses at Baseline and Week 4

End point title	Use of Walking Aids/Orthoses at Baseline and Week 4

End point description:

Subjects were assessed on their use of walking aids and orthoses at baseline, at Weeks 4 and 12 after each Dysport injection, at discretionary visits at Weeks 16, 20 and 24 of each cycle and at the EOS/EW visit. Outcome measure is reported per cycle at baseline and Week 4 (n = number of subjects with data available for analysis). Number of subjects with no walking aid/orthoses were included in the 'No Walking Aid' category and number of subjects with any kind of walking aid/orthosis (including single point cane, tripod cane, ankle foot orthosis or other type of walking aid/orthosis) were combined into the 'Walking Aid' category.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	345			
Units: Subjects				
No Walking Aid at Baseline - Cycle 1 (n=345)	101			
Walking Aid at Baseline - Cycle 1 (n=345)	244			

No Walking Aid at Week 4 - Cycle 1 (n=341)	99			
Walking Aid at Week 4 - Cycle 1 (n=341)	242			
No Walking Aid at Baseline - Cycle 2 (n=297)	84			
Walking Aid at Baseline - Cycle 2 (n=297)	213			
No Walking Aid at Week 4 - Cycle 2 (n=292)	80			
Walking Aid at Week 4 - Cycle 2 (n=292)	212			
No Walking Aid at Baseline - Cycle 3 (n=224)	56			
Walking Aid at Baseline - Cycle 3 (n=224)	168			
No Walking Aid at Week 4 - Cycle 3 (n=206)	59			
Walking Aid at Week 4 - Cycle 3 (n=206)	147			
No Walking Aid at Baseline - Cycle 4 (n=139)	40			
Walking Aid at Baseline - Cycle 4 (n=139)	99			
No Walking Aid at Week 4 - Cycle 4 (n=97)	33			
Walking Aid at Week 4 - Cycle 4 (n=97)	64			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 24 +/- 2 weeks

Adverse event reporting additional description:

An AE was reported as a TEAE if it arose or the intensity increased during the treatment phase of this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Total Dysport

Reporting group description:

Subjects who had completed Study 140 continued to receive open label treatment with Dysport in Study 142 for a maximum of 4 additional treatment cycles, with a minimum interval of 12 weeks between treatment cycles.
All subjects were administered an appropriate dosage of Dysport (1500 Units [U] or 1000 U) by intramuscular (i.m.) injection in the lower limb on Day 1 of treatment Cycle 1. Subjects requiring retreatment were treated during follow up visits, in accordance with meeting pre-specified criteria and investigator judgement.
From treatment Cycle 3 onwards, subjects with co-existing upper limb spasticity were able to receive concomitant injections of Dysport into at least one upper limb muscle at a dose not exceeding 500 U.

Serious adverse events	Total Dysport		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 345 (12.46%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			

subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Venous thrombosis				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery dissection				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				

subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	2 / 345 (0.58%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	5 / 345 (1.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 345 (0.58%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	2 / 345 (0.58%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 345 (0.58%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal polyp			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Anxiety				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc degeneration				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	3 / 345 (0.87%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	3 / 345 (0.87%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 345 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Anal abscess			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 345 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Total Dysport		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 345 (20.00%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	42 / 345 (12.17%)		
occurrences (all)	52		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	36 / 345 (10.43%)		
occurrences (all)	41		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2012	Protocol Amendment 2 - Made the following changes: • The study exclusion criteria were clarified to exclude subjects who had undergone previous surgery to treat spasticity of the affected lower limb (instead of those who had received previous surgery on muscles and ligaments, tendons or nerve trunks of the treated lower limb). • A new exclusion criterion was added to exclude treatment with intrathecal baclofen during the course of the study. • Subjects not requiring a new treatment cycle at the Week 24 follow up visit of treatment Cycle 1 or 2 (instead of Cycle 1 and potentially Cycles 2 and 3) were required to have follow up visits every 4 weeks until a new treatment cycle was required or they reached 12 months follow up. • The Central Laboratory for putative antibody testing was changed from Ipsen Pharma SA (Barcelona, Spain) to Kymos Pharma Services SL (Barcelona, Spain); however, the bioanalytical test remained the same. • The 12 Lead ECG was to be recorded with the subject in a supine position after 5 minutes rest instead of in a prone position after 30 minutes rest. • Oral baclofen was added to the permitted concomitant medications. • The sponsor's Medically Responsible Person was changed.
10 January 2014	Protocol Amendment 5 - Made the following changes: • The pharmacovigilance emergency contacts and telephone numbers were updated. • Subjects were allowed to receive a fourth treatment cycle in Study 142 after the 12 month total follow up duration (including Study 140) in order to complement the long-term safety database. In order to receive the fourth treatment cycle in Study 142, subjects must have received 3 open label treatment cycles within the total 12 month follow up period (including Study 140) and be eligible for retreatment no later than Week 16 of treatment Cycle 3. • The follow up duration was extended to a maximum of 18 months to ensure that the subjects receiving a fourth treatment cycle after Week 52 were monitored for 12 weeks following their last treatment. • The EOS visit was amended to the Week 12 visit of the last treatment cycle administered. • The overall EOS definition was amended to incorporate the change in EOS visit to Week 12. • It was clarified that measurement of the passive range of motion at the affected hip, knee and ankle must be performed on Day 1 of Study 142. • A time window was added to the study visits in the observational phase. • Interim descriptive analyses were allowed, if required.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported