Clinical trial results:
A PHASE III, PROSPECTIVE, MULTICENTRE, OPEN LABEL, EXTENSION STUDY ASSESSING THE LONG TERM SAFETY AND EFFICACY OF REPEATED TREATMENT WITH DYSPORT USED IN THE TREATMENT OF LOWER LIMB SPASTICITY IN CHILDREN WITH DYNAMIC EQUINUS FOOT DEFORMITY DUE TO CEREBRAL PALSY

Summary

EudraCT number	2010-019102-17
Trial protocol	FR PL Outside EU/EEA
Global end of trial date	14 January 2015

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	Y-55-52120-147

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma SAS
Sponsor organisation address	65 Quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Paediatric Neurology, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, Paediatric Neurology, Ipsen Pharma SAS, 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	01 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2015
Global end of trial reached?	Yes
Global end of trial date	14 January 2015
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 long term safety of repeated treatments with Dysport used in the treatment of lower limb spasticity in children with dynamic equinus foot deformity due to CP.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (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 with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 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	Poland: 66
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Chile: 16
Country: Number of subjects enrolled	Mexico: 34
Country: Number of subjects enrolled	Turkey: 56
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	216
EEA total number of subjects	68

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)	193

Adolescents (12-17 years)	23
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed as a multicentre study at 27 investigational sites in France, Mexico, Turkey, Poland, Chile and the United States of America (USA). Twenty six sites recruited at least one subject and the other site was inactive.

Pre-assignment

Screening details:

Of 216 subjects enrolled into this open label study from 141 Study, 203 subjects went straight into Cycle 1. 13 subjects were not considered eligible for retreatment at end of Study 141 (all of whom had received Dysport) and per study design they entered into observational phase of study 147. Of these 13, 4 subjects entered cycle 1 at a later date.

Period 1

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

Arms

Arm title	Total Dysport

Arm description:

Dysport was injected into the affected gastrocnemius soleus complex (GSC) with / without Hamstring injections at doses ranging between 5U/kg to 20U/kg for one leg and 10U/kg to 30U/kg for both legs

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

Dosage and administration details:

Dysport was injected into the affected gastrocnemius soleus complex (GSC) with / without Hamstring injections at doses ranging between 5U/kg to 20U/kg for one leg and 10U/kg to 30U/kg for both legs

Number of subjects in period 1	Total Dysport
Started	216
Cycle 1	207
Cycle 2	175 [1]
Cycle 3	86 [2]
Cycle 4	11 [3]
Completed	194
Not completed	22
Adverse Event	1
Other	12
Lost to follow-up	2

Consent withdrawn	6
Lack of efficacy	1

Notes:

[1] - 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: Of 207 subjects who started in cycle 1, only 175 subjects entered cycle 2. (8 subjects withdrew at cycle 1, 24 subjects completed study after cycle 1)
[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: Of 207 subjects who started in cycle 1, only 86 subjects entered cycle 3. (16 subjects withdrew at cycles 1 and 2, 105 subjects completed study after cycles 1 and 2)
[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: Of 207 subjects who started in cycle 1, only 11 subjects entered cycle 4. (19 subjects withdrew at cycles 1,2 and 3, 177 subjects completed study after cycles 1, 2 and 3)

Baseline characteristics

Reporting groups	
Reporting group title	Open Label Study

Reporting group description: -

Reporting group values	Open Label Study	Total	
Number of subjects	216	216	
Age categorical Units: Subjects			
2 - 9 years	183	183	
10 - 17 years	33	33	
Age continuous Units: years			
arithmetic mean	5.9		
standard deviation	± 3.3	-	
Gender categorical Units: Subjects			
Female	86	86	
Male	130	130	
Race Units: Subjects			
Black/African American	5	5	
Caucasian/White	159	159	
American Indian/Alaska native	1	1	
Multiple	51	51	
Ethnicity Units: Subjects			
Hispanic/Latino	59	59	
Not Hispanic/Latino	157	157	

End points

End points reporting groups

Reporting group title	Total Dysport
Reporting group description:	
Dysport was injected into the affected gastrocnemius soleus complex (GSC) with / without Hamstring injections at doses ranging between 5U/kg to 20U/kg for one leg and 10U/kg to 30U/kg for both legs	
Subject analysis set title	Treatment Cycle 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population	
Subject analysis set title	Treatment Cycle 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population.	
Subject analysis set title	Treatment Cycle 3
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population.	
Subject analysis set title	Dysport All Doses
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population.	

Primary: Number of subjects with Treatment Emergent Adverse Events Reported in the Double Blind (DB) + Open Label (OL) Period

End point title	Number of subjects with Treatment Emergent Adverse Events Reported in the Double Blind (DB) + Open Label (OL) Period[1]

End point description:

Safety Population.

N=216, One Subject received placebo in the double blind study and two treatment cycles of Dysport in this open label study. However, both Dysport treatments were outside of the ranges specified and therefore has been excluded from the tables since all Subjects with dosage outside of the ranges specified (i.e. Cycle 1: <=7.5 or >12.5 U/kg (1 leg), <=15 or >25 U/kg (2 legs), Cycles 2-4: <=7.5 or >17.5 U/kg (1 leg), <=15 or >35 U/kg (2 legs)) were to be excluded.

Treatment Emergent Adverse Event (TEAE); Serious Adverse Event (SAE)

End point type	Primary

End point timeframe:

From baseline (Day 1) till end of study (week 40)

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	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	215			
Units: Number of subjects				
Any TEAEs	177			
Intensity of TEAES - at least one severe	5			

Intensity of TEAES - at least one moderate	91			
Intensity of TEAES - at least one mild	151			
Intensity of TEAES - at least one missing	1			
Causality of TEAES - At least one related	29			
Causality of TEAES - At least one not related	172			
Causality of TEAES - At least one missing	0			
Causality & intensity-at least 1 related & severe	0			
Causality & intensity-atleast 1 related & moderate	9			
Causality & intensity-at least 1 related & mild	23			
Causality&intensity-atleast 1 not related & severe	5			
Causality&intensity-atleast 1 not related&moderate	87			
Causality & intensity-atleast 1 not related & mild	145			
Any TEAEs leading to study withdrawal	1			
Any TEAEs leading to Death	0			
Any SAEs	7			
Any Non-serious TEAEs	175			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (in the double blind study) in the MAS score in the GSC assessed at the ankle joint of the (most) affected lower limb

End point title	Mean change from baseline (in the double blind study) in the MAS score in the GSC assessed at the ankle joint of the (most) affected lower limb

End point description:

ITT (Intent to treat) Population.

The baseline value for the 'change from cycle baseline in the open label study' was defined as the baseline (Day 1) of the current treatment cycle.

n=number of subjects with data.

Modified Ashworth Scale (MAS): A 6-point scale which measures the intensity of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. Investigator will grade muscle tone in the Gastrocnemius-soleus complex (GSC) from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=170)	-1 (± 0.9)			
Treatment Cycle 1, Week 12 (n=157)	-0.8 (± 0.8)			
Treatment Cycle 2, Week 4 (n=122)	-1.1 (± 0.9)			
Treatment Cycle 2, Week 12 (n=93)	-0.9 (± 0.9)			
Treatment Cycle 3, Week 4 (n=66)	-1 (± 0.8)			
Treatment Cycle 3, Week 12 (n=35)	-0.7 (± 1)			
Treatment Cycle 4, Week 4 (n=8)	-0.4 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in the hamstrings) in the MAS score in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point title	Mean change from baseline (prior to the first injection cycle in the hamstrings) in the MAS score in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point description:

ITT Population. Baseline: The baseline value used for this table was defined as the value obtained prior to the first injection in the hamstrings.

Modified Ashworth Scale (MAS): A 6-point scale which measures the intensity of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. Investigator will grade muscle tone in the Gastrocnemius-soleus complex (GSC) from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=25)	-0.6 (± 0.7)			
Treatment Cycle 1, Week 12 (n=24)	-0.8 (± 0.8)			
Treatment Cycle 2, Week 4 (n=33)	-0.5 (± 0.9)			
Treatment Cycle 2, Week 12 (n=21)	-0.3 (± 0.9)			
Treatment Cycle 3, Week 4 (n=13)	-0.2 (± 0.8)			
Treatment Cycle 3, Week 12 (n=5)	-0.6 (± 0.5)			
Treatment Cycle 4, Week 4 (n=2)	-0.5 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in upper limb muscle groups) in the mean MAS score for all injected upper limb muscle groups from Treatment Cycle 2 onwards

End point title	Mean change from baseline (prior to the first injection cycle in upper limb muscle groups) in the mean MAS score for all injected upper limb muscle groups from Treatment Cycle 2 onwards

End point description:

ITT Population.

The baseline value used for this table was defined as the value obtained prior to the first injection in the upper limb(s).
No subjects were treated in the upper limb in Treatment Cycle 4.

TC = Treatment Cycle.

n = number of subjects with data.

TC 3 - Elbow Flexors at week 12 - value for standard deviation is not applicable as number of subject is 1.

Modified Ashworth Scale (MAS): A 6-point scale which measures the intensity of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. Investigator will grade muscle tone in the Gastrocnemius-soleus complex (GSC) from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: Units on a scale				
arithmetic mean (standard deviation)				
TC 2: Elbow Flexors at week 4 (n=14)	-1.2 (± 0.9)			
TC 2: Elbow Flexors at week 12 (n=12)	-1.1 (± 0.8)			
TC 2: Wrist Flexors at week 4 (n=11)	-1.6 (± 0.8)			
TC 2: Wrist Flexors at week 12 (n=8)	-1 (± 0.9)			
TC 3: Elbow Flexors at week 4 (n=2)	1 (± 0)			
TC 3: Elbow Flexors at week 12 (n=1)	-1 (± 0)			
TC 3: Wrist Flexors at week 4 (n=5)	-1.4 (± 0.9)			
TC 3: Wrist Flexors at week 12 (n=2)	-1.5 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean PGA (Physician's Global Assessment) score

End point title	Mean PGA (Physician's Global Assessment) score

End point description:

ITT Population.

Physician's Global Assessment (PGA) Scale of the Treatment Response: Global assessment of treatment response will be assessed by asking the Investigator the following question: "how would you rate the response to treatment in the subject's lower limb(s) since the last injection?" Answers will be made on a 9 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).

Global assessment of treatment response is based on changes since the first injection in the double blind study.
Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At week 4 and week 12.

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	195			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1 at week 4 (n=195)	1.5 (± 0.9)			
Treatment Cycle 1 at week 12 (n=180)	1 (± 1.2)			
Treatment Cycle 2 at week 4 (n=159)	1.5 (± 1)			
Treatment Cycle 2 at week 12 (n=116)	0.9 (± 1.3)			
Treatment Cycle 3 at week 4 (n=78)	1.4 (± 0.9)			
Treatment Cycle 3 at week 12 (n=37)	0.7 (± 1.4)			
Treatment Cycle 4 at week 4 (n=8)	0.5 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean GAS (Goal Attainment Scale) score

End point title	Mean GAS (Goal Attainment Scale) score

End point description:

ITT Population.

Goal Attainment Scale (GAS): A functional scale used to measure progress towards individual therapy goals. Individual goals will be defined for each subject by the physician, and the child's parents (caregiver) where applicable, prior to treatment. Post-baseline, the GAS for each goal will be rated using a defined scale (-2: Much less than expected outcome, -1: somewhat less than expected outcome, 0: expected outcome, 1: somewhat more than expected outcome, and 2: Much more than expected outcome).

Individual goals were defined prior to treatment in each treatment period. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	194			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1 at week 4 (n=194)	50.6 (± 11)			
Treatment Cycle 1 at week 12 (n=178)	50.7 (± 10.1)			
Treatment Cycle 2 at week 4 (n=158)	51.2 (± 11)			
Treatment Cycle 2 at week 12 (n=116)	51.7 (± 10.5)			
Treatment Cycle 3 at week 4 (n=78)	48.3 (± 10.7)			
Treatment Cycle 3 at week 12 (n=36)	45.8 (± 8.9)			
Treatment Cycle 4 at week 4 (n=8)	44.9 (± 9.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in XV1 derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point title	Mean change from treatment cycle baseline (cycle Day 1) in XV1 derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point description:

ITT Population.

The DB (Double blind) baseline is presented for each treatment cycle as it represents the baseline data just for the subjects entering into each treatment cycle. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	169			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=169)	2.6 (± 9)			
Treatment Cycle 1, Week 12 (n=156)	1.4 (± 9.2)			
Treatment Cycle 2, Week 4 (n=121)	1.4 (± 9.2)			
Treatment Cycle 2, Week 12 (n=92)	0.4 (± 10.9)			
Treatment Cycle 3, Week 4 (n=66)	0.5 (± 10.1)			
Treatment Cycle 3, Week 12 (n=35)	-1.1 (± 10.4)			
Treatment Cycle 4, Week 4 (n=8)	-5 (± 9.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in XV3 derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point title	Mean change from treatment cycle baseline (cycle Day 1) in XV3 derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point description:

ITT Population.

The DB baseline is presented for each treatment cycle as it represents the baseline data just for the subjects entering into each treatment cycle. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	168			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=168)	12.2 (± 13.7)			
Treatment Cycle 1, Week 12 (n=155)	9.9 (± 13.7)			
Treatment Cycle 2, Week 4 (n=119)	13.3 (± 12.6)			

Treatment Cycle 2, Week 12 (n=92)	11.4 (± 13.9)			
Treatment Cycle 3, Week 4 (n=65)	12.7 (± 13.4)			
Treatment Cycle 3, Week 12 (n=35)	9.9 (± 14.5)			
Treatment Cycle 4, Week 4 (n=8)	4.4 (± 11.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in X derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point title	Mean change from treatment cycle baseline (cycle Day 1) in X derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point description:

ITT Population.

The DB baseline is presented for each treatment cycle as it represents the baseline data just for the subjects entering into each treatment cycle. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	168			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=168)	-9.7 (± 12.6)			
Treatment Cycle 1, Week 12 (n=155)	-8.5 (± 11.9)			
Treatment Cycle 2, Week 4 (n=119)	-12 (± 12)			
Treatment Cycle 2, Week 12 (n=92)	-10.9 (± 12.8)			
Treatment Cycle 3, Week 4 (n=65)	-12.2 (± 11.6)			
Treatment Cycle 3, Week 12 (n=35)	-11 (± 13.4)			
Treatment Cycle 4, Week 4 (n=8)	-9.4 (± 8.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in Y, derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point title	Mean change from treatment cycle baseline (cycle Day 1) in Y,

	derived from the TS, in the GSC assessed at the ankle joint of the (most) affected lower limb

End point description:

ITT Population.

The DB baseline is presented for each treatment cycle as it represents the baseline data just for the subjects entering into each treatment cycle. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	169			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=169)	-0.4 (± 0.7)			
Treatment Cycle 1, Week 12 (n=155)	-0.3 (± 0.6)			
Treatment Cycle 2, Week 4 (n=120)	-0.4 (± 0.7)			
Treatment Cycle 2, Week 12 (n=92)	-0.3 (± 0.6)			
Treatment Cycle 3, Week 4 (n=66)	-0.4 (± 0.6)			
Treatment Cycle 3, Week 12 (n=35)	-0.3 (± 0.6)			
Treatment Cycle 4, Week 4 (n=8)	-0.3 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in the hamstrings) in XV1, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point title	Mean change from baseline (prior to the first injection cycle in the hamstrings) in XV1, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point description:

ITT Population.

Subjects with dosage outside of the ranges specified (i.e. ≤3 or >12.5 U/kg) were excluded from the table, including the Dysport all doses.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=26)	3.2 (± 10)			
Treatment Cycle 1, Week 12 (n=24)	6.9 (± 10.4)			
Treatment Cycle 2, Week 4 (n=33)	3 (± 11.4)			
Treatment Cycle 2, Week 12 (n=21)	5.5 (± 11.4)			
Treatment Cycle 3, Week 4 (n=13)	3.8 (± 12.1)			
Treatment Cycle 3, Week 12 (n=5)	2 (± 7.6)			
Treatment Cycle 4, Week 4 (n=2)	5 (± 7.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in the hamstrings) in XV3, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point title	Mean change from baseline (prior to the first injection cycle in the hamstrings) in XV3, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point description:

ITT Population.

Subjects with dosage outside of the ranges specified (i.e. ≤3 or >12.5 U/kg) were excluded from the table, including the Dysport all doses.

n=number of subjects with data.
DB = Double blind.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=26)	10.1 (± 14.8)			
Treatment Cycle 1, Week 12 (n=24)	13.3 (± 16.3)			
Treatment Cycle 2, Week 4 (n=33)	8.2 (± 15.1)			

Treatment Cycle 2, Week 12 (n=21)	12.4 (± 16.5)			
Treatment Cycle 3, Week 4 (n=13)	11.9 (± 22.3)			
Treatment Cycle 3, Week 12 (n=5)	30 (± 24.5)			
Treatment Cycle 4, Week 4 (n=2)	5 (± 7.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in the hamstrings) in X, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point title	Mean change from baseline (prior to the first injection cycle in the hamstrings) in X, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point description:

ITT Population.

Subjects with dosage outside of the ranges specified (i.e. ≤3 or >12.5 U/kg) were excluded from the table, including the Dysport all doses.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Degrees				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=26)	-6.9 (± 11.3)			
Treatment Cycle 1, Week 12 (n=24)	-6.5 (± 11.8)			
Treatment Cycle 2, Week 4 (n=33)	-5.2 (± 12)			
Treatment Cycle 2, Week 12 (n=21)	-6.9 (± 11.8)			
Treatment Cycle 3, Week 4 (n=13)	-8.1 (± 13.6)			
Treatment Cycle 3, Week 12 (n=5)	-28 (± 20.8)			
Treatment Cycle 4, Week 4 (n=2)	0 (± 14.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline (prior to the first injection cycle in the hamstrings) in Y, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point title	Mean change from baseline (prior to the first injection cycle in the hamstrings) in Y, derived from the TS, in the knee flexors assessed at the knee joint of the (most) affected lower limb

End point description:

ITT Population.

Subjects with dosage outside of the ranges specified (i.e. ≤3 or >12.5 U/kg) were excluded from the table, including the Dysport all doses.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=26)	-0.1 (± 0.6)			
Treatment Cycle 1, Week 12 (n=24)	-0.1 (± 0.5)			
Treatment Cycle 2, Week 4 (n=33)	0 (± 0.6)			
Treatment Cycle 2, Week 12 (n=21)	-0.1 (± 0.6)			
Treatment Cycle 3, Week 4 (n=13)	-0.1 (± 0.3)			
Treatment Cycle 3, Week 12 (n=5)	-0.4 (± 0.9)			
Treatment Cycle 4, Week 4 (n=2)	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in the OGS total score of the (most) affected leg

End point title	Mean change from treatment cycle baseline (cycle Day 1) in the OGS total score of the (most) affected leg

End point description:

ITT Population.

The DB baseline is presented for each treatment cycle as it represents the baseline data just for the subjects entering into each treatment cycle. Subjects with dosage outside of the ranges specified (i.e. ≤7.5 or >17.5 U/kg) were excluded from the table.

The OGS is a measurement tool that objectively measures to quantify positive and negative features (impairments) of the upper motor neurone syndrome [27]. The OGS is useful when children are too young or insufficiently cooperative for instrumented gait analysis. It is based on the Physicians Rating Scale but has some modifications to improve its sensitivity to detect changes following administration of BTX-A (Botulinum Toxin Type A).

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 4 and week 12

End point values	Dysport All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	178			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Treatment Cycle 1, Week 4 (n=178)	1 (± 3)			
Treatment Cycle 1, Week 12 (n=166)	0.3 (± 2.8)			
Treatment Cycle 2, Week 4 (n=142)	1.4 (± 3)			
Treatment Cycle 2, Week 12 (n=104)	0.8 (± 2.8)			
Treatment Cycle 3, Week 4 (n=70)	1.4 (± 3.2)			
Treatment Cycle 3, Week 12 (n=35)	1 (± 2.6)			
Treatment Cycle 4, Week 4 (n=8)	0.3 (± 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in the PedsQL score (Cerebral Palsy Module Scores) at each study visit except Week 4

End point title	Mean change from treatment cycle baseline (cycle Day 1) in the PedsQL score (Cerebral Palsy Module Scores) at each study visit except Week 4

End point description:

ITT Population.

The PedsQL is a validated quality of life questionnaire, designed for children from 2 to 18 years of age. It has a disease specific CP module that is relevant to the study population and complements the core modules.

Open Label (Dysport All Doses) - Treatment Cycle 1, 2 and 3

Baseline is baseline data from the double blind study.

S and C = Speech and communication.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 12

End point values	Treatment Cycle 1	Treatment Cycle 2	Treatment Cycle 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	179	120	39	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Daily activities at week 12 (n=178, n=119, n=39)	6.9 (± 18.6)	9.2 (± 20.8)	14.4 (± 19)	
Movement and balance at week 12 (n=179,n=120,n=39)	7.7 (± 21)	8.9 (± 19.6)	13.5 (± 19.3)	
Fatigue at week 12 (n=178, n=120, n=39)	4.7 (± 19)	5 (± 18.4)	9 (± 17)	
Pain and hurt at week 12 (n=179, n=120, n=39)	3.5 (± 17.9)	4.5 (± 16.2)	2.7 (± 21.3)	
School activities at week 12 (n=103, n=71, n=26)	3.8 (± 24.5)	5.1 (± 20.4)	7.7 (± 14.5)	
Eating activities at week 12 (n=178, n=120, n=39)	2 (± 15.2)	2.1 (± 14.9)	2.7 (± 10.8)	
S and C at week 12 (n=103, n=72, n=26)	2.5 (± 17.4)	2.3 (± 16.1)	5.8 (± 16.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from treatment cycle baseline (cycle Day 1) in the PedsQL score (Generic Core Scores) at each study visit except Week 4

End point title	Mean change from treatment cycle baseline (cycle Day 1) in the PedsQL score (Generic Core Scores) at each study visit except Week 4

End point description:

ITT Population.

The PedsQL is a validated quality of life questionnaire, designed for children from 2 to 18 years of age. It has a disease specific CP module that is relevant to the study population and complements the core modules.

Open Label (Dysport All Doses) - Treatment Cycle 1, 2 and 3.

Baseline is baseline data from the double blind study.

PhHS = Physical health summary

PHS = Psychosocial health summary.

n=number of subjects with data.

End point type	Secondary

End point timeframe:

At baseline (Day 1), week 12

End point values	Treatment Cycle 1	Treatment Cycle 2	Treatment Cycle 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	174	119	39	
Units: Units on a scale				
arithmetic mean (standard deviation)				
PhHS at week 12 (n=173, n=119, n=39)	7.8 (± 17.2)	6.1 (± 20.9)	8 (± 20.6)	
PHS at week 12 (n=174, n=118, n=39)	4.1 (± 13.5)	4.6 (± 13.8)	8.9 (± 12.1)	
Total Scale at week 12 (n=173, n=119, n=39)	5.5 (± 12.5)	5.2 (± 13.9)	8.6 (± 13.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to end of study (week 40)

Adverse event reporting additional description:

DB+OL Period Safety Popln N=216. Subjects with dosage outside specified ranges[Cycle 1:<=7.5 or>12.5U/kg(1 leg),<=15 or>25U/kg(2 legs),Cycles 2-4:<=7.5 or>17.5U/kg(1 leg),<=15 or>35U/kg (2 legs)] were to be excluded.One Subject who received placebo in DB & 2 cycles Dysport in OL was excluded from tables as both Dysport treatments were outside range

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Dysport All Doses

Reporting group description: -

Serious adverse events	Dysport All Doses		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 215 (3.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Status Epilepticus			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Complex Partial Seizures			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial Seizures			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			

subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 215 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 215 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 215 (0.47%)		
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	Dysport All Doses		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 215 (68.37%)		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	34 / 215 (15.81%)		
occurrences (all)	43		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 215 (7.44%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	12 / 215 (5.58%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	8 / 215 (3.72%)		
occurrences (all)	10		
Cough			
subjects affected / exposed	20 / 215 (9.30%)		
occurrences (all)	24		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	12 / 215 (5.58%)		
occurrences (all)	13		
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	46 / 215 (21.40%)		
occurrences (all)	71		
Nasopharyngitis			
subjects affected / exposed	47 / 215 (21.86%)		
occurrences (all)	65		
Influenza			
subjects affected / exposed	20 / 215 (9.30%)		
occurrences (all)	28		
Pharyngitis			
subjects affected / exposed	25 / 215 (11.63%)		
occurrences (all)	32		
Bronchitis			

subjects affected / exposed	19 / 215 (8.84%)		
occurrences (all)	23		
Viral Infection			
subjects affected / exposed	3 / 215 (1.40%)		
occurrences (all)	6		
Varicella			
subjects affected / exposed	12 / 215 (5.58%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2011	• The GAS was changed from a 7-point scale to the validated 5-point scale. • Question 8 was omitted from the OGS, as central assessors were to evaluateand score each video in an independent manner and would not have thebaseline videos for comparison to score Question 8 which assesses change from baseline. • The injection technique was modified to add the use of ultrasound as a complimentary muscle localisation method to electrical stimulation. • Injection volume for the lower quadrant of gastrocnemius changed to optional and this volume could be utilised in other lower limb injection sites according to clinical presentation of spasticity. This change was based on a publication on neuromuscular endplate concentration in lower limb. • Clarification was added to the study rationale in response to French Central Ethics Committee's request. • A new contact number was added due to change of office reception number.
12 July 2012	• The pharmacovigilance/emergency contact details for the USA and Latin America were updated. • Exclusion criterion 1 was modified to clarify the terminology for the exclusion of subjects based on the assessment of fixed myocontracture. • Exclusion criterion 3 was modified to clarify the exclusion of subjects with a need for surgery due to spasticity. • Written informed consent details were modified to clarify that either one or both parent(s)/guardian(s) would sign the ICF according to local legislation. • Study treatment was to be administered within 24 hours of Day 1 visit assessments of each treatment cycle. • Ipsen Pharma was replaced by Kymos Pharma as the central laboratory used for processing antibody samples. • 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 Clinical Development Data Sciences Department were amended to Statistics Department.
18 November 2013	• The Sponsor’s Co-ordinating and Monitoring Office details were updated. • The pharmacovigilance/emergency contact details for the UK, USA and Latin America were updated. • Deleted informed consent information in Section 4.1.3 to be consistent with Section 5.2. • To allow an interim analyses, if required, for registration purposes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported