Clinical trial results:
A PHASE III, MULTICENTRE, DOUBLE BLIND, PROSPECTIVE, RANDOMISED, PLACEBO CONTROLLED STUDY ASSESSING THE EFFICACY AND SAFETY OF DYSPORT USED IN THE TREATMENT OF LOWER LIMB SPASTICITY IN CHILDREN WITH DYNAMIC EQUINUS FOOT DEFORMITY DUE TO CEREBRAL PALSY

Summary

EudraCT number	2009-017709-12
Trial protocol	FR PL
Global end of trial date	25 June 2014

Results information

Result version number	v2 (current)
This version publication date	23 May 2025
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Data validation

Trial information

Trial identification

Sponsor protocol code	Y-55-52120-141

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01249417
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, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2014
Global end of trial reached?	Yes
Global end of trial date	25 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective will be to assess the efficacy of Dysport compared to placebo at Week 4 on the mean change from baseline in ankle joint hypertonicity in children with dynamic equinus foot deformity associated with cerebral palsy (CP).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Placebo

Actual start date of recruitment	05 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 74
Country: Number of subjects enrolled	Chile: 16
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Turkey: 62
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	241
EEA total number of subjects	74

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)	218
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:

Each center that participated in the study was expected to randomize between 5 and 25 subjects. It was planned to have at least 2 participating centers per country.

Pre-assignment

Screening details:

A total of 241 subjects were randomised to the study. The safety population included 239 subjects who were treated. Out of the 239 treated subjects, 4 subjects were excluded from the Intent-to-Treat (ITT) population because no modified ashworth scale (MAS) score was obtained at the baseline visit and/or at Week 4.

Period 1

Period 1 title	Randomized population
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dysport 10 U/Kg

Arm description:

10 units per kilogram (U/Kg) per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 milliliter (ml) per leg.
Botulinum type A toxin (Dysport®): Intramuscular (I.M.) (in the muscle) injection on Day 1 of a single treatment cycle.

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

Dosage and administration details:

Dysport 10 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Arm title	Dysport 15 U/Kg

Arm description:

15 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg.
Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.

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

Dosage and administration details:

Dysport 15 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Arm title	Placebo

Arm description:

Total volume to be injected per lower limb - 2ml. Either 1 or both lower limbs can be treated.
Placebo: I.M. injection on Day 1 of a single treatment cycle.

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Number of subjects in period 1	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo
Started	80	80	81
Treated	80	80	79
Completed	79	79	77
Not completed	1	1	4
No MAS score at baseline and/or Week 4	1	1	2
Study treatment not received	-	-	2

Period 2

Period 2 title	Treatment phase - ITT population
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dysport 10 U/Kg

Arm description:

10 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.

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

Dosage and administration details:

Dysport 10 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Arm title	Dysport 15 U/Kg

Arm description:

15 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.

Arm type	Experimental

Investigational medicinal product name	Botulinum type A toxin (Dysport)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dysport 15 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Arm title	Placebo

Arm description:

Total volume to be injected per lower limb - 2 ml. Either 1 or both lower limbs can be treated.
Placebo: I.M. injection on Day 1 of a single treatment cycle.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristic values were based on the ITT population, defined as all randomized subjects who received at least 1 injection of study treatment and who had a MAS score in the GSC assessed both at baseline and at Week 4.

Number of subjects in period 2[2]	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo
Started	79	79	77
Completed	78	75	73
Not completed	1	4	4
Consent withdrawn by subject	1	3	1
Adverse event, non-fatal	-	-	1
Not specified	-	-	1
Lost to follow-up	-	1	1

Notes:

[2] - 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: Only subjects who completed the Randomized phase were entered to Treatment phase of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Dysport 10 U/Kg
Reporting group description:	
10 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Dysport 15 U/Kg
Reporting group description:	
15 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Placebo
Reporting group description:	
Total volume to be injected per lower limb - 2 ml. Either 1 or both lower limbs can be treated. Placebo: I.M. injection on Day 1 of a single treatment cycle.	

Reporting group values	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo
Number of subjects	79	79	77
Age categorical Units: Subjects			
Children (2-9 years)	67	67	65
Children (10-17 years)	12	12	12
Age continuous Units: years			
arithmetic mean	6	5.7	5.9
standard deviation	± 3.3	± 3.2	± 3.5
Gender categorical Units: Subjects			
Female	45	48	48
Male	34	31	29
Race Units: Subjects			
Black/African American	2	0	5
Caucasian/White	57	60	55
American Indian/Alaskan Native	1	0	0
Multiple	19	19	17
Ethnicity Units: Subjects			
Hispanic/Latino	21	21	20
Not Hispanic/Latino	58	58	57
Botulinum toxin Status Units: Subjects			
Naive	40	41	41
Non-naive	39	38	36
Number of legs being treated Units: Subjects			
1 Leg injected	42	50	47
2 Leg injected	37	29	30
GMFCS Level			
Subjects were staged according to the following Gross Motor Function Classification System (GMFCS)			

criteria: level 1 (walks without limitations [best outcome]), level 2 (walks with limitations) and level 3 (walks using a hand held mobility device [worst outcome]). Only subjects classified as GMFCS levels 1 to 3 were eligible for entry into the study.			
Units: Subjects			
GMFCS level 1	46	45	40
GMFCS level 2	24	24	30
GMFCS level 3	9	10	7
Height			
Units: centimeter			
arithmetic mean	117.1	111.6	114.6
standard deviation	± 20.7	± 18.5	± 19.7
Weight			
Units: kg			
arithmetic mean	23.1	21.1	22.6
standard deviation	± 13.4	± 10.7	± 11.9
Body Mass Index (BMI)			
Units: kg/meter square			
arithmetic mean	15.8	16.1	16.2
standard deviation	± 2.9	± 2.7	± 2.7
MAS score			
The MAS is a 6-point scale which measures the intensity of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. The Investigator graded muscle tone in the gastrocnemius-soleus complex (GSC) from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).			
Units: Units on scale			
arithmetic mean	3.1	3.1	3.2
standard deviation	± 0.3	± 0.3	± 0.4

Reporting group values	Total		
Number of subjects	235		
Age categorical			
Units: Subjects			
Children (2-9 years)	199		
Children (10-17 years)	36		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	141		
Male	94		
Race			
Units: Subjects			
Black/African American	7		
Caucasian/White	172		
American Indian/Alaskan Native	1		
Multiple	55		
Ethnicity			
Units: Subjects			
Hispanic/Latino	62		
Not Hispanic/Latino	173		
Botulinum toxin Status			

Units: Subjects			
Naive	122		
Non-naive	113		
Number of legs being treated Units: Subjects			
1 Leg injected	139		
2 Leg injected	96		
GMFCS Level			
Subjects were staged according to the following Gross Motor Function Classification System (GMFCS) criteria: level 1 (walks without limitations [best outcome]), level 2 (walks with limitations) and level 3 (walks using a hand held mobility device [worst outcome]). Only subjects classified as GMFCS levels 1 to 3 were eligible for entry into the study.			
Units: Subjects			
GMFCS level 1	131		
GMFCS level 2	78		
GMFCS level 3	26		
Height Units: centimeter arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Body Mass Index (BMI) Units: kg/meter square arithmetic mean standard deviation	- -		
MAS score			
The MAS is a 6-point scale which measures the intensity of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. The Investigator graded muscle tone in the gastrocnemius-soleus complex (GSC) from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).			
Units: Units on scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Dysport 10 U/Kg
Reporting group description:	
10 units per kilogram (U/Kg) per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 milliliter (ml) per leg. Botulinum type A toxin (Dysport®): Intramuscular (I.M.) (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Dysport 15 U/Kg
Reporting group description:	
15 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Placebo
Reporting group description:	
Total volume to be injected per lower limb - 2ml. Either 1 or both lower limbs can be treated. Placebo: I.M. injection on Day 1 of a single treatment cycle.	
Reporting group title	Dysport 10 U/Kg
Reporting group description:	
10 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Dysport 15 U/Kg
Reporting group description:	
15 U/Kg per lower limb. Either 1 or both lower limbs can be treated. Total volume injected, 2 ml per leg. Botulinum type A toxin (Dysport®): I.M. (in the muscle) injection on Day 1 of a single treatment cycle.	
Reporting group title	Placebo
Reporting group description:	
Total volume to be injected per lower limb - 2 ml. Either 1 or both lower limbs can be treated. Placebo: I.M. injection on Day 1 of a single treatment cycle.	

Primary: Change in MAS Score in the Gastrocnemius-soleus Complex (GSC) at the Ankle Joint of the (Most) Affected Lower Limb

End point title	Change in MAS Score in the Gastrocnemius-soleus Complex (GSC) at the Ankle Joint of the (Most) Affected Lower Limb
End point description:	
The MAS is 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 GSC from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension). ITT population, defined as all randomized subjects who received at least 1 injection of study treatment and who had a MAS score in the GSC assessed both at baseline and at Week 4.	
End point type	Primary
End point timeframe:	
Change from baseline to Week 4	

End point values	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	77	
Units: Units on a scale				
least squares mean (confidence interval 95%)	-0.86 (-1.07 to -0.65)	-0.97 (-1.18 to -0.76)	-0.48 (-0.69 to -0.27)	

Statistical analyses

Statistical analysis title	Dysport 10 U/kg/leg compared to Placebo

Statistical analysis description:

MAS: Dysport 10 U/kg/leg compared to Placebo at Week 4. Least square (LS) means for each treatment group and treatment comparisons, as well as the p-values were obtained from an analysis of covariance (ANCOVA) on the change from baseline with treatment, baseline MAS score, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Dysport 10 U/Kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.13

Statistical analysis title	Dysport 15 U/kg/leg compared to Placebo

Statistical analysis description:

MAS: Dysport compared to placebo at Week 4. LS means for each treatment group and treatment comparisons, as well as the p-values were obtained from an ANCOVA on the change from baseline with treatment, baseline MAS score, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Placebo v Dysport 15 U/Kg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.23

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

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

End point description:

PGA Scale of the Treatment Response: Global assessment of treatment response 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). ITT population, defined as all randomized subjects who received at least 1 injection of study treatment and who had a MAS score in the GSC assessed both at baseline and at Week 4.

End point type	Secondary

End point timeframe:

Week 4

End point values	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	77	
Units: Units on a scale				
least squares mean (confidence interval 95%)	1.54 (1.28 to 1.81)	1.5 (1.23 to 1.77)	0.73 (0.46 to 0.99)	

Statistical analyses

Statistical analysis title	Dysport 10 U/kg/leg compared to Placebo

Statistical analysis description:

PGA: Dysport 10 U/kg/leg compared to placebo at Week 4. LS means for each treatment group and treatment comparisons, as well as the p-values were obtained from an analysis of variance (ANOVA) on the visit value with treatment, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Placebo v Dysport 10 U/Kg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Difference in LS means
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.14

Statistical analysis title	Dysport 15 U/kg/leg compared to Placebo

Statistical analysis description:

PGA: Dysport 15 U/kg/leg compared to placebo at Week 4. LS means for each treatment group and treatment comparisons, as well as the p-values were obtained from an ANOVA on the visit value with treatment, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Placebo v Dysport 15 U/Kg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Difference in LS means
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.1

Secondary: Goal Attainment Scale (GAS) Score

End point title	Goal Attainment Scale (GAS) Score

End point description:

GAS is a functional scale used to measure progress towards individual therapy goals. Individual goals 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 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). ITT population, defined as all randomized subjects who received at least 1 injection of study treatment and who had a MAS score in the GSC assessed both at baseline and at Week 4.

End point type	Secondary

End point timeframe:

Week 4

End point values	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	77	
Units: Units on a scale				
least squares mean (confidence interval 95%)	51.53 (49.05 to 54.01)	50.86 (48.36 to 53.36)	46.21 (43.7 to 48.72)	

Statistical analyses

Statistical analysis title	Dysport 10 U/kg/leg compared to Placebo

Statistical analysis description:

GAS: Dysport 10 U/kg/leg compared to Placebo. LS means for each treatment group and treatment comparisons, as well as the p-values were obtained from an ANOVA on the visit value with treatment, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Dysport 10 U/Kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANOVA
Parameter estimate	Difference in LS means
Point estimate	5.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.31
upper limit	8.32

Statistical analysis title	Dysport 15 U/kg/leg compared to Placebo

Statistical analysis description:

GAS: Dysport 15 U/kg/leg compared to Placebo. LS means for each treatment group and treatment comparisons, as well as the p-values were obtained from an ANOVA on the visit value with treatment, age range at baseline, Botulinum toxin status at baseline and center as covariates.

Comparison groups	Placebo v Dysport 15 U/Kg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0031
Method	ANOVA
Parameter estimate	Difference in LS means
Point estimate	4.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.59
upper limit	7.71

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 28 of follow-up	
Adverse event reporting additional description:	
The safety population, defined as all randomized subjects who received at least 1 injection of study treatment, was used for the analysis of adverse events (AEs).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Dysport 10 U/Kg
Reporting group description:	
Dysport 10 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.	
Reporting group title	Dysport 15 U/Kg
Reporting group description:	
Dysport 15 U/Kg I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.	
Reporting group title	Placebo
Reporting group description:	
Placebo I.M. injection on either 1 or both lower limbs (2 ml per leg), single treatment.	

Serious adverse events	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	4 / 79 (5.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			

subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dysport 10 U/Kg	Dysport 15 U/Kg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 80 (63.75%)	51 / 80 (63.75%)	42 / 79 (53.16%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	2 / 80 (2.50%)	0 / 80 (0.00%)	0 / 79 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	2 / 79 (2.53%)
occurrences (all)	1	0	2
Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 80 (2.50%)	3 / 80 (3.75%)	0 / 79 (0.00%)
occurrences (all)	3	4	0
Headache			

subjects affected / exposed	0 / 80 (0.00%)	2 / 80 (2.50%)	1 / 79 (1.27%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 80 (7.50%)	8 / 80 (10.00%)	4 / 79 (5.06%)
occurrences (all)	7	8	4
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 80 (3.75%)	4 / 80 (5.00%)	4 / 79 (5.06%)
occurrences (all)	3	5	4
Diarrhoea			
subjects affected / exposed	2 / 80 (2.50%)	2 / 80 (2.50%)	1 / 79 (1.27%)
occurrences (all)	2	2	1
Nausea			
subjects affected / exposed	2 / 80 (2.50%)	1 / 80 (1.25%)	1 / 79 (1.27%)
occurrences (all)	3	3	2
Abdominal pain upper			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	2 / 79 (2.53%)
occurrences (all)	1	0	2
Abdominal pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	2 / 79 (2.53%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 80 (10.00%)	6 / 80 (7.50%)	5 / 79 (6.33%)
occurrences (all)	10	6	5
Oropharyngeal pain			
subjects affected / exposed	1 / 80 (1.25%)	2 / 80 (2.50%)	0 / 79 (0.00%)
occurrences (all)	1	2	0
Rhinorrhoea			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	2 / 79 (2.53%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	2 / 80 (2.50%)	3 / 80 (3.75%)	4 / 79 (5.06%)
occurrences (all)	2	3	4
Muscular weakness			
subjects affected / exposed	2 / 80 (2.50%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences (all)	2	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 80 (7.50%)	13 / 80 (16.25%)	10 / 79 (12.66%)
occurrences (all)	8	15	11
Nasopharyngitis			
subjects affected / exposed	10 / 80 (12.50%)	9 / 80 (11.25%)	4 / 79 (5.06%)
occurrences (all)	13	10	8
Influenza			
subjects affected / exposed	5 / 80 (6.25%)	6 / 80 (7.50%)	6 / 79 (7.59%)
occurrences (all)	6	9	7
Bronchitis			
subjects affected / exposed	3 / 80 (3.75%)	2 / 80 (2.50%)	2 / 79 (2.53%)
occurrences (all)	4	2	2
Gastroenteritis viral			
subjects affected / exposed	1 / 80 (1.25%)	2 / 80 (2.50%)	0 / 79 (0.00%)
occurrences (all)	1	2	0
Ear infection			
subjects affected / exposed	0 / 80 (0.00%)	2 / 80 (2.50%)	2 / 79 (2.53%)
occurrences (all)	0	4	2
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 80 (0.00%)	2 / 80 (2.50%)	0 / 79 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	6 / 80 (7.50%)	1 / 80 (1.25%)	3 / 79 (3.80%)
occurrences (all)	7	1	3
Rhinitis			
subjects affected / exposed	3 / 80 (3.75%)	1 / 80 (1.25%)	3 / 79 (3.80%)
occurrences (all)	3	1	3
Urinary tract infection			

subjects affected / exposed	2 / 80 (2.50%)	1 / 80 (1.25%)	3 / 79 (3.80%)
occurrences (all)	2	1	3
Respiratory tract infection viral			
subjects affected / exposed	2 / 80 (2.50%)	1 / 80 (1.25%)	0 / 79 (0.00%)
occurrences (all)	2	1	0
Viral infection			
subjects affected / exposed	1 / 80 (1.25%)	1 / 80 (1.25%)	4 / 79 (5.06%)
occurrences (all)	1	2	5
Varicella			
subjects affected / exposed	4 / 80 (5.00%)	0 / 80 (0.00%)	1 / 79 (1.27%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2011	Amendment 1: • 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 evaluate and score each video in an independent manner and would not have the baseline 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. • 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 2011	Amendment 2: • The statistical methodology for the primary efficacy analysis was modified from a Hochberg procedure to a hierarchical testing procedure following feedback from the Food and Drug Administration. • Statistical sections were updated to ensure consistency between the Dysport protocols. • Written informed consent details were modified to clarify that either one or both parent(s)/guardian(s) would sign the informed consent form according to local legislation.
12 July 2012	Amendment 3: • The pharmacovigilance/emergency contact details for the USA and Latin America were updated. • Exclusion criterion 3 was modified to clarify the terminology for the exclusion of subjects based on the assessment of fixed myocontracture. • Exclusion criterion 7 was modified to clarify the exclusion of subjects with a need for surgery due to spasticity. • Exclusion criterion 7 was modified to clarify the exclusion of subjects with previous injection of alcohol or phenol. • 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.
25 July 2013	Amendment 4: • The 3-step hierarchical testing procedure was replaced by a 4-step hierarchical testing procedure in the section: Statistical Methodology for the Efficacy Analysis in View of Registration in the USA, as agreed upon with the Food and Drug Administration. • As a result of the agreement upon a 4-step hierarchical testing procedure, the sample size to demonstrate a statistically significant treatment effect on the mean Physician’s Global Assessment score was recalculated. • The pharmacovigilance/emergency contact details for the USA and Latin America were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported