Clinical trial results:
A Phase III Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Dysport® for the Treatment of Cervical Dystonia

Summary

EudraCT number	2005-000709-70
Trial protocol	DE
Global end of trial date	07 September 2006

Results information

Result version number	v1 (current)
This version publication date	06 February 2016
First version publication date	06 February 2016

Trial information

Trial identification

Sponsor protocol code	Y-47-52120-051

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ipsen Group
Sponsor organisation address	27 Maple Street, Milford, MA, United States, 01757
Public contact	Medical Director, Neurology, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen, 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	19 October 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2006
Global end of trial reached?	Yes
Global end of trial date	07 September 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of intramuscular administration of Dysport (500 units) compared to placebo for the treatment of cervical dystonia

Protection of trial subjects:

The study was conducted in accordance with the applicable Food and Drug Administration (FDA) regulations and/or guidelines, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki. Dysport® for Injection (hereinafter referred to as Dysport) is an injectable form of Botulinum Toxin Type A (BTX-A). Dysport is licensed in many European countries for use in the treatment of a number of focal dystonias, including blepharospasm, spasmodic torticollis (cervical dystonia), and relief of hemifacial spasm.
Clinical studies conducted to date have identified 500 units of Dysport as the optimal dose for the treatment of the signs and symptoms of cervical dystonia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	116
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	96
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first enrollment: 10 October 2005 and Date of last completed: 07 September 2006. The study was conducted at sixteen centers in the USA and four centers in Russia.

Pre-assignment

Screening details:

A total of 127 subjects were screened across 20 centers. 116 subjects were randomized with 55 and 61 in the Dysport and placebo treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dysport

Arm description:

A single dose of Dysport was administered by intramuscular injection to a maximum of four clinically indicated muscles. The total dose was 500 Dysport units in a single dosing session.

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

Dosage and administration details:

A single dose of 500 units of Dysport

Arm title	Placebo

Arm description:

A single dose of 500 units of placebo by intramuscular injection

Principal Investigator (PI)

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

Dosage and administration details:

A single dose of 500 units of placebo by intramuscular injection

Number of subjects in period 1	Dysport	Placebo
Started	55	61
Completed	45	38
Not completed	10	23
Consent withdrawn by subject	2	-
PI & Subject Schedule Conflicts	1	-
Lost to follow-up	1	-
No Longer Wanted to do Blood Draws	1	-
Lack of efficacy	5	23

Baseline characteristics

Reporting groups	
Reporting group title	Dysport
Reporting group description:	
A single dose of Dysport was administered by intramuscular injection to a maximum of four clinically indicated muscles. The total dose was 500 Dysport units in a single dosing session.	
Reporting group title	Placebo
Reporting group description:	
A single dose of 500 units of placebo by intramuscular injection	
Principal Investigator (PI)	

Reporting group values	Dysport	Placebo	Total
Number of subjects	55	61	116
Age categorical			
Units: Subjects			
Between 18 and 65 years	46	50	96
>=65 years	9	11	20
Age continuous			
Units: years			
arithmetic mean	51.9	53.9	
standard deviation	± 13.4	± 12.5	-
Gender categorical			
Units: Subjects			
Female	37	38	75
Male	18	23	41
Race			
Units: Subjects			
Caucasian/White	55	61	116
Ethnicity			
Units: Subjects			
Hispanic/Latino	3	4	7
Not Hispanic/Latino	52	57	109
Height			
Dysport: N= 53 Placebo: N= 60			
Units: cm			
arithmetic mean	167	170	
standard deviation	± 10.3	± 8.5	-
Weight			
Dysport: N= 55 Placebo: N= 60			
Units: kg			
arithmetic mean	73.4	77.4	
standard deviation	± 13.8	± 15	-
TWSTRS Total Score			
Units: Points on a scale			
arithmetic mean	43.83	45.81	
standard deviation	± 7.97	± 8.78	-

Subject’s VAS for Symptom Assessment			
Dysport: N= 55 Placebo: N= 57			
Units: Points on a scale			
arithmetic mean	67.7	63.6	
standard deviation	± 19.7	± 18.9	-
Investigator’s VAS for Symptom Assessment			
Dysport: N= 54 Placebo: N= 59			
Units: Points on a scale			
arithmetic mean	62.3	65.3	
standard deviation	± 15.8	± 18	-
SF-36 Scores - Mental Health Summary			
Dysport: N= 54 Placebo: N= 59 Short Form 36 Quality of Life questionnaire (SF-36)			
Units: Points on a scale			
arithmetic mean	44.52	43.31	
standard deviation	± 10.41	± 11.14	-
SF-36 Scores - Physical Health Summary			
Dysport: N= 54 Placebo: N= 59			
Units: Points on a scale			
arithmetic mean	39.42	43.18	
standard deviation	± 8.84	± 7.89	-

End points

End points reporting groups

Reporting group title	Dysport
Reporting group description:	
A single dose of Dysport was administered by intramuscular injection to a maximum of four clinically indicated muscles. The total dose was 500 Dysport units in a single dosing session.	
Reporting group title	Placebo
Reporting group description:	
A single dose of 500 units of placebo by intramuscular injection Principal Investigator (PI)	

Primary: Change from Baseline in TWSTRS Total Score at week 4

End point title	Change from Baseline in TWSTRS Total Score at week 4
End point description:	
Intention-to Treat (ITT) Population Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) TWSTRS is comprised of three different components which are severity, disability & pain. There is an ordinal scale for each component and the score range for each is the following: for severity from 0 (absence of severity) to 35 (max severity), for disability from 0 (no disability) to 30 (max disability) and for pain from 0 (no pain) to 20 (max pain). TWSTRS total score is the sum of the 3 component scores, with a range from 0 to a maximum of 85. The change in TWSTRS total score is the score at week 4 minus the score at baseline. The analysis was performed on the intention to treat population which consisted of 55 subjects receiving Dysport and 61 Placebo. There were 4 subjects for Dysport and 3 for placebo who were not assessed on TWSTRS score at Week 4. As there was no imputation of missing TWSTRS score values, these 7 subjects were not taken into account.	
End point type	Primary
End point timeframe:	
Baseline (week 0) and week 4	

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: points on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=51,58)	-13.99 (± 12.33)	-5.23 (± 9.33)		

Statistical analyses

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 4
Statistical analysis description:	
Baseline TWSTRS total scores are analysed for all subjects of ITT population, while the analysis at Week	

4 excludes the scores for the 7 subjects who were not assessed.
Mean difference = difference in adjusted least squares mean (Dysport - Placebo).

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Change from Baseline in TWSTRS Total Score week 8 and 12

End point title	Change from Baseline in TWSTRS Total Score week 8 and 12

End point description:

Week 8: The analysis was performed on the intention to treat population which consisted of 55 subjects receiving Dysport and 61 Placebo. There were 9 subjects for Dysport and 15 for placebo who were not assessed on TWSTRS score at Week 8. As there was no imputation of missing TWSTRS score values, these 24 subjects were not taken into account.

Week 12: The analysis was performed on the intention to treat population which consisted of 55 subjects receiving Dysport and 61 Placebo. There were 10 subjects for Dysport and 17 for placebo who were not assessed on TWSTRS score at Week 12. As there was no imputation of missing TWSTRS score values, these 27 subjects were not taken into account.

End point type	Secondary

End point timeframe:

Baseline (week 0), week 8 and week 12

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: points on a scale				
arithmetic mean (standard deviation)				
Week 8 (N=46,46)	-13.82 (± 11.53)	-5.59 (± 11.37)		
Week 12 (N=45,44)	-6.98 (± 11.12)	-4.53 (± 7.75)		

Statistical analyses

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 8

Statistical analysis description:

Baseline TWSTRS total scores are analysed for all subjects of ITT population, while the Week 8 analysis excludes the scores for the 24 subjects who were not assessed.

Mean difference = difference in adjusted least squares mean (Dysport - Placebo).

Comparison groups	Dysport v Placebo

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 12

Statistical analysis description:

Baseline TWSTRS total scores are analysed for all subjects of ITT population, while the Week 12 analysis excludes the scores for the 27 subjects who were not assessed.

Mean difference = difference in adjusted least squares mean (Dysport - Placebo).

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	ANCOVA

Secondary: Change from Baseline in Subject’s VAS for Symptom Assessment

End point title	Change from Baseline in Subject’s VAS for Symptom Assessment

End point description:

Visual Analog Scale (VAS): The assessment was a continuous 100 mm horizonal line with a scale of 0 mm (no symptoms)to 100 mm (worst possible symptoms).
Week 4:Analysis was performed on ITT population which consisted of 55 subjects on Dysport and 61 Placebo.There were 5 subjects on Dysport and 8 on placebo who were not assessed on the change in subject VAS score for CD symptoms at Week 4.There was no imputation of missing VAS scores, so these 13 subjects were not taken into account.
Week 8:Analysis was performed on ITT population which consisted of 55 subjects receiving Dysport and 61 Placebo.There were 3 subjects for Dysport and 5 for placebo who were not assessed on the change in investigator VAS score at Week 4. As there was no imputation of missing VAS scores, these 8 subjects were not taken into account.
Week 12:Analysis was performed on ITT population which consisted of 55 subjects on Dysport and 61 on Placebo.Missing assessments at Week 8 were imputed using LOCF Methodolgy.

End point type	Secondary

End point timeframe:

Baseline (week 0), weeks 4, 8 and 12

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: points on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=50,53)	-24.2 (± 29.5)	-6.7 (± 20.8)		
Week 8 (N=55,57)	-24.6 (± 30)	-5.4 (± 25.4)		
Week 12 (N=55,57)	-14.4 (± 25.2)	-4.6 (± 23.3)		

Statistical analyses

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 4

Statistical analysis description:

Analysis at baseline (and on change at Week 4) excludes 4 subjects (and 13 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 8

Statistical analysis description:

Analysis at baseline (and on change at Week 8) excludes 4 subjects (and 4 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 12

Statistical analysis description:

Analysis at baseline (and on change at Week 12) excludes 4 subjects (and 4 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA

Secondary: Change from Baseline in Investigator’s VAS for Symptom Assessment

End point title	Change from Baseline in Investigator's VAS for Symptom Assessment

End point description:

Week 4: Analysis was performed on intention to treat population which consisted of 55 subjects receiving Dysport and 61 Placebo. There were 3 subjects for Dysport and 5 for placebo who were not assessed on the change in investigator VAS score at Week 4. As there was no imputation of missing VAS scores, these 8 subjects were not taken into account.
Week 8: Analysis was performed on intention to treat population which consisted of 55 subjects on Dysport and 61 on Placebo. Missing assessments at Week 8 were imputed using Last Observation Carried Forward (LOCF) methodology. There was no imputation for 3 patients with missing baseline and Week 4 values.
Week 12: Analysis was performed on intention to treat population which consisted of 55 subjects on Dysport and 61 on Placebo. Missing assessments at Week 12 were imputed using Last Observation Carried Forward (LOCF) methodology. There was no imputation for 3 patients with missing baseline, Week 4 and Week 8 values.

End point type	Secondary

End point timeframe:

Baseline (week 0), weeks 4, 8 and 12,

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: points on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=52,56)	-23.1 (± 22.1)	-9.1 (± 20.2)		
Week 8 (N=54,59)	-20.5 (± 22.7)	-5 (± 21.3)		
Week 12 (N=54,59)	-8.5 (± 18.9)	-5.8 (± 15.8)		

Statistical analyses

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 4

Statistical analysis description:

Analysis at baseline (and on change at Week 4) excludes 3 subjects (and 8 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 8

Statistical analysis description:

Analysis at baseline (and on change at Week 8) excludes 3 subjects (and 3 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 12

Statistical analysis description:

Analysis at baseline (and on change at Week 12) excludes 3 subjects (and 3 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	ANCOVA

Secondary: Change from Baseline in SF-36 Scores

End point title	Change from Baseline in SF-36 Scores

End point description:

Mental and Physical Health Summaries (ITT Population)
SF-36 is a Quality of Life scale comprising eight individual domains. The QoL score for each domain is on a scale from 0 (worst health possible) to 100 (best health possible). SF-36 Mental Health Summary Score is derived from four individual domains (vitality, social functioning, role limitations due to emotional problems and mental health).
SF-36 Physical Health Summary Score is derived from four individual domains (physical functioning, role physical, bodily pain and general health).
MHS and PHS: Analysis was performed on intention to treat population which consisted of 55 subjects on Dysport and 61 on Placebo. There were 13 subjects on Dysport and 24 on placebo who were not assessed on the change in mental and physical health summary at Week 8. There was no imputation of missing scores, so these 37 subjects were not taken into account.

End point type	Secondary

End point timeframe:

Baseline (week 0) and at week 8

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: points on a scale				
arithmetic mean (standard deviation)				
Week 8: Mental Health Summary (N=42,37)	4.11 (± 9.18)	2.48 (± 8.12)		
Week 8: Physical Health Summary (N=42,37)	4.37 (± 5.46)	-0.64 (± 6.41)		

Statistical analyses

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 8

Statistical analysis description:

Mental Health Summary (MHS)
Analysis at baseline (and on change at Week 8) excludes 3 subjects (and 37 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	ANCOVA

Statistical analysis title	Treatment Difference (Dysport & Placebo) - Week 8

Statistical analysis description:

Physical Health Summary (PHS)
Analysis at baseline (and on change at Week 8) excludes 3 subjects (and 37 subjects respectively) of ITT population who were not assessed. Mean difference=difference in adjusted least squares mean (Dysport-placebo)

Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA

Secondary: Number of Subjects Considered by the Investigator to be Overall Treatment Successes

End point title	Number of Subjects Considered by the Investigator to be Overall Treatment Successes

End point description:

Overall treatment success was defined by a global efficacy assessment of “better” or “much better” and a global safety assessment of no worse than “moderate”.

End point type	Secondary

End point timeframe:

At week 12

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: participants	32	10		

Statistical analyses

Statistical analysis title	Dysport - Placebo
Comparison groups	Dysport v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Odds Ratio

Notes:

[1] - The odds ratio represents the odds of success on Dysport versus Placebo stratified for strata and country

Other pre-specified: Number of Subjects with Adverse Event

End point title	Number of Subjects with Adverse Event

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 12 Months

End point values	Dysport	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	61		
Units: Number of subjects				
number (not applicable)				
Any adverse event	26	27		
Any treatment related adverse event	12	9		
Any severe adverse event	4	4		
Any severe treatment related adverse event	4	2		
Any serious adverse event	0	1		
Any adverse events leading to withdrawal	0	0		
Adverse event leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 Months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0
Reporting groups	
Reporting group title	Dysport
Reporting group description:	
A single dose of Dysport was administered by intramuscular injection to a maximum of four clinically indicated muscles. The total dose was 500 Dysport units in a single dosing session	
Reporting group title	Placebo
Reporting group description:	
A single dose of 500 units of placebo by intramuscular injection	

Serious adverse events	Dysport	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dysport	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 55 (20.00%)	5 / 61 (8.20%)	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	3 / 55 (5.45%)	2 / 61 (3.28%)	
occurrences (all)	3	2	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	5 / 55 (9.09%)	0 / 61 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 61 (4.92%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2006	Changes were mostly administrative, but also included an update to the Subject Informed Consent form, providing further information on the potential for Adverse Event (AEs) due to study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported