



Clinical trial results:

A phase III, randomised, double blind and open label phase, active and placebo controlled study comparing the short term efficacy of two formulations of clostridium botulinum type A toxin (Dysport and Dysport NG) to placebo, and assessing the short and long term efficacy and safety of Dysport NG following repeated treatments of subjects with cervical dystonia (CD).

Summary

EudraCT number	2010-019907-43
Trial protocol	PT CZ DE BE AT HU
Global end of trial date	04 June 2013

Results information

Result version number	v1 (current)
This version publication date	02 June 2016
First version publication date	02 June 2016

Trial information

Trial identification

Sponsor protocol code	Y-52-52120-134
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01261611
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2012
Global end of trial reached?	Yes
Global end of trial date	04 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objectives will be assessed in terms of improvement of the subject's CD at a pre-defined time point after treatment. The primary study objectives are to demonstrate the superiority of Dysport NG to placebo in terms of efficacy and to test the non-inferior efficacy of Dysport NG, when compared to Dysport, in CD subjects. In addition to testing for the primary study objectives, the superiority in terms of efficacy of Dysport versus placebo, will be assessed.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

A large body of evidence demonstrates the safety and efficacy of Dysport across several clinical indications. This study was the first use of Dysport NG in humans with CD. The active substance (BTX-A-HAC) in Dysport NG was the same as in the currently marketed Dysport product and had the same mechanism of action. Dysport NG was, therefore, expected to have the same efficacy and safety profile in humans as Dysport, with the advantage of eliminating the potential risk of transmission of infective agents, by the substitution of plant and synthetic products for human and animal-derived products. However, due to the change of excipient, thorough assessment of the safety and efficacy of Dysport NG is necessary.

Previous clinical studies indicate that the maximum effect of Dysport and maximum improvements in CD are observed approximately 4 weeks post treatment, after which there is a gradual return to baseline disease status. The Week 4 follow up visit after the first treatment cycle was therefore, chosen as the primary time point of interest.

Retreatment is necessary in order to maintain the beneficial effect and the long term treatment of CD. Previously conducted long term studies demonstrate the maintenance of the therapeutic effect of Dysport following repeated treatments, with a favourable short and long term safety and immunogenicity profile.

Actual start date of recruitment	27 April 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	Australia: 2
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	Poland: 68

Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 58
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Hungary: 44
Worldwide total number of subjects	369
EEA total number of subjects	269

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)	328
From 65 to 84 years	40
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients recruited at 61 centres in Australia, Austria, Belgium, Czech Republic, France, Germany, Hungary, Poland, Portugal, Russia and Ukraine.

Pre-assignment

Screening details:

382 subjects screened, 369 randomised due to 13 screen failures.

Period 1

Period 1 title	Treatment Cycle 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Dysport NG
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Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

500U (1ml) administered as intramuscular injection on day 1 of treatment cycle 1.

Arm title	Dysport
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Arm description:

1 treatment cycle of Dysport

Arm type	Active comparator
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 500U (1ml) injected as intramuscular injection on day 1 of treatment cycle 1.

Arm title	Placebo
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Arm description:

1 treatment cycle of placebo.

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

Dosage and administration details:

1ml administered as, intramuscular injection on day 1 of treatment cycle 1.

Number of subjects in period 1	Dysport NG	Dysport	Placebo
Started	156	159	54
Completed	152	156	52
Not completed	4	3	2
Protocol violation	-	-	2
Adverse event	-	1	-
Withdrawal by Subject	3	2	-
Lost to follow-up	1	-	-

Period 2

Period 2 title	Treatment Cycle 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dysport NG
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Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

500U (1ml) administered as intramuscular injection on day 1 of treatment cycle 2.

Number of subjects in period 2^[1]	Dysport NG
Started	359
Completed	346
Not completed	13
Protocol Violations	2
Not otherwise specified	2
Withdrawal by Subject	4
Completed study	4
Adverse Events	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of 360 subjects who completed double blind period (Dysport NG / Dysport / Placebo arms) 359 subjects entered open label period (only one arm: Dysport NG). One subject was never retreated and then stayed at cycle 1 during all the study.

Period 3

Period 3 title	Treatment Cycle 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dysport NG
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Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

250U (0.5ml), 500U (1ml) or 750U (1.5ml) administered as intramuscular injection on day 1 of treatment cycle 3.

Number of subjects in period 3	Dysport NG
Started	346
Completed	316
Not completed	30
Lost to Follow-up	1
Withdrawal by Subject	4
Completed study	24

Adverse Events	1
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Period 4

Period 4 title	Treatment Cycle 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dysport NG
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Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

250U (0.5ml), 500U (1ml), 750U (1.5ml) or 1000U (2ml) administered as intramuscular injection on day 1 of treatment cycle 4.

Number of subjects in period 4	Dysport NG
Started	316
Completed	220
Not completed	96
Lost to Follow-up	2
Not otherwise specified	3
Withdrawal by Subject	3
Adverse Events	1
Completed study	87

Period 5

Period 5 title	Treatment Cycle 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dysport NG
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Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

250U (0.5ml), 500U (1ml), 750U (1.5ml) or 1000U (2ml) administered as intramuscular injection on day 1 of treatment cycle 5.

Number of subjects in period 5	Dysport NG
Started	220
Completed	217
Not completed	3
Lost to Follow-up	1
Withdrawal by Subject	1
Adverse Events	1

Baseline characteristics

Reporting groups

Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport
Reporting group description: 1 treatment cycle of Dysport	
Reporting group title	Placebo
Reporting group description: 1 treatment cycle of placebo.	

Reporting group values	Dysport NG	Dysport	Placebo
Number of subjects	156	159	54
Age categorical Units: Subjects			

Age continuous			
ITT population was all randomised subjects who received at least one injection of study treatment regardless of the amount of study treatment administered.			
Units: years			
arithmetic mean	51.6	49.1	49.7
standard deviation	± 12.4	± 12	± 10.8
Gender categorical			
ITT population			
Units: Subjects			
Female	100	101	34
Male	56	58	20
Race (NIH/OMB)			
ITT population			
Units: Subjects			
Asian	0	0	1
Black or African American	0	1	1
White	154	154	49
Unknown or Not Reported	2	4	3
Time since diagnosis of CD, years			
Units: years			
arithmetic mean	7.13	6.88	6.25
standard deviation	± 7.95	± 7.49	± 7.31
Baseline TWSTRS score			
Units: unit on scale			
arithmetic mean	44.56	46.23	47.02
standard deviation	± 9.2	± 8.82	± 9.19

Reporting group values	Total		
Number of subjects	369		

Age categorical			
Units: Subjects			
Age continuous			
ITT population was all randomised subjects who received at least one injection of study treatment regardless of the amount of study treatment administered.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
ITT population			
Units: Subjects			
Female	235		
Male	134		
Race (NIH/OMB)			
ITT population			
Units: Subjects			
Asian	1		
Black or African American	2		
White	357		
Unknown or Not Reported	9		
Time since diagnosis of CD, years			
Units: years			
arithmetic mean			
standard deviation	-		
Baseline TWSTRS score			
Units: unit on scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport
Reporting group description: 1 treatment cycle of Dysport	
Reporting group title	Placebo
Reporting group description: 1 treatment cycle of placebo.	
Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Reporting group title	Dysport NG
Reporting group description: Up to 5 treatment cycles of Dysport NG	
Subject analysis set title	Dysport NG
Subject analysis set type	Intention-to-treat
Subject analysis set description: All doses	

Primary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score Following First Treatment Cycle

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score Following First Treatment Cycle
End point description: TWSTRS is comprised of three different components namely severity, disability and pain. There is an ordinal scale score and range for each component. Severity scores range from 0 (absence of severity) to 35 (maximum severity), Disability scores range from 0 (no disability) to 30 (maximum disability) and pain scores range from 0 (no pain) to 20 (maximum pain). TWSTRS total score is the sum of the 3 component scores ranging from 0 to a maximum of 85. Analysis based on number of subjects in the Intent to Treat (ITT) population.	
End point type	Primary
End point timeframe: Baseline and Week 4	

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-12.46 (-14.3 to -10.62)	-13.99 (-15.78 to -12.21)	-3.93 (-6.74 to -1.12)	

Statistical analyses

Statistical analysis title	LS mean difference - Dysport NG vs Placebo
Comparison groups	Dysport NG v Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	ANCOVA

Notes:

[1] - An ANCOVA on the change from baseline with treatment, baseline TWSTRS total score, BTX status at baseline and pooled centre as explanatory variables had been performed.

Statistical analysis title	LS mean difference - Dysport vs Placebo
Comparison groups	Dysport v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001
Method	ANCOVA

Notes:

[2] - An ANCOVA on the change from baseline with treatment, baseline TWSTRS total score, BTX status at baseline and pooled centre as explanatory variables had been performed.

Statistical analysis title	LS mean difference - Dysport NG vs Dysport
Comparison groups	Dysport NG v Dysport
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	LS mean difference
Point estimate	1.532
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.819
upper limit	3.883

Notes:

[3] - An ANCOVA on the change from baseline with treatment, baseline TWSTRS total score, BTX status at baseline and pooled centre as explanatory variables had been performed. The non-inferiority margin was 3 points.

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity Subscale Score Following First Treatment Cycle

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis
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End point description:

TWSTRS Severity scores range from 0 (absence of severity) to 35 (maximum severity).

Analysis based on number of subjects in the Intent to Treat (ITT) population.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-6.2 (-7 to -5.4)	-6.6 (-7.3 to -5.8)	-1.9 (-3.1 to -0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Disability Subscale Score Following First Treatment Cycle

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Disability Subscale Score Following First Treatment Cycle
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End point description:

TWSTRS Disability scores range from 0 (no disability) to 30 (maximum disability).

Analysis based on number of subjects in the Intent to Treat (ITT) population.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.3 (-4.1 to -2.6)	-3.9 (-4.7 to -3.2)	-0.8 (-1.9 to 0.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Pain Subscale Score Following First Treatment Cycle

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Pain Subscale Score Following First Treatment Cycle
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End point description:

TWSTRS Pain scores range from 0 (no pain) to 20 (maximum pain).

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.1 (-3.7 to -2.51)	-3.44 (-4.03 to -2.86)	-1.21 (-2.12 to -0.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject Visual Analogue Score (VAS) for Pain From Cervical Dystonia Following First Treatment Cycle

End point title	Change From Baseline in Subject Visual Analogue Score (VAS) for Pain From Cervical Dystonia Following First Treatment Cycle
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End point description:

The assessment was made on a continuous 100-mm horizontal line with a scale range of 0 mm (no pain) to 100 mm (worst possible pain).

Analysis based on number of subjects in the Intent to Treat (ITT) population.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-14.8 (-19 to -10.7)	-19.2 (-23.3 to -15.2)	-3.4 (-9.8 to 3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject Visual Analogue Score (VAS) for Symptoms of Cervical Dystonia Following First Treatment Cycle

End point title	Change From Baseline in Subject Visual Analogue Score (VAS) for Symptoms of Cervical Dystonia Following First Treatment Cycle
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End point description:

The assessment was made on a continuous 100-mm horizontal line with a scale range of 0 mm (no symptoms) to 100mm (worst possible symptoms).

Analysis based on number of subjects in the Intent to Treat (ITT) population.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	159	54	
Units: units on a scale				
least squares mean (confidence interval 95%)	-18.7 (-22.7 to -14.7)	-23.6 (-27.5 to -19.7)	-3.3 (-9.4 to 2.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Treatment Responders Following First Treatment Cycle

End point title	Percentage of Treatment Responders Following First Treatment Cycle
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End point description:

Analysis based on number of subjects in the Intent to Treat (ITT) population.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

End point values	Dysport NG	Dysport	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	156	54	
Units: percentage of participants				
number (not applicable)	45.8	55.8	20.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score for Treatment Cycles 2 to 5

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score for Treatment Cycles 2 to 5
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End point description:

The change in TWSTRS total score is the score at week 4 minus the score at baseline.

Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.

End point type	Secondary
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End point timeframe:

Treatment cycle Baseline and Week 4

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Cycle 2 (n=359)	-15.35 (-16.36 to -14.34)			
Cycle 3 (n=346)	-14.85 (-15.86 to -13.84)			
Cycle 4 (n=316)	-15.58 (-16.61 to -14.55)			
Cycle 5 (n=220)	-15.28 (-16.42 to -14.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity Score for Treatment Cycles 2 to 5

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity Score for Treatment Cycles 2 to 5
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End point description:

TWSTRS Severity scores range from 0 (absence of severity) to 35 (maximum severity).

Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.

End point type	Secondary
End point timeframe:	
Treatment cycle Baseline and Week 4	

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	349			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Cycle 2 (n=359)	-7.2 (-7.6 to -6.7)			
Cycle 3 (n=346)	-7.1 (-7.5 to -6.6)			
Cycle 4 (n=316)	-7.3 (-7.7 to -6.8)			
Cycle 5 (n=220)	-7 (-7.5 to -6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Disability Score for Treatment Cycles 2 to 5

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Disability Score for Treatment Cycles 2 to 5
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End point description:

TWSTRS Disability scores range from 0 (no disability) to 30 (maximum disability).

Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.

End point type	Secondary
End point timeframe:	
Treatment cycle Baseline and Week 4	

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				

Cycle 2 (n=359)	-4.7 (-5.2 to -4.3)			
Cycle 3 (n=346)	-4.6 (-5 to -4.1)			
Cycle 4 (n=316)	-5 (-5.5 to -4.5)			
Cycle 5 (n=220)	-4.9 (-5.5 to -4.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Pain Subscale Score for Treatment Cycles 2 to 5

End point title	Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Pain Subscale Score for Treatment Cycles 2 to 5
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End point description:

TWSTRS Pain scores range from 0 (no pain) to 20 (maximum pain).

Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.

End point type	Secondary
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End point timeframe:

Treatment cycle Baseline and Week 4

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Cycle 2 (n=359)	-3.45 (-3.8 to -3.1)			
Cycle 3 (n=346)	-3.21 (-3.57 to -2.85)			
Cycle 4 (n=316)	-3.34 (-3.69 to -2.98)			
Cycle 5 (n=220)	-3.41 (-3.79 to -3.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject Visual Analogue Score (VAS) for Pain From Cervical Dystonia for Treatment Cycles 2 to 5

End point title	Change From Baseline in Subject Visual Analogue Score (VAS)
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End point description:

The assessment was made on a continuous 100-mm horizontal line with a scale range of 0 mm (no pain) to 100 mm (worst possible pain).

End point type	Secondary
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End point timeframe:

Treatment cycle Baseline and Week 4

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Cycle 2 (n=359)	-20.1 (-22.5 to -17.6)			
Cycle 3 (n=346)	-17.8 (-20.4 to -15.2)			
Cycle 4 (n=316)	-18 (-20.5 to -15.4)			
Cycle 5 (n=220)	-16.1 (-19.3 to -12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject Visual Analogue Score (VAS) for Symptoms of Cervical Dystonia for Treatment Cycles 2 to 5

End point title	Change From Baseline in Subject Visual Analogue Score (VAS) for Symptoms of Cervical Dystonia for Treatment Cycles 2 to 5
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End point description:

The assessment was made on a continuous 100-mm horizontal line with a scale of 0 mm (no symptoms) to 100 mm (worst possible symptoms).

Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.

End point type	Secondary
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End point timeframe:

Treatment cycle Baseline and Week 4

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Cycle 2 (n=359)	-24 (-26.4 to -21.7)			
Cycle 3 (n=346)	-18.9 (-21.4 to -16.4)			
Cycle 4 (n=316)	-21 (-23.5 to -18.5)			
Cycle 5 (n=220)	-18.2 (-21.2 to -15.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Treatment Responders for Treatment Cycles 2 to 5

End point title	Percentage of Treatment Responders for Treatment Cycles 2 to 5
End point description:	
Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle.	
End point type	Secondary
End point timeframe:	
Treatment cycle Baseline and Week 4	

End point values	Dysport NG			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: percentage of participants				
number (not applicable)				
Cycle 2 (n=359)	58.5			
Cycle 3 (n=346)	56.8			
Cycle 4 (n=316)	63.5			
Cycle 5 (n=220)	57.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 years

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Dysport NG, 250 U
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Reporting group description: -

Reporting group title	Dysport NG, 500 U
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Reporting group description: -

Reporting group title	Dysport NG, 750 U
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Reporting group description: -

Reporting group title	Dysport NG, 1000 U
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Reporting group description: -

Reporting group title	Dysport, 500 U
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Dysport NG, 250 U	Dysport NG, 500 U	Dysport NG, 750 U
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	16 / 363 (4.41%)	3 / 210 (1.43%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			

subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paget-Schroetter syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			

subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Endocrine disorders			
Thyroid cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Proctitis infectious			
subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal abscess			

subjects affected / exposed	0 / 4 (0.00%)	1 / 363 (0.28%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 363 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dysport NG, 1000 U	Dysport, 500 U	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	3 / 156 (1.92%)	0 / 55 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 57 (0.00%)	1 / 156 (0.64%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 156 (0.64%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	0 / 57 (0.00%)	1 / 156 (0.64%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			

subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paget-Schroetter syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 156 (0.00%)	0 / 55 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 57 (1.75%)	0 / 156 (0.00%)	0 / 55 (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
Rectal perforation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 57 (0.00%)	1 / 156 (0.64%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroid cyst			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Proctitis infectious			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal abscess			
subjects affected / exposed	0 / 57 (0.00%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 57 (0.00%)	1 / 156 (0.64%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dysport NG, 250 U	Dysport NG, 500 U	Dysport NG, 750 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	59 / 363 (16.25%)	29 / 210 (13.81%)
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	38 / 363 (10.47%)	20 / 210 (9.52%)
occurrences (all)	0	54	25
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 4 (25.00%)	11 / 363 (3.03%)	13 / 210 (6.19%)
occurrences (all)	1	15	14
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	21 / 363 (5.79%)	9 / 210 (4.29%)
occurrences (all)	0	26	9

Non-serious adverse events	Dysport NG, 1000 U	Dysport, 500 U	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 57 (12.28%)	15 / 156 (9.62%)	1 / 55 (1.82%)
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	5 / 57 (8.77%)	11 / 156 (7.05%)	0 / 55 (0.00%)
occurrences (all)	5	11	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	6 / 57 (10.53%)	0 / 156 (0.00%)	0 / 55 (0.00%)
occurrences (all)	6	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 57 (3.51%)	4 / 156 (2.56%)	1 / 55 (1.82%)
occurrences (all)	2	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2012	Protocol Amendment 5 (Substantial): The protocol was amended to update the contact information for the Sponsor's Medical and Clinical contacts, remove the pharmacovigilance/emergency contact details from the US, to replace Ipsen Pharma with Kymos Pharma as a CRO for processing binding antibody samples and ensure consistency across all studies with regard to the IB used for assessment of expectedness.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported