



Clinical trial results:

A phase III, multicentre, prospective, open label extension study to assess the long term safety and efficacy of repeated treatment of Dysport intramuscular injections used for the treatment of upper limb spasticity in adult subjects with spastic hemiparesis due to stroke or traumatic brain injury

Summary

EudraCT number	2010-019162-83
Trial protocol	BE CZ SK PL IT HU
Global end of trial date	09 December 2014

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	Y-52-52120-148
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	24 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2014
Global end of trial reached?	Yes
Global end of trial date	09 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 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	Russian Federation: 19
Country: Number of subjects enrolled	United States: 101
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	258
EEA total number of subjects	138

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)	204
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was designed as a multicentre study and included 34 investigational sites in Belgium, the Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia and the United States of America (US) that included at least one subject.

Pre-assignment

Screening details:

Of 227 subjects who completed Study 145, 4 subjects entered observational phase and never received open label treatment with Dysport in Study 148. Remaining 223 subjects were eligible for retreatment and were rolled over to study 148. In addition, of 34 de novo subjects screened, 31 subjects were eligible and included in this study.

Period 1

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

Arms

Arm title	Total Dysport
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Arm description:

Of 227 subjects who completed study 145, 223 Subjects rolled over to this study (4 subjects entered an observational phase at the end of Study 145). Of 34 subjects screened for De-Novo study, only 31 were treated with open label Botulinum type A toxin (Dysport) dose of 1000 Units (U) in Cycle 1 and from Cycle 2 onwards Dysport 500 / 1000 / 1500 U

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

Dosage and administration details:

A vials containing 500 U of botulinum toxin type A reconstituted with sodium chloride 5.0 ml for 500 U and 1000 U Dysport, and 7.5ml for 1500U Dysport Intramuscular injection.

Number of subjects in period 1 ^[1]	Total Dysport
Started	254
Cycle 1	254
Cycle 2	229
Cycle 3	175 ^[2]
Cycle 4	81 ^[3]
Cycle 5	11 ^[4]

Completed	222
Not completed	32
Observational phase	1
Adverse Event	5
Other	5
Consent withdrawn	18
Lack of efficacy	3

Notes:

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

Justification: Worldwide data is reported for safety population of 258 subjects and baseline data is reported for 254 subjects for ITT population (this excludes 4 subjects who entered observational phase in study 148 and never received open label treatment with Dysport in Study 148).

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

Justification: Of 254 subjects who started in cycle 1, only 175 subjects entered cycle 3. (24 subjects withdrew at cycles 1 & 2, 54 subjects ended study after 12 months follow-up and 1 subject entered observational phase)

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

Justification: Of 254 subjects who started in cycle 1, only 81 subjects entered cycle 4. (30 subjects withdrew at cycles 1, 2 & 3, 142 subjects ended study after 12 months follow-up and 1 subject entered observational phase)

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

Justification: Of 254 subjects who started in cycle 1, only 11 subjects entered cycle 5. (31 subjects withdrew at cycles 1, 2, 3 & 4, 211 subjects ended study after 12 months follow-up and 1 subject entered observational phase)

Baseline characteristics

Reporting groups

Reporting group title	Total Dysport
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Reporting group description:

Of 227 subjects who completed study 145, 223 Subjects rolled over to this study (4 subjects entered an observational phase at the end of Study 145). Of 34 subjects screened for De-Novo study, only 31 were treated with open label Botulinum type A toxin (Dysport) dose of 1000 Units (U) in Cycle 1 and from Cycle 2 onwards Dysport 500 / 1000 / 1500 U

Reporting group values	Total Dysport	Total	
Number of subjects	254	254	
Age categorical			
Units: Subjects			
<65 years	201	201	
>=65 years	53	53	
Age continuous			
Units: years			
arithmetic mean	52.4		
standard deviation	± 14	-	
Gender categorical			
Units: Subjects			
Female	91	91	
Male	163	163	
Race			
Units: Subjects			
Asian	7	7	
Black / African American	27	27	
Caucasian / White	218	218	
Multiple	2	2	
Ethnicity			
Units: Subjects			
Hispanic or Latino	16	16	
Not Hispanic or Latino	238	238	

End points

End points reporting groups

Reporting group title	Total Dysport
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Reporting group description:

Of 227 subjects who completed study 145, 223 Subjects rolled over to this study (4 subjects entered an observational phase at the end of Study 145). Of 34 subjects screened for De-Novo study, only 31 were treated with open label Botulinum type A toxin (Dysport) dose of 1000 Units (U) in Cycle 1 and from Cycle 2 onwards Dysport 500 / 1000 / 1500 U

Primary: Assessment of the long term safety of Treatment Emergent Adverse Events

End point title	Assessment of the long term safety of Treatment Emergent Adverse Events ^[1]
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End point description:

TEAEs (treatment emergent adverse event)

AESIs (adverse event of special interest)

SAEs (serious adverse event)

Safety population are all enrolled subjects who provided informed consent to participate in this open label study.

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Number of subjects				
TEAEs: Cycle 1 (n=254)	102			
TEAEs: Cycle 2 (n=229)	62			
TEAEs: Cycle 3 (n=175)	47			
TEAEs: Cycle 4 (n=81)	11			
TEAEs: Cycle 5 (n=11)	2			
Treatment related TEAE: Cycle 1 (n=254)	18			
Treatment related TEAE: Cycle 2 (n=229)	8			
Treatment related TEAE: Cycle 3 (n=175)	5			
Treatment related TEAE: Cycle 4 (n=81)	2			
Treatment related TEAE: Cycle 5 (n=11)	0			
Severe TEAEs: Cycle 1 (n=254)	14			
Severe TEAEs: Cycle 2 (n=229)	8			
Severe TEAEs: Cycle 3 (n=175)	4			
Severe TEAEs: Cycle 4 (n=81)	1			

Severe TEAEs: Cycle 5 (n=11)	0			
TEAEs Leading to Withdrawal: Cycle 1 (n=254)	2			
TEAEs Leading to Withdrawal: Cycle 2 (n=229)	1			
TEAEs Leading to Withdrawal: Cycle 3 (n=175)	2			
TEAEs Leading to Withdrawal: Cycle 4 (n=81)	0			
TEAEs Leading to Withdrawal: Cycle 5 (n=11)	0			
AESIs: Cycle 1 (n=254)	2			
AESIs: Cycle 2 (n=229)	0			
AESIs: Cycle 3 (n=175)	0			
AESIs: Cycle 4 (n=81)	0			
AESIs: Cycle 5 (n=11)	0			
SAEs: Cycle 1 (n=254)	10			
SAEs: Cycle 2 (n=229)	6			
SAEs: Cycle 3 (n=175)	6			
SAEs: Cycle 4 (n=81)	1			
SAEs: Cycle 5 (n=11)	0			
Fatal SAEs: Cycle 1 (n=254)	1			
Fatal SAEs: Cycle 2 (n=229)	1			
Fatal SAEs: Cycle 3 (n=175)	1			
Fatal SAEs: Cycle 4 (n=81)	0			
Fatal SAEs: Cycle 5 (n=11)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in Diastolic and Systolic BP

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in Diastolic and Systolic BP ^[2]
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End point description:

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: mm Hg				
arithmetic mean (full range (min-max))				
Diastolic BP (n=238)	0 (-29 to 34)			

Systolic BP (n=238)	-2.8 (-63 to 41)			
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Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in Heart Rate

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in Heart Rate ^[3]
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End point description:

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: bpm				
arithmetic mean (full range (min-max))				
Heart rate (n=239)	2.5 (-28 to 30)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in RBC count

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in RBC count ^[4]
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End point description:

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Tera/L				
arithmetic mean (full range (min-max))				
RBC Count (n=219)	0.03 (-1.15 to 1.06)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in Haemoglobin and MCHC

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in Haemoglobin and MCHC ^[5]
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End point description:

MCHC (mean corpuscular haemoglobin concentration)

Haematology Variables

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: g/L				
arithmetic mean (full range (min-max))				
Haemoglobin (n=219)	-0.7 (-33 to 37)			
MCHC (n=219)	-0.8 (-26 to 34)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in Haematocrit

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in Haematocrit ^[6]
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End point description:
Haematology Variables

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: N/A				
arithmetic mean (full range (min-max))				
Haematocrit (n=219)	-0.0011 (-0.104 to 0.087)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in MCH

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in MCH ^[7]
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End point description:

MCH (mean corpuscular haemoglobin)

Haematology Variables

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: pg				
arithmetic mean (full range (min-max))				
MCH (n=219)	-0.33 (-5 to 4.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in MCV

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in MCV ^[8]
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End point description:

MCV (mean corpuscular volume)

Haematology Variables

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: fL				
arithmetic mean (full range (min-max))				
MCV (n=219)	-0.77 (-9.9 to 8.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in WBC count, Neutrophils, Lymphocytes and Platelets

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in WBC count, Neutrophils, Lymphocytes and Platelets ^[9]
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End point description:

WBC (white blood cell)

Haematology Variables

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Giga/L				
arithmetic mean (full range (min-max))				
WBC count (n=219)	0.04 (-6.5 to 5.2)			
Neutrophils (n=219)	0 (-6.8 to 5.6)			
Lymphocytes (n=219)	0.01 (-1.9 to 1.2)			
Platelets (n=214)	3.2 (-142 to 249)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from baseline to end of study (EOS)/early withdrawal in 12 lead Electrocardiogram (ECG)

End point title	Mean change from baseline to end of study (EOS)/early withdrawal in 12 lead Electrocardiogram (ECG) ^[10]
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End point description:

Safety population

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: milliseconds (ms)				
arithmetic mean (standard deviation)				
QT Duration - Baseline (n=233)	403.6 (± 31.9)			
QT Duration - Change from Baseline to EOS (n=210)	-6.3 (± 22.1)			
QTcF - Baseline (n=233)	417.8 (± 22.9)			
QTcF - Change from Baseline to EOS (n=210)	-1 (± 15.5)			
QTcB - Baseline (n=233)	425.6 (± 25.5)			
QTcB - Change from Baseline to EOS (n=210)	1.9 (± 20.2)			
QRS Duration - Baseline (n=235)	94.9 (± 15.3)			
QRS Duration - Change from Baseline to EOS (n=210)	-0.4 (± 6.4)			
PR Duration - Baseline (n=233)	165.6 (± 25.4)			
PR Duration - Change from Baseline to EOS (n=210)	-0.3 (± 13.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in ALP, SGOT, SGPT and GGT

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in ALP, SGOT, SGPT and GGT ^[11]
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End point description:

ALP=alkaline phosphatase; GGT=gamma glutamyl transferase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase.

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: IU/L				
arithmetic mean (full range (min-max))				
ALP (n=226)	-0.6 (-39 to 83)			
SGOT (n=226)	1.4 (-32 to 45)			
SGPT (n=226)	1.2 (-81 to 57)			
GGT (n=226)	1.5 (-105 to 195)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in Total Bilirubin and Creatinine

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in Total Bilirubin and Creatinine ^[12]
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End point description:

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: µmol/L				
arithmetic mean (full range (min-max))				
Total Bilirubin (n=226)	-0.27 (-18.7 to 12.2)			
Creatinine (n=226)	-3.7 (-115 to 35)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline to End of Study/Early Withdrawal in BUN and Fasting Blood Glucose

End point title	Mean Change from Baseline to End of Study/Early Withdrawal in BUN and Fasting Blood Glucose ^[13]
End point description:	
BUN=blood urea nitrogen	
End point type	Primary
End point timeframe:	
Up to visit V20 (week 52)	

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: mmol/L				
arithmetic mean (full range (min-max))				
BUN (n=226)	-0.033 (-12.85 to 8.93)			
Fasting Blood Glucose (n=101)	0.132 (-3.66 to 7.94)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from baseline to end of study/early withdrawal in 12 lead ECG - Heart Rate

End point title	Mean change from baseline to end of study/early withdrawal in 12 lead ECG - Heart Rate ^[14]
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End point description:

Safety population

EOS= End of Study

bpm = beats per minute

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: bpm				
arithmetic mean (standard deviation)				
Baseline (n=243)	68.2 (± 11.3)			
Change from Baseline to EOS (n=226)	2.7 (± 10.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with Botulinum Toxin A Binding and Neutralising Putative Antibodies

End point title	Number of subjects with Botulinum Toxin A Binding and Neutralising Putative Antibodies ^[15]
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End point description:

Number of subjects who were positive / Negative at baseline and positive post baseline for binding and neutralizing

Safety population

+ve = positive

-ve = negative

End point type	Primary
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End point timeframe:

Up to visit V20 (week 52)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Number of subjects				
+ve at baseline – binding	5			
-ve at baseline & +ve post baseline-binding	20			
+ve at baseline – neutralizing	4			
-ve at baseline & +ve post baseline-Neutralizing	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline MAS in the overall PTMG for upper limb

End point title	Mean change from baseline MAS in the overall PTMG for upper limb
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End point description:

The MAS consists of 6 grades: 0, 1, 1+, 2, 3, or 4 that can be applied to muscles of both the upper and lower limbs. The MAS was applied by the rater by stretching the joint through its full available range over 1 second.

The intention to treat (ITT) population was defined as all enrolled subjects who received at least one injection of study medication in this open label extension study.

PTMG (Primary Targeted Muscle Group)
MAS (Modified Ashworth Scale Score)

End point type	Secondary
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End point timeframe:

At week 4 (visit 2)

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Unit in scale				
arithmetic mean (standard deviation)				
Study 145 (n=152)	-1.2 (± 1)			
Cycle 1 (n=252)	-1.4 (± 1.1)			
Cycle 2 (n=226)	-1.6 (± 1.2)			
Cycle 3 (n=163)	-1.5 (± 1.1)			
Cycle 4 (n=80)	-1.4 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with at least one grade reduction in MAS for overall PTMG

End point title	Percentage of subjects with at least one grade reduction in MAS for overall PTMG
End point description: ITT population.	
End point type	Secondary
End point timeframe: At week 4	

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Percentage of subjects				
number (not applicable)				
One Grade Reduction from Baseline:Study 145(n=152)	75			
One Grade Reduction from Baseline: Cycle 1(n=254)	77.6			
One Grade Reduction from Baseline: Cycle 2(n=229)	79.5			
One Grade Reduction from Baseline: Cycle 3(n=175)	77.1			
One Grade Reduction from Baseline: Cycle 4(n=81)	75.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians Global Assessment of Treatment Response

End point title	Physicians Global Assessment of Treatment Response
End point description: Physician's Global Assessment is 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	
End point type	Secondary
End point timeframe: At week 4	

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Study 145 (n=151)	1.5 (± 1.1)			
Cycle 1 (n=253)	1.7 (± 1)			
Cycle 2 (n=227)	1.9 (± 1)			
Cycle 3 (n=167)	1.9 (± 1)			
Cycle 4 (n=80)	2 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Disability Assessment Scale Score for the Principal Target of Treatment

End point title	Mean change from baseline in Disability Assessment Scale Score for the Principal Target of Treatment
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End point description:

Disability Assessment Scale is a 4-point scale, the extent of functional impairment in four functional domains (dressing, hygiene, limb position and pain) was rated as follows: 0=no disability, 1=mild disability (noticeable but does not interfere significantly with normal activities), 2=moderate disability (normal activities require increased effort and/or assistance) and 3=severe disability (normal activities limited).

ITT population

End point type	Secondary
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End point timeframe:

At week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Scale in units				
arithmetic mean (standard deviation)				
Study 145 (n=151)	-0.7 (± 0.8)			
Cycle 1 (n=252)	-0.9 (± 0.8)			
Cycle 2 (n=226)	-1.1 (± 0.8)			
Cycle 3 (n=166)	-1.1 (± 0.8)			
Cycle 4 (n=80)	-1.1 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with at least one grade reduction in DAS for PTT

End point title	Percentage of subjects with at least one grade reduction in DAS for PTT
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End point description:

ITT population

DAS (Disability Assessment Scale)

PTT (Principal Target of Treatment)

End point type	Secondary
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End point timeframe:

At week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
number (not applicable)				
PTT: Study 145 (n=152)	55.3			
PTT: Cycle 1 (n=254)	68.5			
PTT: Cycle 2 (n=229)	75.1			
PTT: Cycle 3 (n=175)	73.7			
PTT: Cycle 4 (n=81)	74.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline for X (angle of spasticity) of the TS in extrinsic finger flexors as PTMG

End point title	Mean change from baseline for X (angle of spasticity) of the TS in extrinsic finger flexors as PTMG
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End point description:

The TS was used to measure spasticity in the shoulder extensors, elbow flexors, wrist flexors and extrinsic finger flexors. Assessments were made at slow (V1) and fast (V3) speeds of stretch. The angle of arrest at slow speed (XV1), the angle of catch at fast speed (XV3) and the spasticity grade (Y) at fast speed were recorded in the eCRF. The spasticity angle was automatically calculated in the eCRF as the difference between the angle of arrest at slow speed (XV1) and the angle of catch at fast speed (XV3). The spasticity grade (Y) is an ordinal variable that grades the intensity of the muscle reaction to fast stretch.

TS (Tardieu Scale)

PTMG (Primary Targeted Muscle group)

ITT population

End point type	Secondary
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End point timeframe:

At week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Angle of Spasticity (X): Study 145 (n=88)	-23.5 (± 48.3)			
Angle of Spasticity (X): Cycle 1 (n=144)	-33.5 (± 54)			
Angle of Spasticity (X): Cycle 2 (n=133)	-33.9 (± 55.9)			
Angle of Spasticity (X): Cycle 3 (n=98)	-43.3 (± 57.8)			
Angle of Spasticity (X): Cycle 4 (n=56)	-35.9 (± 48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline for X (angle of spasticity) of the TS in elbow flexors as PTMG

End point title	Mean change from baseline for X (angle of spasticity) of the TS in elbow flexors as PTMG
End point description:	
ITT population	
End point type	Secondary
End point timeframe:	
At week 4	

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Angle of Spasticity (X): Study 145 (n=43)	-25.7 (± 24.5)			
Angle of Spasticity (X): Cycle 1 (n=69)	-26.4 (± 24.9)			
Angle of Spasticity (X): Cycle 2 (n=59)	-31 (± 27.7)			
Angle of Spasticity (X): Cycle 3 (n=42)	-33.3 (± 26)			
Angle of Spasticity (X): Cycle 4 (n=14)	-46.4 (± 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline for X (angle of spasticity) of the TS in wrist flexors as PTMG

End point title	Mean change from baseline for X (angle of spasticity) of the TS in wrist flexors as PTMG
End point description: ITT population	
End point type	Secondary
End point timeframe: At week 4	

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Angle of Spasticity (X): Study 145 (n=21)	-19.8 (± 30)			
Angle of Spasticity (X): Cycle 1 (n=39)	-23.3 (± 32.5)			
Angle of Spasticity (X): Cycle 2 (n=34)	-28.8 (± 37.1)			
Angle of Spasticity (X): Cycle 3 (n=23)	-21.7 (± 35.2)			
Angle of Spasticity (X): Cycle 4 (n=10)	-13.5 (± 29.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in active range of motion (AROM) in the 3 possible PTMGs

End point title	Mean change from baseline in active range of motion (AROM) in the 3 possible PTMGs
End point description: ITT population	
The active range of extension achieved by the subjects moving each joint without assistance was measured at baseline and at all subsequent study visits during each cycle. A goniometer was used for measurements in the elbow and wrist flexors but not for measurements in the extrinsic finger flexors.	
End point type	Secondary
End point timeframe: At week 4	

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Extrinsic Finger Flexors: Study 145 (n=88)	19.8 (± 28.8)			

Extrinsic Finger Flexors: Cycle 1 (n=144)	31.3 (± 40.9)			
Extrinsic Finger Flexors: Cycle 2 (n=133)	34.4 (± 45)			
Extrinsic Finger Flexors: Cycle 3 (n=98)	33.5 (± 47.1)			
Extrinsic Finger Flexors: Cycle 4 (n=56)	38 (± 53.4)			
Elbow Flexors: Study 145 (n=43)	14.3 (± 22.3)			
Elbow Flexors: Cycle 1 (n=69)	10.7 (± 25.5)			
Elbow Flexors: Cycle 2 (n=59)	17.6 (± 23.3)			
Elbow Flexors: Cycle 3 (n=42)	14.5 (± 24.1)			
Elbow Flexors: Cycle 4 (n=14)	13.6 (± 20.6)			
Wrist Flexors: Study 145 (n=21)	21.8 (± 24.6)			
Wrist Flexors: Cycle 1 (n=39)	17.3 (± 28.6)			
Wrist Flexors: Cycle 2 (n=34)	23 (± 32.7)			
Wrist Flexors: Cycle 3 (n=23)	22 (± 30.9)			
Wrist Flexors: Cycle 4 (n=10)	3 (± 25.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Ease of Applying a Splint

End point title	Mean change from baseline in Ease of Applying a Splint
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End point description:

The ease of applying a splint was evaluated on a 6-point scale (0: no splint needed, -1: splint needed and applied with no difficulty, -2: splint needed and applied with mild difficulty, -3: splint needed and applied with moderate difficulty, -4: splint needed and applied with severe difficulty, -5: splint needed, but unable to apply).

ITT population

End point type	Secondary
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End point timeframe:

At week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Study 145 (n=149)	-0.3 (± 1)			
Cycle 1 (n=218)	-0.4 (± 1.1)			
Cycle 2 (n=196)	-0.4 (± 1.3)			
Cycle 3 (n=137)	-0.4 (± 1.4)			
Cycle 4 (n=56)	-0.4 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Modified Frenchay Scale (MFS)

End point title	Mean change from baseline in Modified Frenchay Scale (MFS)
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End point description:

ITT population

The MFS was used to measure upper limb active function. Each subject was videotaped while performing specific tasks. The videos were sent to a central provider and were read and scored by two independent readers blinded to the timing of the video and to treatment. These central assessments were used for the analysis of efficacy endpoints

End point type	Secondary
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End point timeframe:

At week 4

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units in scale				
arithmetic mean (standard deviation)				
Study 145 (n=152)	0.21 (± 0.53)			
Cycle 1 (n=219)	0.4 (± 0.77)			
Cycle 2 (n=190)	0.51 (± 0.8)			
Cycle 3 (n=138)	0.44 (± 0.82)			
Cycle 4 (n=56)	0.4 (± 0.75)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean Change from Baseline in Short Form (36) Health Survey (SF-36) Quality of Life
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End point description:

ITT population

Subjects were asked to complete the SF 36 questionnaires prior to the study treatment at baseline and at the end of study/early withdrawal visit. The SF 36 is a generic nonpreference based health status measure. This instrument assessed subject health across eight dimensions, which are specific health domains such as physical functioning, social functioning and vitality.

Physical Component Summary (PCS); Mental Component Summary (MCS); Change = Change from Baseline

End point type	Secondary
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End point timeframe:

Baseline (Cycle 1 Day 1) and Final visit (up to year 1)

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units on scale				
arithmetic mean (standard deviation)				
PCS Baseline - Double-blind study 145 (n=145)	37.89 (± 8.85)			
PCS Change - Double-blind study 145 (n=137)	0.95 (± 6.04)			
PCS Baseline - Open label study 148 (n=244)	37.49 (± 8.94)			
PCS Change - Open label study 148 (n=229)	1.07 (± 6.76)			
MCS Baseline - Double-blind study 145 (n=145)	47.77 (± 13.43)			
MCS Change - Double-blind study 145 (n=137)	0.41 (± 10.05)			
MCS Baseline - Open label study 148 (n=244)	46.88 (± 13.09)			
MCS Change - Open label study 148 (n=229)	0.96 (± 11.11)			

Statistical analyses

No statistical analyses for this end point

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

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

ITT population

Subjects were asked to complete the EQ 5D Quality of Life (QoL) questionnaires prior to the study treatment at baseline and at the end of study/early withdrawal visit. The EQ 5D index is a generic preference based measure of health related QoL producing utility scores that represent subject preferences for particular health states. This instrument rated subject health state looking at five specific dimensions such as mobility, self-care, usual activity, pain/discomfort and anxiety/depression and scored their general health state.

Double Blind (DB); Open Label (OL); Visual Analogue Scale (VAS); Change = Change from Baseline

End point type	Secondary
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End point timeframe:

Baseline (Cycle 1 Day 1) and Final visit (up to year 1)

End point values	Total Dysport			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Units on scale				
arithmetic mean (standard deviation)				
Anxiety/Depression Baseline-DB study 145 (n=150)	1.8 (± 0.9)			
Anxiety/Depression Change - DB study 145 (n=140)	0 (± 0.8)			
Anxiety/Depression Baseline - OL study 148 (n=249)	1.9 (± 0.9)			
Anxiety/Depression Change - OL study 148 (n=231)	-0.1 (± 0.9)			
Mobility Baseline - DB study 145 (n=150)	2.7 (± 0.9)			
Mobility Change - DB study 145 (n=140)	0 (± 0.8)			
Mobility Baseline - OL study 148 (n=249)	2.8 (± 0.9)			
Mobility Change - OL study 148 (n=231)	0 (± 0.8)			
Pain/Discomfort Baseline - DB study 145 (n=150)	2.1 (± 1)			
Pain/Discomfort Change - DB study 145 (n=140)	-0.1 (± 0.9)			
Pain/Discomfort Baseline - OL study 148 (n=249)	2.1 (± 1)			
Pain/Discomfort Change - OL study 148 (n=231)	-0.2 (± 0.9)			
Self-Care Baseline - DB study 145 (n=150)	2.5 (± 1)			
Self-Care Change - DB study 145 (n=140)	0 (± 0.9)			
Self-Care Baseline - OL study 148 (n=249)	2.4 (± 1)			
Self-Care Change - OL study 148 (n=231)	0 (± 0.8)			
Usual Activities Baseline - DB study 145 (n=150)	2.8 (± 1)			
Usual Activities Change - DB study 145 (n=140)	-0.1 (± 0.9)			
Usual Activities Baseline - OL study 148 (n=249)	2.8 (± 1)			
Usual Activities Change - OL study 148 (n=231)	-0.2 (± 1)			
VAS Baseline - DB study 145 (n=150)	63.4 (± 20.3)			
VAS Change - DB study 145 (n=140)	2.4 (± 17.3)			
VAS - OL study 148 (n=249)	63.6 (± 19.7)			
VAS Change - OL study 148 (n=231)	2.8 (± 19)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to visit 20 (week 52)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Total Dysport
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Reporting group description:

223 Subjects who rolled over from study 145 plus 31 subjects from observational De-Novo study entered this open label Botulinum type A toxin (Dysport) dose of 1000 Units (U) in Cycle 1 and from Cycle 2 onwards Dysport 500 / 1000 / 1500 U

Serious adverse events	Total Dysport		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 254 (8.27%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Prostate cancer			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device malfunction			

subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasal polyps			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Affective disorder			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Suicidal ideation			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ulna fracture			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		

Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Nephrogenic anaemia			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Total Dysport		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 254 (55.91%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	20 / 254 (7.87%)		
occurrences (all)	25		
Hand fracture			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	3		
Contusion			
subjects affected / exposed	4 / 254 (1.57%)		
occurrences (all)	4		
Humerus fracture			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 254 (1.57%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 254 (2.36%)		
occurrences (all)	6		
Epilepsy			

subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	6		
Paraesthesia			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 254 (1.97%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	7 / 254 (2.76%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	5		
Peripheral swelling			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	4 / 254 (1.57%)		
occurrences (all)	4		
Injection site bruising			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	4		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 4		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 4		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 5		
Depression subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	14 / 254 (5.51%) 18		
Muscular weakness subjects affected / exposed occurrences (all)	13 / 254 (5.12%) 14		
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 5		
Arthralgia subjects affected / exposed occurrences (all)	8 / 254 (3.15%) 9		

Joint swelling subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Back pain subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 5		
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 254 (2.36%) 7		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 254 (2.36%) 10		
Influenza subjects affected / exposed occurrences (all)	4 / 254 (1.57%) 4		
Sinusitis subjects affected / exposed occurrences (all)	4 / 254 (1.57%) 4		
Cystitis subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Gastroenteritis viral subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Herpes zoster subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		
Upper respiratory tract subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2012	Protocol Amendment 2 - Made the following changes: •The sponsor's Medically Responsible Person was changed. •Pronator muscles were excluded from the MAS and TS assessments. •The study entry criteria was simplified to exclude subjects who had undergone previous surgery to treat spasticity of the affected upper limb (instead of those who had received previous surgery on muscles, ligaments, tendons, nerve trunks or bones of the upper limb). •A new exclusion criterion was added to exclude treatment with intrathecal baclofen during the course of the study. •Subjects not requiring a new treatment cycle at the Week 24 follow up visit of Treatment Cycle 1 or 2 (instead of Cycle 1 and potentially Cycle 2) were required to have follow up visits every 4 weeks until a new treatment cycle was required or they reached 12 months follow up. •The Central Laboratory was changed. •12-lead ECG was to be recorded after 5 minutes rest instead of after 30 minutes rest. •Section 9.6 concerning dosage of concomitant medications was amended to include oral baclofen. •Item 9 of the Modified Frenchay Scale was altered to specify that the affected hand was to hold the fork for this task.
25 April 2013	Protocol Amendment 4 - Made the following changes: •The Sponsor's Co-ordinating and Monitoring Officer was changed. •The protocol was substantially updated to include de novo patients as well as rollover subjects from Study 145. The changes specified included: -The study design was amended to include the definition of baseline for MAS de novo patients, the maximum number of treatment cycles in the extension study for the rollover and de novo subjects, the start time of the first treatment cycle for the two populations and the maximum study duration. -Separate inclusion criteria were provided for rollover and de novo subjects -The start of the observation period was specified separately for rollover and de novo subjects. -A separate definition was provided for the selection of primary targeted muscle groups in the de novo subjects. -Separate schedules of assessment were defined for de novo and rollover subjects. -Separate conditions were defined for rollover and de novo subjects who required injections within 2 weeks of the Week 12 visit of any treatment cycle. -Separate study flow diagrams were provided for rollover and de novo subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported