



Clinical trial results:

A PHASE III, MULTICENTRE, RANDOMISED, DOUBLE BLIND, PARALLEL GROUP, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF ONE OR MORE INTRADETRUSOR TREATMENTS OF 600 OR 800 UNITS OF DYSPORT® FOR THE TREATMENT OF URINARY INCONTINENCE IN SUBJECTS WITH NEUROGENIC DETRUSOR OVERACTIVITY DUE TO SPINAL CORD INJURY OR MULTIPLE SCLEROSIS

Summary

EudraCT number	2015-000507-44
Trial protocol	DE BE ES FR LT
Global end of trial date	04 July 2019

Results information

Result version number	v1 (current)
This version publication date	15 July 2020
First version publication date	15 July 2020

Trial information

Trial identification

Sponsor protocol code	D-FR-52120-223
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02660359
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, Ipsen Innovation, clinical.trials@ipsen.com
Scientific contact	Medical Director, 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	04 July 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of two doses of Dysport® (600 Units [U] and 800 U) in adult subjects with urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) due to spinal cord injury (SCI) or multiple sclerosis (MS) and who had not been adequately managed with oral medication and routinely required clean intermittent catheterisation to manage their bladder function.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2016
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	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Brazil: 47
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Colombia: 22
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Peru: 17
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	Ukraine: 5
Worldwide total number of subjects	258
EEA total number of subjects	60

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)	240
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 258 subjects with UI, caused by NDO due to SCI or MS, were enrolled at 67 study sites worldwide. One of the 258 randomised subjects did not receive any treatment. The study was terminated early by the sponsor due to lack of recruitment.

Pre-assignment

Screening details:

Subjects were randomised to 1 of 4 sequences: A) placebo in a double-blind placebo-controlled (DBPC) cycle then Dysport® 600 U in subsequent double-blind cycles: B) placebo in DBPC cycle then Dysport® 800 U in subsequent cycles: C) Dysport® 600 U in all cycles: D) Dysport® 800 U in all cycles. The minimum retreatment interval was 12 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects were administered placebo on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 millilitres (mL) divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

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

Dosage and administration details:

Placebo was injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each.

Arm title	Dysport® 600 U
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Arm description:

Subjects were administered Dysport® 600 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

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

Dosage and administration details:

Dysport® 600 U was injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each.

Arm title	Dysport® 800 U
Arm description:	
Subjects were administered Dysport® 800 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.	
Arm type	Experimental
Investigational medicinal product name	Dysport®
Investigational medicinal product code	
Other name	AbobotulinumtoxinA
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dysport® 800 U was injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each.

Number of subjects in period 1^[1]	Placebo	Dysport® 600 U	Dysport® 800 U
Started	86	86	85
Completed	0	0	1
Not completed	86	86	84
Consent withdrawn by subject	7	5	8
Adverse event, non-fatal	-	1	-
Sponsor Decision to Terminate Study	73	75	71
Unspecified	2	1	3
Lost to follow-up	3	3	-
Lack of efficacy	1	1	1
Protocol deviation	-	-	1

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: The Baseline Period is based on the 257 subjects that received treatment. One of the 258 randomised subjects did not receive any treatment and is therefore excluded from baseline analyses. This subject is included in the Worldwide Enrolled population but data was not available on the patient's age and so the patient has been included in the larger 18-64 years age group for validation purposes.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects were administered placebo on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 millilitres (mL) divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 600 U
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Reporting group description:

Subjects were administered Dysport® 600 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 800 U
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Reporting group description:

Subjects were administered Dysport® 800 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group values	Placebo	Dysport® 600 U	Dysport® 800 U
Number of subjects	86	86	85
Age categorical Units: Subjects			
Adults (18-64 years)	80	82	77
From 65-84 years	6	4	8
Age continuous Units: years			
arithmetic mean	42.2	42.5	42.0
standard deviation	± 13.16	± 12.10	± 14.72
Gender categorical Units: Subjects			
Female	36	29	30
Male	50	57	55
Race Units: Subjects			
American Indian or Alaska Native	8	13	9
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	2	4	4
White	55	52	56
Other	11	6	7
Multiple	7	5	3
Missing	3	6	5
Aetiology of NDO Units: Subjects			

SCI	62	64	65
MS	24	22	20

Reporting group values	Total		
Number of subjects	257		
Age categorical Units: Subjects			
Adults (18-64 years)	239		
From 65-84 years	18		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	95		
Male	162		
Race Units: Subjects			
American Indian or Alaska Native	30		
Asian	0		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	10		
White	163		
Other	24		
Multiple	15		
Missing	14		
Aetiology of NDO Units: Subjects			
SCI	191		
MS	66		

End points

End points reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects were administered placebo on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 millilitres (mL) divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 600 U
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Reporting group description:

Subjects were administered Dysport® 600 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 800 U
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Reporting group description:

Subjects were administered Dysport® 800 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Primary: Mean Change From Baseline in Weekly Number of UI Episodes at Week 6 of DBPC Cycle

End point title	Mean Change From Baseline in Weekly Number of UI Episodes at Week 6 of DBPC Cycle
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End point description:

The weekly number of UI episodes was measured using a 7-day bladder diary. Bladder diaries that contained data recorded on at least 5 days were included in the analysis. The least square (LS) mean of the change in weekly number of UI episodes at 6 weeks after the first study treatment was calculated using a mixed model repeated measures (MMRM) analysis. Results are presented for the modified intention to treat (mITT) population (all randomised subjects who received at least 1 administration of study treatment). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Primary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	82	73	
Units: Weekly UI episodes				
least squares mean (standard error)	-12.86 (± 1.95)	-21.83 (± 1.91)	-22.62 (± 1.88)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U to Placebo
Statistical analysis description: Treatment group, visit (Week 6), treatment-by-visit interaction, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [Botulinum toxin [BTX]-naïve or BTX-non-naïve]) and study baseline value (weekly number of UI episodes) as fixed effect variables, and subject as a random effect.	
Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-8.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	-4.44

Notes:

[1] - If both p-values for the 2 primary tests (the test of Dysport® 800 U vs. placebo and the test of Dysport® 600 U vs. placebo) were lower than 0.05, both were declared statistically significant. If 1 of the primary tests had a p-value greater than or equal to 0.05, then the other test was declared statistically significant if its p-value was lower than 0.025 and only the significant dose continued in the hierarchal testing strategy.

Statistical analysis title	Comparison of Dysport® 800 U to Placebo
Statistical analysis description: Treatment group, visit (Week 6), treatment-by-visit interaction, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [Botulinum toxin [BTX]-naïve or BTX-non-naïve]) and study baseline value (weekly number of UI episodes) as fixed effect variables, and subject as a random effect.	
Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-9.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.41
upper limit	-5.12

Notes:

[2] - If both p-values for the 2 primary tests (the test of Dysport® 800 U vs. placebo and the test of Dysport® 600 U vs. placebo) were lower than 0.05, both were declared statistically significant. If 1 of the primary tests had a p-value greater than or equal to 0.05, then the other test was declared statistically significant if its p-value was lower than 0.025 and only the significant dose continued in the hierarchal testing strategy.

Secondary: Percentage of Subjects With No Episodes of UI at Week 6 of DBPC Cycle

End point title	Percentage of Subjects With No Episodes of UI at Week 6 of DBPC Cycle
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End point description:

The weekly number of UI episodes was measured using a 7-day bladder diary. Bladder diaries that contained data recorded on at least 5 days were included in the analysis. The number of subjects with no UI episodes at 6 weeks after the first study treatment was recorded. Percentage of subjects with no episodes of UI ($\geq 100\%$ Improvement) was calculated as: Total number of subjects with no weekly number of UI episodes at Week 6 / Total number of subjects with any number of UI events at Week 6. Results are presented for the mITT population (all randomised subjects who received at least 1 administration of study treatment). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	82	73	
Units: Percentage of Subjects				
number (not applicable)	1.3	36.6	26.0	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0002
Method	Generalised linear mixed model (GLMM)
Parameter estimate	Odds ratio (OR)
Point estimate	45.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.09
upper limit	340.69

Notes:

[3] - This secondary endpoint was included in the hierarchical analysis and was tested for both doses at the 0.05 level using a hierarchical methodology.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 800 U
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Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.0009
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	31.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.17
upper limit	240.58

Notes:

[4] - This secondary endpoint was included in the hierarchical analysis and was tested for both doses at the 0.05 level using a hierarchical methodology.

Secondary: Percentage of Subjects with a UI Response at Improvement Levels $\geq 30\%$, $\geq 50\%$, and $\geq 75\%$ at Week 6 of the DBPC Cycle

End point title	Percentage of Subjects with a UI Response at Improvement Levels $\geq 30\%$, $\geq 50\%$, and $\geq 75\%$ at Week 6 of the DBPC Cycle
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End point description:

The weekly number of UI episodes was measured using a 7-day bladder diary. Bladder diaries that contained data recorded on at least 5 days were included in the analysis. The percentage of subjects showing an improvement of $\geq 30\%$, $\geq 50\%$ and $\geq 75\%$ was calculated as: Total number of subjects with UI response level $\geq 30\%$ or $\geq 50\%$ or $\geq 75\%$ improvement at Week 6 / Total number of subjects with any UI response at Week 6. Results are presented for the mITT population: all randomised subjects who received at least 1 administration of study treatment. Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	82	73	
Units: Percentage of Subjects				
number (not applicable)				
$\geq 30\%$ Improvement	55.3	81.7	76.7	
$\geq 50\%$ Improvement	38.2	72.0	61.6	
$\geq 75\%$ Improvement	17.1	62.2	50.7	

Statistical analyses

Statistical analysis title	Treatment comparison at $\geq 30\%$ Improvement
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Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0007
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	3.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	7.34

Notes:

[5] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Treatment comparison at ≥30% Improvement
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Statistical analysis description:

Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.0037
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	6.07

Notes:

[6] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Treatment comparison at ≥50% Improvement
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Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	3.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.03
upper limit	7.79

Notes:

[7] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Treatment comparison at $\geq 50\%$ Improvement
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Statistical analysis description:

Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.0034
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	5.33

Notes:

[8] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Treatment comparison at $\geq 75\%$ Improvement
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Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	7.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	15.58

Notes:

[9] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Treatment comparison at $\geq 75\%$ Improvement
Statistical analysis description: Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.	
Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	5.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.48
upper limit	11.24

Notes:

[10] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Secondary: Median Time Between Treatments

End point title	Median Time Between Treatments
End point description: Duration of effect for time between treatments was calculated by: (the date of the first retreatment visit - date of first treatment administration in the DBPC cycle). The median number of days between treatments was determined and subjects with no retreatment were censored at the last visit. Results are presented for the mITT population (all randomised subjects who received at least 1 administration of study treatment). Subjects were analysed as randomised (planned treatment).	
End point type	Secondary
End point timeframe: Day of first treatment (baseline) and day of retreatment	

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	86	85	
Units: Days				
median (full range (min-max))	132.0 (8 to 644)	238.5 (57 to 651)	210.0 (56 to 649)	

Statistical analyses

Secondary: Mean Change From Baseline in Volume Per Void at Week 6 of DBPC Cycle

End point title	Mean Change From Baseline in Volume Per Void at Week 6 of DBPC Cycle
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End point description:

The volume per void was measured during one 24-hour period of the 7-day bladder diary. The LS mean of the change in volume per void at 6 weeks after the first study treatment was calculated using a MMRM analysis. Results are presented for the mITT population (all randomised subjects who received at least 1 administration of study treatment). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	77	72	
Units: mL				
least squares mean (standard error)	-6.00 (± 17.80)	90.14 (± 17.45)	84.78 (± 17.22)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
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Statistical analysis description:

Treatment group, visit (Week 6), treatment-by-visit interaction, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and study baseline value (total volume per void) as fixed effect variables, and subject as a random effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	96.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.1
upper limit	139.19

Notes:

[11] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
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Statistical analysis description:

Treatment group, visit (Week 6), treatment-by-visit interaction, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and study baseline value (total volume per void) as fixed effect variables, and subject as a random effect.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	90.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.07
upper limit	134.48

Notes:

[12] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Secondary: Mean Change From Baseline in Maximum Cystometric Capacity (MCC) at Week 6 of DBPC Cycle

End point title	Mean Change From Baseline in Maximum Cystometric Capacity (MCC) at Week 6 of DBPC Cycle
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End point description:

Subjects included in the urodynamic subset (84.9% of randomised subjects) had a standardised urodynamic filling cystometry assessment at baseline (Screening) and again at Week 6 to determine the MCC. The LS mean of the change in MCC at 6 weeks after the first study treatment was calculated using an analysis of covariance (ANCOVA). Results are presented for the urodynamic population (all subjects in the mITT population included in the urodynamic subset at randomisation). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	76	63	
Units: mL				
least squares mean (standard error)	3.5 (± 22.83)	178.5 (± 21.38)	171.9 (± 21.58)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-

naïve or BTX-non-naïve]) and baseline value of MCC as covariates.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	175
Confidence interval	
level	95 %
sides	2-sided
lower limit	122.9
upper limit	227

Notes:

[13] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and baseline value of MCC as covariates.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	168.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	113.6
upper limit	223.1

Notes:

[14] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Secondary: Mean Change From Baseline in Maximum Detrusor Pressure (MDP) During Storage at Week 6 of DBPC Cycle

End point title	Mean Change From Baseline in Maximum Detrusor Pressure (MDP) During Storage at Week 6 of DBPC Cycle
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End point description:

Subjects included in the urodynamic subset (84.9% of randomised subjects) had a standardised urodynamic filling cystometry assessment at baseline (Screening) and again at Week 6 to determine the MDP. The LS mean of the change in MDP at 6 weeks after the first study treatment was calculated using an ANCOVA. Results are presented for the urodynamic population (all subjects in the mITT population included in the urodynamic subset at randomisation). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	71	57	
Units: centimetres of water				
least squares mean (standard error)	-3.7 (± 3.84)	-36.7 (± 3.48)	-36.2 (± 3.51)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
Statistical analysis description:	
Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and baseline value of MDP as covariates.	
Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.5
upper limit	-24.4

Notes:

[15] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
Statistical analysis description:	
Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and baseline value of MDP as covariates.	
Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-32.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.5
upper limit	-23.4

Notes:

[16] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Secondary: Mean Change From Baseline in Volume at First Involuntary Detrusor Contraction (Vol@1stIDC) at Week 6 of DBPC Cycle

End point title	Mean Change From Baseline in Volume at First Involuntary Detrusor Contraction (Vol@1stIDC) at Week 6 of DBPC Cycle
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End point description:

Subjects included in the urodynamic subset (84.9% of randomised subjects) had a standardised urodynamic filling cystometry assessment at baseline (Screening) and again at Week 6 to determine the Vol@1stIDC which is the instilled volume when first IDC commences. Subjects who did not exhibit a post-treatment IDC at Week 6 had Vol@1stIDC imputed using the recorded corrected MCC volume at Week 6. The LS mean of the change in Vol@1stIDC at 6 weeks after the first study treatment was calculated using an ANCOVA. Results are presented for the urodynamic population (all subjects in the mITT population included in the urodynamic subset at randomisation). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	72	58	
Units: mL				
least squares mean (standard error)	15.9 (± 23.34)	168.7 (± 22.09)	185.5 (± 22.80)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naïve or BTX-non-naïve]) and baseline value of Vol@1stIDC as covariates.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	152.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	99.2
upper limit	206.5

Notes:

[17] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
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Statistical analysis description:

Treatment group, recorded stratification factors (aetiology of NDO [SCI or MS], prior intradetrusor [BTX-naive or BTX-non-naive]) and baseline value of Vol@1stIDC as covariates.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	169.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	111.7
upper limit	227.6

Notes:

[18] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Secondary: Percentage of Subjects With No Involuntary Detrusor Contractions (IDCs) During Storage at Week 6 of DBPC Cycle

End point title	Percentage of Subjects With No Involuntary Detrusor Contractions (IDCs) During Storage at Week 6 of DBPC Cycle
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End point description:

Subjects included in the urodynamic subset (84.9% of randomised subjects) had a standardised urodynamic filling cystometry assessment at baseline (Screening) and again at Week 6 to determine the occurrence of IDCs. The percentage of subjects without IDCs at 6 weeks after the first study treatment was recorded. Results are presented for the urodynamic population (all subjects in the mITT population included in the urodynamic subset at randomisation). Subjects were analysed as randomised (planned treatment). Only subjects with data available for analysis at Week 6 of DBPC cycle are presented.

End point type	Secondary
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End point timeframe:

Baseline and Week 6 of DBPC Cycle

End point values	Placebo	Dysport® 600 U	Dysport® 800 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	74	58	
Units: Percentage of Subjects				
number (not applicable)	3.4	52.7	50.0	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo
Statistical analysis description:	
Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.	
Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	31.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.05
upper limit	137.09

Notes:

[19] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Statistical analysis title	Comparison of Dysport® 800 U with Placebo
Statistical analysis description:	
Treatment group, recorded stratification factors, visit, treatment-by-visit interaction, study baseline-by-visit interaction and study baseline weekly number of UI episodes as fixed effect.	
Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	28.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.24
upper limit	126.25

Notes:

[20] - This secondary endpoint was not included within the hierarchical testing procedure and was analysed for exploratory purposes only to compare each Dysport® dose to placebo at a 0.05 type one error rate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events are presented for the full DBPC cycle (i.e. approximately 32 weeks for both Dysport® groups and approximately 19 weeks for the Placebo group).

Adverse event reporting additional description:

The safety population included all subjects who received at least 1 administration of study treatment (including only partial administration). Safety subjects were analysed according to their actual treatment received. Number of deaths (all causes) is presented for the duration of the study (up to a maximum of 115 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects were administered placebo on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 600 U
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Reporting group description:

Subjects were administered Dysport® 600 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Reporting group title	Dysport® 800 U
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Reporting group description:

Subjects were administered Dysport® 800 U on Day 1 of the DBPC cycle. All study treatments were injected into the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each. Subjects were followed-up by telephone at Week 1 and Week 4; and attended clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits were scheduled every 12 weeks until end of study, or until retreatment was required.

Serious adverse events	Placebo	Dysport® 600 U	Dysport® 800 U
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	9 / 87 (10.34%)	8 / 85 (9.41%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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 / 85 (0.00%)	1 / 87 (1.15%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Multiple sclerosis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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			
Urinary tract infection			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Osteomyelitis chronic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Perineal abscess			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Soft tissue infection			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Testicular abscess			

subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (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
Urosepsis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dysport® 600 U	Dysport® 800 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 85 (40.00%)	40 / 87 (45.98%)	42 / 85 (49.41%)
Investigations			
Nitrite urine present			
subjects affected / exposed	2 / 85 (2.35%)	2 / 87 (2.30%)	0 / 85 (0.00%)
occurrences (all)	2	2	0
Blood urine present			
subjects affected / exposed	2 / 85 (2.35%)	0 / 87 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Anaesthetic complication cardiac			
subjects affected / exposed	0 / 85 (0.00%)	2 / 87 (2.30%)	1 / 85 (1.18%)
occurrences (all)	0	2	1
Vascular disorders			

Haemorrhage subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 87 (2.30%) 2	1 / 85 (1.18%) 1
Hypotension subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	2 / 87 (2.30%) 2	1 / 85 (1.18%) 1
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	1 / 87 (1.15%) 1	3 / 85 (3.53%) 5
Muscle spasticity subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 87 (2.30%) 2	1 / 85 (1.18%) 1
Neuralgia subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 87 (2.30%) 2	0 / 85 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	0 / 87 (0.00%) 0	0 / 85 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 87 (2.30%) 2	1 / 85 (1.18%) 1
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	3 / 87 (3.45%) 5	2 / 85 (2.35%) 2
Fatigue subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	1 / 87 (1.15%) 1	2 / 85 (2.35%) 2
Malaise subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	2 / 87 (2.30%) 2	0 / 85 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 3	3 / 87 (3.45%) 7	4 / 85 (4.71%) 4
Constipation subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	4 / 87 (4.60%) 4	2 / 85 (2.35%) 2
Abdominal pain subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	1 / 87 (1.15%) 2	2 / 85 (2.35%) 2
Abdominal pain lower subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	0 / 87 (0.00%) 0	2 / 85 (2.35%) 2
Nausea subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 87 (2.30%) 2	0 / 85 (0.00%) 0
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	0 / 87 (0.00%) 0	2 / 85 (2.35%) 2
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	0 / 87 (0.00%) 0	2 / 85 (2.35%) 2
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	4 / 85 (4.71%) 4	5 / 87 (5.75%) 5	4 / 85 (4.71%) 4
Leukocyturia subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	1 / 87 (1.15%) 1	2 / 85 (2.35%) 3
Bladder pain subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	1 / 87 (1.15%) 1	0 / 85 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	3 / 87 (3.45%) 5	5 / 85 (5.88%) 6

Arthralgia			
subjects affected / exposed	0 / 85 (0.00%)	2 / 87 (2.30%)	1 / 85 (1.18%)
occurrences (all)	0	3	1
Myalgia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	17 / 85 (20.00%)	19 / 87 (21.84%)	22 / 85 (25.88%)
occurrences (all)	21	24	34
Bacteriuria			
subjects affected / exposed	0 / 85 (0.00%)	6 / 87 (6.90%)	1 / 85 (1.18%)
occurrences (all)	0	6	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 85 (1.18%)	0 / 87 (0.00%)	4 / 85 (4.71%)
occurrences (all)	1	0	4
Influenza			
subjects affected / exposed	5 / 85 (5.88%)	2 / 87 (2.30%)	1 / 85 (1.18%)
occurrences (all)	5	2	1
Nasopharyngitis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 87 (1.15%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Pharyngitis			
subjects affected / exposed	2 / 85 (2.35%)	1 / 87 (1.15%)	1 / 85 (1.18%)
occurrences (all)	2	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2018	Amendment included the following changes: <ul style="list-style-type: none">• Decrease in sample size from 408 to 330 subjects; statistical power lowered from 90% to 80%.• Clarification added regarding the primary analysis (i.e. previously referred to as an 'interim' analysis).• Removal of the internal data monitoring committee.• Clarification added throughout the protocol regarding description of the Screening period (i.e. time between Screening Visit 1 and Screening Visit 2, as well as time between Screening and administration of study treatment).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was terminated early by the sponsor on 04 October 2018, due to slow subject recruitment (258 subjects randomised compared to 330 planned subjects). Only primary and key secondary efficacy analyses were performed.

Notes: