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	2015-003471-30
Trial protocol	RO PT CZ IT NL PL
Global end of trial date	14 February 2019

Results information

Result version number	v2 (current)
This version publication date	16 May 2021
First version publication date	01 March 2020
Version creation reason	• New data added to full data set New data added

Trial information

Trial identification

Sponsor protocol code	D-FR-52120-222

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02660138
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	14 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2018
Global end of trial reached?	Yes
Global end of trial date	14 February 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	29 March 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	Turkey: 31
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Romania: 30
Worldwide total number of subjects	226
EEA total number of subjects	99

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)	205
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 227 subjects with UI, caused by NDO due to SCI or MS, were enrolled at 64 study sites worldwide. One of the 226 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 Units (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 re-treatment 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	Subject, Investigator, Monitor, Carer

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

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	AbobotulinumtoxinA
Other name	
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	AbobotulinumtoxinA
Other name	
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	Placebo	Dysport® 600 U	Dysport® 800 U
Started	76	75	75
Completed	6	2	3
Not completed	70	73	72
Consent withdrawn by subject	7	6	6
Adverse event, non-fatal	-	3	2
Sponsor Decision to Terminate Study	57	57	62
Unspecified	1	1	-
Lost to follow-up	4	4	1
Lack of efficacy	1	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

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

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

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	76	75	75
Age categorical Units: Subjects			
Adults (18-64 years)	68	71	66
From 65-84 years	8	4	9
Age continuous Units: years			
arithmetic mean	45.9	43.0	46.8
standard deviation	± 13.15	± 12.38	± 13.58
Gender categorical Units: Subjects			
Female	38	27	30
Male	38	48	45
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	3	4

White	65	70	64
More than one race	1	0	0
Unknown or Not Reported	2	0	3
Aetiology of NDO Units: Subjects			
SCI	51	49	48
MS	25	26	27

Reporting group values	Total		
Number of subjects	226		
Age categorical Units: Subjects			
Adults (18-64 years)	205		
From 65-84 years	21		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	95		
Male	131		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	10		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	11		
White	199		
More than one race	1		
Unknown or Not Reported	5		
Aetiology of NDO Units: Subjects			
SCI	148		
MS	78		

End points

End points reporting groups

Reporting group title	Placebo

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

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

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

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

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	64	62	67	
Units: Weekly UI episodes				
least squares mean (standard error)	-12.7 (± 2.01)	-23.5 (± 2.04)	-24.9 (± 1.97)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U to Placebo

Statistical analysis description:

Treatment group, visit (Week 2, Week 6 and Week 12), 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	126
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-10.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.36
upper limit	-5.31

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.

Statistical analysis title	Comparison of Dysport® 800 U to Placebo

Statistical analysis description:

Treatment group, visit (Week 2, Week 6 and Week 12), 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	131
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-12.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.65
upper limit	-6.73

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.

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

End point description:

All 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 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

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	66	60	70	
Units: mL				
least squares mean (standard error)	-8.5 (± 18.06)	152.4 (± 19.10)	180.7 (± 17.70)	

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 MCC as covariates.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	160.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	109.9
upper limit	211.9

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

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	136
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	189.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	140.1
upper limit	238.2

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

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

End point description:

All 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 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

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	58	54	65	
Units: centimetres of water				
least squares mean (standard error)	-5.4 (± 2.83)	-29.8 (± 2.96)	-34.1 (± 2.71)	

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	112
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-16.4

Notes:

[5] - 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

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	123
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.2
upper limit	-21.1

Notes:

[6] - 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: 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

End point description:

All 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 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

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	63	56	66	
Units: mL				
least squares mean (standard error)	14.0 (± 19.45)	169.4 (± 20.72)	195.7 (± 19.12)	

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 Vol@1stIDC as covariates.

Comparison groups	Dysport® 600 U v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	155.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	100.5
upper limit	210.4

Notes:

[7] - 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

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® 800 U

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	181.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	129.2
upper limit	234.3

Notes:

[8] - 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: Number of Subjects With No Episodes of UI at Week 6 of DBPC Cycle

End point title	Number of Subjects With No Episodes of UI at Week 6 of DBPC Cycle

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.
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

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	64	62	67	
Units: subjects	3	21	21	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo

Statistical analysis description:

Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	126
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0006
Method	Generalised linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	9.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.72
upper limit	35.6

Notes:

[9] - 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

Statistical analysis description:

Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	131
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0003
Method	Generalised linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	10.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.05
upper limit	39.61

Notes:

[10] - 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: Number of Subjects With No IDCs During Storage at Week 6 of DBPC Cycle

End point title	Number of Subjects With No IDCs During Storage at Week 6 of DBPC Cycle

End point description:

All subjects had a standardised urodynamic filling cystometry assessment at baseline (screening) and again at Week 6 to determine the occurrence of IDCs. The number of subjects without IDCs at 6 weeks after the first study treatment was recorded.
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

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	63	60	71	
Units: subjects	6	20	42	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo

Statistical analysis description:

Treatment group, and recorded stratification factors (aetiology of NDO, previous BTX-A usage) and study baseline (prior intradetrusor BTX-A usage for UI) as explanatory variables.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	16.24
Variability estimate	Standard deviation

Notes:

[11] - 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

Statistical analysis description:

Treatment group, and recorded stratification factors (aetiology of NDO, previous BTX-A usage) and study baseline (prior intradetrusor BTX-A usage for UI) as explanatory variables.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.82
upper limit	44.43

Variability estimate	Standard deviation

Notes:

[12] - 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: 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

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

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	60	65	
Units: mL				
least squares mean (standard error)	2.3 (± 14.92)	87.1 (± 15.10)	112.8 (± 14.50)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U with Placebo

Statistical analysis description:

Treatment group, visit (Week 2, Week 6 and Week 12), 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	122
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	84.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	43.73
upper limit	125.89

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

Statistical analysis description:

Treatment group, visit (Week 2, Week 6 and Week 12), 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	127
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	110.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.17
upper limit	150.98

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: Number of Subjects with a UI Response at Improvement Levels ≥30%, ≥50%, and ≥75% at Week 6 of the DBPC Cycle

End point title	Number of Subjects with a UI Response at Improvement Levels ≥30%, ≥50%, and ≥75% at Week 6 of the DBPC Cycle

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 showing an improvement of ≥30%, ≥50% and ≥75% were recorded. 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

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	64	62	67	
Units: Subjects				
≥30% Improvement	32	50	52	
≥50% Improvement	19	47	50	
≥75% Improvement	9	39	44	

Statistical analyses

Statistical analysis title	Treatment comparison at ≥30% Improvement

Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	126
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0007
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	8.86

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	Treatment comparison at ≥30% Improvement

Statistical analysis description:

Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	131
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.0012
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	7.86

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.

Statistical analysis title	Treatment comparison at ≥50% Improvement

Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	126
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	8.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.56
upper limit	18.09

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	Treatment comparison at ≥50% Improvement

Statistical analysis description:

Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	131
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	8.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.66
upper limit	18.47

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.

Statistical analysis title	Treatment comparison at ≥75% Improvement

Statistical analysis description:

Dysport® 600 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	126
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.59
upper limit	24.95

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	Treatment comparison at ≥75% Improvement

Statistical analysis description:

Dysport® 800 U versus Placebo. Treatment group, recorded stratification factors, visit (Week 2, Week 6 and Week 12), 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	131
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.0001
Method	GLMM
Parameter estimate	Odds ratio (OR)
Point estimate	12.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	29.56

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.

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 based on the Kaplan-Meier method. 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	76	75	75	
Units: Days				
median (full range (min-max))	120.5 (44 to 616)	215.0 (37 to 590)	224.0 (82 to 647)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Incontinence Quality of Life (I-QoL) Questionnaire Total Summary Score at Week 6 of DBPC Cycle

End point title	Mean Change from Baseline in Incontinence Quality of Life (I-QoL) Questionnaire Total Summary Score at Week 6 of DBPC Cycle

End point description:

The I-QoL questionnaire is a validated, disease-specific questionnaire designed to measure the effect of UI on subjects' QoL. It consists of 22 items in 3 domains (avoidance and limiting behaviour, psychosocial impact and social embarrassment). Subjects used a 5-point response scale for each of the 22 items with values ranging from 1 (extremely) to 5 (not at all). The total summary score was transformed to a 100 point scale ranging from 0 to 100, with higher scores indicating a better QoL. The LS mean of the change in the I-QoL total summary score 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

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	71	61	68	
Units: score on a scale				
least squares mean (standard error)	5.8 (± 2.52)	19.1 (± 2.63)	23.0 (± 2.51)	

Statistical analyses

Statistical analysis title	Comparison of Dysport® 600 U to Placebo

Statistical analysis description:

Treatment group, visit (Week 6 and Week 12), 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 (I-QoL summary total score) as fixed variables, and subject as a random effect.

Comparison groups	Placebo v Dysport® 600 U
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0003
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.22
upper limit	20.37

Notes:

[21] - 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 to Placebo

Statistical analysis description:

Treatment group, visit (Week 6 and Week 12), 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 (I-QoL summary total score) as fixed variables, and subject as a random effect.

Comparison groups	Placebo v Dysport® 800 U
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	17.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.36
upper limit	24.15

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events are presented for the full DBPC cycle (i.e. approximately 35 weeks for both Dysport® groups and approximately 25 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 113 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

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® 800 U

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 title	Dysport® 600 U

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.

Serious adverse events	Placebo	Dysport® 800 U	Dysport® 600 U
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 76 (10.53%)	6 / 77 (7.79%)	9 / 73 (12.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to abdominal cavity			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	0 / 73 (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
Hypertension			

subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 76 (3.95%)	1 / 77 (1.30%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	0 / 73 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	0 / 73 (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
Cystitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	0 / 73 (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
Epididymitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	0 / 73 (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			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fournier's gangrene			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dysport® 800 U	Dysport® 600 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 76 (30.26%)	23 / 77 (29.87%)	20 / 73 (27.40%)
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	3 / 76 (3.95%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences (all)	3	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	3 / 73 (4.11%)
occurrences (all)	1	2	3
Dysuria			
subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	2 / 73 (2.74%)
occurrences (all)	1	2	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 76 (17.11%)	21 / 77 (27.27%)	13 / 73 (17.81%)
occurrences (all)	26	27	26
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 77 (0.00%)	1 / 73 (1.37%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2018	• 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 01 October 2018, due to low subject recruitment.

Notes: