



## 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          | v1            |
| This version publication date  | 01 March 2020 |
| First version publication date | 01 March 2020 |

### 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 | Korea, Republic of: 10 |
| Country: Number of subjects enrolled | United States: 76      |
| Country: Number of subjects enrolled | Turkey: 31             |
| Country: Number of subjects enrolled | Canada: 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            |
| Country: Number of subjects enrolled | Czech Republic: 23     |
| Country: Number of subjects enrolled | Italy: 22              |
| 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     |
| <b>Arm title</b>             | 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.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | 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.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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 |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>             | 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) | -12.59 (± 2.02) | -23.52 (± 2.04) | -24.89 (± 1.98) |  |

## 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  | 126                                     |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority <sup>[1]</sup>              |
| P-value  | = 0.0001                                |
| Method   | MMRM                                    |
| Parameter estimate   | LS Mean Difference                      |
| Point estimate   | -10.93                                  |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | -16.47                                  |
| upper limit  | -5.38                                   |

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 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  | 131                                     |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority <sup>[2]</sup>              |
| P-value  | < 0.0001                                |
| Method   | MMRM                                    |
| Parameter estimate   | LS Mean Difference                      |
| Point estimate   | -12.3                                   |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | -17.78                                  |
| upper limit  | -6.82                                   |

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 <sup>[3]</sup> |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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 <sup>[4]</sup>                |
| 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   |  |

|                                     |                 |                 |                 |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| <b>End point values</b>             | 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**

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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 <sup>[5]</sup>                |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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 <sup>[6]</sup>                |
| 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 <sup>[7]</sup>                |
| 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 <sup>[8]</sup>                |
| 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, 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 <sup>[9]</sup>     |
| P-value                                 | = 0.0006                       |
| Method                                  | Generalised linear mixed model |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 9.73                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.7                            |
| upper limit                             | 35.11                          |

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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Comparison of Dysport® 800 U with Placebo |
| Statistical analysis description:<br>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  | 131                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | superiority <sup>[10]</sup>               |
| P-value  | = 0.0003                                  |
| Method   | Generalised linear mixed model            |
| Parameter estimate   | Odds ratio (OR)                           |
| Point estimate   | 10.96                                     |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | 3.05                                      |
| upper limit  | 39.36                                     |

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:<br>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.<br>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:<br>Baseline and Week 6 of DBPC Cycle  |  |

| <b>End point values</b>     | Placebo         | Dysport® 600 U  | Dysport® 800 U  |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 61              | 54              | 68              |  |
| Units: subjects             | 6               | 20              | 42              |  |

## **Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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   | 115                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority <sup>[11]</sup>               |
| P-value   | = 0.0004                                  |
| Method  | Regression, Logistic                      |
| Parameter estimate  | Odds ratio (OR)                           |
| Point estimate  | 6.85                                      |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 2.35                                      |
| upper limit   | 20.01                                     |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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   | 129                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority <sup>[12]</sup>               |
| P-value   | < 0.0001                                  |
| Method  | Regression, Logistic                      |
| Parameter estimate  | Odds ratio (OR)                           |
| Point estimate  | 17.35                                     |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 6.14                                      |
| upper limit   | 49.04                                     |
| 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         | 61              | 60              | 64               |  |
| Units: mL                           |                 |                 |                  |  |
| least squares mean (standard error) | 2.27 (± 15.12)  | 87.05 (± 15.18) | 114.12 (± 14.67) |  |

## Statistical analyses

| Statistical analysis title  | Comparison of Dysport® 600 U with Placebo |
|---|---|
| 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   | 121                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority <sup>[13]</sup>               |
| P-value   | < 0.0001                                  |
| Method  | MMRM                                      |
| Parameter estimate  | LS Mean Difference                        |
| Point estimate  | 84.78                                     |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 43.28                                     |
| upper limit   | 126.27                                    |

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 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 | 125                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[14]</sup> |
| P-value                                 | < 0.0001                    |
| Method                                  | MMRM                        |
| Parameter estimate                      | LS Mean Difference          |
| Point estimate                          | 111.85                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 70.87                       |
| upper limit                             | 152.82                      |

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

| <b>End point values</b>     | 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              | 48              | 50              |  |
| ≥75% Improvement            | 9               | 39              | 44              |  |

### **Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Treatment comparison at ≥30% Improvement |
|-----------------------------------|--|

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 | 126                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[15]</sup> |
| P-value                                 | = 0.0005                    |
| Method                                  | GLMM                        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 4.13                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.86                        |
| upper limit                             | 9.15                        |

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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Treatment comparison at ≥30% 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 | 131                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[16]</sup> |
| P-value                                 | = 0.0009                    |
| Method                                  | GLMM                        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 3.75                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.73                        |
| upper limit                             | 8.13                        |

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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Treatment comparison at ≥50% Improvement |
|-----------------------------------|--|

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 | 126                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[17]</sup> |
| P-value                                 | < 0.0001                    |
| Method                                  | GLMM                        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 8.75                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 3.86    |
| upper limit         | 19.83   |

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.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Treatment comparison at $\geq 50\%$ 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 | 131                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[18]</sup> |
| P-value                                 | < 0.0001                    |
| Method                                  | GLMM                        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 8.08                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 3.62                        |
| upper limit                             | 18.04                       |

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.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Treatment comparison at $\geq 75\%$ Improvement |
|-----------------------------------|---|

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 | 126                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[19]</sup> |
| P-value                                 | < 0.0001                    |
| Method                                  | GLMM                        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 10.55                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 4.53                        |
| upper limit                             | 24.54                       |

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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Treatment comparison at $\geq 75\%$ Improvement |
| Statistical analysis description:<br>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   | 131   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | superiority <sup>[20]</sup>                     |
| P-value   | < 0.0001  |
| Method  | GLMM  |
| Parameter estimate  | Odds ratio (OR)                                 |
| Point estimate  | 12.45   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 5.33  |
| upper limit   | 29.08   |

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:<br>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:<br>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



## 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® 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.

| Serious adverse events                            | Placebo         | Dysport® 600 U  | Dysport® 800 U |
|---|-----------------|-----------------|----------------|
| Total subjects affected by serious adverse events |                 |                 |                |
| subjects affected / exposed                       | 8 / 76 (10.53%) | 9 / 73 (12.33%) | 6 / 77 (7.79%) |
| 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%) | 1 / 73 (1.37%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications                      |                |                |                |
| Multiple injuries   |                |                |                |
| subjects affected / exposed   | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (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          |
| Road traffic accident   |                |                |                |
| subjects affected / exposed   | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Fibula fracture   |                |                |                |
| subjects affected / exposed   | 1 / 76 (1.32%) | 0 / 73 (0.00%) | 0 / 77 (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 / 73 (0.00%) | 0 / 77 (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 / 73 (0.00%) | 0 / 77 (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%) | 0 / 73 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypertension  |                |                |                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (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          |
| General disorders and administration site conditions |                |                |                |
| Systemic inflammatory response syndrome              |                |                |                |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                           |                |                |                |
| Ileus  |                |                |                |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (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          |
| Reproductive system and breast disorders             |                |                |                |
| Uterine polyp  |                |                |                |
| subjects affected / exposed                          | 1 / 76 (1.32%) | 0 / 73 (0.00%) | 0 / 77 (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 / 73 (1.37%) | 1 / 77 (1.30%) |
| 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%) | 1 / 73 (1.37%) | 0 / 77 (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          |
| Musculoskeletal and connective tissue disorders      |                |                |                |
| Muscular weakness                                    |                |                |                |
| subjects affected / exposed                          | 1 / 76 (1.32%) | 0 / 73 (0.00%) | 0 / 77 (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%) | 1 / 73 (1.37%) | 0 / 77 (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                     | 3 / 76 (3.95%) | 3 / 73 (4.11%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 5          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 73 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Clostridium difficile infection                 |                |                |                |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 73 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cystitis  |                |                |                |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 73 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epididymitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (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          |
| Erysipelas                                      |                |                |                |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 73 (0.00%) | 1 / 77 (1.30%) |
| 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 / 76 (0.00%) | 1 / 73 (1.37%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 16 April 2018 | <ul style="list-style-type: none"><li>• Decrease in sample size from 408 to 330 subjects; statistical power lowered from 90% to 80%.</li><li>• Clarification added regarding the primary analysis (i.e. previously referred to as an 'interim' analysis).</li><li>• Removal of the internal data monitoring committee.</li><li>• 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).</li></ul> |

Notes:

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### 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. Only primary and key secondary efficacy analyses were performed.

Notes: