



## Clinical trial results:

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

### Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | Y-52-52120-134 |
|-----------------------|----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

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

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

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

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

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

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 27 April 2011 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 2           |
| Country: Number of subjects enrolled | Russian Federation: 36 |
| Country: Number of subjects enrolled | Ukraine: 62            |
| Country: Number of subjects enrolled | Poland: 68             |

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

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 328 |
| From 65 to 84 years                       | 40  |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Dysport NG |

Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

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

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

Arm description:

1 treatment cycle of Dysport

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

Dosage and administration details:

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

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

Arm description:

1 treatment cycle of placebo.

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

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**Dosage and administration details:**

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

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

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**Period 2**

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

**Arms**

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Dysport NG |
|------------------|------------|

Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

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

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Dysport NG |
|-----------------------------------------------------|------------|
| Started                                             | 359        |
| Completed                                           | 346        |
| Not completed                                       | 13         |
| Protocol Violations                                 | 2          |
| Not otherwise specified                             | 2          |
| Withdrawal by Subject                               | 4          |
| Completed study                                     | 4          |
| Adverse Events                                      | 1          |

Notes:

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

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

### Period 3

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

### Arms

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Dysport NG |
|------------------|------------|

Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

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

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

|                |   |
|----------------|---|
| Adverse Events | 1 |
|----------------|---|

#### Period 4

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

#### Arms

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Dysport NG |
|------------------|------------|

Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

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

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

**Period 5**

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

**Arms**

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Dysport NG |
|------------------|------------|

Arm description:

Up to 5 treatment cycles of Dysport NG

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

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

|                                                                        |            |
|------------------------------------------------------------------------|------------|
| Reporting group title                                                  | Dysport NG |
| Reporting group description:<br>Up to 5 treatment cycles of Dysport NG |            |
| Reporting group title                                                  | Dysport    |
| Reporting group description:<br>1 treatment cycle of Dysport           |            |
| Reporting group title                                                  | Placebo    |
| Reporting group description:<br>1 treatment cycle of placebo.          |            |

| Reporting group values             | Dysport NG | Dysport | Placebo |
|------------------------------------|------------|---------|---------|
| Number of subjects                 | 156        | 159     | 54      |
| Age categorical<br>Units: Subjects |            |         |         |

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

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 369   |  |  |

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

## End points

### End points reporting groups

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

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

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

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

## Statistical analyses

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Change From Baseline in Toronto Western Spasmodic Torticollis |
|-----------------|---------------------------------------------------------------|

End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

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

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**Statistical analyses**

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No statistical analyses for this end point

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

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

End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

---

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Treatment Responders Following First Treatment Cycle

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Percentage of Treatment Responders Following First Treatment Cycle |
|-----------------|--------------------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment cycle Baseline and Week 4

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                                                                                                 |                                                                                                                                     |
|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                 | Change From Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Pain Subscale Score for Treatment Cycles 2 to 5 |
| End point description:                                                                          |                                                                                                                                     |
| TWSTRS Pain scores range from 0 (no pain) to 20 (maximum pain).                                 |                                                                                                                                     |
| Analysis based on number (n) of subjects in the Intent to Treat (ITT) population in each Cycle. |                                                                                                                                     |
| End point type                                                                                  | Secondary                                                                                                                           |
| End point timeframe:                                                                            |                                                                                                                                     |
| Treatment cycle Baseline and Week 4                                                             |                                                                                                                                     |

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Change From Baseline in Subject Visual Analogue Score (VAS) |
|-----------------|-------------------------------------------------------------|

## End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Treatment cycle Baseline and Week 4

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

## Statistical analyses

No statistical analyses for this end point

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

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

## End point description:

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

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Treatment cycle Baseline and Week 4

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

### Statistical analyses

No statistical analyses for this end point

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

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

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

2 years

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Dysport NG, 250 U |
|-----------------------|-------------------|

Reporting group description: -

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Dysport NG, 500 U |
|-----------------------|-------------------|

Reporting group description: -

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Dysport NG, 750 U |
|-----------------------|-------------------|

Reporting group description: -

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Dysport NG, 1000 U |
|-----------------------|--------------------|

Reporting group description: -

|                       |                |
|-----------------------|----------------|
| Reporting group title | Dysport, 500 U |
|-----------------------|----------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

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

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

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

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

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

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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported