



## Clinical trial results:

**A phase III, multicentre, double-blind, prospective, randomised, placebo controlled study, assessing the efficacy and safety of Dysport used for the treatment of lower limb spasticity in adult subjects with hemiparesis due to stroke or traumatic brain injury**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2009-015868-34    |
| Trial protocol           | BE CZ SK IT PT HU |
| Global end of trial date | 13 May 2014       |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 17 August 2017  |
| First version publication date | 01 August 2015  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Following the system outage last year; this completed record had been indicated as "Removed from public view". No applicable reason provided in options above therefore 'correction of full data set' chosen. |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | Y-55-52120-140 |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01249404 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Ipsen Pharma SAS  |
| Sponsor organisation address | 65 quai Georges Gorse, Boulogne-Billancourt, France, 92100    |
| Public contact               | Medical Director, Ipsen Pharma SAS, clinical.trials@ipsen.com |
| Scientific contact           | Medical Director, Ipsen Pharma SAS, 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                       | 10 April 2015 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 13 May 2014   |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary study objective is to assess the efficacy of Dysport compared to placebo at Week 4 on the change from baseline in the gastrocnemius-soleus complex (GSC) muscle tone (knee extended) in hemiparetic subjects with lower limb spasticity due to stroke or traumatic brain injury.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Placebo

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 29 March 2011    |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 6 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 86             |
| Country: Number of subjects enrolled | Portugal: 12           |
| Country: Number of subjects enrolled | Slovakia: 16           |
| Country: Number of subjects enrolled | Belgium: 19            |
| Country: Number of subjects enrolled | Czech Republic: 18     |
| Country: Number of subjects enrolled | France: 54             |
| Country: Number of subjects enrolled | Hungary: 15            |
| Country: Number of subjects enrolled | Italy: 24              |
| Country: Number of subjects enrolled | Australia: 43          |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | United States: 68      |
| Worldwide total number of subjects   | 385                    |
| EEA total number of subjects         | 244                    |

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)                      | 319 |
| From 65 to 84 years                       | 66  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter study conducted in 62 investigational sites. Subjects were screened at 53 centers and in 52 centers subjects were randomized to receive study treatment.

### Pre-assignment

Screening details:

Subjects randomized were 388 and 385 subjects who received treatment were included in the safety population. Only 381 subjects were included in the intent-to-treat (ITT) population. Subjects excluded from ITT population were 7 (including 4 subjects due to no MAS score at the baseline and/or at Week 4).

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 456 <sup>[1]</sup> |
| Number of subjects completed | 388                |

### Pre-assignment subject non-completion reasons

|                            |                        |
|----------------------------|------------------------|
| Reason: Number of subjects | Screening Failures: 68 |
|----------------------------|------------------------|

Notes:

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

Justification: The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Either resolve this issue or provide a justification.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Randomised Population   |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

### Arms

|                              |                |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes            |
| <b>Arm title</b>             | Dysport 1000 U |

Arm description:

Dysport 1000 U intramuscular injection single treatment cycle on day 1

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

Dosage and administration details:

Dysport 1000 U intramuscular injection single treatment cycle on day 1

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Dysport 1500 U |
|------------------|----------------|

Arm description:

Dysport 1500 U intramuscular injection single treatment cycle on day 1

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name                                 | Dysport                           |
| Investigational medicinal product code                                 |                                   |
| Other name   |                                   |
| Pharmaceutical forms   | Powder for solution for injection |
| Routes of administration   | Intramuscular use                 |
| Dosage and administration details:                                     |                                   |
| Dysport 1500 U intramuscular injection single treatment cycle on day 1 |                                   |
| <b>Arm title</b>   | Placebo                           |

Arm description:

Placebo intramuscular injection single treatment cycle on day 1

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

Dosage and administration details:

Placebo intramuscular injection single treatment cycle on day 1

| <b>Number of subjects in period 1</b>  | Dysport 1000 U | Dysport 1500 U | Placebo |
|--|----------------|----------------|---------|
| Started                                | 127            | 129            | 132     |
| Completed                              | 125            | 128            | 128     |
| Not completed                          | 2              | 1              | 4       |
| Did not meet entry criteria            | -              | -              | 2       |
| No functional need for Dysport         | -              | 1              | -       |
| No MAS score at baseline and/or Week 4 | 2              | -              | 2       |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Treatment phase - ITT   |
| Is this the baseline period? | Yes <sup>[2]</sup>      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

## Arms

|  |                |
|--|----------------|
| Are arms mutually exclusive?   | Yes            |
| <b>Arm title</b>   | Dysport 1000 U |
| Arm description:   |                |
| Dysport 1000 U intramuscular injection single treatment cycle on day 1 |                |
| Arm type   | Experimental   |

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name                                 | Dysport                           |
| Investigational medicinal product code                                 |                                   |
| Other name   |                                   |
| Pharmaceutical forms   | Powder for solution for injection |
| Routes of administration   | Intramuscular use                 |
| Dosage and administration details:                                     |                                   |
| Dysport 1000 U intramuscular injection single treatment cycle on day 1 |                                   |
| <b>Arm title</b>   | Dysport 1500 U                    |

Arm description:

Dysport 1500 U intramuscular injection single treatment cycle on day 1

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

Dosage and administration details:

Dysport 1500 U intramuscular injection single treatment cycle on day 1

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

Arm description:

Placebo intramuscular injection single treatment cycle on day 1

|  |                    |
|--|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo Comparator |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Injection          |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

Placebo intramuscular injection single treatment cycle on day 1

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is not the baseline period. It is expected that period 1 will be the baseline period. Either resolve this issue or provide a justification

| <b>Number of subjects in period 2<sup>[3]</sup></b> | Dysport 1000 U | Dysport 1500 U | Placebo |
|---|----------------|----------------|---------|
| Started   | 125            | 128            | 128     |
| Completed   | 120            | 121            | 125     |
| Not completed                                       | 5              | 7              | 3       |
| Consent withdrawn by subject                        | 2              | 2              | -       |
| Adverse event, non-fatal                            | 2              | 2              | 2       |
| Unspecified   | 1              | 3              | 1       |

Notes:

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

Justification: The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Either resolve this issue or provide a justification.

## Baseline characteristics

### Reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Dysport 1000 U |
| Reporting group description:   |                |
| Dysport 1000 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Dysport 1500 U |
| Reporting group description:   |                |
| Dysport 1500 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Placebo        |
| Reporting group description:   |                |
| Placebo intramuscular injection single treatment cycle on day 1        |                |

| Reporting group values | Dysport 1000 U | Dysport 1500 U | Placebo |
|------------------------|----------------|----------------|---------|
| Number of subjects     | 125            | 128            | 128     |
| Age categorical        |                |                |         |
| Units: Subjects        |                |                |         |
| Adults (18-80 years)   | 125            | 128            | 128     |
| Age continuous         |                |                |         |
| ITT Population         |                |                |         |
| Units: years           |                |                |         |
| arithmetic mean        | 53.2           | 53.3           | 51.4    |
| standard deviation     | ± 13.2         | ± 12           | ± 12.9  |
| Gender categorical     |                |                |         |
| Units: Subjects        |                |                |         |
| Female                 | 38             | 49             | 38      |
| Male                   | 87             | 79             | 90      |
| Race                   |                |                |         |
| ITT Population         |                |                |         |
| Units: Subjects        |                |                |         |
| Asian                  | 3              | 4              | 3       |
| African American       | 5              | 13             | 5       |
| Caucasian/White        | 116            | 109            | 119     |
| Hawaiian/Pacific       | 0              | 1              | 0       |
| Multiple               | 1              | 1              | 1       |
| Ethnicity              |                |                |         |
| ITT Population         |                |                |         |
| Units: Subjects        |                |                |         |
| Hispanic               | 14             | 11             | 11      |
| Not Hispanic           | 111            | 117            | 117     |
| Weight                 |                |                |         |
| ITT Population         |                |                |         |
| Units: kg              |                |                |         |
| arithmetic mean        | 79.6           | 80.1           | 79.7    |
| standard deviation     | ± 16.5         | ± 14.8         | ± 17.9  |
| BMI                    |                |                |         |
| ITT Population         |                |                |         |
| Units: kg/m2           |                |                |         |
| arithmetic mean        | 27.3           | 27.3           | 27.4    |

|  |        |        |       |
|--|--------|--------|-------|
| standard deviation                             | ± 5    | ± 4.1  | ± 5.2 |
| MAS score at Baseline                          |        |        |       |
| Units: Units on a scale                        |        |        |       |
| arithmetic mean                                | 3.8    | 3.7    | 3.9   |
| standard deviation                             | ± 0.5  | ± 0.5  | ± 0.5 |
| Barefoot Comfortable Walking Speed at Baseline |        |        |       |
| Units: m/s                                     |        |        |       |
| arithmetic mean                                | 0.44   | 0.47   | 0.45  |
| standard deviation                             | ± 0.23 | ± 0.22 | ± 0.2 |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | Total |  |  |
| Number of subjects            | 381   |  |  |
| Age categorical               |       |  |  |
| Units: Subjects               |       |  |  |
| Adults (18-80 years)          | 381   |  |  |
| Age continuous                |       |  |  |
| ITT Population                |       |  |  |
| Units: years                  |       |  |  |
| arithmetic mean               | -     |  |  |
| standard deviation            |       |  |  |
| Gender categorical            |       |  |  |
| Units: Subjects               |       |  |  |
| Female                        | 125   |  |  |
| Male                          | 256   |  |  |
| Race                          |       |  |  |
| ITT Population                |       |  |  |
| Units: Subjects               |       |  |  |
| Asian                         | 10    |  |  |
| African American              | 23    |  |  |
| Caucasian/White               | 344   |  |  |
| Hawaiian/Pacific              | 1     |  |  |
| Multiple                      | 3     |  |  |
| Ethnicity                     |       |  |  |
| ITT Population                |       |  |  |
| Units: Subjects               |       |  |  |
| Hispanic                      | 36    |  |  |
| Not Hispanic                  | 345   |  |  |
| Weight                        |       |  |  |
| ITT Population                |       |  |  |
| Units: kg                     |       |  |  |
| arithmetic mean               | -     |  |  |
| standard deviation            |       |  |  |
| BMI                           |       |  |  |
| ITT Population                |       |  |  |
| Units: kg/m2                  |       |  |  |
| arithmetic mean               | -     |  |  |
| standard deviation            |       |  |  |
| MAS score at Baseline         |       |  |  |
| Units: Units on a scale       |       |  |  |
| arithmetic mean               | -     |  |  |
| standard deviation            |       |  |  |



|  |   |  |  |
|--|---|--|--|
| Barefoot Comfortable Walking Speed at Baseline |   |  |  |
| Units: m/s                                     |   |  |  |
| arithmetic mean                                |   |  |  |
| standard deviation                             | - |  |  |

## End points

### End points reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Dysport 1000 U |
| Reporting group description:<br>Dysport 1000 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Dysport 1500 U |
| Reporting group description:<br>Dysport 1500 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Placebo        |
| Reporting group description:<br>Placebo intramuscular injection single treatment cycle on day 1        |                |
| Reporting group title  | Dysport 1000 U |
| Reporting group description:<br>Dysport 1000 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Dysport 1500 U |
| Reporting group description:<br>Dysport 1500 U intramuscular injection single treatment cycle on day 1 |                |
| Reporting group title  | Placebo        |
| Reporting group description:<br>Placebo intramuscular injection single treatment cycle on day 1        |                |

### Primary: Change from baseline in Modified Ashworth Scale (MAS) score in the Gastrocnemius Soleus Complex (Knee Extended)

|  |  |
|--|--|
| End point title  | Change from baseline in Modified Ashworth Scale (MAS) score in the Gastrocnemius Soleus Complex (Knee Extended) <sup>[1]</sup> |
| End point description:<br>Intention to treat (ITT) population  |  |
| MAS is a 6-point scale which measures the amount of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. A low score indicated little or no stiffness (best). A high score indicated severe stiffness (worse). The number of participants in each score category is presented |  |
| End point type   | Primary  |
| End point timeframe:<br>At week 4  |  |

Notes:

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

Justification: No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Either resolve this issue or provide a justification.

| End point values                             | Dysport 1000 U      | Dysport 1500 U      | Placebo             |  |
|--|---------------------|---------------------|---------------------|--|
| Subject group type                           | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                  | 125                 | 128                 | 128                 |  |
| Units: Units on a scale                      |                     |                     |                     |  |
| least squares mean (confidence interval 95%) |                     |                     |                     |  |
| MAS score change from Baseline to Week 4     | -0.6 (-0.8 to -0.5) | -0.8 (-0.9 to -0.7) | -0.5 (-0.7 to -0.4) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Physician's Global Assessment of Treatment Response

|                 |   |
|-----------------|---|
| End point title | Physician's Global Assessment of Treatment Response |
|-----------------|---|

End point description:

ITT Population

Physician's Global Assessment (PGA) is a 9 points scale used to assess global overall treatment response by the investigator (-4: markedly worse, -3: much worse, -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved and +4: markedly improved).

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

End point timeframe:

At week 4

| End point values                             | Dysport 1000<br>U | Dysport 1500<br>U | Placebo          |  |
|--|-------------------|-------------------|------------------|--|
| Subject group type                           | Reporting group   | Reporting group   | Reporting group  |  |
| Number of subjects analysed                  | 125               | 128               | 128              |  |
| Units: Units on a scale                      |                   |                   |                  |  |
| least squares mean (confidence interval 95%) | 0.9 (0.7 to 1.1)  | 0.9 (0.7 to 1.1)  | 0.7 (0.5 to 0.9) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Comfortable Barefoot Walking Speed (Without Walking Aids)

|                 |   |
|-----------------|---|
| End point title | Change from baseline in Comfortable Barefoot Walking Speed (Without Walking Aids) |
|-----------------|---|

End point description:

ITT Population

Barefoot Comfortable Walking (BCW)

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

End point timeframe:

At week 4

| <b>End point values</b>                      | Dysport 1000<br>U   | Dysport 1500<br>U   | Placebo             |  |
|--|---------------------|---------------------|---------------------|--|
| Subject group type                           | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                  | 124                 | 127                 | 126                 |  |
| Units: m/s                                   |                     |                     |                     |  |
| least squares mean (confidence interval 95%) |                     |                     |                     |  |
| BCW Speed from Baseline to Week 4            | 0.05 (0.03 to 0.07) | 0.04 (0.03 to 0.06) | 0.05 (0.03 to 0.07) |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 24 ±2 weeks

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

### Dictionary used

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

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

### Reporting groups

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

Reporting group description:

Safety Population

|                       |                |
|-----------------------|----------------|
| Reporting group title | Dysport 1500 U |
|-----------------------|----------------|

Reporting group description:

Safety Population

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

Reporting group description:

Safety Population

| Serious adverse events  | Dysport 1000 U  | Dysport 1500 U  | Placebo         |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                 |                 |
| subjects affected / exposed   | 5 / 127 (3.94%) | 5 / 128 (3.91%) | 7 / 130 (5.38%) |
| number of deaths (all causes)                                       | 0               | 0               | 2               |
| number of deaths resulting from adverse events                      | 0               | 0               | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Pancreatic carcinoma  |                 |                 |                 |
| subjects affected / exposed   | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 130 (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           |
| Injury, poisoning and procedural complications                      |                 |                 |                 |
| Femur fracture  |                 |                 |                 |
| subjects affected / exposed   | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 130 (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           |
| Humerus fracture  |                 |                 |                 |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 127 (0.79%)                           | 0 / 128 (0.00%) | 0 / 130 (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           |
| Femoral neck fracture                           |   |                 |                 |
| subjects affected / exposed                     | 0 / 127 (0.00%)                           | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0                                     | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                     | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |   |                 |                 |
| Atrial septal defect                            |   |                 |                 |
| subjects affected / exposed                     | 0 / 127 (0.00%)                           | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0                                     | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                     | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |   |                 |                 |
| Sinus tachycardia                               |   |                 |                 |
| subjects affected / exposed                     | 1 / 127 (0.79%)                           | 0 / 128 (0.00%) | 0 / 130 (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           |
| Nervous system disorders                        |   |                 |                 |
| Cerebrovascular accident                        | Additional description: Safety Population |                 |                 |
| subjects affected / exposed                     | 0 / 127 (0.00%)                           | 1 / 128 (0.78%) | 0 / 130 (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           |
| Convulsion                                      |   |                 |                 |
| subjects affected / exposed                     | 2 / 127 (1.57%)                           | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2                                     | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                     | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |   |                 |                 |
| subjects affected / exposed                     | 0 / 127 (0.00%)                           | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0                                     | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                     | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |   |                 |                 |
| subjects affected / exposed                     | 0 / 127 (0.00%)                           | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0                                     | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                     | 0 / 0           | 0 / 1           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Blood and lymphatic system disorders                 |                 |                 |                 |
| Anaemia  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Pulmonary embolism                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Musculoskeletal and connective tissue disorders      |                 |                 |                 |
| Muscular weakness                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 130 (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                          |                 |                 |                 |
| Appendicitis   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 130 (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           |
| Post procedural infection                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Dysport 1000 U                            | Dysport 1500 U    | Placebo           |
|---|---|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |   |                   |                   |
| subjects affected / exposed                           | 55 / 127 (43.31%)                         | 52 / 128 (40.63%) | 41 / 130 (31.54%) |
| Injury, poisoning and procedural complications        |   |                   |                   |
| Fall  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 12 / 127 (9.45%)                          | 8 / 128 (6.25%)   | 4 / 130 (3.08%)   |
| occurrences (all)                                     | 14  | 9                 | 8                 |
| Nervous system disorders                              |   |                   |                   |
| Headache  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 0 / 127 (0.00%)                           | 4 / 128 (3.13%)   | 1 / 130 (0.77%)   |
| occurrences (all)                                     | 0   | 5                 | 1                 |
| Convulsion  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 4 / 127 (3.15%)                           | 0 / 128 (0.00%)   | 1 / 130 (0.77%)   |
| occurrences (all)                                     | 4   | 0                 | 1                 |
| Paraesthesia  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 2 / 127 (1.57%)                           | 0 / 128 (0.00%)   | 3 / 130 (2.31%)   |
| occurrences (all)                                     | 2   | 0                 | 3                 |
| General disorders and administration site conditions  |   |                   |                   |
| Fatigue   | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 1 / 127 (0.79%)                           | 5 / 128 (3.91%)   | 0 / 130 (0.00%)   |
| occurrences (all)                                     | 2   | 5                 | 0                 |
| Asthenia  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 3 / 127 (2.36%)                           | 1 / 128 (0.78%)   | 1 / 130 (0.77%)   |
| occurrences (all)                                     | 3   | 1                 | 2                 |
| Influenza like illness                                | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 3 / 127 (2.36%)                           | 0 / 128 (0.00%)   | 0 / 130 (0.00%)   |
| occurrences (all)                                     | 3   | 0                 | 0                 |
| Psychiatric disorders                                 |   |                   |                   |
| Depression  | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 2 / 127 (1.57%)                           | 4 / 128 (3.13%)   | 0 / 130 (0.00%)   |
| occurrences (all)                                     | 2   | 4                 | 0                 |
| Musculoskeletal and connective tissue disorders       |   |                   |                   |
| Pain in extremity                                     | Additional description: Safety Population |                   |                   |
| subjects affected / exposed                           | 7 / 127 (5.51%)                           | 8 / 128 (6.25%)   | 3 / 130 (2.31%)   |
| occurrences (all)                                     | 7   | 9                 | 3                 |
| Muscular weakness                                     | Additional description: Safety Population |                   |                   |



|  |   |                      |                      |
|--|---|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 127 (2.36%)<br>3                      | 8 / 128 (6.25%)<br>9 | 4 / 130 (3.08%)<br>4 |
| Arthralgia                                       | Additional description: Safety Population |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 5 / 127 (3.94%)<br>5                      | 3 / 128 (2.34%)<br>4 | 1 / 130 (0.77%)<br>1 |
| Myalgia  | Additional description: Safety Population |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 3 / 127 (2.36%)<br>3                      | 2 / 128 (1.56%)<br>2 | 2 / 130 (1.54%)<br>2 |
| Back pain  |   |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 4 / 127 (3.15%)<br>4                      | 0 / 128 (0.00%)<br>0 | 2 / 130 (1.54%)<br>2 |
| Infections and infestations                      |   |                      |                      |
| Nasopharyngitis                                  | Additional description: Safety Population |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                      | 3 / 128 (2.34%)<br>3 | 2 / 130 (1.54%)<br>2 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 18 April 2011    | Amendment 2:<br>The procedure for blinding and breaking the blind was clarified.<br>The statistical methodology for the primary and first secondary efficacy endpoints was modified to account for separate registration in US and non-US countries.  |
| 09 February 2012 | Amendment 3:<br>The definition of naïve and non naïve subjects was clarified following questions raised by the investigators. A naïve subject was one who had never received any BTX in the affected lower limb.<br>Criterion 6, regarding exclusion due to surgery was clarified and made more specific to refer only to surgery for spasticity on the affected lower limb.<br>Exclusion criterion 19 was added to exclude the use of intrathecal baclofen during the course of the study or during the 4 weeks before entering the study.<br>The study duration was amended to reflect new timelines and a delay in subject recruitment.  |
| 12 July 2012     | Amendment 4:<br>Inclusion criterion 3 was altered to allow entry into the study of subjects with a nonevolutive lesion diagnosed before the stroke and in the same cerebral hemisphere.<br>Inclusion criterion 7 was altered to include subjects with a spasticity angle greater than or equal to 5 degrees (instead of greater than 5 degrees) in the GSC of the affected leg as assessed by the TS.<br>The wording of Section 9.5 was amended to clarify the meaning and take into account all possibilities regarding used and unused treatments and empty boxes for destruction.<br>References to sponsor's CDDS Department were amended to Statistics Department.<br>The pharmacovigilance/emergency contact details for the USA were updated. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported