



Clinical trial results:

Phase II, Randomised, Double-blind, Dose-ranging Study in Children and Young People to determine the Optimal Dose of Botulinum Toxin Type-A (Dysport®) in Managing the Symptoms of Hip Muscle Spasticity due to Cerebral Palsy.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2005-001794-10 |
| Trial protocol | GB |
| Global end of trial date | 17 March 2008 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 22 April 2017 |
| First version publication date | 22 April 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | Y-97-52120-727 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00455637 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ipsen Ltd. |
| Sponsor organisation address | Bath Road, Slough, United Kingdom, |
| Public contact | Medical Director, Ipsen Ltd., clinical.trials@ipsen.com |
| Scientific contact | Medical Director, Ipsen Ltd., 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? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 March 2008 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 March 2008 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 March 2008 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To compare the effectiveness of 3 doses of Dysport® (5, 10 or 15 units per kilogram [kg] per hip) in the management of chronic bilateral hip pain due to Cerebral Palsy in children/young people.

Protection of trial subjects:

The clinical study was conducted in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, under the ethical principles laid down in the Declaration of Helsinki. In addition, this clinical study adhered to all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 16 April 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Worldwide total number of subjects | 6 |
| EEA total number of subjects | 6 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 2 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 1 centre in the United Kingdom. A recommendation from the ethics committee to allow only patients with bilateral hip pain to be included significantly reduced the original patient pool. A total of 6 eligible children/young people were enrolled. The study was prematurely terminated with only 6 patients recruited.

Pre-assignment

Screening details:

A screening visit was performed 4 weeks before study entry. All 6 screened subjects were enrolled in the study.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dysport® 5 units/kg/hip |

Arm description:

Dysport® was administered at 5 units/kg/hip up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had clinically significant (CS) pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Dysport® |
| Investigational medicinal product code | |
| Other name | Clostridium botulinum type A toxin haemagglutinin complex, Abobotulinum toxin A |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Dysport® was presented as a white lyophilised powder for reconstitution, containing 500 units (nominal) Clostridium botulinum type A toxin haemagglutinin complex together with 125 micrograms (mcg) of human serum albumin and 2.5 milligrams (mg) of lactose in a glass vial. Once reconstituted, the study medication was administered by intramuscular injection into the Adductor Magnus, Iliopsoas and the Medial Hamstring or Rectus Femorus group.

| | |
|------------------|--------------------------|
| Arm title | Dysport® 10 units/kg/hip |
|------------------|--------------------------|

Arm description:

Dysport® was administered at 10 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

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

| | |
|--|---|
| Investigational medicinal product name | Dysport® |
| Investigational medicinal product code | |
| Other name | Clostridium botulinum type A toxin haemagglutinin complex, Abobotulinum toxin A |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Dysport® was presented as a white lyophilised powder for reconstitution, containing 500 units (nominal) Clostridium botulinum type A toxin haemagglutinin complex together with 125 mcg of human serum albumin and 2.5 mg of lactose in a glass vial. Once reconstituted, the study medication was administered by intramuscular injection into the Adductor Magnus, Iliopsoas and the Medial Hamstring or Rectus Femorus group.

| | |
|------------------|--------------------------|
| Arm title | Dysport® 15 units/kg/hip |
|------------------|--------------------------|

Arm description:

Dysport® was administered at 15 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Dysport® |
| Investigational medicinal product code | |
| Other name | Clostridium botulinum type A toxin haemagglutinin complex, Abobotulinum toxin A |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Dysport® was presented as a white lyophilised powder for reconstitution, containing 500 units (nominal) Clostridium botulinum type A toxin haemagglutinin complex together with 125 mcg of human serum albumin and 2.5 mg of lactose in a glass vial. Once reconstituted, the study medication was administered by intramuscular injection into the Adductor Magnus, Iliopsoas and the Medial Hamstring or Rectus Femorus group.

| Number of subjects in period 1 | Dysport® 5 units/kg/hip | Dysport® 10 units/kg/hip | Dysport® 15 units/kg/hip |
|---------------------------------------|-------------------------|--------------------------|--------------------------|
| Started | 2 | 2 | 2 |
| Completed | 2 | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dysport® 5 units/kg/hip |
|-----------------------|-------------------------|

Reporting group description:

Dysport® was administered at 5 units/kg/hip up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had clinically significant (CS) pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|-----------------------|--------------------------|
| Reporting group title | Dysport® 10 units/kg/hip |
|-----------------------|--------------------------|

Reporting group description:

Dysport® was administered at 10 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|-----------------------|--------------------------|
| Reporting group title | Dysport® 15 units/kg/hip |
|-----------------------|--------------------------|

Reporting group description:

Dysport® was administered at 15 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| Reporting group values | Dysport® 5 units/kg/hip | Dysport® 10 units/kg/hip | Dysport® 15 units/kg/hip |
|--|-------------------------|--------------------------|--------------------------|
| Number of subjects | 2 | 2 | 2 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 1 | 1 |
| Adolescents (12-17 years) | 2 | 1 | 1 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 2 | 0 |
| Male | 2 | 0 | 2 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 6 | | |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | | | |

| | | | |
|---|---|--|--|
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 2 | | |
| Adolescents (12-17 years) | 4 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 2 | | |
| Male | 4 | | |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | Dysport® 5 units/kg/hip |
| Reporting group description: Dysport® was administered at 5 units/kg/hip up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had clinically significant (CS) pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20. | |
| Reporting group title | Dysport® 10 units/kg/hip |
| Reporting group description: Dysport® was administered at 10 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20. | |
| Reporting group title | Dysport® 15 units/kg/hip |
| Reporting group description: Dysport® was administered at 15 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20. | |

Primary: Change in Score in the Paediatric Pain Profile (PPP) from Baseline to Week 4.

| | |
|---|--|
| End point title | Change in Score in the Paediatric Pain Profile (PPP) from Baseline to Week 4. ^[1] |
| End point description: The PPP completed by the patient's parent/guardian was assessed by the Investigator at Screening, Baseline and at Weeks 4, 12, 16 and 20. The primary end point was the change in score in the PPP at Week 4 in comparison to Baseline. | |
| End point type | Primary |
| End point timeframe: 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 Analysis Performed.

| End point values | Dysport® 5 units/kg/hip | Dysport® 10 units/kg/hip | Dysport® 15 units/kg/hip | |
|-----------------------------|-------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| Units: Not Applicable | | | | |

Notes:

[2] - Due to the small sample of patients, end point data was listed only. No summarised results reported.

[3] - Due to the small sample of patients, end point data was listed only. No summarised results reported.

[4] - Due to the small sample of patients, end point data was listed only. No summarised results reported.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 20

Adverse event reporting additional description:

Adverse events (AEs) were monitored from the time that the patient gave informed consent to the end of the study. Treatment-emergent AEs (TEAEs) are reported.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dysport® 5 units/kg/hip |
|-----------------------|-------------------------|

Reporting group description:

Dysport® was administered at 5 units/kg/hip up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|-----------------------|--------------------------|
| Reporting group title | Dysport® 15 units/kg/hip |
|-----------------------|--------------------------|

Reporting group description:

Dysport® was administered at 15 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| | |
|-----------------------|--------------------------|
| Reporting group title | Dysport® 10 units/kg/hip |
|-----------------------|--------------------------|

Reporting group description:

Dysport® was administered at 10 units/kg/hip, up to a maximum total dose of 1000 units in a single treatment. Only patients with bilateral hip pain were entered onto the study, therefore the total dosage was divided between both hips. Patients had follow-up visits at 4, 12 and 16 (and if applicable 20) weeks post injection. Patients completed the study at Week 16 if they had CS pain. If the patient did not have CS pain at Week 16, the patient continued in the study for a further 4 weeks and completed the study at Week 20.

| Serious adverse events | Dysport® 5 units/kg/hip | Dysport® 15 units/kg/hip | Dysport® 10 units/kg/hip |
|---|-------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 2 (0.00%) | 0 / 2 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Dysport® 5 units/kg/hip | Dysport® 15 units/kg/hip | Dysport® 10 units/kg/hip |
|---|------------------------------------|-------------------------------------|-------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 2 / 2 (100.00%) | 1 / 2 (50.00%) |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 2 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 January 2006 | <p>The study was altered to reduce the study to a single treatment with 1 of 3 doses of Dysport® for up to 20 weeks.</p> <ul style="list-style-type: none">• The protocol was amended to indicate that a single dose would be given and not a repeat dose.• The evaluation of effectiveness of Dysport® in the management of hip pain was altered to show that change in score in the PPP at all other assessment timepoints and not just the change from baseline to the Week 12 and Week 16 assessments would be assessed.• Assessment of the effect of Dysport® treatment on hip migration percentage as measured on X-ray on completion of the study (Week 28) in comparison to Baseline was removed.• Comparison of the duration of efficacy for the three doses by recording the return of CS pain was added.• The study design was changed to double-blind.• The study duration was changed from 32 to 24 weeks.• It was specified that if the patient was still free from CS pain at Week 16 they would return for a further study visit at Week 20 and that a new diary would be dispensed except at the patient's final visit (Week 16 or Week 20).• The sleep questionnaire was to be completed at Week 12 in addition to Weeks 4 and 16.• Patients were to complete the study at Week 16. If the patient did not have CS pain at Week 16, the patient was to remain in the study for a further 4 weeks and complete an additional final study visit at Week 20.• Sample size considerations were revised.• A section detailing withdrawal criteria and procedures was added. |
| 07 July 2006 | <p>The Independent Ethics Committee suggested that the study was amended to include patients with bilateral hip pain only. The protocol was altered to reflect these accepted changes. This change significantly reduced the original patient pool.</p> |
| 24 November 2006 | <p>Study was re-classified from Phase IV to Phase II as it fell outside the product license for Dysport® in the UK. This change had no impact on study conduct.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to the small patient pool, it was difficult to find eligible patients and the study was prematurely terminated with only 6 patients recruited. No analyses of aggregated patient data was performed and only listings were produced for this study.

Notes: