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	The study was altered to reduce the study to a single treatment with 1 of 3 doses of Dysport® for up to 20 weeks. • 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	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.
24 November 2006	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.

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: