Clinical trial results:
Post-operative pain in children with cerebral palsy following major hip surgery: a double blind randomised placebo controlled trial of pre-operative Botulinum toxin type A. [The Post-Operative Pain in cerebral Palsy (POPPIES) trial]

Summary

EudraCT number	2010-023240-33
Trial protocol	GB
Global end of trial date	07 January 2015

Results information

Result version number	v1 (current)
This version publication date	04 August 2019
First version publication date	04 August 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (Final Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	POPPIES

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01437644
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Dr Fabian Norman-Taylor, Guy's and St Thomas' NHS Foundation Trust, 0044 020 7188 4658, fabian.norman-taylor@gstt.nhs.uk
Scientific contact	Dr Fabian Norman-Taylor, Guy's and St Thomas' NHS Foundation Trust, 0044 020 7188 4658, fabian.norman-taylor@gstt.nhs.uk

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	07 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2015
Global end of trial reached?	Yes
Global end of trial date	07 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the benefit to children with cerebral palsy of having botulinum toxin injections prior to major hip surgery, in order to reduce their post-operative pain.

To describe the pain experience of children with cerebral palsy undergoing major hip surgery.

Protection of trial subjects:

A single dose of active drug or placebo was administered immediately prior to surgery.
The injections were given to the anaesthetised child before the surgical procedure began.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	21 September 2011
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	26
Adolescents (12-17 years)	28
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical paediatric hospital in London between 2011 and 2015

Pre-assignment

Screening details:

Inclusion Criteria
1. The child has displaced hips requiring bony orthopaedic surgery (osteotomy) due to cerebral palsy
2. Is between the ages of 2 and 15 years (inclusive).
3. Has a GMFCS level of IV or V
4. Has a diagnosis of hypertonic cerebral palsy (or a diagnosis consistent with this nomenclature)
5. Does not communicate verbally

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, Carer

Blinding implementation details:

The surgeon or physician will administer medication in syringes containing the trial drug which he is unable to identify as active drug or placebo. The trial drug will be drawn up in six identical syringes for administration to the six muscle groups targeted with either 2 units per kilogram of Botulinum Toxin A or an equivalent volume of normal saline.

Arms

Are arms mutually exclusive?	Yes
Arm title	ACTIVE

Arm description:

Injections of Botulinum neurotoxin A were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings
and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

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

Dosage and administration details:

2 administration and units of Botox® per kilogram c at each site, up to a total of 50 units each site, and a total maximum of 300 units per child. Administered by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was anaesthetised on the day of surgery.

Arm title	PLACEBO

Arm description:

Injections of normal saline were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings
and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

Arm type	Placebo

Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The volume of saline to be prepared per syringe is decided by referring to the study dosing chart and checking the volume related to the child's weight. This chart will be available to the pharmacist, study nurse and anaesthetist to double check in each case.

Number of subjects in period 1	ACTIVE	PLACEBO
Started	27	27
Completed	24	26
Not completed	3	1
Adverse event, serious fatal	-	1
Lost to follow-up	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
<7 years	26	26	
> 7 years	28	28	
Gender categorical Units: Subjects			
Female	23	23	
Male	31	31	

End points

End points reporting groups

Reporting group title	ACTIVE

Reporting group description:

Injections of Botulinum neurotoxin A were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings
and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

Reporting group title	PLACEBO

Reporting group description:

Injections of normal saline were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings
and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

Primary: Post-operative pain score using a validated numerical system (PPP).

End point title	Post-operative pain score using a validated numerical system (PPP).[1]

End point description:

The primary endpoint is the change in pain score during the six weeks following the operation. Pain will be measured using a validated questionnaire, the Paediatric Pain Profile. This scores pain by rating twenty different items of observed behaviour on an ordinal scale of 0 to 3 with a composite score of 0 to 60. It has been validated in children with severe cerebral palsy

End point type	Primary

End point timeframe:

Until six weeks post operation.

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: Please see attached document for full results.

End point values	ACTIVE	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	27		
Units: whole	24	27		

Attachments (see zip file)	Results/POPPIES PUBLICATION.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary

End point title	Secondary

End point description:

Secondary endpoints
The following assessments will be made pre-operatively, at 6 weeks, at 3 months and at 6 months post-surgery:

- Clinical examination of the hips with measurement of ranges of movement
- X-ray measurement of hip displacement using the Migration Index (%), and dysplasia using the Acetabular Index (degrees).
- Quality of life using the CP-CHILD questionnaire

The following secondary endpoints will also be recorded:
- Immediate post-operative pain measured each day while in hospital by a simple parent (or carer) visual analogue scale (and continued weekly at home by the parents or carers for the first six weeks post-operatively with the help of the weekly telephone call).
- Drugs prescribed and given on the ward (from the drug chart).
- Length of hospital stay in days
- Estimated analgesia requirement by recall of analgesia use in the 24 hours prior to each weekly pain assessment during the weekly telephone call.

End point type	Secondary

End point timeframe:

Until 6 weeks post operation.

End point values	ACTIVE	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: whole	27	27		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

0 to six months post operation.

Adverse event reporting additional description:

Ongoing assessment during inpatient stay then follow up as out patient

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	BTX-A
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were 302 adverse events in total (n=156 inBoNT-A group). Of these, none were related to the trial drug, and 219 were unremarkable postoperative findings.There was no evidence of a relationship between trial arm and intensity of adverse events (v2=0.83,p=0.66).

Serious adverse events	BTX-A	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 27 (22.22%)	10 / 27 (37.04%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Surgical and medical procedures			
Hospitalisation - Chest Infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical replacement of loose screw in hip			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical repair of bony protrusion in hip joint			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testes exploration -- de-torsion			

subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 27 (3.70%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar Pontine Giloma			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension & Hypoxia during surgery	Additional description: Hip surgery abandoned post administration of anaesthesia and IMP due to hypoxia and hypotension.		
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hospitalisation - due to constipation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation - due to vomiting & dehydration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture Left arm			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound Infection			

subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital admission - Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prolonged Hospitalisation - Urinary Tract Infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BTX-A	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30644541