Clinical trial results:
BOTOX® Treatment in Adult Patients with Upper Limb Spasticity

Summary

EudraCT number	2013-002346-37
Trial protocol	GB HU
Global end of trial date	14 December 2015

Results information

Result version number	v1 (current)
This version publication date	10 February 2017
First version publication date	10 February 2017

Trial information

Trial identification

Sponsor protocol code	191622-127

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02145676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.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	03 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2015
Global end of trial reached?	Yes
Global end of trial date	14 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a safety and efficacy study of onabotulinumtoxinA in poststroke patients with upper limb spasticity.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2014
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	Canada: 1
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	53
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	41
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Each patient was screened for a period of up to 4 weeks prior to randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	onabotulinumtoxinA 500U

Arm description:

OnabotulinumtoxinA 500U injected into predefined muscles of the study limb on Day 1.

Arm type	Experimental
Investigational medicinal product name	onabotulinumtoxinA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

OnabotulinumtoxinA 500U injected into predefined muscles of the study limb on Day 1.

Arm title	onabotulinumtoxinA 300U

Arm description:

OnabotulinumtoxinA 300U injected into predefined muscles of the study limb on Day 1.

Arm type	Experimental
Investigational medicinal product name	onabotulinumtoxinA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

OnabotulinumtoxinA 300U injected into predefined muscles of the study limb on Day 1.

Arm title	placebo (normal saline)

Arm description:

Placebo (normal saline) injected into predefined muscles of the study limb 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 (normal saline) injected into predefined muscles of the study limb on Day 1.

Number of subjects in period 1	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)
Started	17	18	18
Completed	17	18	18

Baseline characteristics

Reporting groups	
Reporting group title	onabotulinumtoxinA 500U
Reporting group description:	
OnabotulinumtoxinA 500U injected into predefined muscles of the study limb on Day 1.	
Reporting group title	onabotulinumtoxinA 300U
Reporting group description:	
OnabotulinumtoxinA 300U injected into predefined muscles of the study limb on Day 1.	
Reporting group title	placebo (normal saline)
Reporting group description:	
Placebo (normal saline) injected into predefined muscles of the study limb on Day 1.	

Reporting group values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)
Number of subjects	17	18	18
Age categorical Units: Subjects			
Adults (18-64 years)	12	14	15
From 65-84 years	5	4	3
Age Continuous | Units: Years			
arithmetic mean	58.8	59.7	56.2
standard deviation	± 11.46	± 10.36	± 8.3
Gender, Male/Female Units: Participants			
Female	4	8	10
Male	13	10	8

Reporting group values	Total		
Number of subjects	53		
Age categorical Units: Subjects			
Adults (18-64 years)	41		
From 65-84 years	12		
Age Continuous | Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Participants			
Female	22		
Male	31		

End points

End points reporting groups

Reporting group title	onabotulinumtoxinA 500U
Reporting group description:	
OnabotulinumtoxinA 500U injected into predefined muscles of the study limb on Day 1.	
Reporting group title	onabotulinumtoxinA 300U
Reporting group description:	
OnabotulinumtoxinA 300U injected into predefined muscles of the study limb on Day 1.	
Reporting group title	placebo (normal saline)
Reporting group description:	
Placebo (normal saline) injected into predefined muscles of the study limb on Day 1.	

Primary: Change from Baseline in the Modified Ashworth Scale-Bohannon (MAS-B) Score of Elbow Flexors Using a 6-Point Scale

End point title	Change from Baseline in the Modified Ashworth Scale-Bohannon (MAS-B) Score of Elbow Flexors Using a 6-Point Scale[1]

End point description:

The MAS-B is a 6-point scale used to evaluate spasticity based on grading the resistance encountered in the elbow flexors by passively moving the elbow flexor muscles through their range of motion. The score ranges from 0 (no increase in muscle tone) to 4 (affected part(s) rigid in flexion or extension). Scores are converted to a 0 to 5 grade. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Primary

End point timeframe:

Baseline, Week 6

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 is reported for this outcome measure.

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	4.12 (± 0.332)	4.06 (± 0.236)	4.17 (± 0.383)	
Change from Baseline at Week 6 (N=16, 18, 17)	-1.62 (± 1.455)	-1.47 (± 1.247)	-0.74 (± 0.97)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the MAS-B Score of Shoulder Adductors Using a 6-Point Scale

End point title	Change from Baseline in the MAS-B Score of Shoulder

	Adductors Using a 6-Point Scale

End point description:

The MAS-B is a 6-point scale used to evaluate spasticity based on grading the resistance encountered in the shoulder adductors by passively moving the shoulder adductor muscles through their range of motion. The score ranges from 0 (no increase in muscle tone) to 4 (affected part(s) rigid in flexion or extension). Scores are converted to a 0 to 5 grade. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	4 (± 0)	4.06 (± 0.236)	4 (± 0)	
Change from Baseline at Week 6 (N=16, 18, 17)	-1.59 (± 1.263)	-1.39 (± 1.042)	-1.44 (± 1.004)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pain on an 11-Point Scale

End point title	Change from Baseline in Pain on an 11-Point Scale

End point description:

The patient is asked to select a number that best describes his/her pain in the treated areas of the study limb on an 11-point scale from 0 = "no pain" to 10 = "pain as bad as can be imagined". Patients are instructed to recall their average pain in the study limb during the 48-hour period prior to the visit. Patients with a baseline pain score >0 are included in the analyses. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	10	13	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	4.89 (± 2.714)	6.05 (± 3.197)	5.13 (± 3.586)	
Change from Baseline at Week 6 (N=11, 10, 11)	-2.08 (± 3.585)	-2.51 (± 4.606)	-2.64 (± 3.857)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Dressing Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point title	Change from Baseline in the Dressing Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point description:

The SIA-UL asks the patient to assess the impact of upper limb spasticity in his/her daily life on a 19-item scale. The scale covers impacts on activities of dressing, showering/bathing, and self-care. The SIA score ranged from 0 (not at all difficult) to 4 (extremely difficult) for each question. The dressing domain was calculated based on the average of 2 questions.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	2.61 (± 1.346)	2.91 (± 1.123)	2.82 (± 1.092)	
Change from Baseline at Week 6 (N=16, 18, 17)	-0.36 (± 0.854)	-0.27 (± 0.932)	-0.55 (± 1.082)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Showering/Bathing Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point title	Change from Baseline in the Showering/Bathing Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point description:

The SIA-UL asks the patient to assess the impact of upper limb spasticity his/her daily life on a 19-item scale. The scale covers impacts on activities of dressing, showering/bathing, and self-care. The SIA score ranged from 0 (not at all difficult) to 4 (extremely difficult) for each question. The showering/bathing domain was based on a single question.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	2.71 (± 1.231)	2.69 (± 1.263)	2.58 (± 1.188)	
Change from Baseline at Week 6 (N=16, 18, 17)	-0.62 (± 1.147)	-0.36 (± 1.247)	-0.51 (± 1.064)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Self-Care Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point title	Change from Baseline in the Self-Care Domain Score on the Spasticity Impact Assessment-Upper Limb (SIA-UL)

End point description:

The SIA-UL asks the patient to assess the impact of upper limb spasticity in his/her daily life on a 19-item scale. The scale covers impacts on activities of dressing, showering/bathing, and self-care. The SIA score ranged from 0 (not at all difficult) to 4 (extremely difficult) for each question. The self-care domain was calculated based on the average of 4 questions.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	onabotulinumtoxinA 500U	onabotulinumtoxinA 300U	placebo (normal saline)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	2.58 (± 1.234)	2.61 (± 1.189)	2.61 (± 1.086)	
Change from Baseline at Week 6 (N=16, 18, 17)	-0.26 (± 0.779)	-0.21 (± 0.667)	-0.48 (± 1.094)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from signing the informed consent to the end of study (Week 16).

Adverse event reporting additional description:

The Safety Population included all enrolled patients who received a treatment injection. The Safety Population was used to assess adverse events and serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	onabotulinumtoxinA 500U

Reporting group description:

OnabotulinumtoxinA 500U injected into predefined muscles of the study limb on Day 1.

Reporting group title	placebo (normal saline)

Reporting group description:

Placebo (normal saline) injected into predefined muscles of the study limb on Day 1.

Reporting group title	onabotulinumtoxinA 300U

Reporting group description:

OnabotulinumtoxinA 300U injected into predefined muscles of the study limb on Day 1.

Serious adverse events	onabotulinumtoxinA 500U	placebo (normal saline)	onabotulinumtoxinA 300U
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 17 (11.76%)	3 / 18 (16.67%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (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			
Seizure			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	onabotulinumtoxinA 500U	placebo (normal saline)	onabotulinumtoxinA 300U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	7 / 18 (38.89%)	5 / 18 (27.78%)
Investigations			
Electromyogram abnormal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pulmonary function test decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Wrist fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Head injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Seizure			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Seasonal allergy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Large intestine polyp			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Muscular weakness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Sialoadenitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Tooth abscess			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
01 April 2014	The pectoralis minor muscle was removed from the injection paradigm, and its associated dose and volume were reallocated to the pectoralis major muscle.
01 July 2014	Retreatment was removed as an option and the planned EU study sites were eliminated from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported