Clinical trial results:
BOTOX® Treatment in Pediatric Lower Limb Spasticity: Open-label Study

Summary

EudraCT number	2012-000084-24
Trial protocol	DE PL HU IT
Global end of trial date	25 August 2018

Results information

Result version number	v1 (current)
This version publication date	13 March 2019
First version publication date	13 March 2019

Trial information

Trial identification

Sponsor protocol code	191622-112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01603641
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Ltd.
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, clinicaltrials@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	25 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term safety of repeated doses of BOTOX® (botulinum toxin type A) for the treatment of paediatric lower 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	05 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 133
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Korea, Republic of: 93
Country: Number of subjects enrolled	United States: 81
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Philippines: 4
Worldwide total number of subjects	370
EEA total number of subjects	151

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)	313

Adolescents (12-17 years)	57
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Paediatric participants with lower limb spasticity who were previously treated with BOTOX® in study191622-111 [NCT01603628] and de novo participants received up to 5 BOTOX® treatments in this study.

Pre-assignment period milestones

Number of subjects started	370
Number of subjects completed	367

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Receive Treatment: 3

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	BOTOX®

Arm description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

Arm type	Experimental
Investigational medicinal product name	BOTOX®
Investigational medicinal product code	
Other name	Botulinum Toxin Type A OnabotulinumtoxinA
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received intramuscular injections of BOTOX® into the lower and/or upper limbs at a minimum of 12 weeks apart for a maximum of 5 treatments.

Number of subjects in period 1[1]	BOTOX®
Started	367
Modified Intent-to-treat Population	366
Completed	335
Not completed	32
Adverse Event	1
Personal Reasons	18
Lost to follow-up	6
Other Miscellaneous Reasons	6
Lack of efficacy	1

Notes:

[1] - 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: Baseline characteristics were available for safety population, which included all treated participants.

Baseline characteristics

Reporting groups	
Reporting group title	BOTOX®

Reporting group description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

Reporting group values	BOTOX®	Total	
Number of subjects	367	367	
Age categorical Units: Subjects			
2 - 11 years	311	311	
12 - 17 years	56	56	
Age Continuous Units: years			
arithmetic mean	6.9		
standard deviation	± 3.8	-	
Sex: Female, Male Units: Subjects			
Female	167	167	
Male	200	200	
Race/Ethnicity, Customized Units: Subjects			
White	224	224	
Black	9	9	
Asian	109	109	
Hispanic	21	21	
Other	4	4	

End points

End points reporting groups

Reporting group title	BOTOX®

Reporting group description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

Primary: Percentage of Participants with at Least One Treatment-emergent Adverse Event (TEAE)

End point title	Percentage of Participants with at Least One Treatment-emergent Adverse Event (TEAE)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. A TEAE was an AE that occurred after receiving the first dose of investigational product or an AE present prior to first dose but increased in severity during the Treatment Period. Safety population included all treated participants.

End point type	Primary

End point timeframe:

From first dose of study drug up to 12 weeks post last dose (Up to 60 weeks)

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: Statistical analysis was not planned for this endpoint.

End point values	BOTOX®			
Subject group type	Reporting group			
Number of subjects analysed	367			
Units: percentage of participants				
number (not applicable)	65.4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 12 weeks post last dose (Up to 60 weeks)

Adverse event reporting additional description:

Safety Population included all treated participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	BOTOX®

Reporting group description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

Serious adverse events	BOTOX®		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 367 (6.54%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			

subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	4 / 367 (1.09%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hemiplegia			
subjects affected / exposed	2 / 367 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 367 (0.54%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	2 / 367 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Entropion			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Strabismus			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract			

subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	4 / 367 (1.09%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 367 (1.09%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 367 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 367 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BOTOX®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 367 (39.51%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	27 / 367 (7.36%)		
occurrences (all)	40		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	67 / 367 (18.26%)		
occurrences (all)	135		
Nasopharyngitis			
subjects affected / exposed	65 / 367 (17.71%)		
occurrences (all)	101		
Bronchitis			
subjects affected / exposed	21 / 367 (5.72%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2012	•Revised the pronator teres dose from 2 U/kg to 1.5 U/kg and the number of sites from 2 to 1 •Revised approximate volume of blood collection for hematology and chemistry laboratory assessments from 5 millilitres (mL) to 7 mL (participants weighing < 15 kg) and from 12 to 14 mL (participants weighing ≥ 15 kg) to meet revised central laboratory requirements.
28 November 2012	•Added language for diplegic participants, allowing injection of a dose up to 10 U/kg and not to exceed 340 U during Treatment Cycles 2 to 5 when both lower limbs were treated •Changed designation of visit for Exclusion Criterion 23 regarding history of fracture in the study upper limb within 12 months from "prior to the screening visit" to "prior to the Day 1 visit," for consistency with other criteria •For Treatment Cycle 1 for de novo participants, clarified that 8 U/kg was to be injected either in the single study lower limb or divided between both study lower limbs only for diplegic participants; for Treatment Cycles 2 through 5 for all participants, clarified the description of dose limitations • Clarified that participants who met the retreatment criteria "may be reinjected" rather than "should be reinjected" •Clarified language regarding retreatment visits, including determination of whether the dose was clinically appropriate or dose reduction relative to the last injection received was required •Added for Modified Tardieu Scale (MTS) that it should be done with knee extended • For de novo participants, revised to specify Modified Ashworth Scale – Bohannon (MAS-B) was to be done in the ankle of the study limb(s) only (deleted the knee) •Added MAS-B for knee flexors and any other muscles in the treatment plan •Deleted Edinburgh Visual Gait (EVG) score at subsequent Treatment/Retreatment Visit •At Early Discontinuation, corrected "Study Week 42" to "Study Week 48" •Revised language to allow therapists to perform MAS-B.
28 January 2014	•Specified that Columbia-Suicide Severity Rating Scale (C-SSRS) was to be performed as a safety measure for participants ≥ 6 years of age at Day 1, and provided description of scale, data handling, and reference information. Request from US Food and Drug Administration (FDA) •Added a +14-day window to Study Week 48 visit •Modified Exclusion Criterion 13a regarding seizure frequency for exclusion •Modified Exclusion Criterion 14 regarding vulnerable respiratory state •Added Exclusion Criterion 29 to exclude participants with significant suicidality from treatment •Added collection of patient-reported benefit of injection •Clarified that anti-epileptics were permissible during the study •Amended retreatment criteria to specify that participants who experienced certain adverse events, including compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation, would not receive further study treatments •Removed requirement of true equinus foot deformity •Updated serious adverse event (SAE) language •Clarified that physician investigator, not investigator, was to conduct Clinical Global Impression of Overall Change (CGI) by Physician.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported