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

Summary

EudraCT number	2012-000043-27
Trial protocol	DE PL HU IT
Global end of trial date	03 September 2018

Results information

Result version number	v1 (current)
This version publication date	16 March 2019
First version publication date	16 March 2019

Trial information

Trial identification

Sponsor protocol code	191622-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01603615
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, 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	03 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 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 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	30 October 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: 75
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Turkey: 2
Worldwide total number of subjects	220
EEA total number of subjects	83

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)	165

Adolescents (12-17 years)	55
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 Upper Limb Spasticity who were previously treated with BOTOX® in study 191622-101 [NCT01603602] and de novo participants received up to 5 BOTOX® treatments in this study.

Pre-assignment period milestones

Number of subjects started	220
Number of subjects completed	213

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Receive Treatment: 7

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 a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in 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 upper and/or lower limb at a minimum of 12 weeks apart for a maximum of 5 treatments.

Number of subjects in period 1[1]	BOTOX®
Started	213
Completed	186
Not completed	27
Personal Reasons	17
Lost to follow-up	9
Other Miscellaneous Reasons	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 a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in previous study.

Reporting group values	BOTOX®	Total	
Number of subjects	213	213	
Age categorical Units: Subjects			
2 - 11 years	159	159	
12 - 17 years	54	54	
Age Continuous Units: years			
arithmetic mean	8.3		
standard deviation	± 4.1	-	
Sex: Female, Male Units: Subjects			
Female	85	85	
Male	128	128	
Race/Ethnicity, Customized Units: Subjects			
White	130	130	
Black	9	9	
Asian	61	61	
Hispanic	10	10	
Other	3	3	

End points

End points reporting groups

Reporting group title	BOTOX®

Reporting group description:

Participants received a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in 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	213			
Units: percentage of participants				
number (not applicable)	58.7			

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	19.0

Reporting groups

Reporting group title	BOTOX®

Reporting group description:

Participants received a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in previous study.

Serious adverse events	BOTOX®		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 213 (6.10%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 213 (0.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hemiplegia			

subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dental caries			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint contracture			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
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	57 / 213 (26.76%)		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	13 / 213 (6.10%) 14		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 29 / 213 (13.62%) 38 22 / 213 (10.33%) 30		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2012	•Revised to clarify the ideal order of Clinical Global Impression of Overall Change (CGI) and spasticity assessments •Revised the heading from "(2 to 4 Weeks Before Study Day 1)" to "(Up to 4 Weeks Before Study Day 1)" in order to match the schedule of events •Revised approximate volume of blood collection for haematology and chemistry from 5 to 7 mL based on the revised central laboratory requirements.
07 December 2012	•Added language for triplegic participants, to allow dose up to 10 U/kg and not to exceed 340 U to be injected during treatment cycles 2 to 5 when only both lower limbs were treated •Changed exclusion criteria 21 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 •Added to the wording that requires a participant to remain on a stable dose of antispastic medications: to the extent possible unless judged by the investigator to be clinically inappropriate for clarification in Prohibited Medications/Treatments •Added at the study Day 1 visit for both de novo and rollover, the site accessed the IVRS/IWRS to enroll the participant in Method of assignment •The wordings were revised in Treatment Regimen and Dosing to "If a participant met the retreatment criteria, including no indication of an unacceptable safety risk, and it was considered to be clinically appropriate by the investigator, the participant should receive at least 6 U/kg in the study upper limb every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle •Clarified title (Maximum Per-muscle, Per-limb, and Total Body Dose), added row for total maximum dose for both lower limbs, and added footnote to indicate that only 1 upper limb is to be injected •Added For purposes of dose calculation, the participants weight would be rounded to the nearest whole kilogram •Revised to "Participants should may be retreated" if they met the retreatment criteria •Added that study Day 1 is treatment 1/ day 1 for participants who received treatment on that day •Added obtaining study medication kit numbers from and entering exit status to the IVRS/IWRS •Passive range of motion was performed as part of the Modified Tardieu Scale (MTS) and therefore did not need to be identified as a separate procedure.
07 December 2012	•For de novo participants revised to specify (Modified Ashworth Scale-Bohannon) MAS-B was to be done on the elbow and wrist of the study limb •Revised study week 42 to study week 48 in "Early Discontinuation of Patients" section •Added that participants will be withdrawn from the study if they develop a medically significant hypersensitivity reaction to the study drug such as angioedema or anaphylaxis, or if a participant becomes pregnant during the study •Added the same investigator should perform this measure at each visit, if possible in section 12.1.10 MAS for consistency across evaluation •Deleted description of how to measure R1 and R2 in section 12.1.11 MTS.

01 August 2016	•Specified that the Columbia-Suicide Severity Rating Scale (C-SSRS) is 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 as requested by the United States Food and Drug Administration's (US FDA's) Division of Neurology Products •Added a +14-day window to study week 48 visit •Modified Exclusion Criterion 11a regarding seizure frequency for exclusion •Modified Exclusion Criterion 12 regarding vulnerable respiratory state •Added Exclusion Criterion 27 to exclude participants with significant suicidality from treatment •Added patient-reported benefit of injection •Added a sentence on use of anti-epileptics •Amended retreatment criteria to specify that participants who experience certain adverse events will not receive further study treatments •Revised paragraph regarding retreatment for participant with adverse events of compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation •Clarified that passive range of motion can be performed during the MTS •Clarified to remove time frame for blood sample collection •Clarified regarding patient not receiving treatment or retreatment •Clarification on requirements for weight measurements and that weight must be measured in kilograms •Added "temporal, rectal" to body temperature •Revised MAS-B description to say "study specified" instead of "non-study-specified" velocity and provided detail on scoring to clarify that we do instruct the sites on a specific velocity for MAS-B assessment •Clarified "investigator" to "physician investigator."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported