Clinical trial results:
BOTOX® Treatment in Adult Patients With Poststroke Lower Limb Spasticity

Summary

EudraCT number	2011-004980-63
Trial protocol	HU DE GB CZ PL
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	07 September 2016
First version publication date	07 September 2016

Trial information

Trial identification

Sponsor protocol code	191622-116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01575054
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	14 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To primary objective of this trial was to evaluate the efficacy and safety of a single treatment of BOTOX compared with placebo in the treatment of adult poststroke lower limb spasticity involving the ankle plantar flexors.

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	23 May 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	United States: 84
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Czech Republic: 28
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Poland: 136
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Korea, Republic of: 56
Worldwide total number of subjects	468
EEA total number of subjects	246

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	344
From 65 to 84 years	124
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened up to 42 days prior to randomization on Day 1.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	botulinum toxin Type A

Arm description:

Double-Blind Study Phase (12 weeks): On Day 1, botulinum toxin Type A 300 U will be given by intramuscular injections into specified muscles of the lower limb, and an optional dose of 100 U may be injected into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

Arm type	Experimental
Investigational medicinal product name	BOTOX®
Investigational medicinal product code	
Other name	onabotulinumtoxinA, botulinum toxin Type A
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Double-Blind Study Phase (12 weeks): On Day 1, botulinum toxin Type A 300 U will be given by intramuscular injections into specified muscles of the lower limb, and an optional dose of 100 U may be injected into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

Arm title	Normal Saline (Placebo) Followed by botulinum toxin Type A

Arm description:

Double-Blind Study Phase (12 weeks): On Day 1, normal saline (placebo) will be given by intramuscular injections into specified muscles of the lower limb, and optional injections may be administered into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

Arm type	Placebo followed by experimental
Investigational medicinal product name	Normal Saline (Placebo) Followed by botulinum toxin Type A
Investigational medicinal product code	
Other name	BOTOX®
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Double-Blind Study Phase (12 weeks): On Day 1, normal saline (placebo) will be given by intramuscular injections into specified muscles of the lower limb, and optional injections may be administered into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

Number of subjects in period 1	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A
Started	233	235
Completed	204	209
Not completed	29	26
Other Reasons	5	3
Adverse event, non-fatal	9	8
Personal Reasons	10	11
Lost to follow-up	3	3
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	botulinum toxin Type A
Reporting group description:	
Double-Blind Study Phase (12 weeks): On Day 1, botulinum toxin Type A 300 U will be given by intramuscular injections into specified muscles of the lower limb, and an optional dose of 100 U may be injected into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.	
Reporting group title	Normal Saline (Placebo) Followed by botulinum toxin Type A
Reporting group description:	
Double-Blind Study Phase (12 weeks): On Day 1, normal saline (placebo) will be given by intramuscular injections into specified muscles of the lower limb, and optional injections may be administered into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.	

Reporting group values	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A	Total
Number of subjects	233	235	468
Age categorical Units: Subjects			
Adults (18-64 years)	173	171	344
From 65-84 years	60	64	124
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	56	57	
standard deviation	± 12.6	± 11.88	-
Gender, Male/Female Units: Participants			
Female	85	80	165
Male	148	155	303

End points

End points reporting groups

Reporting group title	botulinum toxin Type A

Reporting group description:

Double-Blind Study Phase (12 weeks): On Day 1, botulinum toxin Type A 300 U will be given by intramuscular injections into specified muscles of the lower limb, and an optional dose of 100 U may be injected into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

Reporting group title	Normal Saline (Placebo) Followed by botulinum toxin Type A

Reporting group description:

Double-Blind Study Phase (12 weeks): On Day 1, normal saline (placebo) will be given by intramuscular injections into specified muscles of the lower limb, and optional injections may be administered into additional lower limb muscles. Open Label Study Phase: Up to 3 treatments with botulinum toxin Type A up to 400 U will be given by intramuscular injections to the lower limb approximately every 12 weeks over a 42 week period.

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

End point title	Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Score of Ankle Plantar 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 ankle flexors by passively moving the ankle plantar 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. The average of the weeks 4 and 6 MAS-B ankle change from baseline is the primary end point. 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, 6 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: The MAS-B change from baseline was analyzed by ANCOVA with treatment and study center as factors, and baseline ankle MAS-B (3 vs 4) and muscles injected (mandatory muscles only vs mandatory muscles plus toe muscles vs mandatory muscles plus rectus femoris) as covariates.

End point values	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	235		
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	4.1 (± 0.27)	4.1 (± 0.25)		
Change from Baseline at 6 weeks	-0.81 (± 0.874)	-0.61 (± 0.835)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) of Overall Change by Physician Using a 9-Point Scale

End point title	Clinical Global Impression (CGI) of Overall Change by Physician Using a 9-Point Scale

End point description:

The CGI is a 9-point scale evaluating change from baseline status by the Physician. Scores range from +4 (very marked improvement) to -4 (very marked worsening). The average of the weeks 4 and 6 CGI by Physician score is used as a secondary end point. Higher scores indicate a greater improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, 6 weeks

End point values	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	235		
Units: Scores on a Scale				
least squares mean (standard deviation)	0.86 (± 0.953)	0.65 (± 0.902)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Pain Score While Walking on the 11-Point Pain Scale

End point title	Change from Baseline in Average Pain Score While Walking on the 11-Point Pain Scale

End point description:

The patient is asked to select a number that best describes his/her pain while walking 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.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	164		
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline	4.5 (± 1.95)	4.5 (± 2.13)		
Change from Baseline at Week 6 (N=175, 158)	-0.8 (± 2.3)	-1.1 (± 2.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Score of Optional Muscles Using a 6-Point Scale

End point title	Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Score of Optional Muscles 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 optional muscles by passively moving the muscles through their range of motion. Optional muscles treated include: Rectus Femoris, Flexor Digitorum Longus, Flexor Hallucis Longus, and Extensor Hallucis. The scores range 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	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	133		
Units: Scores on a Scale				
least squares mean (standard deviation)				
Baseline Rectus Femoris (N=25, 25)	3.3 (± 0.58)	3.2 (± 0.59)		
Chng from BL at Wk6 in Rectus Femoris (N=24,25)	-0.9 (± 0.87)	-1 (± 1.14)		
Baseline Flexor Digitorum Longus (N=86,88)	3.3 (± 0.76)	3.4 (± 0.7)		
Chng from BL at Wk6 in Digitorum Longus (N=85,84)	-0.9 (± 1.11)	-0.8 (± 1.22)		
Baseline Flexor Hallucis Longus (N=73,67)	3.1 (± 0.81)	3.2 (± 0.83)		
Chng frm BL at Wk6 Flexor Hallucis Longus(N=72,66)	-1 (± 1.3)	-0.6 (± 1.2)		

Baseline Extensor Hallucis (N=23,13)	3.6 (± 0.49)	3.6 (± 0.51)		
Chng from BL at Wk6 in Extensor Hallucis (N=23,13)	-1.3 (± 1.22)	-1.3 (± 1.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Goal Attainment Scores on the 6-Point Physician-Assessed Goal Attainment Scale (GAS)

End point title	Goal Attainment Scores on the 6-Point Physician-Assessed Goal Attainment Scale (GAS)

End point description:

The physician-assessed GAS is an individualized, goal-oriented 6-point scale used to track functional improvement toward active and passive goals. GAS scoring ranged from −3 to 2 (−3 = worse than start; 0 = expected goal/attained the defined therapeutic goal; 2 = much more than expected/improvements clearly exceeded the defined therapeutic goal). Active and Passive Goal scores are presented.

End point type	Secondary

End point timeframe:

Week 8

End point values	botulinum toxin Type A	Normal Saline (Placebo) Followed by botulinum toxin Type A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	235		
Units: Scores on a Scale				
least squares mean (standard deviation)				
Active Goals (N=226, 228)	-0.8 (± 1.34)	-1 (± 1.33)		
Passive Goals (N=214, 217)	-0.5 (± 1.42)	-0.8 (± 1.33)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were monitored from informed consent signature to the end of study for each subject.

Adverse event reporting additional description:

The safety population during the 12-week double-blind phase included all enrolled patients who received at least 1 treatment injection in the study. The double-blind safety population is used to assess adverse events and serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	botulinum toxin Type A

Reporting group description:

Double-Blind Study Phase (12 weeks): On Day 1, botulinum toxin Type A 300 U will be given by intramuscular injections into specified muscles of the lower limb, and an optional dose of 100 U may be injected into additional lower limb muscles.

Reporting group title	Normal Saline (Placebo)

Reporting group description:

Double-Blind Study Phase (12 weeks): On Day 1, normal saline (placebo) will be given by intramuscular injections into specified muscles of the lower limb, and optional injections may be administered into additional lower limb muscles.

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 no non-serious AEs that met the 5% reporting level.

Serious adverse events	botulinum toxin Type A	Normal Saline (Placebo)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 231 (4.33%)	9 / 233 (3.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bullous lung disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 231 (0.87%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barbiturates positive			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opiates positive			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bifascicular block			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bundle branch block right			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 231 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 231 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	botulinum toxin Type A	Normal Saline (Placebo)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 231 (0.00%)	0 / 233 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2012	1) Patients with contralateral spasticity of clinical significance were excluded; 2) Physical therapy was limited to the study limb and only stated modalities were excluded; 3) An exclusion criterion was added to allow initiation of physical therapy or use of splints prior to randomization, but not afterwards; 4) An exclusion criterion was added to exclude patients with significant weakness in the contralateral leg; 5) An exclusion criterion was added to exclude any other surgeries that may have created scar tissues and could have confounded the efficacy results; 6) A requirement to the secondary efficacy measures was added that the distribution of baseline (randomization) MAS B ankle score throughout enrollment would be monitored to ensure that at least 75% of the enrolled patients had a baseline MAS B ankle score of 3; 7) The measure on MAS B for optional muscles and the Pain scale was changed from "other efficacy measure" to a secondary efficacy measure; 8) A requirement that GAS was to be rated both by the physician and patient was added; and 9) Collection of a BDI-II score at baseline was added.
01 August 2012	1) It was clarified that the BDI-II was to be administered at selected sites only.
01 July 2013	1) The C-SSRS assessment was specified to be performed at all visits; 2) An exclusion criterion was added to exclude patients with significant suicidality from treatment; 3) The CGI by Physician was added as a primary measure; 4) An imputation method was added for the primary efficacy variable; and 5) A subgroup analysis for the 400 U total dose group was added.
01 September 2013	1) Study center was added as a factor to the ANCOVA model for the primary and secondary efficacy analyses; 2) The sample size was revised; and 3) The imputation method was modified to use within-group means.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported