EU Clinical Trials Register

Clinical trial results:
BOTOX® Treatment in Pediatric Lower Limb Spasticity: Double-blind Study

Summary

EudraCT number	2012-000042-35
Trial protocol	DE PL HU IT
Global end of trial date	28 June 2017

Results information

Result version number	v1 (current)
This version publication date	24 June 2018
First version publication date	24 June 2018

Trial information

Trial identification

Sponsor protocol code	191622-111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01603628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	1st Floor Marlow International The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Allergan Limited, EU Regulatory Department, +44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	EU Regulatory Department, 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)	
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	28 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety and efficacy of BOTOX® (botulinum toxin Type A) in pediatric participants with 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	11 September 2012
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	Poland: 137
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Korea, Republic of: 96
Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Philippines: 4
Worldwide total number of subjects	384
EEA total number of subjects	156

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)	326
Adolescents (12-17 years)	58
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:

Pediatric participants with lower limb spasticity were randomized 1:1:1 to one of three treatment groups: BOTOX® 4 or 8 U/kg (unit per kilogram) or placebo.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BOTOX® 8 U/kg

Arm description:

Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 8 units (U) per kg of body weight (8 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly physical therapy (PT).

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® (botulinum toxin Type A) into specified muscles of the lower limb.

Arm title	BOTOX® 4 U/kg

Arm description:

Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 U per kg of body weight (4 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly PT.

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® (botulinum toxin Type A) into specified muscles of the lower limb.

Arm title	Placebo

Arm description:

Participants received intramuscular injections of normal saline (placebo) into specified muscles of the lower limb. Participants received weekly PT.

Arm type	Placebo

Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	0.9% Saline Solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received intramuscular injections into specified muscles of the upper limb.

Number of subjects in period 1	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo
Started	128	126	130
Completed	125	123	128
Not completed	3	3	2
Personal Reasons	1	1	2
Other Miscellaneous Reason	1	-	-
Lost to follow-up	-	1	-
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	BOTOX® 8 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 8 units (U) per kg of body weight (8 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly physical therapy (PT).	
Reporting group title	BOTOX® 4 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 U per kg of body weight (4 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly PT.	
Reporting group title	Placebo
Reporting group description:	
Participants received intramuscular injections of normal saline (placebo) into specified muscles of the lower limb. Participants received weekly PT.	

Reporting group values	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo
Number of subjects	128	126	130
Age categorical			
Units: Subjects			
Children (2-11 years)	108	110	108
Adolescents (12-17 years)	20	16	22
Age Continuous			
Units: years			
arithmetic mean	6.7	6.4	6.6
standard deviation	± 3.9	± 3.6	± 3.9
Sex: Female, Male			
Units: Subjects			
Female	57	58	62
Male	71	68	68
Modified Ashworth Scale-Bohannon (MAS-B) Ankle Score with Knee Extended			
The MAS-B evaluates spasticity, grading the resistance encountered in the principal muscle group (elbow and wrist) by passively moving a limb through its range of motion at a specified velocity. The resistance encountered to passive stretch was graded on a 6-point scale: 0=no increase in muscle tone (best) to 4=affected part(s) rigid in flexion or extension (worst). 2 participants in the Placebo arm are not included in the analysis.			
Units: score on a scale			
arithmetic mean	3.5	3.5	3.5
standard deviation	± 0.52	± 0.53	± 0.50

Reporting group values	Total		
Number of subjects	384		
Age categorical			
Units: Subjects			
Children (2-11 years)	326		
Adolescents (12-17 years)	58		

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	177		
Male	207		
Modified Ashworth Scale-Bohannon (MAS-B) Ankle Score with Knee Extended			
The MAS-B evaluates spasticity, grading the resistance encountered in the principal muscle group (elbow and wrist) by passively moving a limb through its range of motion at a specified velocity. The resistance encountered to passive stretch was graded on a 6-point scale: 0=no increase in muscle tone (best) to 4=affected part(s) rigid in flexion or extension (worst). 2 participants in the Placebo arm are not included in the analysis.			
Units: score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	BOTOX® 8 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 8 units (U) per kg of body weight (8 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly physical therapy (PT).	
Reporting group title	BOTOX® 4 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 U per kg of body weight (4 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly PT.	
Reporting group title	Placebo
Reporting group description:	
Participants received intramuscular injections of normal saline (placebo) into specified muscles of the lower limb. Participants received weekly PT.	
Subject analysis set title	BOTOX® 8 U/kg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 8 units (U) per kg of body weight (8 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly physical therapy (PT).	
Subject analysis set title	BOTOX® 4 U/kg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 U per kg of body weight (4 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly PT.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received intramuscular injections of normal saline (placebo) into specified muscles of the lower limb. Participants received weekly PT.	

Primary: Average Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Ankle Score with Knee Extended at Weeks 4 and 6

End point title	Average Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Ankle Score with Knee Extended at Weeks 4 and 6
End point description:	
The MAS-B was used to evaluate spasticity based on grading the resistance encountered in the principal muscle group (elbow and wrist) by means of passively moving a limb through its range of motion at a study specified velocity. The resistance encountered to passive stretch was graded using a 6-point scale where: 0=no increase in muscle tone (best) to 4=affected part(s) rigid in flexion or extension (worst). The scores at Weeks 4 and 6 were averaged. A Mixed Model Repeated Measures (MMRM) model was used for analysis. A negative change from Baseline indicates improvement. Participants from the mITT population, all randomized participants with a valid MAS-B baseline ankle score with knee extended and at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B of the ankle score with knee extended and the CGI by physician, with data available for analysis.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to Weeks 4 and 6	

End point values	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	119	125	
Units: score on a scale				
least squares mean (standard error)	-1.06 (± 0.071)	-1.01 (± 0.072)	-0.80 (± 0.071)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [1]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.453
upper limit	-0.063

Notes:

[1] - MMRM including baseline MAS-B ankle score (knee extended) as a covariate and factors of age, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age is represented by stratification categories.

Statistical analysis title	Statistical Analysis 2
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [2]
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.405
upper limit	-0.018

Notes:

[2] - MMRM including baseline MAS-B ankle score (knee extended) as a covariate and factors of age, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age is represented by stratification categories.

Secondary: Average Clinical Global Impression (CGI) of Overall Change by Physician at Weeks 4 and 6

End point title	Average Clinical Global Impression (CGI) of Overall Change by Physician at Weeks 4 and 6

End point description:

The CGI of overall change (improvement or worsening) was assessed by the physician considering the participant's clinical condition and severity of side effects using a 9-point scale where: -4=very marked worsening to +4=very marked improvement. The scores at Weeks 4 and 6 were averaged. A Mixed Model Repeated Measures (MMRM) model was used for analysis.

Participants from the mITT population, all randomized participants with a valid MAS-B baseline ankle score with knee extended and at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B of the ankle score with knee extended and the CGI by physician, with data available for analysis.

End point type	Secondary

End point timeframe:	
Weeks 4 and 6	

End point values	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	118	124	
Units: score on a scale				
least squares mean (standard error)	1.65 (± 0.090)	1.49 (± 0.091)	1.36 (± 0.089)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [3]
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.532

Notes:

[3] - MMRM including baseline MAS-B ankle score (knee extended) as a covariate and factors of age, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age is represented by stratification categories.

Statistical analysis title	Statistical Analysis 2
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.299 [4]
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.115
upper limit	0.374

Notes:

[4] - MMRM including baseline MAS-B ankle score (knee extended) as a covariate and factors of age, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age is represented by stratification categories.

Secondary: Goal Attainment Score (GAS) as Assessed by Physician Using a 6-Point Scale

End point title	Goal Attainment Score (GAS) as Assessed by Physician Using a 6-Point Scale

End point description:

Two functional goals, one active and one passive, were selected by the participant and family in consultation with the physician investigator and/or treating physical therapist relative to the lower limb impairment due to spasticity. The physician assessed the achievement of the goals using a 6-point scale: where -3=worse than start to +2=much more than expected: improvements clearly exceed the defined therapeutic goal. An Analysis of Covariance (ANCOVA) model was used for analysis.
The Modified ITT population includes all randomized participants with a valid MAS-B baseline ankle score with knee extended and at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B of the ankle score with knee extended and the CGI by physician, with data available for analysis.

End point type	Secondary

End point timeframe:

Weeks 8 and 12

End point values	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	127	125	129	
Units: score on a scale				
least squares mean (standard error)				
Week 8, Active Goal (n=121, 121, 127)	0.10 (± 0.108)	-0.03 (± 0.108)	-0.31 (± 0.105)	
Week 8, Passive Goal (n=120, 121, 127)	0.19 (± 0.115)	0.18 (± 0.114)	-0.26 (± 0.111)	
Week 12, Active Goal (n=124, 123, 128)	0.37 (± 0.112)	0.09 (± 0.113)	-0.12 (± 0.111)	
Week 12, Passive Goal (n=124, 123, 128)	0.40 (± 0.114)	0.27 (± 0.114)	0.00 (± 0.112)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 8, Active Goal

Comparison groups	BOTOX® 8 U/kg v Placebo

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.126
upper limit	0.704

Notes:

[5] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 8, Active Goal

Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.573

Notes:

[6] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 8, Passive Goal

Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.145
upper limit	0.756

Notes:

[7] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 8, Passive Goal	
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	0.74

Notes:

[8] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 12, Active Goal	
Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [9]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.191
upper limit	0.797

Notes:

[9] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 12, Active Goal

Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153 [10]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	0.541

Notes:

[10] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 12, Passive Goal

Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.711

Notes:

[11] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 12, Passive Goal

Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.571

Notes:

[12] - ANCOVA model including baseline MAS-B ankle score with knee extended as a covariate and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories.

Secondary: Change from Baseline in Severity of Spasticity of the Ankle with Knee Extended and Knee Flexed (R2-R1) Calculated Using the Modified Tardieu Scale (MTS)

End point title	Change from Baseline in Severity of Spasticity of the Ankle with Knee Extended and Knee Flexed (R2-R1) Calculated Using the Modified Tardieu Scale (MTS)

End point description:

The MTS measured the difference between slow and fast range of motion (R2-R1) and respective change from baseline to each posttreatment visit. The MTS of the ankle determined the passive range of movement at different movement velocities, V1 (as slow as possible) and V3 (as fast as possible) with the relative difference between a slow and fast velocity passive stretch determining the dynamic component of the muscle contracture for the joint. The investigator measured 2 joint angles by goniometer: the R1 angle which is the angle of catch after a V3 stretch and the R2 angle defined as the passive joint range of movement following a V1 stretch. The R2–R1 value indicated the level of the dynamic component of spasticity in the joint. The difference between R2 and R1 range of motion and respective change from baseline to each posttreatment office visit on the MTS was derived. An Analysis of Covariance (ANCOVA) model was used for analysis. The mITT population was used for analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 2, 4, 6, 8 and 12

End point values	BOTOX® 8 U/kg	BOTOX® 4 U/kg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	127	125	129	
Units: angle				
least squares mean (standard error)				
Change from Baseline to Week 2 (n=126, 124, 129)	-4.44 (± 1.023)	-5.69 (± 1.024)	-2.44 (± 1.0101)	
Change from Baseline to Week 4 (n-124, 121, 126)	-6.11 (± 1.134)	-6.80 (± 1.135)	-4.69 (± 1.121)	
Change from Baseline to Week 6 (n=126, 121, 126)	-6.65 (± 1.029)	-7.23 (± 1.049)	-3.32 (± 1.029)	
Change from Baseline to Week 8 (n=122, 123, 127)	-5.42 (± 1.317)	-5.82 (± 1.308)	-3.36 (± 1.291)	
Change from Baseline to Week 12 (n=125, 123, 128)	-4.59 (± 1.070)	-3.07 (± 1.074)	-1.98 (± 1.057)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline to Week 2

Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.768
upper limit	0.779

Notes:

[13] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change from Baseline to Week 2

Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.974
upper limit	-0.524

Notes:

[14] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Change from Baseline to Week 4

Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363 [15]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.489
upper limit	1.648

Notes:

[15] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Change from Baseline to Week 4

Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171 [16]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.127
upper limit	0.914

Notes:

[16] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Change from Baseline to Week 6

Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.143
upper limit	-0.525

Notes:

[17] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:	
Change from Baseline to Week 6	
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [18]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.688
upper limit	-1.148

Notes:

[18] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Change from Baseline to Week 8	
Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.254 [19]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.621
upper limit	1.491

Notes:

[19] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Change from Baseline to Week 8	
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165 [20]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.935
upper limit	1.014

Notes:

[20] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Change from Baseline to Week 12	
Comparison groups	BOTOX® 8 U/kg v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 [21]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.517
upper limit	0.296

Notes:

[21] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Change from Baseline to Week 12	
Comparison groups	BOTOX® 4 U/kg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451 [22]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.944
upper limit	1.758

Notes:

[22] - ANCOVA model including baseline MTS ankle score with knee extended as a covariate and factors of age group, treatment group, study center, and previous botulinum toxin exposure where age group is represented by stratification categories.

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Baseline (Day 1) to the end of study (Week 12)	
Adverse event reporting additional description:	
The Safety Population, all treated participants based on the treatment received, was used to determine the number of participants at risk for Serious Adverse Events and Adverse Events.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	BOTOX® 8 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 8 U per kg of body weight (8 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly physical therapy (PT).	
Reporting group title	Placebo
Reporting group description:	
Participants received intramuscular injections of normal saline (placebo) into specified muscles of the lower limb. Participants received weekly PT.	
Reporting group title	BOTOX® 4 U/kg
Reporting group description:	
Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 U per kg of body weight (4 U/kg) into specified muscles of the lower limb on Day 1. Participants received weekly PT.	

Serious adverse events	BOTOX® 8 U/kg	Placebo	BOTOX® 4 U/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 128 (0.00%)	4 / 128 (3.13%)	3 / 126 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 128 (0.00%)	0 / 128 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 128 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Seizure	BOTOX® 8 U/kg	Placebo	BOTOX® 4 U/kg
subjects affected / exposed	0 / 128 (0.00%)	2 / 128 (1.56%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular Pain			
subjects affected / exposed	0 / 128 (0.00%)	1 / 128 (0.78%)	0 / 126 (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
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	0 / 128 (0.00%)	0 / 128 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastoeneteritis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 128 (0.78%)	0 / 126 (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

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

Non-serious adverse events	BOTOX® 8 U/kg	Placebo	BOTOX® 4 U/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 128 (18.75%)	35 / 128 (27.34%)	26 / 126 (20.63%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 128 (3.91%)	7 / 128 (5.47%)	8 / 126 (6.35%)
occurrences (all)	5	14	8
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	12 / 128 (9.38%)	22 / 128 (17.19%)	14 / 126 (11.11%)
occurrences (all)	12	56	19
Upper respiratory tract infection			
subjects affected / exposed	8 / 128 (6.25%)	9 / 128 (7.03%)	10 / 126 (7.94%)
occurrences (all)	9	20	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2012	-The primary efficacy analyses were reworded to specify that if a pairwise comparison in MAS-B was not statistically significant, the corresponding pairwise comparison in CGI by Physician would not be considered statistically significant regardless of the actual p-value. -Addition of Section 7.7 Additional Analysis/Inference for US FDA to clarify when dose effectiveness would be concluded. This change addressed US FDA (United States Food and Drug Administration) comments during Special Protocol Assessment review. -Revised approximate volume of blood collection for hematology and chemistry laboratory assessments from 5 to 7 mL (milliliters) (participants weighing < 15 kg) and from 12 to 14 mL (participants weighing ≥ 15 kg) to meet revised central laboratory requirements. -Revised participant-reported onset of spasticity symptom relief question from "have you noticed any treatment effect…" to "have you noticed any effect…" to minimize potential bias based on central IRB requirement.
28 January 2014	-Amended primarily to add assessment of suicidal ideation/behavior using the C-SSRS as a standard safety measure required by the US FDA's Division of Neurology Products. -Added distinction between US FDA and non-US FDA clinical hypotheses and analyses. -Added participant-reported benefit of injection as an efficacy measure. -Specified that 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 FDA. -Revised Inclusion Criterion and screening procedure to remove requirement of true equinus foot deformity referenced in Rodda and Graham. Clarified gait pattern analysis not required to confirm equinus foot deformity. -Revised Exclusion Criterion to remove definition of significant knee spasticity. -Modified Exclusion Criterion regarding seizure frequency for exclusion. -Added Exclusion Criterion to exclude participants with significant suicidality from treatment so as to avoid data confounding. -Clarified that participants could stay in the study even if prohibited medication was administered -Clarified MTS scale description by adding "with knee extended and knee flexed". -Changed multiple testing procedure to gatekeeping procedure to control type I error rate -Removed pairwise comparison for higher dose versus lower dose to incorporate US FDA recommendation. -Removed overall test for among group comparison. Gatekeeping procedure sufficient to control type I error rate -Removed subgroup efficacy analyses by type of anesthesia. -Revised sample size calculation to base the calculation on 2 sample t test as the overall test for among group comparison was removed. -Removed requirement that urine pregnancy test must be performed prior to study treatment. -Updated serious adverse event reporting procedures -Revised MAS-B description so the assessment could be performed by other qualified site personnel.

25 July 2016	-Protocol amended primarily to modify the statistical methods (introduction of the Hochberg procedure, change in imputation methods, and sensitivity analyses) to reflect the simultaneous changes being made to Protocol 191622-101. -The ITT population was replaced with the mITT population (defined as all randomized participants with a valid MAS-B at baseline of the principal muscle group and ≥ 1 postbaseline measurement at Weeks 2, 4, or 6 for the MAS-B of the principal muscle group and CGI by Physician). Revised based on US FDA recommendation. -Added a responder status based on +1 score of CGI by Physician. -Changed sensitivity analyses of MAS-B and CGI by Physician to use the MI method for missing values instead of observed cases and deleted sensitivity analyses using LOCF. Revised to address US FDA feedback. -Changed primary MAS-B analysis and coprimary MAS-B and CGI by Physician (for US FDA) analyses to use MMRM with observed data; ANCOVA with MI and observed data was used as sensitivity analyses. Revised to address US FDA feedback. -Deleted subgroup analyses of adverse events because deemed unnecessary. -Changed multiple testing procedure (gatekeeping procedure) to Hochberg procedure for the coprimary analysis (for US FDA) to control type I error rate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported