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

Summary

EudraCT number	2012-000062-38
Trial protocol	DE PL HU IT
Global end of trial date	06 July 2017

Results information

Result version number	v1 (current)
This version publication date	11 June 2018
First version publication date	11 June 2018

Trial information

Trial identification

Sponsor protocol code	191622-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01603602
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	EU Regulatory Department, Allergan Limited, +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	06 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 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 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	12 July 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	United States: 63
Country: Number of subjects enrolled	Poland: 79
Country: Number of subjects enrolled	Korea, Republic of: 48
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Turkey: 2
Worldwide total number of subjects	235
EEA total number of subjects	88

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)	182
Adolescents (12-17 years)	53
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 upper limb spasticity were randomized 1:1:1 to one of three treatment groups: BOTOX® 3 or 6 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® 6 U/kg

Arm description:

Intramuscular injections of BOTOX® (botulinum toxin Type A) 6 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly occupational therapy (OT).

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 upper limb.

Arm title	BOTOX® 3 U/kg

Arm description:

Intramuscular injections of BOTOX® (botulinum toxin Type A) 3 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly OT.

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 upper limb.

Arm title	Placebo

Arm description:

Intramuscular injections of normal saline (placebo) into specified muscles of the upper limb on Day 1. Participants received weekly OT.

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® 6 U/kg	BOTOX® 3 U/kg	Placebo
Started	77	78	80
Completed	75	78	79
Not completed	2	0	1
Adverse event, non-fatal	1	-	-
Personal Reasons	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BOTOX® 6 U/kg
Reporting group description:	
Intramuscular injections of BOTOX® (botulinum toxin Type A) 6 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly occupational therapy (OT).	
Reporting group title	BOTOX® 3 U/kg
Reporting group description:	
Intramuscular injections of BOTOX® (botulinum toxin Type A) 3 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly OT.	
Reporting group title	Placebo
Reporting group description:	
Intramuscular injections of normal saline (placebo) into specified muscles of the upper limb on Day 1. Participants received weekly OT.	

Reporting group values	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo
Number of subjects	77	78	80
Age categorical Units: Subjects			
Children (2-11 years)	61	56	65
Adolescents (12-17 years)	16	22	15
Age Continuous Units: years			
arithmetic mean	7.6	8.3	7.8
standard deviation	± 3.66	± 4.48	± 4.06
Sex: Female, Male Units: Subjects			
Female	27	36	32
Male	50	42	48
Modified Ashworth Scale-Bohannon (MAS-B) Score of the Principal Muscle Group Change			
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). 1 Participant in the Placebo arm was not included in the analysis.			
Units: score on a scale			
arithmetic mean	3.3	3.3	3.3
standard deviation	± 0.45	± 0.45	± 0.44

Reporting group values	Total		
Number of subjects	235		
Age categorical Units: Subjects			
Children (2-11 years)	182		
Adolescents (12-17 years)	53		
Age Continuous Units: years			
arithmetic mean			

standard deviation	-		

Sex: Female, Male Units: Subjects			
Female	95		
Male	140		
Modified Ashworth Scale-Bohannon (MAS-B) Score of the Principal Muscle Group Change			
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). 1 Participant in the Placebo arm was not included in the analysis.			
Units: score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	BOTOX® 6 U/kg
Reporting group description:	
Intramuscular injections of BOTOX® (botulinum toxin Type A) 6 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly occupational therapy (OT).	
Reporting group title	BOTOX® 3 U/kg
Reporting group description:	
Intramuscular injections of BOTOX® (botulinum toxin Type A) 3 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly OT.	
Reporting group title	Placebo
Reporting group description:	
Intramuscular injections of normal saline (placebo) into specified muscles of the upper limb on Day 1. Participants received weekly OT.	

Primary: Average Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Score of the Principal Muscle Group at Weeks 4 and 6

End point title	Average Change from Baseline in Modified Ashworth Scale-Bohannon (MAS-B) Score of the Principal Muscle Group 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 Modified Intent-to treat (mITT) population, all randomized participants with a valid MAS-B baseline score and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principal muscle group 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® 6 U/kg	BOTOX® 3 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	76	75	
Units: score on a scale				
least squares mean (standard error)	-1.87 (± 0.102)	-1.92 (± 0.101)	-1.21 (± 0.102)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOTOX® 6 U/kg v Placebo

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.938
upper limit	-0.379

Notes:

[1] - MMRM model with baseline MAS-B score as covariate; factors of age, principal muscle group, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure, stratified by age and principal muscle group categories.

Statistical analysis title	Statistical Analysis 2
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.992
upper limit	-0.426

Notes:

[2] - MMRM model with baseline MAS-B score as covariate; factors of age, principal muscle group, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure, stratified by age and principal muscle group 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 MMRM model was used for analysis.
Participants from the mITT population were used for analysis and included all randomized participants with a valid MAS-B baseline score and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principal muscle group and the CGI by physician, with data available for analysis at the given time-point.

End point type	Secondary

End point timeframe:

Weeks 4 and 6

End point values	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	76	75	
Units: score on a scale				
least squares mean (standard error)	1.87 (± 0.108)	1.88 (± 0.108)	1.66 (± 0.108)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155 [3]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.082
upper limit	0.511

Notes:

[3] - MMRM model with baseline MAS-B score as covariate; factors of age, principal muscle group, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure, stratified by age and principal muscle group categories.

Statistical analysis title	Statistical Analysis 2
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.147 [4]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.079
upper limit	0.523

Notes:

[4] - MMRM model with baseline MAS-B score as covariate; factors of age, principal muscle group, treatment, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure, stratified by age and principal muscle group categories.

Secondary: Average Change from Baseline in MAS-B Score of the Finger Flexor Muscle Group at Weeks 4 and 6

End point title	Average Change from Baseline in MAS-B Score of the Finger Flexor Muscle Group at Weeks 4 and 6

End point description:

The MAS-B was used to evaluate spasticity based on grading the resistance encountered in the finger flexor muscle group 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. An Analysis of Covariance (ANCOVA) model was used for analysis. A negative change from Baseline indicates improvement.
Participants from the mITT population were used for analysis and included all randomized participants with a valid MAS-B baseline score and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principal muscle group and the CGI by physician, with data available for analysis at the given time-point.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 4 and 6

End point values	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	29	
Units: score on a scale				
least squares mean (standard error)	-1.41 (± 0.184)	-1.46 (± 0.169)	-1.02 (± 0.170)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.861
upper limit	0.091

Notes:

[5] - ANCOVA model including baseline MAS-B score of finger flexor muscle group 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
Comparison groups	BOTOX® 3 U/kg v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.933
upper limit	0.051

Notes:

[6] - ANCOVA model including baseline MAS-B score of finger flexor muscle group 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: 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 ANCOVA model was used for analysis. Participants from the mITT population were used for analysis and included all randomized participants with a valid MAS-B baseline score and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principal muscle group and the CGI by physician, with data available for analysis. The number of subjects analysed in each arm at each time point is indicated by n.

End point type	Secondary

End point timeframe:

Week 8 and 12

End point values	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	78	79	
Units: score on a scale				
least squares mean (standard error)				
Week 8, Active Goal (n=75, 76, 77)	0.11 (± 0.148)	0.12 (± 0.148)	0.21 (± 0.148)	
Week 8, Passive Goal (n=75, 76, 77)	0.30 (± 0.146)	0.23 (± 0.146)	0.06 (± 0.146)	
Week 12, Active Goal (n=73, 78, 79)	0.49 (± 0.143)	0.26 (± 0.139)	0.52 (± 0.139)	
Week 12, Passive Goal (n=72, 78, 79)	0.71 (± 0.143)	0.31 (± 0.139)	0.11 (± 0.139)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Week 8, Active Goal	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.498
upper limit	0.305

Notes:

[7] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Week 8, Active Goal	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.658 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.502
upper limit	0.318

Notes:

[8] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 8, Passive Goal	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 [9]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.162
upper limit	0.635

Notes:

[9] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 8, Passive Goal	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412 [10]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.237
upper limit	0.576

Notes:

[10] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 12, Active Goal	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.904 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.408
upper limit	0.361

Notes:

[11] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:	
Week 12, Active Goal	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.641
upper limit	0.135

Notes:

[12] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 12, Passive Goal	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.978

Notes:

[13] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 12, Passive Goal	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.194
upper limit	0.58

Notes:

[14] - ANCOVA model including baseline MAS-B score as a covariate; factors of age, principal muscle group, treatment, study center and previous botulinum toxin exposure where age and principal muscle group were represented by stratification categories.

Secondary: Change from Baseline in Severity of Spasticity of the Principal Muscle Group (R2-R1) Calculated Using the Modified Tardieu Scale (MTS)

End point title	Change from Baseline in Severity of Spasticity of the Principal Muscle Group (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 was used to determine 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 a fast velocity passive stretch determining the dynamic component of the muscle contracture for the joint. At each visit, the investigator measured 2 joint angles by goniometer: the R1 angle which is the angle of catch after a fast velocity (V3) stretch and the R2 angle defined as the passive joint range of movement following a slow velocity (V1) stretch. The R2–R1 value indicated the level of the dynamic component of spasticity in the joint. The difference between slow (R2) and fast (R1) range of motion and respective change from baseline to each posttreatment visit on the MTS was derived. The mITT population was used for analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 6

End point values	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	78	79	
Units: angle				
least squares mean (standard error)				
Change to Week 2, Elbow(n=48, 48, 44)	33.27 (± 5.246)	29.58 (± 5.268)	21.17 (± 5.602)	
Change to Week 4, Elbow (n=48, 47, 47)	31.49 (± 4.116)	28.63 (± 4.160)	16.78 (± 4.272)	
Change to Week 6, Elbow (n=46, 48, 47)	37.62 (± 4.372)	28.00 (± 4.268)	16.65 (± 4.408)	
Change to Week 8, Elbow (n=47, 48, 48)	31.17 (± 4.238)	23.14 (± 4.188)	15.92 (± 4.276)	
Change to Week 12, Elbow (n=46, 48, 48)	14.69 (± 3.828)	14.06 (± 3.775)	10.19 (± 3.854)	
Change to Week 2, Wrist (n=29, 30, 30)	-15.72 (± 4.096)	-24.20 (± 3.831)	-9.60 (± 3.877)	
Change to Week 4, Wrist (n=28, 30, 31)	-22.97 (± 4.965)	-25.43 (± 4.557)	-12.33 (± 4.447)	
Change to Week 6, Wrist (n=28, 30, 30)	-24.33 (± 5.036)	-18.47 (± 4.641)	-7.22 (± 4.570)	
Change to Week 8, Wrist (n=29, 30, 30)	-20.87 (± 4.621)	-18.90 (± 4.307)	-3.16 (± 4.303)	
Change to Week 12, Wrist (n=29, 30, 31)	-16.87 (± 4.927)	-15.14 (± 4.607)	-1.62 (± 4.509)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change from Baseline to Week 2, Elbow	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.117 [15]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.089
upper limit	27.293

Notes:

[15] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273 [16]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	8.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.717
upper limit	23.527

Notes:

[16] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 6 U/kg v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	14.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.958
upper limit	26.458

Notes:

[17] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [18]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	11.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.203
upper limit	23.504

Notes:

[18] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	20.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.801
upper limit	33.137

Notes:

[19] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064 [20]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	11.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.662
upper limit	23.362

Notes:

[20] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [21]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	15.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.317
upper limit	27.178

Notes:

[21] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow	
Comparison groups	BOTOX® 3 U/kg v Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225 [22]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	7.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.488
upper limit	18.934

Notes:

[22] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow

Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409 [23]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.239
upper limit	15.236

Notes:

[23] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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, Elbow

Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 [24]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.69
upper limit	14.419

Notes:

[24] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
Change from Baseline to Week 2, Wrist	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263 [25]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-6.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.962
upper limit	4.706

Notes:

[25] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 12
Statistical analysis description:	
Change from Baseline to Week 2, Wrist	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.846
upper limit	-3.36

Notes:

[26] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 13
Statistical analysis description:	
Change from Baseline to Week 4, Wrist	
Comparison groups	BOTOX® 6 U/kg v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098 [27]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-10.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.277
upper limit	1.996

Notes:

[27] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 14
Statistical analysis description:	
Change from Baseline to Week 4, Wrist	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051 [28]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-13.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.26
upper limit	0.068

Notes:

[28] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 15
Statistical analysis description:	
Change from Baseline to Week 6, Wrist	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [29]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-17.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.031
upper limit	-4.189

Notes:

[29] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 16
Statistical analysis description:	
Change from Baseline to Week 6, Wrist	
Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098 [30]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-11.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.622
upper limit	2.131

Notes:

[30] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 17
Statistical analysis description:	
Change from Baseline to Week 8, Wrist	
Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [31]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-17.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.888
upper limit	-5.537

Notes:

[31] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 18
Statistical analysis description:	
Change from Baseline to Week 8, Wrist	
Comparison groups	BOTOX® 3 U/kg v Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-15.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.293
upper limit	-3.194

Notes:

[32] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Change from Baseline to Week 12, Wrist

Comparison groups	BOTOX® 6 U/kg v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [33]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-15.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.01
upper limit	-2.492

Notes:

[33] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and botulinum toxin exposure where age group is represented by stratification categories.

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Change from Baseline to Week 12, Wrist

Comparison groups	BOTOX® 3 U/kg v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [34]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-13.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.797
upper limit	-0.243

Notes:

[34] - ANCOVA model including baseline MTS as a covariate and factors of age group, treatment group, study center and 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 end of the 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® 6 U/kg

Reporting group description:

Intramuscular injections of BOTOX® (botulinum toxin Type A) 6 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly occupational therapy (OT).

Reporting group title	BOTOX® 3 U/kg

Reporting group description:

Intramuscular injections of BOTOX® (botulinum toxin Type A) 3 U/kg into specified muscles of the upper limb on Day 1. Participants received weekly occupational therapy (OT).

Reporting group title	Placebo

Reporting group description:

Intramuscular injections of normal saline (placebo) into specified muscles of the upper limb on Day 1. Participants received weekly OT.

Serious adverse events	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 77 (3.90%)	1 / 78 (1.28%)	1 / 79 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Stomatitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 78 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infectious mononucleosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BOTOX® 6 U/kg	BOTOX® 3 U/kg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 77 (19.48%)	12 / 78 (15.38%)	17 / 79 (21.52%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 77 (1.30%)	2 / 78 (2.56%)	4 / 79 (5.06%)
occurrences (all)	1	3	8
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 77 (2.60%)	3 / 78 (3.85%)	5 / 79 (6.33%)
occurrences (all)	2	4	10
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 77 (2.60%)	1 / 78 (1.28%)	4 / 79 (5.06%)
occurrences (all)	2	1	12
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 77 (9.09%)	4 / 78 (5.13%)	2 / 79 (2.53%)
occurrences (all)	8	4	4
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 77 (7.79%)	4 / 78 (5.13%)	5 / 79 (6.33%)
occurrences (all)	7	5	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2012	Amendment 1: -Corrected typographical error regarding the maximum dose allowed in the 3 U/kg group to read "not to exceed 100 U" -Clarified that in the primary efficacy analyses, 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 -Added clarification of when dose effectiveness would be concluded to address comments by US FDA (United States Food and Drug Administration) during the Special Protocol Assessment review -Clarified the ideal order in the timing of the CGI by Physician and spasticity assessments -Revised the question for the Patient-reported Onset of Spasticity Symptom Relief assessment from "have you noticed any treatment effect" to "have you noticed any effect" to minimize potential bias
28 January 2014	Amendment 2: -Added distinction between US FDA and non-US FDA clinical hypotheses, measures, and analyses -Specified that the C-SSRS (Columbia Suicide Severity Rating Scale) 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 -Added participant-reported benefit of injection question -Modified Exclusion regarding seizure frequency for exclusion -Modified Exclusion regarding vulnerable respiratory state -Added Exclusion to exclude participants with significant risk of suicide from treatment -Added a statement that participants may have stayed in the study even if a prohibited medication was administered -Clarified that school-based therapy, if relevant per local legislation, was permitted during the study -Added "or EMG" to the devices for muscle localization techniques -The original multiple testing procedure (Fisher's Protected Testing procedure) was changed to a gatekeeping procedure to control type I error rate -Pairwise comparison for high dose (BOTOX 6 U/kg) versus low dose (BOTOX 3 U/kg) was removed to incorporate US FDA recommendation -Overall test for among-group comparison was removed since the gatekeeping procedure for the 2 pairwise comparisons was sufficient -Clarified that CGI by Physician was removed for non-US FDA primary analyses and was added for non-US FDA analyses as a secondary measure -Removed subgroup efficacy analyses by type of anesthesia -Revised sample size calculation to base the calculation on a 2-sample t-test -Removed passive range of motion bullet to indicate that assessment of passive range of motion could be performed as part of the MTS using the angle of slow stretch (R2) -Clarified that MAS-B and MTS for finger flexors were to be analyzed for the subgroup of participants with wrist identified as the principal muscle group
22 July 2016	Amendment 3: -Number of participants and sample size calculations were revised such that the estimated number of participants needed to complete study decreased from 351 to 213 based on adjusted treatment differences from upper limb studies -The intent-to-treat (ITT) population was replaced with the mITT population based on US FDA recommendation -Text describing sensitivity analyses was edited to spell out the covariate and factors in the MMRM model -Edited text and figure to specify that the principal muscle group should have been the wrist in participants with the same MAS-B scores in the elbow and the wrist at baseline -Added a responder status based on +1 score of CGI by Physician -The sensitivity analyses of MAS-B and CGI were changed to use the MI method for missing values instead of observed cases; sensitivity analyses using last observation carried forward (LOCF) were removed -The primary MAS-B analysis and US FDA coprimary MAS-B and CGI analyses were changed to use MMRM with observed data; ANCOVA with MI and observed data were used as sensitivity analyses -Subgroup analyses of AEs were deleted -Changed the multiple testing procedure (gatekeeping procedure) to the Hochberg procedure for the coprimary analysis for US FDA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported