# 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<br>Units: Subjects | | | |
| Children (2-11 years) | 108 | 110 | 108 |
| Adolescents (12-17 years) | 20 | 16 | 22 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 6.7 | 6.4 | 6.6 |
| standard deviation | ± 3.9 | ± 3.6 | ± 3.9 |
| Sex: Female, Male<br>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<br>Units: Subjects | | | |
| Children (2-11 years) | 326 | | |
| Adolescents (12-17 years) | 58 | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female<br>Male | 177<br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |

## 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.<br>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 | | | |
| 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.<br>-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.<br>-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.<br>-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.<br>-Added distinction between US FDA and non-US FDA clinical hypotheses and analyses.<br>-Added participant-reported benefit of injection as an efficacy measure.<br>-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.<br>-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.<br>-Revised Exclusion Criterion to remove definition of significant knee spasticity.<br>-Modified Exclusion Criterion regarding seizure frequency for exclusion.<br>-Added Exclusion Criterion to exclude participants with significant suicidality from treatment so as to avoid data confounding.<br>-Clarified that participants could stay in the study even if prohibited medication was administered<br>-Clarified MTS scale description by adding "with knee extended and knee flexed".<br>-Changed multiple testing procedure to gatekeeping procedure to control type I error rate<br>-Removed pairwise comparison for higher dose versus lower dose to incorporate US FDA recommendation.<br>-Removed overall test for among group comparison. Gatekeeping procedure sufficient to control type I error rate<br>-Removed subgroup efficacy analyses by type of anesthesia.<br>-Revised sample size calculation to base the calculation on 2 sample t test as the overall test for among group comparison was removed.<br>-Removed requirement that urine pregnancy test must be performed prior to study treatment.<br>-Updated serious adverse event reporting procedures<br>-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.<br>-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.<br>-Added a responder status based on +1 score of CGI by Physician.<br>-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.<br>-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.<br>-Deleted subgroup analyses of adverse events because deemed unnecessary.<br>-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