



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

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-000084-24 |
| Trial protocol | DE PL HU IT |
| Global end of trial date | 25 August 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 13 March 2019 |
| First version publication date | 13 March 2019 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 191622-112 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01603641 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Allergan Ltd. |
| Sponsor organisation address | 1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL |
| Public contact | Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com |
| Scientific contact | Therapeutic Area Head, Allergan plc, 001 862-261-7000, clinicaltrials@allergan.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 August 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 August 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term safety of repeated doses of BOTOX® (botulinum toxin type A) for the treatment of paediatric 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 | 05 November 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 133 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | Korea, Republic of: 93 |
| Country: Number of subjects enrolled | United States: 81 |
| Country: Number of subjects enrolled | Russian Federation: 26 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | Thailand: 7 |
| Country: Number of subjects enrolled | Philippines: 4 |
| Worldwide total number of subjects | 370 |
| EEA total number of subjects | 151 |

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) | 313 |

| | |
|---------------------------|----|
| Adolescents (12-17 years) | 57 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Paediatric participants with lower limb spasticity who were previously treated with BOTOX® in study191622-111 [NCT01603628] and de novo participants received up to 5 BOTOX® treatments in this study.

Pre-assignment period milestones

| | |
|----------------------------|-----|
| Number of subjects started | 370 |
|----------------------------|-----|

| | |
|------------------------------|-----|
| Number of subjects completed | 367 |
|------------------------------|-----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|------------------------------|
| Reason: Number of subjects | Did Not Receive Treatment: 3 |
|----------------------------|------------------------------|

Period 1

| | |
|----------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
|----------------|--------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-----------------------------|
| Allocation method | Non-randomised - controlled |
|-------------------|-----------------------------|

| | |
|---------------|-------------|
| Blinding used | Not blinded |
|---------------|-------------|

Arms

| | |
|-----------|--------|
| Arm title | BOTOX® |
|-----------|--------|

Arm description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------|
| Investigational medicinal product name | BOTOX® |
|--|--------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | Botulinum Toxin Type A OnabotulinumtoxinA |
|------------|--|

| | |
|----------------------|-----------------------------------|
| Pharmaceutical forms | Powder for solution for injection |
|----------------------|-----------------------------------|

| | |
|--------------------------|-------------------|
| Routes of administration | Intramuscular use |
|--------------------------|-------------------|

Dosage and administration details:

Participants received intramuscular injections of BOTOX® into the lower and/or upper limbs at a minimum of 12 weeks apart for a maximum of 5 treatments.

| Number of subjects in period 1^[1] | BOTOX® |
|---|---------------|
| Started | 367 |
| Modified Intent-to-treat Population | 366 |
| Completed | 335 |
| Not completed | 32 |
| Adverse Event | 1 |
| Personal Reasons | 18 |
| Lost to follow-up | 6 |
| Other Miscellaneous Reasons | 6 |
| Lack of efficacy | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics were available for safety population, which included all treated participants.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | BOTOX® |
|-----------------------|--------|

Reporting group description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

| Reporting group values | BOTOX® | Total | |
|----------------------------|--------|-------|--|
| Number of subjects | 367 | 367 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 2 - 11 years | 311 | 311 | |
| 12 - 17 years | 56 | 56 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 6.9 | | |
| standard deviation | ± 3.8 | - | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 167 | 167 | |
| Male | 200 | 200 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 224 | 224 | |
| Black | 9 | 9 | |
| Asian | 109 | 109 | |
| Hispanic | 21 | 21 | |
| Other | 4 | 4 | |

End points

End points reporting groups

| | |
|---|--------|
| Reporting group title | BOTOX® |
| Reporting group description: Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study. | |

Primary: Percentage of Participants with at Least One Treatment-emergent Adverse Event (TEAE)

| | |
|-----------------|---|
| End point title | Percentage of Participants with at Least One Treatment-emergent Adverse Event (TEAE) ^[1] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. A TEAE was an AE that occurred after receiving the first dose of investigational product or an AE present prior to first dose but increased in severity during the Treatment Period. Safety population included all treated participants.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From first dose of study drug up to 12 weeks post last dose (Up to 60 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

| End point values | BOTOX® | | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 367 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 65.4 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 12 weeks post last dose (Up to 60 weeks)

Adverse event reporting additional description:

Safety Population included all treated participants.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | BOTOX® |
|-----------------------|--------|

Reporting group description:

Participants received maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into a single lower limb muscles or divided between both lower limb muscles or into the lower limb muscles and/or upper limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment not to exceed a maximum of 8 unit per kilogram (U/kg) of body weight (not to exceed 300 U) in treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 4 or 8 U/kg into the lower limb in the previous study or were de novo participants who were not enrolled in the previous study.

| Serious adverse events | BOTOX® | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 367 (6.54%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Febrile convulsion | | | |
| subjects affected / exposed | 4 / 367 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiplegia | | | |
| subjects affected / exposed | 2 / 367 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 367 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status epilepticus | | | |
| subjects affected / exposed | 2 / 367 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Entropion | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Strabismus | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cataract | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 367 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 367 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 367 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 367 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | BOTOX® | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 145 / 367 (39.51%) | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 367 (7.36%) | | |
| occurrences (all) | 40 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 67 / 367 (18.26%) | | |
| occurrences (all) | 135 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 65 / 367 (17.71%) | | |
| occurrences (all) | 101 | | |
| Bronchitis | | | |
| subjects affected / exposed | 21 / 367 (5.72%) | | |
| occurrences (all) | 22 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 April 2012 | <ul style="list-style-type: none">•Revised the pronator teres dose from 2 U/kg to 1.5 U/kg and the number of sites from 2 to 1•Revised approximate volume of blood collection for hematology and chemistry laboratory assessments from 5 millilitres (mL) to 7 mL (participants weighing < 15 kg) and from 12 to 14 mL (participants weighing ≥ 15 kg) to meet revised central laboratory requirements. |
| 28 November 2012 | <ul style="list-style-type: none">•Added language for diplegic participants, allowing injection of a dose up to 10 U/kg and not to exceed 340 U during Treatment Cycles 2 to 5 when both lower limbs were treated•Changed designation of visit for Exclusion Criterion 23 regarding history of fracture in the study upper limb within 12 months from "prior to the screening visit" to "prior to the Day 1 visit," for consistency with other criteria•For Treatment Cycle 1 for de novo participants, clarified that 8 U/kg was to be injected either in the single study lower limb or divided between both study lower limbs only for diplegic participants; for Treatment Cycles 2 through 5 for all participants, clarified the description of dose limitations<ul style="list-style-type: none">• Clarified that participants who met the retreatment criteria "may be reinjected" rather than "should be reinjected"•Clarified language regarding retreatment visits, including determination of whether the dose was clinically appropriate or dose reduction relative to the last injection received was required•Added for Modified Tardieu Scale (MTS) that it should be done with knee extended<ul style="list-style-type: none">• For de novo participants, revised to specify Modified Ashworth Scale – Bohannon (MAS-B) was to be done in the ankle of the study limb(s) only (deleted the knee)•Added MAS-B for knee flexors and any other muscles in the treatment plan•Deleted Edinburgh Visual Gait (EVG) score at subsequent Treatment/Retreatment Visit•At Early Discontinuation, corrected "Study Week 42" to "Study Week 48"•Revised language to allow therapists to perform MAS-B. |
| 28 January 2014 | <ul style="list-style-type: none">•Specified that Columbia-Suicide Severity Rating Scale (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 Food and Drug Administration (FDA)•Added a +14-day window to Study Week 48 visit•Modified Exclusion Criterion 13a regarding seizure frequency for exclusion•Modified Exclusion Criterion 14 regarding vulnerable respiratory state•Added Exclusion Criterion 29 to exclude participants with significant suicidality from treatment•Added collection of patient-reported benefit of injection•Clarified that anti-epileptics were permissible during the study•Amended retreatment criteria to specify that participants who experienced certain adverse events, including compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation, would not receive further study treatments•Removed requirement of true equinus foot deformity•Updated serious adverse event (SAE) language•Clarified that physician investigator, not investigator, was to conduct Clinical Global Impression of Overall Change (CGI) by Physician. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported