



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

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-000043-27    |
| Trial protocol           | DE PL HU IT       |
| Global end of trial date | 03 September 2018 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 16 March 2019 |
| First version publication date | 16 March 2019 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 191622-105 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01603615 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Allergan Ltd.  |
| Sponsor organisation address | 1st Floor, Marlow International, The Parkway, Marlow<br>Buckinghamshire, United Kingdom, SL7 1YL |
| Public contact               | Clinical Trials Registry Team, Allergan plc, 001 8772778566,<br>IR-CTRegistration@allergan.com   |
| Scientific contact           | Therapeutic Area Head, Allergan, 001 862-261-7000,<br>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                       | 03 September 2018 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 03 September 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 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                          | 30 October 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: 75             |
| Country: Number of subjects enrolled | Hungary: 8             |
| Country: Number of subjects enrolled | United States: 58      |
| Country: Number of subjects enrolled | Korea, Republic of: 45 |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | Thailand: 8            |
| Country: Number of subjects enrolled | Philippines: 3         |
| Country: Number of subjects enrolled | Turkey: 2              |
| Worldwide total number of subjects   | 220                    |
| EEA total number of subjects         | 83                     |

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)                     | 165 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 55 |
| 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 Upper Limb Spasticity who were previously treated with BOTOX® in study 191622-101 [NCT01603602] and de novo participants received up to 5 BOTOX® treatments in this study.

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 220 |
| Number of subjects completed | 213 |

### Pre-assignment subject non-completion reasons

|                            |                              |
|----------------------------|------------------------------|
| Reason: Number of subjects | Did Not Receive Treatment: 7 |
|----------------------------|------------------------------|

### 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 a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in 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 upper and/or lower limb at a minimum of 12 weeks apart for a maximum of 5 treatments.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>BOTOX®</b> |
|---|---------------|
| Started   | 213           |
| Completed   | 186           |
| Not completed                                       | 27            |
| Personal Reasons                                    | 17            |
| Lost to follow-up                                   | 9             |
| Other Miscellaneous Reasons                         | 1             |

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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 a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in previous study.

| Reporting group values     | BOTOX® | Total |  |
|----------------------------|--------|-------|--|
| Number of subjects         | 213    | 213   |  |
| Age categorical            |        |       |  |
| Units: Subjects            |        |       |  |
| 2 - 11 years               | 159    | 159   |  |
| 12 - 17 years              | 54     | 54    |  |
| Age Continuous             |        |       |  |
| Units: years               |        |       |  |
| arithmetic mean            | 8.3    |       |  |
| standard deviation         | ± 4.1  | -     |  |
| Sex: Female, Male          |        |       |  |
| Units: Subjects            |        |       |  |
| Female                     | 85     | 85    |  |
| Male                       | 128    | 128   |  |
| Race/Ethnicity, Customized |        |       |  |
| Units: Subjects            |        |       |  |
| White                      | 130    | 130   |  |
| Black                      | 9      | 9     |  |
| Asian                      | 61     | 61    |  |
| Hispanic                   | 10     | 10    |  |
| Other                      | 3      | 3     |  |

## End points

### End points reporting groups

|   |        |
|---|--------|
| Reporting group title   | BOTOX® |
| Reporting group description:  |        |
| Participants received a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in 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) <sup>[1]</sup> |
|-----------------|---|

#### 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       | 213             |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           | 58.7            |  |  |  |

### 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 | 19.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received a maximum of 5 treatments of intramuscular injections of BOTOX® (botulinum toxin Type A) into upper limb and/or lower limb muscles at a minimum of 12 weeks apart. Treatment dosing was according to investigator judgment, de novo participants received at least 6 U/kg of body weight or a maximum of 8 U/kg of body weight (not to exceed 300 U). Rollover participants received up to a maximum of 8 U/kg of body weight (not to exceed 300 U) for treatment Cycle 1. Dose could be increased to a maximum of 10 U/kg (not to exceed 340 U) in treatment Cycles 2-5. Rolled over participants received intramuscular injections of BOTOX® (botulinum toxin Type A) 3 or 6 U/kg into upper limb in previous study or were de novo participants who were not enrolled in previous study.

| Serious adverse events                            | BOTOX®           |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 13 / 213 (6.10%) |  |  |
| number of deaths (all causes)                     | 0                |  |  |
| number of deaths resulting from adverse events    | 0                |  |  |
| Congenital, familial and genetic disorders        |                  |  |  |
| Cryptorchism                                      |                  |  |  |
| subjects affected / exposed                       | 1 / 213 (0.47%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Nervous system disorders                          |                  |  |  |
| Epilepsy  |                  |  |  |
| subjects affected / exposed                       | 2 / 213 (0.94%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 3            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Hemiplegia  |                  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Seizure   |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Status epilepticus                              |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Partial seizures                                |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Food poisoning                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dental caries                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Joint contracture                               |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Juvenile idiopathic arthritis                   |                 |  |  |
| subjects affected / exposed                     | 1 / 213 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |   |  |  |
|---|---|--|--|
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all    | <br><br>1 / 213 (0.47%)<br>0 / 1<br>0 / 0 |  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br>1 / 213 (0.47%)<br>0 / 1<br>0 / 0     |  |  |
| Respiratory tract infection viral<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | <br>1 / 213 (0.47%)<br>0 / 1<br>0 / 0     |  |  |
| Meningitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br>1 / 213 (0.47%)<br>0 / 1<br>0 / 0     |  |  |
| Metabolism and nutrition disorders<br>Dehydration<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>1 / 213 (0.47%)<br>0 / 1<br>0 / 0 |  |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                     | <br>1 / 213 (0.47%)<br>0 / 1<br>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                           | 57 / 213 (26.76%) |  |  |
| Respiratory, thoracic and mediastinal disorders       |                   |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)  | 13 / 213 (6.10%)<br>14  |  |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 29 / 213 (13.62%)<br>38 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 22 / 213 (10.33%)<br>30 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 30 March 2012    | <ul style="list-style-type: none"><li>•Revised to clarify the ideal order of Clinical Global Impression of Overall Change (CGI) and spasticity assessments</li><li>•Revised the heading from "(2 to 4 Weeks Before Study Day 1)" to "(Up to 4 Weeks Before Study Day 1)" in order to match the schedule of events</li><li>•Revised approximate volume of blood collection for haematology and chemistry from 5 to 7 mL based on the revised central laboratory requirements.</li></ul>   |
| 07 December 2012 | <ul style="list-style-type: none"><li>•Added language for triplegic participants, to allow dose up to 10 U/kg and not to exceed 340 U to be injected during treatment cycles 2 to 5 when only both lower limbs were treated</li><li>•Changed exclusion criteria 21 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</li><li>•Added to the wording that requires a participant to remain on a stable dose of antispastic medications: to the extent possible unless judged by the investigator to be clinically inappropriate for clarification in Prohibited Medications/Treatments</li><li>•Added at the study Day 1 visit for both de novo and rollover, the site accessed the IVRS/IWRS to enroll the participant in Method of assignment</li><li>•The wordings were revised in Treatment Regimen and Dosing to "If a participant met the retreatment criteria, including no indication of an unacceptable safety risk, and it was considered to be clinically appropriate by the investigator, the participant should receive at least 6 U/kg in the study upper limb every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle</li><li>•Clarified title (Maximum Per-muscle, Per-limb, and Total Body Dose), added row for total maximum dose for both lower limbs, and added footnote to indicate that only 1 upper limb is to be injected</li><li>•Added For purposes of dose calculation, the participants weight would be rounded to the nearest whole kilogram</li><li>•Revised to "Participants should may be retreated" if they met the retreatment criteria</li><li>•Added that study Day 1 is treatment 1/ day 1 for participants who received treatment on that day</li><li>•Added obtaining study medication kit numbers from and entering exit status to the IVRS/IWRS</li><li>•Passive range of motion was performed as part of the Modified Tardieu Scale (MTS) and therefore did not need to be identified as a separate procedure.</li></ul> |
| 07 December 2012 | <ul style="list-style-type: none"><li>•For de novo participants revised to specify (Modified Ashworth Scale-Bohannon) MAS-B was to be done on the elbow and wrist of the study limb</li><li>•Revised study week 42 to study week 48 in "Early Discontinuation of Patients" section</li><li>•Added that participants will be withdrawn from the study if they develop a medically significant hypersensitivity reaction to the study drug such as angioedema or anaphylaxis, or if a participant becomes pregnant during the study</li><li>•Added the same investigator should perform this measure at each visit, if possible in section 12.1.10 MAS for consistency across evaluation</li><li>•Deleted description of how to measure R1 and R2 in section 12.1.11 MTS.</li></ul>  |

|                |   |
|----------------|---|
| 01 August 2016 | <ul style="list-style-type: none"> <li>•Specified that the Columbia-Suicide Severity Rating Scale (C-SSRS) is to be performed as a safety measure for participants &gt; 6 years of age at day 1, and provided description of scale, data handling, and reference information as requested by the United States Food and Drug Administration's (US FDA's) Division of Neurology Products</li> <li>•Added a +14-day window to study week 48 visit</li> <li>•Modified Exclusion Criterion 11a regarding seizure frequency for exclusion</li> <li>•Modified Exclusion Criterion 12 regarding vulnerable respiratory state</li> <li>•Added Exclusion Criterion 27 to exclude participants with significant suicidality from treatment</li> <li>•Added patient-reported benefit of injection</li> <li>•Added a sentence on use of anti-epileptics</li> <li>•Amended retreatment criteria to specify that participants who experience certain adverse events will not receive further study treatments</li> <li>•Revised paragraph regarding retreatment for participant with adverse events of compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation</li> <li>•Clarified that passive range of motion can be performed during the MTS</li> <li>•Clarified to remove time frame for blood sample collection</li> <li>•Clarified regarding patient not receiving treatment or retreatment</li> <li>•Clarification on requirements for weight measurements and that weight must be measured in kilograms</li> <li>•Added "temporal, rectal" to body temperature</li> <li>•Revised MAS-B description to say "study specified" instead of "non-study-specified"</li> <li>velocity and provided detail on scoring to clarify that we do instruct the sites on a specific velocity for MAS-B assessment</li> <li>•Clarified "investigator" to "physician investigator."</li> </ul> |
|----------------|---|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported