



Clinical trial results:

Evaluation of the Safety and Efficacy of Treatment With BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for Subjects With Facial Rhytides (Forehead Lines, Glabellar Lines, Lateral Canthal Lines)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001815-38 |
| Trial protocol | DE GB BE |
| Global end of trial date | 20 April 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 20 January 2018 |
| First version publication date | 20 January 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 191622-143 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02261493 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Allergan Limited |
| Sponsor organisation address | Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL |
| Public contact | EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com |
| Scientific contact | EU Regulatory Dept, 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) | 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 | 19 September 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 April 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This is a safety and efficacy study of onabotulinumtoxinA in subjects with upper facial rhytides (forehead lines, glabellar lines, lateral canthal lines [crow's feet lines]).

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 | 27 October 2014 |
| 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 | Belgium: 70 |
| Country: Number of subjects enrolled | Denmark: 217 |
| Country: Number of subjects enrolled | United Kingdom: 96 |
| Country: Number of subjects enrolled | United States: 404 |
| Worldwide total number of subjects | 787 |
| EEA total number of subjects | 383 |

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) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 749 |
| From 65 to 84 years | 38 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were randomized to placebo, onabotulinumtoxinA Dose A, or onabotulinumtoxinA Dose B in Period 1. Subjects randomized to receive placebo or Dose B in Period 1, who subsequently continued to Period 2, received onabotulinumtoxinA Dose A in Period 2.

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 |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A |

Arm description:

Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria, the subject will receive up to 2 treatments with onabotulinumtoxinA Dose A into the protocol-specified areas.

| | |
|--|----------------------------------|
| Arm type | Placebo followed by experimental |
| Investigational medicinal product name | OnabotulinumtoxinA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria, the subject will receive up to 2 treatments with onabotulinumtoxinA Dose A into the protocol-specified areas.

| | |
|------------------|---------------------------|
| Arm title | OnabotulinumtoxinA Dose B |
|------------------|---------------------------|

Arm description:

OnabotulinumtoxinA Dose B injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | OnabotulinumtoxinA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

OnabotulinumtoxinA Dose B injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| | |
|------------------|---------------------------|
| Arm title | OnabotulinumtoxinA Dose A |
|------------------|---------------------------|

Arm description:

OnabotulinumtoxinA Dose A injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

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

| | |
|--|--------------------|
| Investigational medicinal product name | OnabotulinumtoxinA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

OnabotulinumtoxinA Dose A injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| Number of subjects in period 1 | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose B | OnabotulinumtoxinA Dose A |
|--------------------------------|---|---------------------------|---------------------------|
| | | | |
| Started | 156 | 318 | 313 |
| Completed | 126 | 271 | 287 |
| Not completed | 30 | 47 | 26 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | - | 1 | - |
| Pregnancy | 1 | 2 | - |
| Undisclosed alcohol abuse | - | 1 | - |
| Personal Reasons | 14 | 14 | 16 |
| Lost to follow-up | 14 | 27 | 8 |
| Protocol deviation | 1 | - | - |
| Lack of efficacy | - | 1 | - |
| Noncompliance | - | - | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A |
|-----------------------|---|

Reporting group description:

Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria, the subject will receive up to 2 treatments with onabotulinumtoxinA Dose A into the protocol-specified areas.

| | |
|-----------------------|---------------------------|
| Reporting group title | OnabotulinumtoxinA Dose B |
|-----------------------|---------------------------|

Reporting group description:

OnabotulinumtoxinA Dose B injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| | |
|-----------------------|---------------------------|
| Reporting group title | OnabotulinumtoxinA Dose A |
|-----------------------|---------------------------|

Reporting group description:

OnabotulinumtoxinA Dose A injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| Reporting group values | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose B | OnabotulinumtoxinA Dose A |
|--|---|---------------------------|---------------------------|
| Number of subjects | 156 | 318 | 313 |
| Age Categorical Units: Subjects | | | |
| <65 years | 147 | 300 | 302 |
| >=65 years | 9 | 18 | 11 |
| Age continuous Units: years | | | |
| arithmetic mean | 48.1 | 47.6 | 45.5 |
| standard deviation | ± 9.7 | ± 10.3 | ± 9.6 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 140 | 278 | 284 |
| Male | 16 | 40 | 29 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 787 | | |
| Age Categorical Units: Subjects | | | |
| <65 years | 749 | | |
| >=65 years | 38 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 702 | | |
| Male | 85 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A |
| Reporting group description: Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria, the subject will receive up to 2 treatments with onabotulinumtoxinA Dose A into the protocol-specified areas. | |
| Reporting group title | OnabotulinumtoxinA Dose B |
| Reporting group description: OnabotulinumtoxinA Dose B injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments. | |
| Reporting group title | OnabotulinumtoxinA Dose A |
| Reporting group description: OnabotulinumtoxinA Dose A injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments. | |

Primary: Percentage of Subjects with an Investigator Rating of None or Mild on the 4-Grade Forehead Wrinkle Scale (FWS) for Forehead Line Severity at Maximum Eyebrow Elevation

| | |
|---|---|
| End point title | Percentage of Subjects with an Investigator Rating of None or Mild on the 4-Grade Forehead Wrinkle Scale (FWS) for Forehead Line Severity at Maximum Eyebrow Elevation ^[1] |
| End point description: Day 30 | |
| End point type | Primary |
| End point timeframe: The Investigator assessed the severity of the subject's forehead lines at maximum eyebrow elevation using the 4-point FWS, where 0=none, 1=mild, 2=moderate, and 3=severe. The percentage of subjects assessed as "none" or "mild" on the FWS are reported. | |
| 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: No statistical analyses for this end point. | |

| End point values | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose B | OnabotulinumtoxinA Dose A | |
|----------------------------------|---|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 111 | 222 | 235 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 2.7 (-0.3 to 5.7) | 90.5 (86.7 to 94.4) | 93.6 (90.5 to 96.7) | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with a Subject Rating of None or Mild on the 4-Grade FWS for Forehead Line Severity at Maximum Eyebrow Elevation

| | |
|-----------------|--|
| End point title | Percentage of Subjects with a Subject Rating of None or Mild on the 4-Grade FWS for Forehead Line Severity at Maximum Eyebrow Elevation ^[2] |
|-----------------|--|

End point description:

The subject assessed the severity of his/her forehead lines at maximum eyebrow elevation using the 4-point FWS, where 0=none, 1=mild, 2=moderate, and 3=severe. The percentage of subjects assessing forehead lines as "none" or "mild" on the FWS are reported.

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

End point timeframe:

Day 30

Notes:

[2] - 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: No statistical analyses for this end point.

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 111 | 222 | 235 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.6 (0.1 to 7.1) | 81.5 (76.4 to 86.6) | 88.9 (84.9 to 92.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with ≥ 2 -Grade Improvement from Baseline on Both the Investigator's and Subject's FWS Ratings of Forehead Line Severity at Maximum Eyebrow Elevation

| | |
|-----------------|---|
| End point title | Percentage of Subjects with ≥ 2 -Grade Improvement from Baseline on Both the Investigator's and Subject's FWS Ratings of Forehead Line Severity at Maximum Eyebrow Elevation |
|-----------------|---|

End point description:

The Investigator and subject each assessed the severity of the subject's forehead lines at maximum eyebrow elevation using the 4-grade FWS, where 0=none, 1=mild, 2=moderate, and 3=severe. The percentage of subjects with at least a 2-grade improvement from baseline assessed by both the Investigator and the subject are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 30

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 156 | 318 | 313 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 0.6 (-0.6 to 1.9) | 45.6 (40.1 to 51.1) | 53.0 (47.5 to 58.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with ≥ 1 -Grade Improvement from Baseline on the Investigator's FWS Rating of Forehead Line Severity at Rest

| | |
|-----------------|--|
| End point title | Percentage of Subjects with ≥ 1 -Grade Improvement from Baseline on the Investigator's FWS Rating of Forehead Line Severity at Rest |
|-----------------|--|

End point description:

The Investigator assessed the severity of the subject's forehead lines at rest using the 4-grade FWS, where 0=none, 1=mild, 2=moderate, and 3=severe. The percentage of subjects with at least a 1-grade improvement assessed by the Investigator are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 30

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 150 | 310 | 309 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 18.7 (12.4 to 24.9) | 85.2 (81.2 to 89.1) | 84.8 (80.8 to 88.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Mostly Satisfied or Very Satisfied on the 5-Point Facial Line Satisfaction Questionnaire (FLSQ) Item 5

| | |
|-----------------|---|
| End point title | Percentage of Subjects Reporting Mostly Satisfied or Very Satisfied on the 5-Point Facial Line Satisfaction Questionnaire (FLSQ) Item 5 |
|-----------------|---|

End point description:

The FLSQ consists of 13 questions that assess subject satisfaction and appearance-related impacts associated with facial lines. Item 5 on the FLSQ asks "How satisfied are you with the effect your treatment had on your facial lines?" Responses included: very satisfied, mostly satisfied, neither satisfied or dissatisfied, mostly dissatisfied, or very dissatisfied. The percentage of subjects reporting a score of mostly satisfied or very satisfied with treatment are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 60

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 155 | 317 | 313 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.2 (0.4 to 6.0) | 81.4 (77.1 to 85.7) | 87.9 (84.2 to 91.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with ≥ 20 -Point Improvement from Baseline on the Impact Domain of the FLSQ Among Subjects With Baseline Score ≥ 20 Points

| | |
|-----------------|---|
| End point title | Percentage of Subjects with ≥ 20 -Point Improvement from Baseline on the Impact Domain of the FLSQ Among Subjects With Baseline Score ≥ 20 Points |
|-----------------|---|

End point description:

The FLSQ consists of 13 questions that assess subject satisfaction and appearance-related impacts associated with facial lines. The Impact Domain measures the subject's appearance-related and emotional impacts of treatment and is composed of 5 questions with a possible range of scores from 0 (worst) to 100 (best), using a transformed scale. Only subjects with baseline scores ≥ 20 are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 30

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 152 | 310 | 301 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 19.7 (13.4 to | 61.0 (55.5 to | 76.1 (71.3 to | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a ≥ 3 -Point Improvement from Baseline on Item 4 of the 11-Point Facial Line Outcomes (FLO-11) Questionnaire©

| | |
|-----------------|--|
| End point title | Percentage of Subjects with a ≥ 3 -Point Improvement from Baseline on Item 4 of the 11-Point Facial Line Outcomes (FLO-11) Questionnaire© |
|-----------------|--|

End point description:

The FLO-11 assess the subject's psychological and appearance-related impacts associated with facial lines. Item 4 is "I look older than my actual age because of my facial lines" with a range of possible scores from 0 = not at all to 10 = very much. Only subjects with baseline scores ≥ 3 are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 30

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|----------------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 141 | 285 | 288 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 9.9 (5.0 to 14.9) | 66.7 (61.2 to 72.1) | 77.1 (72.2 to 81.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Retreatment Eligibility

| | |
|-----------------|---------------------------------|
| End point title | Time to Retreatment Eligibility |
|-----------------|---------------------------------|

End point description:

Time to retreatment eligibility is defined as the number of days from treatment cycle 1 injection to the return to an Investigator FWS rating of moderate or severe at maximum eyebrow elevation. The FWS is a 4-grade scale, where 0=none, 1=mild, 2=moderate, and 3=severe. Only subjects who achieved a ≥ 2 -grade improvement on both the Investigator and subject FWS ratings at maximum eyebrow elevation on Day 30 are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 Months

| End point values | Placebo (normal saline) followed by Onabotulinumt oxinA Dose A | Onabotulinumt oxinA Dose B | Onabotulinumt oxinA Dose A | |
|-----------------------------|--|-------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1 ^[3] | 143 | 161 | |
| Units: Days | | | | |
| median (standard deviation) | 64.0 (± 999) | 120.0 (± 46.4) | 126.0 (± 53.7) | |

Notes:

[3] - The standard deviations was NA; 999 used as a placeholder.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from signing the informed consent to the end of study.

Adverse event reporting additional description:

The Safety Population includes all subjects who received at least 1 study treatment injection and was used to assess AEs and SAEs. Subjects randomized to receive placebo in Period 1 who subsequently received open-label onabotulinumtoxinA Dose A in Period 2 are included in the onabotulinumtoxinA Dose A group for the Safety analysis.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A |
|-----------------------|---|

Reporting group description:

Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria, the subject will receive up to 2 treatments with onabotulinumtoxinA Dose A into the protocol-specified areas.

| | |
|-----------------------|---------------------------|
| Reporting group title | OnabotulinumtoxinA Dose A |
|-----------------------|---------------------------|

Reporting group description:

OnabotulinumtoxinA Dose A injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| | |
|-----------------------|---------------------------|
| Reporting group title | OnabotulinumtoxinA Dose B |
|-----------------------|---------------------------|

Reporting group description:

OnabotulinumtoxinA Dose B injected into the protocol-specified areas on Day 1. Subjects will receive at least 1 and up to 3 treatments.

| Serious adverse events | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose B |
|---|---|---------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 16 / 746 (2.14%) | 7 / 318 (2.20%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine benign neoplasm | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyoma | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 746 (0.00%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma stage II | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the tongue | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 746 (0.00%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 2 / 318 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural inflammation | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 746 (0.00%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 0 / 746 (0.00%) | 1 / 318 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Tonsillectomy | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Neuritis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Temporal lobe epilepsy | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 2 / 746 (0.27%) | 0 / 318 (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 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Abscess | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 2 / 746 (0.27%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 746 (0.13%) | 0 / 318 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo (normal saline) followed by OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose A | OnabotulinumtoxinA Dose B |
|---|---|---------------------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 156 (13.46%) | 198 / 746 (26.54%) | 90 / 318 (28.30%) |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 156 (5.13%) | 69 / 746 (9.25%) | 30 / 318 (9.43%) |
| occurrences (all) | 10 | 89 | 35 |
| General disorders and administration site conditions | | | |
| Injection site bruising | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 47 / 746 (6.30%) | 26 / 318 (8.18%) |
| occurrences (all) | 5 | 53 | 27 |
| Injection site haematoma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 156 (1.92%) | 34 / 746 (4.56%) | 16 / 318 (5.03%) |
| occurrences (all) | 3 | 39 | 20 |
| Infections and infestations | | | |

| | | | |
|---|-----------------|------------------|------------------|
| Nasopharyngitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 48 / 746 (6.43%) | 18 / 318 (5.66%) |
| occurrences (all) | 5 | 58 | 21 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 03 August 2015 | A) Topical anesthetics were excluded; B) added requirement for subjects to be observed for adverse events for at least 30 minutes following study treatment; C) added analysis method of MI and added sensitivity analyses for primary variables/analyses; D) defined clinical benefit and clarified that responders for FLSQ Impact Domain score only included subjects who had baseline scores ≥ 20 points for secondary efficacy variables/analyses; and E) added FWS ratings of FHL severity at maximum eyebrow elevation based on independent physician reviewers' assessment of photographs for other efficacy variables/analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported