



## Clinical trial results:

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

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-001860-36 |
| Trial protocol           | IE             |
| Global end of trial date | 26 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 | 191622-142 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02261467 |
| 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                       | 12 September 2016 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 26 April 2016     |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 26 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 forehead and glabellar facial rhytides (frown 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                          | 21 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 | Ireland: 16        |
| Country: Number of subjects enrolled | Canada: 132        |
| Country: Number of subjects enrolled | United States: 243 |
| Worldwide total number of subjects   | 391                |
| EEA total number of subjects         | 16                 |

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)                      | 382 |
| From 65 to 84 years                       | 9   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 421 subjects were enrolled in the study, of these, 30 subjects were excluded from the data analyses at one site. The participant flow reflects all subjects included in the data analyses.

### Pre-assignment

Screening details:

Subjects were randomized to either placebo or onabotulinumtoxinA in Period 1. Subjects randomized to receive placebo in Period 1 who subsequently received open-label onabotulinumtoxinA in Period 2 are also included in the onabotulinumtoxinA group for the Safety analysis.

### 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  |
| <b>Arm title</b>             | Placebo followed by OnabotulinumtoxinA in Period 2 |

Arm description:

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

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | OnabotulinumtoxinA |
|------------------|--------------------|

Arm description:

OnabotulinumtoxinA 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 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 followed by<br>OnabotulinumtoxinA<br>in Period 2 | OnabotulinumtoxinA |
|--------------------------------|--|--------------------|
|                                |  |                    |
| Started                        | 101  | 290                |
| Completed                      | 80   | 253                |
| Not completed                  | 21   | 37                 |
| Enrolled in Error              | 1  | -                  |
| Adverse event, non-fatal       | 1  | 1                  |
| Personal Reasons               | 17   | 22                 |
| Lost to follow-up              | 2  | 13                 |
| Protocol deviation             | -  | 1                  |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo followed by OnabotulinumtoxinA in Period 2 |
|-----------------------|--|

Reporting group description:

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

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | OnabotulinumtoxinA |
|-----------------------|--------------------|

Reporting group description:

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

| Reporting group values                 | Placebo followed by OnabotulinumtoxinA in Period 2 | OnabotulinumtoxinA | Total |
|--|--|--------------------|-------|
| Number of subjects                     | 101  | 290                | 391   |
| Age Categorical<br>Units: Subjects     |  |                    |       |
| <65 years                              | 101  | 281                | 382   |
| >=65 years                             | 0  | 9                  | 9     |
| Age continuous<br>Units: years         |  |                    |       |
| arithmetic mean                        | 42.4   | 44.5               |       |
| standard deviation                     | ± 10.6   | ± 11.2             | -     |
| Gender, Male/Female<br>Units: Subjects |  |                    |       |
| Female                                 | 87   | 249                | 336   |
| Male                                   | 14   | 41                 | 55    |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Placebo followed by OnabotulinumtoxinA in Period 2 |
| Reporting group description:<br>Placebo (normal saline) injected into the protocol-specified areas on Day 1. If the subject meets the re-treatment criteria in Period 2, the subject will receive up to 2 open-label treatments with onabotulinumtoxinA into the protocol-specified areas. |  |
| Reporting group title  | OnabotulinumtoxinA                                 |
| Reporting group description:<br>OnabotulinumtoxinA 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 <sup>[1]</sup> |
| End point description:<br>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. |   |
| End point type  | Primary   |
| End point timeframe:<br>Day 30  |   |
| Notes:<br>[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.<br>Justification: No statistical analyses for this end point.   |   |

| End point values                 | Placebo followed by OnabotulinumtoxinA in Period 2 | OnabotulinumtoxinA  |  |  |
|----------------------------------|--|---------------------|--|--|
| Subject group type               | Reporting group                                    | Reporting group     |  |  |
| Number of subjects analysed      | 60   | 194                 |  |  |
| Units: Percentage of Subjects    |  |                     |  |  |
| number (confidence interval 95%) | 1.7 (-1.6 to 4.9)                                  | 94.8 (91.7 to 98.0) |  |  |

### 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 <sup>[2]</sup> |
|-----------------|--|

**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 followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
|----------------------------------|---|---------------------|--|--|
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 60 <sup>[3]</sup>                                   | 194                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 999 (999 to 999)                                    | 87.6 (83.0 to 92.3) |  |  |

**Notes:**

[3] - The number was 0 with NA confidence intervals; 999 used as a placeholder.

**Statistical analyses**

No statistical analyses for this end point

### Secondary: Percentage of Subjects with $\geq 2$ -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 $\geq 2$ -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 followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
|----------------------------------|---|---------------------|--|--|
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 101 <sup>[4]</sup>                                  | 290                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 999 (999 to 999)                                    | 61.4 (55.8 to 67.0) |  |  |

Notes:

[4] - The number was 0 with NA confidence intervals; 999 used as a placeholder.

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with $\geq 1$ -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-point 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

|                                  |   |                     |  |  |
|----------------------------------|---|---------------------|--|--|
| <b>End point values</b>          | Placebo followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 96  | 278                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 19.8 (1.8 to 27.8)                                  | 85.6 (81.5 to 89.7) |  |  |

## 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 followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
|----------------------------------|---|---------------------|--|--|
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 99  | 289                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 1.0 (-1.0 to 3.0)                                   | 90.3 (86.9 to 93.7) |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with $\geq 20$ -Point Improvement from Baseline on the Impact Domain of the FLSQ Among Subjects With Baseline Score $\geq 20$ 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  $\geq 20$  are included in the analysis.

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

End point timeframe:

Baseline, Day 30

| End point values                 | Placebo followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
|----------------------------------|---|---------------------|--|--|
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 90  | 268                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 18.9 (10.8 to 27.0)                                 | 73.9 (68.6 to 79.1) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with a $\geq 3$ -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 $\geq 3$ -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  $\geq 3$  are included in the analysis.

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

End point timeframe:

Baseline, Day 30

| End point values                 | Placebo followed by Onabotulinumt oxinA in Period 2 | Onabotulinumt oxinA |  |  |
|----------------------------------|---|---------------------|--|--|
| Subject group type               | Reporting group                                     | Reporting group     |  |  |
| Number of subjects analysed      | 89  | 246                 |  |  |
| Units: Percentage of Subjects    |   |                     |  |  |
| number (confidence interval 95%) | 11.2 (4.7 to 17.8)                                  | 77.2 (72.0 to 82.5) |  |  |

### 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-point scale, where 0=none, 1=mild, 2=moderate, and 3=severe. Only subjects who achieved a  $\geq 2$ -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

| <b>End point values</b>     | Placebo<br>followed by<br>Onabotulinumt<br>oxinA in Period<br>2 | Onabotulinumt<br>oxinA |  |  |
|-----------------------------|---|------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group        |  |  |
| Number of subjects analysed | 0 <sup>[5]</sup>  | 174                    |  |  |
| Units: Days                 |   |                        |  |  |
| median (standard deviation) | ( )   | 119 (± 52.9)           |  |  |

Notes:

[5] - No subjects met the reporting criteria

### 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 adverse events and serious adverse events. Subjects randomized to receive placebo in Period 1 who subsequently received open-label onabotulinumtoxinA in Period 2 are included in the onabotulinumtoxinA group for the Safety analysis.

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

### Dictionary used

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

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

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | OnabotulinumtoxinA |
|-----------------------|--------------------|

Reporting group description:

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

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo followed by OnabotulinumtoxinA in Period 2 |
|-----------------------|--|

Reporting group description:

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

| Serious adverse events  | OnabotulinumtoxinA | Placebo followed by OnabotulinumtoxinA in Period 2 |  |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events                   |                    |  |  |
| subjects affected / exposed   | 5 / 374 (1.34%)    | 0 / 100 (0.00%)                                    |  |
| number of deaths (all causes)                                       | 0                  | 0  |  |
| number of deaths resulting from adverse events                      | 0                  | 0  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Basal cell carcinoma  |                    |  |  |
| subjects affected / exposed   | 1 / 374 (0.27%)    | 0 / 100 (0.00%)                                    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0  |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0  |  |
| Cardiac disorders   |                    |  |  |
| Angina pectoris   |                    |  |  |
| subjects affected / exposed   | 1 / 374 (0.27%)    | 0 / 100 (0.00%)                                    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0  |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0  |  |
| Nervous system disorders  |                    |  |  |

|   |                                   |                                   |  |
|---|-----------------------------------|-----------------------------------|--|
| Headache<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 374 (0.27%)<br>0 / 1<br>0 / 0 | 0 / 100 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Immune system disorders<br>Anaphylactic reaction<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all        | 1 / 374 (0.27%)<br>0 / 1<br>0 / 0 | 0 / 100 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                     | 1 / 374 (0.27%)<br>0 / 1<br>0 / 0 | 0 / 100 (0.00%)<br>0 / 0<br>0 / 0 |  |

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

| <b>Non-serious adverse events</b>  | OnabotulinumtoxinA      | Placebo followed by OnabotulinumtoxinA in Period 2 |  |
|--|-------------------------|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 92 / 374 (24.60%)       | 12 / 100 (12.00%)                                  |  |
| Nervous system disorders<br>Headache<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 43 / 374 (11.50%)<br>50 | 7 / 100 (7.00%)<br>7                               |  |
| General disorders and administration site conditions<br>Injection site bruising<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 19 / 374 (5.08%)<br>20  | 2 / 100 (2.00%)<br>2                               |  |
| Infections and infestations<br>Nasopharyngitis<br>alternative assessment type: Non-systematic  |                         |  |  |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 30 / 374 (8.02%) | 3 / 100 (3.00%) |  |
| occurrences (all)           | 35               | 3               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 05 August 2015 | A) Excluded use of topical anesthetics; B) added requirement for subjects to be observed for TEAEs for at least 30 minutes following study treatment; C) added analysis method of MI and sensitivity analyses for the primary efficacy variables/analyses; D) defined clinical benefit and clarified that responders for FLSQ Impact Domain score only included subjects who had baseline scores $\geq 20$ points for secondary efficacy variables/analyses; and E) added FWS ratings of FHL severity at maximum eyebrow elevation based on independent physician reviewer assessments of photographs for other efficacy variables/analyses. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported