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 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%)	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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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	

26.1)	66.4)	80.9)

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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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 OnabotulinumtoxinA Dose A	OnabotulinumtoxinA Dose B	OnabotulinumtoxinA 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