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
Arm title	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.

Arm title	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 OnabotulinumtoxinA 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 Units: Subjects			
<65 years	101	281	382
>=65 years	0	9	9
Age continuous Units: years			
arithmetic mean	42.4	44.5	
standard deviation	± 10.6	± 11.2	-
Gender, Male/Female 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:	
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.	

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:	
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:	
Day 30	

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 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[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 followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[3]	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 ≥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 followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[4]	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 ≥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-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

End point values	Placebo followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
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 OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
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 ≥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 followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
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 ≥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 followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
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 ≥ 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 followed by OnabotulinumtoxinA in Period 2	OnabotulinumtoxinA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	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			
alternative assessment type: Non-systematic			
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	
Immune system disorders			
Anaphylactic reaction			
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	
Psychiatric disorders			
Depression			
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	

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported