Clinical trial results:
A Phase III, Randomised, Double Blind, Placebo Controlled and Open Label Phase, Multicentre Study to Investigate the Efficacy and Safety of BTX-A-HAC NG in the Treatment of Moderate to Severe Glabellar Lines, and Assess the Long Term Efficacy and Safety of BTX-A-HAC NG Following Repeated Treatments in this Indication.

Summary

EudraCT number	2014-003841-86
Trial protocol	DE GB
Global end of trial date	02 December 2016

Results information

Result version number	v1 (current)
This version publication date	19 August 2018
First version publication date	19 August 2018

Trial information

Trial identification

Sponsor protocol code	Y-52-52120-214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02493946
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Innovation
Sponsor organisation address	65 quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Neurology, Ipsen Innovation, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen Innovation, clinical.trials@ipsen.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	02 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2015
Global end of trial reached?	Yes
Global end of trial date	02 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess short-term efficacy and safety of a single treatment of Clostridium botulinum toxin type A Haemagglutinin Complex (BTX-A-HAC) solution 50 Units (U) over placebo for the improvement in the appearance of glabellar lines and to assess the long term (LT) safety and efficacy of BTX-A-HAC solution 50 U after repeated injections. The primary objective was to demonstrate the superiority of BTX-A-HAC solution 50 U (0.25 milliltre [mL]) over placebo as measured by the Investigator's live assessment (ILA) of the appearance of the subject's glabellar lines at maximum frown on Day 29 of the double blind (DB) period.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Council for Harmonisation Consolidated Guideline on Good Clinical Practice and Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2015
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	United Kingdom: 24
Country: Number of subjects enrolled	France: 163
Country: Number of subjects enrolled	Germany: 413
Worldwide total number of subjects	600
EEA total number of subjects	600

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)	588
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with moderate or severe glabellar lines were enrolled in 24 sites in France, Germany and the United Kingdom from 23 April 2015. The study was completed in December 2016.

Pre-assignment

Screening details:

605 subjects were screened. 192 were screened for the DB period; 2 were screen failures and 190 were randomised to treatment or placebo. 413 additional subjects were screened for the open label (OL) period, referred to as de novo subjects; 3 were screen failures and 410 received at least one treatment cycle.

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	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	No
Arm title	BTX-A-HAC Solution 50 U - DB Period

Arm description:

During the DB period, subjects were randomised to receive a single treatment of BTX-A-HAC solution 50 U.
50 U (0.25 mL) BTX-A-HAC was administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive further BTX-A-HAC treatment.

Arm type	Experimental
Investigational medicinal product name	BTX-A-HAC Solution 50 U
Investigational medicinal product code	
Other name	Botulinum Toxin Type A, BTX-A-HAC NG
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In each treatment cycle subjects received a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.

Arm title	Placebo - DB Period

Arm description:

During the DB period, subjects were randomised to receive a single treatment of placebo. 0.25 mL placebo was administered as five injections of 0.05 mL each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive BTX-A-HAC treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In each treatment cycle subjects received a single treatment with 0.25 mL placebo administered as five

injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region. Placebo was provided as a liquid identical to BTX-A-HAC solution, containing only the excipients of BTX-A-HAC solution.

Arm title	BTX-A-HAC Solution 50 U - LT Analyses

Arm description:

Eligible subjects who completed the DB Cycle 1 treatment were able to receive further treatment in the OL period (OL Cycles 2 to 5). Additional BTX-naïve (de novo) subjects were enrolled into the OL period to receive treatment with BTX-A-HAC during OL Cycle 1, and if eligible for retreatment de novo subjects received retreatment in OL Cycles 2 to 5.
Each treatment cycle included a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region, and treatments were separated by at least 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BTX-A-HAC Solution 50 U
Investigational medicinal product code	
Other name	Botulinum Toxin Type A, BTX-A-HAC NG
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In each treatment cycle subjects received a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.

Number of subjects in period 1	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period	BTX-A-HAC Solution 50 U - LT Analyses
Started	126	64	595
Completed	118	59	509
Not completed	8	5	86
Consent withdrawn by subject	8	5	74
Site error	-	-	1
Adverse event, non-fatal	-	-	4
Pregnancy	-	-	3
Investigator decision - non-compliance	-	-	2
Lost to follow-up	-	-	1
Investigator decision - non-availability	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BTX-A-HAC Solution 50 U - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of BTX-A-HAC solution 50 U.
50 U (0.25 mL) BTX-A-HAC was administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive further BTX-A-HAC treatment.

Reporting group title	Placebo - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of placebo. 0.25 mL placebo was administered as five injections of 0.05 mL each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive BTX-A-HAC treatment.

Reporting group title	BTX-A-HAC Solution 50 U - LT Analyses

Reporting group description:

Eligible subjects who completed the DB Cycle 1 treatment were able to receive further treatment in the OL period (OL Cycles 2 to 5). Additional BTX-naïve (de novo) subjects were enrolled into the OL period to receive treatment with BTX-A-HAC during OL Cycle 1, and if eligible for retreatment de novo subjects received retreatment in OL Cycles 2 to 5.
Each treatment cycle included a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region, and treatments were separated by at least 12 weeks.

Reporting group values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period	BTX-A-HAC Solution 50 U - LT Analyses
Number of subjects	126	64	595
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn-gestational age < 37 wk	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
From 18 - 64 years	123	64	586
From 65 - 84 years	3	0	9
Over 85 years	0	0	0
Gender categorical Units: Subjects			
Female	115	58	530
Male	11	6	65
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1

White	125	64	589
More than one race	0	0	0
Unknown or Not Reported	0	0	3

Reporting group values	Total		
Number of subjects	600		
Age categorical Units: Subjects			
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		
From 18 - 64 years	588		
From 65 - 84 years	12		
Over 85 years	0		
Gender categorical Units: Subjects			
Female	533		
Male	67		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	594		
More than one race	0		
Unknown or Not Reported	3		

End points

End points reporting groups

Reporting group title	BTX-A-HAC Solution 50 U - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of BTX-A-HAC solution 50 U.
50 U (0.25 mL) BTX-A-HAC was administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive further BTX-A-HAC treatment.

Reporting group title	Placebo - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of placebo. 0.25 mL placebo was administered as five injections of 0.05 mL each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive BTX-A-HAC treatment.

Reporting group title	BTX-A-HAC Solution 50 U - LT Analyses

Reporting group description:

Eligible subjects who completed the DB Cycle 1 treatment were able to receive further treatment in the OL period (OL Cycles 2 to 5). Additional BTX-naïve (de novo) subjects were enrolled into the OL period to receive treatment with BTX-A-HAC during OL Cycle 1, and if eligible for retreatment de novo subjects received retreatment in OL Cycles 2 to 5.
Each treatment cycle included a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region, and treatments were separated by at least 12 weeks.

Primary: The Percentage of Responders at Day 29 Cycle 1 as Measured by ILA of Glabellar Lines at Maximum Frown: DB Period

End point title	The Percentage of Responders at Day 29 Cycle 1 as Measured by ILA of Glabellar Lines at Maximum Frown: DB Period[1]

End point description:

The appearance of glabellar lines at maximum frown was assessed in the DB period at the Day 29 follow-up visit using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline (Day 1 Cycle 1). The percentage of responders at Day 29 Cycle 1 is presented.
Results are presented for the modified intent-to-treat (mITT) population which consisted of all subjects who were randomised, received study treatment (BTX-A-HAC solution or placebo) and completed one post-treatment assessment of the ILA of glabellar lines at maximum frown.

End point type	Primary

End point timeframe:

Day 29 (Cycle 1)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	61		
Units: Percentage of Responders				
number (confidence interval 95%)	81.6 (61.3 to 92.5)	0.8 (0.1 to 4.8)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29

Statistical analysis description:

Treatment difference against placebo in the percentage of responders.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	80.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	73.7
upper limit	88

Notes:

[2] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Secondary: The Percentage of Responders at Each Post-Treatment Visit (Except Day 29 Cycle 1) as Measured by the ILA at Maximum Frown: DB Period

End point title	The Percentage of Responders at Each Post-Treatment Visit (Except Day 29 Cycle 1) as Measured by the ILA at Maximum Frown: DB Period[3]

End point description:

The appearance of glabellar lines at maximum frown was assessed in the DB period at post-treatment follow-up visits using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline (Day 1 Cycle 1). The percentage of responders is presented at Days 8, 57 and 85.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 8, 57 and 85 (Cycle 1).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Percentage of Responders				
number (confidence interval 95%)				
Day 8	75.9 (56.7 to 88.3)	0.9 (0.1 to 5.5)		
Day 57 (n=122; n=60)	74.7 (51.4 to 89.2)	0.6 (0.1 to 4.0)		
Day 85 (n=123; n=59)	55.5 (35.8 to 73.5)	1.8 (0.4 to 8.9)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8
Statistical analysis description:	
Treatment difference against placebo in the percentage of responders at Day 8 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	75
Confidence interval	
level	95 %
sides	2-sided
lower limit	67.1
upper limit	82.8

Notes:

[4] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57
Statistical analysis description:	
Treatment difference against placebo in the percentage of responders at Day 57 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	74.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	66.2
upper limit	82.1

Notes:

[5] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	53.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.2
upper limit	63.1

Notes:

[6] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Secondary: The Percentage of Responders on Day 29 Cycle 1 Who Remained Responders on Days 57 and 85 as Measured by the ILA at Maximum Frown: DB Period

End point title	The Percentage of Responders on Day 29 Cycle 1 Who Remained Responders on Days 57 and 85 as Measured by the ILA at Maximum Frown: DB Period[7]

End point description:

The appearance of glabellar lines at maximum frown was assessed in the DB period at post treatment follow-up visits using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline (Day 1 Cycle 1). The percentage of responders at Day 29 of Cycle 1 who still fulfilled the criteria for a responder at Days 57 and 85 is presented.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 29, 57 and 85 (Cycle 1).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Percentage of Responders				
number (confidence interval 95%)				
Day 57 (n=106; n=1)	87.7 (81.5 to 94.0)	100.0 (100.0 to 100.0)		
Day 85 (n=106; n=1)	63.2 (54.0 to 72.4)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the ILA at Rest: DB Period

End point title	The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the ILA at Rest: DB Period[8]

End point description:

The appearance of glabellar lines at rest was assessed in the DB period at post treatment follow-up visits using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline (Day 1 Cycle 1). The percentage of responders is presented for Days 8, 29, 57 and 85.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Percentage of Responders				
number (confidence interval 95%)				
Day 8 (n=90; n=42)	69.4 (49.2 to 84.2)	11.4 (3.9 to 29.0)		
Day 29 (n=89; n=41)	62.2 (39.0 to 80.9)	5.4 (1.4 to 18.5)		
Day 57 (n=87; n=40)	63.1 (35.2 to 84.4)	0.6 (0.0 to 8.2)		
Day 85 (n=88; n=39)	49.5 (29.0 to 70.1)	6.8 (1.9 to 22.0)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8
Statistical analysis description:	
Treatment difference against placebo in the percentage of responders at Day 8 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	58
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.5
upper limit	71.6

Notes:

[9] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29
Statistical analysis description:	
Treatment difference against placebo in the percentage of responders at Day 29 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	56.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.5
upper limit	69

Notes:

[10] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	62.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.1
upper limit	72.9

Notes:

[11] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	42.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.5
upper limit	55.7

Notes:

[12] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Secondary: The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Self-Assessment (SSA) at Maximum Frown: DB Period

End point title	The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Self-Assessment (SSA) at Maximum Frown: DB Period[13]

End point description:

The appearance of glabellar lines at maximum frown was assessed using the SSA, a validated 4-point categorical scale of glabellar line severity, in the DB period at post-treatment follow-up visits. A responder was defined as having a severity grade of no wrinkles (Grade 0) or mild wrinkles (Grade 1) at maximum frown at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) wrinkles at baseline (Day 1 Cycle 1).

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Percentage of Responders				
number (confidence interval 95%)				
Day 8	63.5 (44.0 to 79.3)	2.3 (0.6 to 9.1)		
Day 29 (n=124; n=61)	68.1 (48.4 to 82.9)	2.3 (0.6 to 8.5)		
Day 57 (n=122; n=60)	71.2 (51.2 to 85.3)	0.7 (0.1 to 6.8)		
Day 85 (n=123; n=60)	34.7 (18.5 to 55.4)	1.7 (0.3 to 8.0)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 8 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	61.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.9
upper limit	70.3

Notes:

[14] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 29 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	65.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	56.8
upper limit	74.8

Notes:

[15] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	70.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.2
upper limit	78.8

Notes:

[16] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	33

Confidence interval	
level	95 %
sides	2-sided
lower limit	24
upper limit	42

Notes:

[17] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Secondary: The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Level of Satisfaction with the Appearance of Their Glabellar Lines: DB Period

End point title	The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Level of Satisfaction with the Appearance of Their Glabellar Lines: DB Period[18]

End point description:

The subject's level of satisfaction with the appearance of their glabellar lines was assessed in the DB period at post-treatment follow-up visits using a 4-point categorical scale. A responder was defined as having a satisfaction rating of very satisfied (Grade 0) or satisfied (Grade 1) at a given visit and a satisfaction rating of dissatisfied (Grade 2) or very dissatisfied (Grade 3) at baseline (Day 1 Cycle 1). The percentage of responders is presented for Days 8, 29, 57 and 85.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Percentage of Responders				
number (confidence interval 95%)				
Day 8	76.3 (59.3 to 87.6)	8.1 (3.0 to 19.7)		
Day 29 (n=124; n=61)	83.1 (67.3 to 92.1)	5.7 (1.9 to 15.7)		
Day 57 (n=122; n= 60)	77.9 (60.0 to 89.2)	3.5 (1.0 to 11.9)		
Day 85 (n=123; n=60)	51.3 (30.7 to 71.4)	0.3 (0.0 to 4.2)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 8 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Linear
Parameter estimate	Treatment difference
Point estimate	68.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.2
upper limit	78.3

Notes:

[19] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 29 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	77.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	68.6
upper limit	86.2

Notes:

[20] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	74.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	65.7
upper limit	83.1

Notes:

[21] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference against placebo in the percentage of responders at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	51
Confidence interval	
level	95 %
sides	2-sided
lower limit	42
upper limit	59.9

Notes:

[22] - The treatment difference and p-value were obtained from a logistic regression on responders with treatment group, gender, baseline severity score on ILA at maximum frown and centre as fixed variables.

Secondary: The Median Time to Onset of Treatment Response Based on the Subject's Diary Card: DB Period

End point title	The Median Time to Onset of Treatment Response Based on the Subject's Diary Card: DB Period[23]

End point description:

Subjects were asked to record their assessment of study treatment response on a diary card on Days 1 to 7 at approximately the same time each day. Subjects were asked to respond 'yes' or 'no' to the following question: 'Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows)?' The time to onset of response was defined as the first day the subject responded 'yes' to this question.

Results are presented for the mITT population.

End point type	Secondary

End point timeframe:

Days 1 to 7 (Cycle 1).

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63[24]		
Units: Days				
median (confidence interval 95%)	2.0 (2.0 to 3.0)	99999999 (99999999 to 99999999)		

Notes:

[24] - 99999999 indicates value was not calculated due to the small number of responders.

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo

Statistical analysis description:

Treatment difference in median time to onset of treatment response.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Cox proportional hazard model

Notes:

[25] - The Hazard ratio calculated with centre, gender and ILA baseline severity score as covariates = 15.296.

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Satisfaction with Facial Appearance Overall Scale: DB Period

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Satisfaction with Facial Appearance Overall Scale: DB Period[26]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the satisfaction with facial appearance overall scale. This consisted of 10 items with 4 possible answers for each: 1 (Very Dissatisfied), 2 (Somewhat Dissatisfied), 3 (Somewhat Satisfied) and 4 (Very Satisfied). The least squares mean change from baseline at post-treatment visits of Rasch transformed scores is presented. The Rasch transformed score was calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 (most dissatisfied) to 100 (most satisfied) using a conversion table.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Scores on a Scale				
least squares mean (standard error)				
Day 8 (n=123; n=62)	9.4 (± 1.72)	0.8 (± 1.93)		
Day 29 (n=123; n=60)	8.1 (± 1.90)	-3.0 (± 2.12)		
Day 57 (n=121; n=59)	11.2 (± 1.83)	0.7 (± 2.03)		
Day 85 (n=122; n=59)	4.7 (± 1.91)	-5.0 (± 2.15)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8
Statistical analysis description:	
Treatment difference (BTX-A-HAC Solution – Placebo) at Day 8 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	12

Notes:

[27] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariates.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29
Statistical analysis description:	
Treatment difference (BTX-A-HAC Solution – Placebo) at Day 29 Cycle 1.	
Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.4
upper limit	14.8

Notes:

[28] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariates.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.8
upper limit	14

Notes:

[29] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariates.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.9
upper limit	13.3

Notes:

[30] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariates.

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Psychological Well-Being Scale: DB Period

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Psychological Well-Being Scale: DB Period[31]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the psychological well-being scale. This consisted of 10 items with 4 possible answers for each: 1

(Definitely disagree), 2 (Somewhat disagree), 3 (Somewhat agree) and 4 (Definitely agree). The least squares mean change from baseline at post-treatment visits of Rasch transformed scores is presented. The Rasch transformed score was calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 (worst) to 100 (best) using a conversion table.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Scores on a Scale				
least squares mean (standard error)				
Day 8 (n=124; n=62)	6.6 (± 2.19)	-2.7 (± 2.46)		
Day 29 (n=123; n=60)	4.5 (± 2.39)	-6.9 (± 2.66)		
Day 57 (n=121; n=59)	6.1 (± 2.41)	-5.1 (± 2.69)		
Day 85 (n=122; n=59)	0.7 (± 2.28)	-7.5 (± 2.57)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 8 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	13.6

Notes:

[32] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 29 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	16

Notes:

[33] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.4
upper limit	15.9

Notes:

[34] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [35]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	12.6

Notes:

[35] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Aging Appearance Appraisal Visual Analogue Scale (VAS): DB Period

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Aging Appearance Appraisal Visual Analogue Scale (VAS): DB Period[36]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the aging appearance appraisal VAS. The VAS ranged from -15 ('I look 15 years younger') to +15 ('I look 15 years older'), with 0 indicating 'I look my age'. Subjects were asked to circle one number on the VAS indicating how many years younger or older they thought they looked compared to their actual age, with lower scores indicating a better outcome and higher scores a worse outcome. The least squares mean change from baseline at post-treatment visits is presented.

Results are presented for the mITT population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1).

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the DB period only and the arm 'BTX-A-HAC Solution 50 U - LT Analyses' represents the OL period.

End point values	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	63		
Units: Scores on a Scale				
least squares mean (standard error)				
Day 8 (n=123; n=62)	-0.8 (± 0.25)	-0.2 (± 0.28)		
Day 29 (n=122; n=60)	-0.8 (± 0.28)	0.3 (± 0.32)		
Day 57 (n=121; n=59)	-0.6 (± 0.34)	0.7 (± 0.39)		
Day 85 (n=122; n=59)	-0.4 (± 0.31)	1.1 (± 0.36)		

Statistical analyses

Statistical analysis title	BTX-A-HAC vs Placebo: Day 8

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 8 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174 [37]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.1

Notes:

[37] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 29

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 29 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.6

Notes:

[38] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 57

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 57 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [39]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	-1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.7

Notes:

[39] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Statistical analysis title	BTX-A-HAC vs Placebo: Day 85

Statistical analysis description:

Treatment difference (BTX-A-HAC Solution – Placebo) at Day 85 Cycle 1.

Comparison groups	BTX-A-HAC Solution 50 U - DB Period v Placebo - DB Period
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [40]
Method	General linear model
Parameter estimate	Treatment difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.8

Notes:

[40] - The general linear model included mean change from baseline as a dependent variable and treatment group, gender and centre as fixed effects, and baseline severity score on ILA at maximum frown as covariate.

Secondary: The Percentage of Responders at Each Post-Treatment Visit as Measured by the ILA at Maximum Frown: LT Analyses

End point title	The Percentage of Responders at Each Post-Treatment Visit as Measured by the ILA at Maximum Frown: LT Analyses[41]

End point description:

The appearance of glabellar lines at maximum frown was assessed in the OL period at post-treatment follow-up visits using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline. The cycle baseline was defined as the last measurement collected prior to the study treatment injection of the corresponding cycle. The percentage of responders at each post-treatment visit for Cycles 1 to 5 are presented. Cycle 1 corresponds to the first administration of BTX-A-HAC solution and includes the DB Cycle 1 of subjects who were treated with BTX-A-HAC solution, the Cycle 1 of de novo subjects and Cycle 2 of subjects who were randomised to receive placebo in the DB period.
The LTA population consisted of all subjects who received at least one injection of BTX-A-HAC solution in the OL period.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 - 5 (up to 15 months).

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Percentage of Responders				
number (confidence interval 95%)				
Cycle 1: Day 8 (n=589)	75.7 (72.3 to 79.2)			
Cycle 1: Day 29 (n=585)	82.2 (79.1 to 85.3)			
Cycle 1: Day 57 (n=575)	69.9 (66.2 to 73.7)			
Cycle 1: Day 85 (n=579)	53.0 (49.0 to 57.1)			
Cycle 2: Day 8 (n=553)	80.8 (77.6 to 84.1)			
Cycle 2: Day 29 (n=547)	84.5 (81.4 to 87.5)			
Cycle 2: Day 57 (n=544)	74.3 (70.6 to 77.9)			
Cycle 2: Day 85 (n=544)	53.7 (49.5 to 57.9)			
Cycle 3: Day 8 (n=483)	86.5 (83.5 to 89.6)			
Cycle 3: Day 29 (n=476)	87.8 (84.9 to 90.8)			
Cycle 3: Day 57 (n=472)	78.6 (74.9 to 82.3)			
Cycle 3: Day 85 (n=472)	56.8 (52.3 to 61.2)			
Cycle 4: Day 8 (n=312)	84.3 (80.3 to 88.3)			
Cycle 4: Day 29 (n=310)	86.1 (82.3 to 90.0)			
Cycle 4: Day 57 (n=306)	76.1 (71.4 to 80.9)			
Cycle 4: Day 85 (n=302)	50.7 (45.0 to 56.3)			
Cycle 5: Day 8 (n=88)	84.1 (76.4 to 91.7)			
Cycle 5: Day 29 (n=87)	82.8 (74.8 to 90.7)			
Cycle 5: Day 57 (n=86)	55.8 (45.3 to 66.3)			
Cycle 5: Day 85 (n=86)	45.3 (34.8 to 55.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Responders at Each Post-Treatment Visit as Measured by the ILA at Rest: LT Analyses

End point title	The Percentage of Responders at Each Post-Treatment Visit as Measured by the ILA at Rest: LT Analyses[42]

End point description:

The appearance of glabellar lines at rest was assessed in the OL period at post-treatment follow-up visits using the ILA, a validated 4-point photographic scale of glabellar line severity. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at baseline. The cycle baseline was defined as the last measurement collected prior to the study treatment injection of the corresponding cycle. The percentage of responders at each post-treatment visit for Cycles 1 to 5 are presented. Cycle 1 corresponds to the first administration of BTX-A-HAC solution and includes the DB Cycle 1 of subjects who were treated with BTX-A-HAC solution, the Cycle 1 of de novo subjects and Cycle 2 of subjects who were randomised to receive placebo in the DB period.

Results are presented for the LTA population. Only subjects with data available at the timepoints of testing are presented.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 - 5 (up to 15 months).

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Percentage of Responders				
number (confidence interval 95%)				
Cycle 1: Day 8 (n=375)	74.1 (69.7 to 78.6)			
Cycle 1: Day 29 (n=372)	81.7 (77.8 to 85.6)			
Cycle 1: Day 57 (n=365)	77.3 (73.0 to 81.6)			
Cycle 1: Day 85 (n=368)	61.1 (56.2 to 66.1)			
Cycle 2: Day 8 (n=239)	74.5 (68.9 to 80.0)			
Cycle 2: Day 29 (n=236)	78.4 (73.1 to 83.6)			
Cycle 2: Day 57 (n=234)	71.4 (65.6 to 77.2)			
Cycle 2: Day 85 (n=234)	47.9 (41.5 to 54.3)			
Cycle 3: Day 8 (n=202)	82.2 (76.9 to 87.5)			
Cycle 3: Day 29 (n=196)	84.2 (79.1 to 89.3)			
Cycle 3: Day 57 (n=195)	80.0 (74.4 to 85.6)			
Cycle 3: Day 85 (n=196)	58.7 (51.8 to 65.6)			
Cycle 4: Day 8 (n=134)	77.6 (70.6 to 84.7)			
Cycle 4: Day 29 (n=134)	81.3 (74.7 to 87.9)			
Cycle 4: Day 57 (n=133)	78.9 (72.0 to 85.9)			
Cycle 4: Day 85 (n=131)	59.5 (51.1 to 67.9)			

Cycle 5: Day 8 (n=42)	85.7 (75.1 to 96.3)			
Cycle 5: Day 29 (n=41)	78.0 (65.4 to 90.7)			
Cycle 5: Day 57 (n=41)	63.4 (48.7 to 78.2)			
Cycle 5: Day 85 (n=41)	56.1 (40.9 to 71.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Responders at Each Post-Treatment Visit as Measured by the SSA at Maximum Frown: LT Analyses

End point title	The Percentage of Responders at Each Post-Treatment Visit as Measured by the SSA at Maximum Frown: LT Analyses[43]

End point description:

The appearance of glabellar lines at maximum frown was assessed using the SSA, a validated 4-point categorical scale of glabellar line severity, in the OL period at post-treatment follow-up visits. A responder was defined as having a severity grade of no wrinkles (Grade 0) or mild wrinkles (Grade 1) at maximum frown at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) wrinkles at baseline. The cycle baseline was defined as the last measurement collected prior to the study treatment injection of the corresponding cycle. The percentage of responders at each post-treatment visit for Cycles 1 to 5 are presented. Cycle 1 corresponds to the first administration of BTX-A-HAC solution and includes the DB Cycle 1 of subjects who were treated with BTX-A-HAC solution, the Cycle 1 of de novo subjects and Cycle 2 of subjects who were randomised to receive placebo in the DB period.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 - 5 (up to 15 months).

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Percentage of Responders				
number (confidence interval 95%)				
Cycle 1: Day 8 (n=589)	62.8 (58.9 to 66.7)			
Cycle 1: Day 29 (n=585)	72.5 (68.9 to 76.1)			
Cycle 1: Day 57 (n=575)	64.3 (60.4 to 68.3)			
Cycle 1: Day 85 (n=578)	43.6 (39.6 to 47.6)			
Cycle 2: Day 8 (n=524)	74.8 (71.1 to 78.5)			

Cycle 2: Day 29 (n=522)	75.3 (71.6 to 79.0)			
Cycle 2: Day 57 (n=518)	69.3 (65.3 to 73.3)			
Cycle 2: Day 85 (n=517)	44.3 (40.0 to 48.6)			
Cycle 3: Day 8 (n=476)	78.8 (75.1 to 82.5)			
Cycle 3: Day 29 (n=469)	80.6 (77.0 to 84.2)			
Cycle 3: Day 57 (n=465)	67.1 (62.8 to 71.4)			
Cycle 3: Day 85 (n=465)	44.9 (40.4 to 49.5)			
Cycle 4: Day 8 (n=310)	80.3 (75.9 to 84.7)			
Cycle 4: Day 29 (n=307)	75.2 (70.4 to 80.1)			
Cycle 4: Day 57 (n=304)	66.1 (60.8 to 71.4)			
Cycle 4: Day 85 (n=300)	47.3 (41.7 to 53.0)			
Cycle 5: Day 8 (n=87)	66.7 (56.8 to 76.6)			
Cycle 5: Day 29 (n=86)	62.8 (52.6 to 73.0)			
Cycle 5: Day 57 (n=85)	49.4 (38.8 to 60.0)			
Cycle 5: Day 85 (n=85)	37.6 (27.3 to 47.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Level of Satisfaction with the Appearance of Their Glabellar Lines: LT Analyses

End point title	The Percentage of Responders at Each Post-Treatment Visit to the Study Centre as Measured by the Subject's Level of Satisfaction with the Appearance of Their Glabellar Lines: LT Analyses[44]

End point description:

The subject's level of satisfaction with the appearance of their glabellar lines was assessed in the OL period at post-treatment follow-up visits of each treatment cycle using a 4-point categorical scale. A responder was defined as having a satisfaction rating of very satisfied (Grade 0) or satisfied (Grade 1) at a given visit and a satisfaction rating of dissatisfied (Grade 2) or very dissatisfied (Grade 3) at baseline. The cycle baseline was defined as the last measurement collected prior to the study treatment injection of the corresponding cycle. The percentage of responders at each post-treatment visit for Cycles 1 to 5 are presented. Cycle 1 corresponds to the first administration of BTX-A-HAC solution and includes the DB Cycle 1 of subjects who were treated with BTX-A-HAC solution, the Cycle 1 of de novo subjects and Cycle 2 of subjects who were randomised to receive placebo in the DB period.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 - 5 (up to 15 months).

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Percentage of Responders				
number (confidence interval 95%)				
Cycle 1: Day 8 (n=589)	78.8 (75.5 to 82.1)			
Cycle 1: Day 29 (n=585)	86.0 (83.2 to 88.8)			
Cycle 1: Day 57 (n=575)	75.8 (72.3 to 79.3)			
Cycle 1: Day 85 (n=579)	56.3 (52.3 to 60.3)			
Cycle 2: Day 8 (n=448)	80.8 (77.2 to 84.5)			
Cycle 2: Day 29 (n=446)	85.2 (81.9 to 88.5)			
Cycle 2: Day 57 (n=442)	79.0 (75.2 to 82.8)			
Cycle 2: Day 85 (n=444)	51.8 (47.2 to 56.4)			
Cycle 3: Day 8 (n=401)	88.3 (85.1 to 91.4)			
Cycle 3: Day 29 (n=395)	87.8 (84.6 to 91.1)			
Cycle 3: Day 57 (n=391)	80.6 (76.6 to 84.5)			
Cycle 3: Day 85 (n=392)	54.6 (49.7 to 59.5)			
Cycle 4: Day 8 (n=263)	87.1 (83.0 to 91.1)			
Cycle 4: Day 29 (n=260)	87.3 (83.3 to 91.4)			
Cycle 4: Day 57 (n=257)	74.3 (69.0 to 79.7)			
Cycle 4: Day 85 (n=254)	58.3 (52.2 to 64.3)			
Cycle 5: Day 8 (n=73)	74.0 (63.9 to 84.0)			
Cycle 5: Day 29 (n=72)	72.2 (61.9 to 82.6)			
Cycle 5: Day 57 (n=71)	60.6 (49.2 to 71.9)			
Cycle 5: Day 85 (n=70)	44.3 (32.6 to 55.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Retreatment in LT Analysis

End point title	Median Time to Retreatment in LT Analysis[45]

End point description:

The median time to onset of the next eligible treatment cycle is presented for Cycles 1 to 4.
Cycle 1 corresponds to the first administration of BTX-A-HAC solution and includes the DB Cycle 1 of subjects who were treated with BTX-A-HAC solution, the Cycle 1 of de novo subjects and Cycle 2 of subjects who were randomised to receive placebo in the DB period.
Subjects who were not subsequently retreated after a given cycle were excluded from the summary of time to retreatment at that cycle.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Cycles 1 - 4 (up to 12 months).

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Days				
median (confidence interval 95%)				
Cycle 1	113.0 (113.0 to 116.0)			
Cycle 2 (n=558)	114.0 (113.0 to 117.0)			
Cycle 3 (n=486)	110.0 (106.0 to 113.0)			
Cycle 4 (n=305)	99.0 (92.0 to 110.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Satisfaction with Facial Appearance Overall Scale: LT Analyses

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Satisfaction with Facial Appearance Overall Scale: LT Analyses[46]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the satisfaction with facial appearance overall scale. This consisted of 10 items with 4 possible answers for each: 1 (Very Dissatisfied), 2 (Somewhat Dissatisfied), 3 (Somewhat Satisfied) and 4 (Very Satisfied). The mean change from baseline at post-treatment visits of Rasch transformed scores is presented. The Rasch transformed score was calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 (most dissatisfied) to 100 (most satisfied) using a conversion

table.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Cycle 1: Day 8 (n=586)	9.2 (± 14.5)			
Cycle 1: Day 29 (n=583)	10.9 (± 15.9)			
Cycle 1: Day 57 (n=517)	9.9 (± 15.4)			
Cycle 1: Day 85 (n=577)	6.6 (± 14.7)			
Cycle 2: Day 8 (n=553)	9.5 (± 14.6)			
Cycle 2: Day 29 (n=546)	9.7 (± 15.1)			
Cycle 2: Day 57 (n=1)	0.0 (± 0.0)			
Cycle 2: Day 85 (n=542)	4.8 (± 12.3)			
Cycle 3: Day 8 (n=484)	10.9 (± 15.0)			
Cycle 3: Day 29 (n=477)	9.9 (± 15.1)			
Cycle 3: Day 57 (n=3)	6.0 (± 4.6)			
Cycle 3: Day 85 (n=474)	5.0 (± 12.7)			
Cycle 4: Day 8 (n=314)	11.2 (± 14.3)			
Cycle 4: Day 29 (n=311)	9.9 (± 13.8)			
Cycle 4: Day 85 (n=308)	5.6 (± 11.8)			
Cycle 5: Day 8 (n=88)	12.0 (± 18.2)			
Cycle 5: Day 29 (n=87)	9.4 (± 17.5)			
Cycle 5: Day 85 (n=85)	5.3 (± 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Psychological Well-Being Scale: LT Analyses

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Psychological Well-Being Scale: LT Analyses[47]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the psychological well-being scale. This consisted of 10 items with 4 possible answers for each: 1 (Definitely disagree), 2 (Somewhat disagree), 3 (Somewhat agree) and 4 (Definitely agree). The mean change from baseline at post-treatment visits of Rasch transformed scores is presented. The Rasch

transformed score was calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 (worst) to 100 (best) using a conversion table.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5.

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Cycle 1: Day 8 (n=588)	6.7 (± 16.9)			
Cycle 1: Day 29 (n=584)	7.2 (± 19.2)			
Cycle 1: Day 57 (n=518)	5.5 (± 18.7)			
Cycle 1: Day 85 (n=578)	2.7 (± 16.9)			
Cycle 2: Day 8 (n=553)	7.8 (± 14.0)			
Cycle 2: Day 29 (n=546)	8.2 (± 15.6)			
Cycle 2: Day 57 (n=1)	0.0 (± 0.0)			
Cycle 2: Day 85 (n=541)	4.6 (± 13.6)			
Cycle 3: Day 8 (n=484)	8.8 (± 15.5)			
Cycle 3: Day 29 (n=477)	9.4 (± 15.3)			
Cycle 3: Day 85 (n=474)	4.4 (± 13.0)			
Cycle 4: Day 8 (n=314)	10.1 (± 16.0)			
Cycle 4: Day 29 (n=309)	8.8 (± 14.9)			
Cycle 4: Day 85 (n=307)	6.3 (± 13.7)			
Cycle 5: Day 8 (n=88)	10.1 (± 17.0)			
Cycle 5: Day 29 (n=87)	8.4 (± 14.4)			
Cycle 5: Day 85 (n=86)	7.0 (± 12.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at All Post-Treatment Visits in the FACE-Q Aging Appearance Appraisal VAS: LT Analyses

End point title	Change from Baseline at All Post-Treatment Visits in the FACE-Q Aging Appearance Appraisal VAS: LT Analyses[48]

End point description:

FACE-Q is a subject-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. One of three scales that was selected for this study was the aging appearance appraisal VAS. The VAS ranged from -15 ('I look 15 years younger') to +15 ('I look 15 years older'), with 0 indicating 'I look my age'. Subjects were asked to circle one number on the VAS indicating how many years younger or older they thought they looked compared to their actual age, with lower scores indicating a better outcome and higher scores a worse outcome. The mean change

from baseline at post-treatment visits is presented.

Results are presented for the LTA population.

End point type	Secondary

End point timeframe:

Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5.

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point presents data for the OL period only and the arms 'BTX-A-HAC Solution 50 U - DB Period' and 'Placebo - DB Period' represent the DB period.

End point values	BTX-A-HAC Solution 50 U - LT Analyses			
Subject group type	Reporting group			
Number of subjects analysed	595			
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Cycle 1: Day 8 (n=586)	-1.0 (± 2.2)			
Cycle 1: Day 29 (n=583)	-1.3 (± 2.5)			
Cycle 1: Day 57 (n=518)	-1.2 (± 2.6)			
Cycle 1: Day 85 (n=578)	-0.8 (± 2.5)			
Cycle 2: Day 8 (n=553)	-0.9 (± 1.8)			
Cycle 2: Day 29 (n=546)	-1.0 (± 1.9)			
Cycle 2: Day 57 (n=1)	0.0 (± 0.0)			
Cycle 3: Day 8 (n=484)	-1.0 (± 1.9)			
Cycle 3: Day 29 (n=477)	-1.0 (± 2.1)			
Cycle 3: Day 57 (n=3)	-0.3 (± 1.5)			
Cycle 3: Day 85 (n=474)	-0.5 (± 1.7)			
Cycle 4: Day 8 (n=314)	-1.1 (± 1.8)			
Cycle 4: Day 29 (n=311)	-0.9 (± 1.8)			
Cycle 4: Day 85 (n=307)	-0.5 (± 1.6)			
Cycle 5: Day 8 (n=88)	-1.3 (± 2.3)			
Cycle 5: Day 29 (n=87)	-1.1 (± 2.0)			
Cycle 5: Day 85 (n=86)	-0.7 (± 1.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from baseline (Day 1 Cycle 1 of DB period/OL period, as applicable) up to end of DB period (for DB period arms) or up to end of Cycle 5 of the OL period (for LT Analyses arm), up to approximately 20 months.

Adverse event reporting additional description:

DB period arms: the safety population for the DB period consisted of all subjects who received at least one injection of study treatment into at least one injection site.
LT Analyses arm: the LTA population included all subjects included in the DB period/de novo subjects who received at least one injection of BTX-A-HAC solution in the OL period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	BTX-A-HAC Solution 50 U - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of BTX-A-HAC solution 50 U.
50 U (0.25 mL) BTX-A-HAC was administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive further BTX-A-HAC treatment.

Reporting group title	Placebo - DB Period

Reporting group description:

During the DB period, subjects were randomised to receive a single treatment of placebo. 0.25 mL placebo was administered as five injections of 0.05 mL each into one of five predefined sites across the glabellar region.
Subjects who completed the DB treatment (Cycle 1) were eligible to continue to the OL period to receive BTX-A-HAC treatment.

Reporting group title	BTX-A-HAC Solution 50 U - LT Analyses

Reporting group description:

Eligible subjects who completed the DB Cycle 1 treatment were able to receive further treatment in the OL period (OL Cycles 2 to 5). Additional BTX-naïve (de novo) subjects were enrolled into the OL period to receive treatment with BTX-A-HAC during OL Cycle 1, and if eligible for retreatment de novo subjects received retreatment in OL Cycles 2 to 5.
Each treatment cycle included a single treatment with 50 U (0.25 mL) BTX-A-HAC administered as five injections of 10 U (0.05 mL) each into one of five predefined sites across the glabellar region, and treatments were separated by at least 12 weeks.

Serious adverse events	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period	BTX-A-HAC Solution 50 U - LT Analyses
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	2 / 64 (3.13%)	34 / 595 (5.71%)
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)			
Myxofibrosarcoma			

subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine carcinoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site extravasation			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 126 (0.00%)	1 / 64 (1.56%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			

subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 126 (0.79%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Post-traumatic stress disorder			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 126 (0.00%)	1 / 64 (1.56%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	2 / 595 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			

subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Holmes-Adie pupil			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune pancreatitis			

subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	2 / 595 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Gastrointestinal infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 126 (0.00%)	1 / 64 (1.56%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis bacterial			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	1 / 595 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BTX-A-HAC Solution 50 U - DB Period	Placebo - DB Period	BTX-A-HAC Solution 50 U - LT Analyses
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 126 (27.78%)	13 / 64 (20.31%)	279 / 595 (46.89%)
Vascular disorders			
Haematoma			
subjects affected / exposed	5 / 126 (3.97%)	0 / 64 (0.00%)	15 / 595 (2.52%)
occurrences (all)	5	0	16
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 126 (10.32%)	4 / 64 (6.25%)	117 / 595 (19.66%)
occurrences (all)	22	4	272
Migraine			
subjects affected / exposed	2 / 126 (1.59%)	0 / 64 (0.00%)	13 / 595 (2.18%)
occurrences (all)	5	0	20
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 126 (2.38%)	0 / 64 (0.00%)	6 / 595 (1.01%)
occurrences (all)	3	0	6
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	15 / 595 (2.52%)
occurrences (all)	0	0	19
Eyelid oedema			

subjects affected / exposed	2 / 126 (1.59%)	0 / 64 (0.00%)	14 / 595 (2.35%)
occurrences (all)	3	0	16
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 126 (1.59%)	1 / 64 (1.56%)	25 / 595 (4.20%)
occurrences (all)	2	3	29
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 126 (10.32%)	8 / 64 (12.50%)	168 / 595 (28.24%)
occurrences (all)	14	10	252
Pharyngitis			
subjects affected / exposed	3 / 126 (2.38%)	0 / 64 (0.00%)	7 / 595 (1.18%)
occurrences (all)	3	0	7
Bronchitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 64 (0.00%)	20 / 595 (3.36%)
occurrences (all)	1	0	21
Sinusitis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 64 (1.56%)	19 / 595 (3.19%)
occurrences (all)	1	2	22
Gastroenteritis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 64 (0.00%)	18 / 595 (3.03%)
occurrences (all)	1	0	19
Influenza			
subjects affected / exposed	0 / 126 (0.00%)	0 / 64 (0.00%)	16 / 595 (2.69%)
occurrences (all)	0	0	17
Cystitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 64 (0.00%)	15 / 595 (2.52%)
occurrences (all)	5	0	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported