Clinical trial results:
A phase III, double blind, randomised, placebo controlled study to assess the efficacy and safety of a single treatment of Clostridium botulinum toxin type A to improve the appearance of moderate to severe glabellar lines

Summary

EudraCT number	2013-002321-34
Trial protocol	DE
Global end of trial date	31 August 2015

Results information

Result version number	v1 (current)
This version publication date	04 March 2018
First version publication date	04 March 2018

Trial information

Trial identification

Sponsor protocol code	Y-52-52120-189

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02353871
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Innovation
Sponsor organisation address	5 Avenue du Canada, Les Ulis, Cedex, France, 91940
Public contact	Medical Director, Neurology, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen, 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	31 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2015
Global end of trial reached?	Yes
Global end of trial date	31 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of a single treatment of an injectable liquid form of Clostridium Botulinum toxin type A haemagglutinin complex (BTX-A-HAC) next generation (NG) at 50 Units (U), used for the improvement in the appearance of moderate to severe glabellar lines at maximum frown.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 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	France: 76
Country: Number of subjects enrolled	Germany: 109
Worldwide total number of subjects	185
EEA total number of subjects	185

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)	183
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with moderate or severe vertical glabellar lines at maximum frown were recruited to nine active sites in France and Germany from January 2015. The study was completed in August 2015.

Pre-assignment

Screening details:

Overall, 190 subjects were screened, five of whom were screening failures. A total of 185 subjects were enrolled and randomised to receive treatment. One of the subjects who was randomised to placebo did not receive study treatment due to violation of an inclusion criterion.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	BTX-A-HAC NG 50 U

Arm description:

Subjects were randomised to receive BTX-A-HAC NG. A total dose of 50 U was injected on Day 1. The total treatment volume (0.25 millilitres [mL]) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region.

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

Dosage and administration details:

Subjects received a single total dose of 50 U BTX-A-HAC NG solution (10 U/0.05 mL) divided into five equal injections (0.05 mL per injection) to be administered into five predefined sites in the glabellar region.

Arm title	Placebo

Arm description:

Subjects were randomised to receive placebo. The total placebo volume (0.25 mL) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region

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:

The placebo solution for injection contained only the excipients of BTX-A-HAC NG. Subjects received a single dose of 0.25 mL divided into five equal injections (0.05 mL per injection) to be administered into five predefined sites in the glabellar region.

Number of subjects in period 1	BTX-A-HAC NG 50 U	Placebo
Started	125	60
Completed	122	51
Not completed	3	9
Lost to follow-up	2	-
Consent withdrawn	1	8
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BTX-A-HAC NG 50 U
Reporting group description:	
Subjects were randomised to receive BTX-A-HAC NG. A total dose of 50 U was injected on Day 1. The total treatment volume (0.25 millilitres [mL]) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region.	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomised to receive placebo. The total placebo volume (0.25 mL) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region	

Reporting group values	BTX-A-HAC NG 50 U	Placebo	Total
Number of subjects	125	60	185
Age categorical			
Units: Subjects			
Age continuous			
Units: Years			
arithmetic mean	47.7	48.0	
standard deviation	± 9.75	± 9.09	-
Gender categorical			
Units: Subjects			
Female	108	52	160
Male	17	8	25
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	125	60	185
Unknown or Not Reported	0	0	0
Race, Customised			
Units: Subjects			
Caucasion/White	124	59	183
Black/African American	0	1	1
Other	1	0	1

End points

End points reporting groups

Reporting group title	BTX-A-HAC NG 50 U

Reporting group description:

Subjects were randomised to receive BTX-A-HAC NG. A total dose of 50 U was injected on Day 1. The total treatment volume (0.25 millilitres [mL]) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region.

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive placebo. The total placebo volume (0.25 mL) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region

Primary: The percentage of responders at Day 29 assessed by the Investigator's live assessment (ILA) of the appearance of glabellar lines at maximum frown.

End point title	The percentage of responders at Day 29 assessed by the Investigator's live assessment (ILA) of the appearance of glabellar lines at maximum frown.

End point description:

The ILA was used to assess the appearance of glabellar lines at maximum frown on Day 29, and consists of a validated 4-point photographic scale:
Grade 0 - none; Grade 1 - mild; Grade 2 - moderate; Grade 3 - severe.

A responder at maximum frown was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at maximum frown on Day 29 and a severity grade of moderate (Grade 2) or severe (Grade 3) at Baseline (Day 1, pretreatment).

The adjusted percentage of responders in each treatment group is presented and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects.

The modified intent-to-treat (mITT) population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Primary

End point timeframe:

Day 1 (Baseline) and Day 29

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	58		
Units: Adjusted percentage of responders				
number (confidence interval 95%)	88.3 (76.1 to 94.7)	1.4 (0.3 to 6.5)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	86.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	80.5
upper limit	93.3

Notes:

[1] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of responders at each post-treatment visit to the study centre (except Day 29) as measured by the ILA at maximum frown.

End point title	The percentage of responders at each post-treatment visit to the study centre (except Day 29) as measured by the ILA at maximum frown.

End point description:

The ILA was used to assess the appearance of glabellar lines at maximum frown on Days 8, 15, 57, 113, 148 and 183 and consists of a validated 4-point photographic scale:
Grade 0 - none; Grade 1 - mild; Grade 2 - moderate; Grade 3 - severe.

A responder at maximum frown was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at maximum frown on a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at Baseline (Day 1, pretreatment).

The adjusted percentage of responders in each treatment group is presented for each post-treatment visit and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Days 1 (Baseline), 8, 15, 57, 85, 113, 148 and 183 (End of Study).

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	59		
Units: Adjusted percentage of responders				
number (confidence interval 95%)				
Day 8 (n=124 BTX-A-HAC; n=57 Placebo)	80.5 (65.3 to 90.0)	1.3 (0.3 to 6.2)		

Day 15 (n=124 BTX-A-HAC; n=59 Placebo)	87.0 (74.5 to 93.9)	1.5 (0.3 to 7.0)		
Day 57 (n=124 BTX-A-HAC; n=58 Placebo)	77.4 (63.0 to 87.3)	1.0 (0.2 to 5.4)		
Day 85 (n=121 BTX-A-HAC; n=57 Placebo)	51.3 (35.1 to 67.3)	1.0 (0.2 to 5.6)		
Day 113 (n=123 BTX-A-HAC; n=56 Placebo)	34.0 (20.5 to 50.7)	0.8 (0.1 to 5.1)		
Day 148 (n=121 BTX-A-HAC; n=51 Placebo)	17.1 (7.9 to 33.1)	1.8 (0.3 to 9.8)		
Day 183 (n=122 BTX-A-HAC; n=51 Placebo)	4.9 (0.9 to 23.2)	0.9 (0.1 to 8.9)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 8

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 8 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	79.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.6
upper limit	86.7

Notes:

[2] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 15

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 15 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	85.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	78.8
upper limit	92.2

Notes:

[3] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	76.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	68.5
upper limit	84.2

Notes:

[4] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	50.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	41
upper limit	59.6

Notes:

[5] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	33.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.5
upper limit	41.9

Notes:

[6] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 148

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 148 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 [7]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	22.9

Notes:

[7] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0441 [8]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	4.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	8.7

Notes:

[8] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of responders on Day 29 who remained responders on Days 57, 85, 113, 148 and 183 as measured by the ILA at maximum frown.

End point title	The percentage of responders on Day 29 who remained responders on Days 57, 85, 113, 148 and 183 as measured by the ILA at maximum frown.

End point description:

The ILA was used to assess the appearance of glabellar lines at maximum frown and consists of a validated 4-point photographic scale: Grade 0 - none; Grade 1 - mild; Grade 2 - moderate; Grade 3 - severe.
A responder at maximum frown was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at maximum frown on a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at Baseline (Day 1). Subjects who were not responders at Day 29 were excluded from the analysis.
The adjusted percentage of remaining responders in each treatment group following Day 29 is presented and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects.
The modified mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Days 57, 85, 113, 148 and 183 (End of Study).

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	2		
Units: Adjusted percentage of responders				
number (confidence interval 95%)				
Day 57 (n=112 BTX-A-HAC; n=2 Placebo)	87.3 (72.4 to 94.8)	47.0 (2.8 to 96.5)		
Day 85 (n=109 BTX-A-HAC; n=2 Placebo)	61.1 (42.5 to 77.0)	4.9 (0.1 to 73.4)		
Day 113 (n=111 BTX-A-HAC; n=2 Placebo)	39.6 (23.9 to 57.9)	24.0 (0.7 to 93.5)		
Day 148 (n=109 BTX-A-HAC; n=2 Placebo)	20.1 (9.0 to 39.0)	32.1 (1.8 to 92.6)		
Day 183 (n=110 BTX-A-HAC; n=2 Placebo)	5.3 (0.9 to 26.6)	8.0 (0.2 to 76.9)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of remaining responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2422 [9]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	40.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	100

Notes:

[9] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of remaining responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0917 [10]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	56.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.8
upper limit	87.5

Notes:

[10] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of remaining responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7064 [11]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	15.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.3
upper limit	75.5

Notes:

[11] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 148

Statistical analysis description:

The difference in the adjusted percentage of remaining responders between the treatment groups at Day 148 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.701 [12]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	-11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.1
upper limit	53.2

Notes:

[12] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of remaining responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7894 [13]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.5
upper limit	35.2

Notes:

[13] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of responders at each post-treatment visit to the study centre as measured by the ILA at rest.

End point title	The percentage of responders at each post-treatment visit to

	the study centre as measured by the ILA at rest.

End point description:

The ILA was used to assess the appearance of glabellar lines at rest and consists of a validated 4-point photographic scale: Grade 0 - none; Grade 1 - mild; Grade 2 - moderate; Grade 3 - severe.

A responder at rest was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at rest at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at Baseline (Day 1).

The adjusted percentage of responders in each treatment group is presented for each post-treatment visit and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects. Day 148 results (BTX-A-HAC NG 50 U) were not calculable due to quasi-complete separation of data point.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Days 1 (Baseline), 8, 15, 29, 57, 85, 113, 148 and 183 (End of Study).

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[14]	59[15]		
Units: Adjusted percentage of responders				
number (confidence interval 95%)				
Day 8 (n=53 BTX-A-HAC; n=31 Placebo)	73.2 (38.4 to 92.3)	2.0 (0.2 to 15.8)		
Day 15 (n=53 BTX-A-HAC; n=32 Placebo)	74.5 (37.7 to 93.3)	1.3 (0.1 to 12.7)		
Day 29 (n=53 BTX-A-HAC; n=32 Placebo)	81.1 (46.5 to 95.5)	1.5 (0.1 to 14.4)		
Day 57 (n=53 BTX-A-HAC; n=32 Placebo)	77.2 (41.7 to 94.1)	0.5 (0.0 to 10.6)		
Day 85 (n=53 BTX-A-HAC; n=32 Placebo)	58.5 (24.0 to 86.2)	0.5 (0.0 to 8.0)		
Day 113 (n=53 BTX-A-HAC; n=31 Placebo)	74.7 (43.5 to 91.8)	4.8 (0.8 to 24.6)		
Day 148 (n=51 BTX-A-HAC; n=29 Placebo)	99999999 (99999999 to 99999999)	99999999 (99999999 to 99999999)		
Day 183 (n=53 BTX-A-HAC; n=29 Placebo)	56.0 (26.4 to 81.9)	10.4 (2.2 to 37.9)		

Notes:

[14] - Not calculable denoted 99999999.

[15] - Not calculable denoted 99999999.

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 8

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 8 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	71.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.2
upper limit	84.1

Notes:

[16] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 15

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 15 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	73.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	60.9
upper limit	85.6

Notes:

[17] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 29

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 29 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	79.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	68.2
upper limit	90.9

Notes:

[18] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	76.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	65.1
upper limit	88.2

Notes:

[19] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	58
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.5
upper limit	71.5

Notes:

[20] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	69.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	56
upper limit	83.8

Notes:

[21] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [22]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	45.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.3
upper limit	63

Notes:

[22] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of subjects with a reduction of two or more grades in the severity of glabellar lines at each post-treatment visit to the study centre as measured by the ILA at maximum frown

End point title	The percentage of subjects with a reduction of two or more grades in the severity of glabellar lines at each post-treatment visit to the study centre as measured by the ILA at maximum frown

End point description:

The ILA was used to assess the appearance of glabellar lines at maximum frown and consists of a validated 4-point photographic scale: Grade 0 - none; Grade 1 - mild; Grade 2 - moderate; Grade 3 - severe.

Adjusted percentages of subjects with a reduction of two or more grades in the severity of glabellar lines at each post-treatment visit compared with Baseline are presented, and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and

baseline ILA score at maximum frown) as fixed effects.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown

End point type	Secondary

End point timeframe:

Days 1 (Baseline), 8, 15, 29, 57, 85, 113, 148 and 183 (End of Study).

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	59		
Units: Adjusted percentage of subjects				
number (confidence interval 95%)				
Day 8 (n=124 BTX-A-HAC; n=57 Placebo)	56.2 (37.1 to 73.6)	0.2 (0.0 to 3.0)		
Day 15 (n=124 BTX-A-HAC; n=59 Placebo)	69.7 (52.0 to 83.0)	0.2 (0.0 to 3.1)		
Day 29 (n=124 BTX-A-HAC; n=58 Placebo)	63.6 (46.4 to 77.9)	0.1 (0.0 to 1.8)		
Day 57 (n=124 BTX-A-HAC; n=58 Placebo)	48.0 (31.6 to 64.9)	0.1 (0.0 to 2.6)		
Day 85 (n=121 BTX-A-HAC; n=57 Placebo)	24.3 (13.4 to 39.9)	0.3 (0.0 to 4.8)		
Day 113 (n=123 BTX-A-HAC; n=56 Placebo)	10.1 (4.3 to 21.7)	0.3 (0.0 to 4.4)		
Day 148 (n=121 BTX-A-HAC; n=51 Placebo)	3.5 (0.8 to 13.5)	0.3 (0.0 to 5.4)		
Day 183 (n=122 BTX-A-HAC; n=51 Placebo)	3.4 (0.8 to 12.6)	1.3 (0.1 to 12.0)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 8

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 8 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	56
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.2
upper limit	64.8

Notes:

[23] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 15

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 15 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	69.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	61.3
upper limit	77.7

Notes:

[24] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 29

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 29 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	63.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	55
upper limit	72

Notes:

[25] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	47.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.1
upper limit	56.7

Notes:

[26] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [27]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.2
upper limit	31.7

Notes:

[27] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065 [28]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	9.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	15.3

Notes:

[28] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 148

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 148 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0643 [29]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	6.8

Notes:

[29] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367 [30]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	6.5

Notes:

[30] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of responders at each post-treatment visit as measured by the subject's self-assessment (SSA) at maximum frown

End point title	The percentage of responders at each post-treatment visit as

	measured by the subject's self-assessment (SSA) at maximum frown

End point description:

The SSA was used to assess the appearance of glabellar lines at maximum frown and consists of a validated 4-point categorical scale: Grade 0 - no wrinkles; Grade 1 - mild wrinkles; Grade 2 - moderate wrinkles; Grade 3 - severe wrinkles.

A responder at maximum frown 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 wrinkles (Grade 2) or severe wrinkles (Grade 3) at Baseline (Day 1, pretreatment).

The adjusted percentage of responders in each treatment group is presented for each post-treatment visit and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Days 1 (Baseline), 8, 15, 29, 57, 85, 113, 148 and 183 (End of Study).

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	59		
Units: Adjusted percentage of responders				
number (confidence interval 95%)				
Day 8 (n=124 BTX-A-HAC; n=57 Placebo)	62.0 (47.2 to 74.9)	5.1 (1.6 to 14.8)		
Day 15 (n=124 BTX-A-HAC; n=59 Placebo)	75.6 (61.8 to 85.6)	4.4 (1.3 to 13.7)		
Day 29 (n=124 BTX-A-HAC; n=58 Placebo)	76.0 (62.2 to 85.9)	5.2 (1.7 to 15.0)		
Day 57 (n=124 BTX-A-HAC; n=58 Placebo)	67.5 (52.4 to 79.6)	2.2 (0.6 to 8.3)		
Day 85 (n=121 BTX-A-HAC; n=57 Placebo)	61.8 (46.1 to 75.3)	3.9 (1.1 to 12.6)		
Day 113 (n=123 BTX-A-HAC; n=56 Placebo)	46.2 (32.8 to 60.2)	9.8 (3.9 to 22.5)		
Day 148 (n=121 BTX-A-HAC; n=51 Placebo)	44.1 (31.2 to 57.7)	13.1 (5.3 to 28.9)		
Day 183 (n=122 BTX-A-HAC; n=51 Placebo)	27.0 (16.4 to 41.1)	6.0 (1.8 to 17.8)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 8

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 8 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	56.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.6
upper limit	67.2

Notes:

[31] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 15

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 15 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	71.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	62
upper limit	80.4

Notes:

[32] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 29

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 29 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	70.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	61.4
upper limit	80.2

Notes:

[33] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	65.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	56.2
upper limit	74.3

Notes:

[34] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	57.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.9
upper limit	67.9

Notes:

[35] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	36.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.7
upper limit	48.2

Notes:

[36] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 148

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 148 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [37]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.1
upper limit	43.7

Notes:

[37] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036 [38]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	21

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.7
upper limit	31.2

Notes:

[38] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The percentage of responders at each post-treatment visit as measured by the subject’s level of satisfaction with the appearance of their glabellar lines

End point title	The percentage of responders at each post-treatment visit as measured by the subject’s level of satisfaction with the appearance of their glabellar lines

End point description:

The subject's level of satisfaction with the appearance of their glabellar lines was assessed with a validated 4-point categorical scale: Grade 0 - very satisfied; Grade 1 - satisfied; Grade 2 - dissatisfied; Grade 3 - very dissatisfied.

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, pretreatment).

The adjusted percentage of responders in each treatment group is presented for each post-treatment visit and was calculated using a multivariate logistic regression model with treatment group, centre and stratification factors (gender and baseline ILA score at maximum frown) as fixed effects.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Day 8, 15, 29, 57, 85, 113, 148 and 183

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	59		
Units: Adjusted percentage of responders				
number (confidence interval 95%)				
Day 8 (n=124 BTX-A-HAC; n=57 Placebo)	72.7 (58.9 to 83.2)	4.9 (1.6 to 14.5)		
Day 15 (n=124 BTX-A-HAC; n=59 Placebo)	80.6 (68.4 to 88.9)	7.9 (3.1 to 19.1)		
Day 29 (n=124 BTX-A-HAC; n=58 Placebo)	80.9 (68.7 to 89.1)	8.3 (3.1 to 20.2)		
Day 57 (n=124 BTX-A-HAC; n=58 Placebo)	74.7 (61.2 to 84.6)	5.9 (2.1 to 15.3)		
Day 85 (n=121 BTX-A-HAC; n=57 Placebo)	70.9 (56.1 to 82.3)	7.3 (2.7 to 18.7)		
Day 113 (n=123 BTX-A-HAC; n=56 Placebo)	61.9 (48.3 to 73.8)	9.8 (4.0 to 22.2)		
Day 148 (n=121 BTX-A-HAC; n=51 Placebo)	58.9 (45.4 to 71.3)	12.3 (5.0 to 27.3)		
Day 183 (n=122 BTX-A-HAC; n=51 Placebo)	49.8 (36.3 to 63.3)	11.3 (4.5 to 25.6)		

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 8

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 8 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	67.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.1
upper limit	77.4

Notes:

[39] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 15

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 15 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [40]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	72.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.9
upper limit	82.5

Notes:

[40] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 29

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 29 is

presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [41]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	72.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.7
upper limit	82.5

Notes:

[41] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 57

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 57 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [42]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	68.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	59
upper limit	78.6

Notes:

[42] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 85

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 85 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [43]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	63.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	53
upper limit	74.1

Notes:

[43] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 113

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 113 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.4
upper limit	63.6

Notes:

[44] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 148

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 148 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [45]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	46.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.1
upper limit	59.2

Notes:

[45] - Statistical tests were two-sided with a type I error rate at 5%.

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo at Day 183

Statistical analysis description:

The difference in the adjusted percentage of responders between the treatment groups at Day 183 is presented.

Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	38.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	26
upper limit	50.9

Notes:

[46] - Statistical tests were two-sided with a type I error rate at 5%.

Secondary: The time to onset of treatment response based on the subject’s diary card.

End point title	The time to onset of treatment response based on the subject’s diary card.

End point description:

The median time to onset of treatment response is presented and was based on the subject's diary card in which subjects were asked to record their assessment of study treatment response on Days 1 to 7. They responded '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 onset of response was defined as the first day the subject responded 'yes'.

The median time to onset of treatment response was not calculable for the placebo treatment group due to the small number of subjects who answered 'yes'.

The mITT population consisted of subjects who had received at least one injection and had a baseline and at least one post-baseline value for the ILA of glabellar lines at maximum frown.

End point type	Secondary

End point timeframe:

Day 1 to 7

End point values	BTX-A-HAC NG 50 U	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	58[47]		
Units: Days				
median (confidence interval 95%)	3.0 (2.0 to 3.0)	99999999 (99999999 to 99999999)		

Notes:

[47] - Not calculable denoted as 99999999.

Statistical analyses

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo- Log rank
Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Statistical analysis title	BTX-A-HAC NG 50 U versus Placebo - Cox analysis
Comparison groups	BTX-A-HAC NG 50 U v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cox proportional hazard model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from Day 1 until end of study (Day 183)/early withdrawal (approximately 7 months).

Adverse event reporting additional description:

Adverse events were reported for the safety population which consisted of all randomised subjects who received at least one injection of study treatment into at least one injection site.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	BTX-A-HAC NG 50 U

Reporting group description:

Subjects were randomised to receive Botulinum toxin type A haemagglutinin complex (BTX-A-HAC) next generation (NG). A single total dose of 50 U was injected on Day 1. The total treatment volume (0.25 millilitres [mL]) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region.

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive placebo. A single total dose of 50 U was injected on Day 1. The total treatment volume (0.25 mL) was divided into five injections (0.05 mL per injection) injected into five predefined sites across the glabellar region

Serious adverse events	BTX-A-HAC NG 50 U	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 125 (1.60%)	1 / 59 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Mydriasis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Foot deformity			
subjects affected / exposed	1 / 125 (0.80%)	0 / 59 (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: 1 %

Non-serious adverse events	BTX-A-HAC NG 50 U	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 125 (32.80%)	17 / 59 (28.81%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Spinal column injury			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 125 (14.40%)	2 / 59 (3.39%)	
occurrences (all)	27	2	
Balance disorder			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	10 / 125 (8.00%)	3 / 59 (5.08%)	
occurrences (all)	10	3	
Eye disorders			

Eyelid oedema			
subjects affected / exposed	2 / 125 (1.60%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Blepharochalasis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Brow ptosis			
subjects affected / exposed	3 / 125 (2.40%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Papule			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Pruritis generalised			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Tendon calcification			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 125 (8.00%)	5 / 59 (8.47%)	
occurrences (all)	10	6	
Influenza			
subjects affected / exposed	3 / 125 (2.40%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Tonsillitis			

subjects affected / exposed	3 / 125 (2.40%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Cystitis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Oral herpes			
subjects affected / exposed	2 / 125 (1.60%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Bronchitis			
subjects affected / exposed	1 / 125 (0.80%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	1 / 125 (0.80%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 125 (0.80%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Subcutaneous abscess			
subjects affected / exposed	0 / 125 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	

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