



## 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,<br>clinical.trials@ipsen.com |
| Scientific contact           | Medical Director, Neurology, Ipsen Innovation,<br>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 millilitre [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                                  |
| <b>Arm title</b>             | 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.

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

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

| <b>Number of subjects in period 1</b>    | 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   |

| <b>Reporting group values</b>              | Total |  |  |
|--|-------|--|--|
| Number of subjects                         | 600   |  |  |
| Age categorical<br>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<br>Units: Subjects      |       |  |  |
| Female                                     | 533   |  |  |
| Male                                       | 67    |  |  |
| Race (NIH/OMB)<br>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:<br>During the DB period, subjects were randomised to receive a single treatment of BTX-A-HAC solution 50 U.<br>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.<br>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:<br>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.<br>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:<br>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.<br>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 <sup>[1]</sup> |
| End point description:<br>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.<br>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:<br>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.



|                                  |                                     |                     |  |  |
|----------------------------------|-------------------------------------|---------------------|--|--|
| <b>End point values</b>          | 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>                                     | 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 <sup>[2]</sup>                                   |
| 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 <sup>[3]</sup> |
|-----------------|---|

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<br>Solution 50 U -<br>DB Period | Placebo - DB<br>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<br>88.3)                    | 0.9 (0.1 to 5.5)       |  |  |
| Day 57 (n=122; n=60)             | 74.7 (51.4 to<br>89.2)                    | 0.6 (0.1 to 4.0)       |  |  |
| Day 85 (n=123; n=59)             | 55.5 (35.8 to<br>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 <sup>[4]</sup>                                   |
| 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 <sup>[5]</sup>                                   |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[6]</sup>                                   |
| 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 <sup>[7]</sup> |
|-----------------|--|

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<br>Solution 50 U -<br>DB Period | Placebo - DB<br>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<br>94.0)                    | 100.0 (100.0<br>to 100.0) |  |  |
| Day 85 (n=106; n=1)              | 63.2 (54.0 to<br>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 <sup>[8]</sup> |
|-----------------|--|

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<br>Solution 50 U -<br>DB Period | Placebo - DB<br>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<br>84.2)                    | 11.4 (3.9 to<br>29.0)  |  |  |
| Day 29 (n=89; n=41)              | 62.2 (39.0 to<br>80.9)                    | 5.4 (1.4 to<br>18.5)   |  |  |
| Day 57 (n=87; n=40)              | 63.1 (35.2 to<br>84.4)                    | 0.6 (0.0 to 8.2)       |  |  |
| Day 85 (n=88; n=39)              | 49.5 (29.0 to<br>70.1)                    | 6.8 (1.9 to<br>22.0)   |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | BTX-A-HAC vs Placebo: Day 8                               |
| Statistical analysis description:<br>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 <sup>[9]</sup>                                   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | BTX-A-HAC vs Placebo: Day 29                              |
| Statistical analysis description:<br>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 <sup>[10]</sup>                                  |
| 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.

|  |                              |
|--|------------------------------|
| <b>Statistical analysis title</b>  | BTX-A-HAC vs Placebo: Day 57 |
| Statistical analysis description:<br>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 <sup>[11]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[12]</sup>                                  |
| 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 <sup>[13]</sup> |
|-----------------|--|

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 <sup>[14]</sup>                                  |
| 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 <sup>[15]</sup> |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[16]</sup>                                  |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[17]</sup>                                  |
| 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 <sup>[18]</sup> |
|-----------------|--|

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 <sup>[19]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[20]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[21]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[22]</sup>                                  |
| 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 <sup>[23]</sup> |
|-----------------|---|

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.

|                                  |                                     |                                 |  |  |
|----------------------------------|-------------------------------------|---------------------------------|--|--|
| <b>End point values</b>          | BTX-A-HAC Solution 50 U - DB Period | Placebo - DB Period             |  |  |
| Subject group type               | Reporting group                     | Reporting group                 |  |  |
| Number of subjects analysed      | 125                                 | 63 <sup>[24]</sup>              |  |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>                                   | 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 <sup>[25]</sup>                                  |
| 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 <sup>[26]</sup> |
|-----------------|--|

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<br>Solution 50 U -<br>DB Period | Placebo - DB<br>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:<br>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 <sup>[27]</sup>                                  |
| 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:<br>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 <sup>[28]</sup>                                  |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | BTX-A-HAC vs Placebo: Day 57                              |
| Statistical analysis description:<br>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 <sup>[29]</sup>                                  |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | BTX-A-HAC vs Placebo: Day 85                              |
| Statistical analysis description:<br>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 <sup>[30]</sup>                                  |
| 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 <sup>[31]</sup> |
|-----------------|---|

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 <sup>[32]</sup>                                  |
| 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 <sup>[33]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[34]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[35]</sup>                                  |
| 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 <sup>[36]</sup> |
|-----------------|---|

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 <sup>[37]</sup> |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>                                      | 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 <sup>[38]</sup>                                  |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>                                      | 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 <sup>[39]</sup>                                  |
| 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.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[40]</sup>                                  |
| 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 <sup>[41]</sup> |
|-----------------|--|

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.

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | BTX-A-HAC<br>Solution 50 U -<br>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 <sup>[42]</sup> |
|-----------------|---|

**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.

| <b>End point values</b>          | BTX-A-HAC<br>Solution 50 U -<br>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 <sup>[43]</sup> |
|-----------------|--|

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 <sup>[44]</sup> |
|-----------------|--|

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<br>Solution 50 U -<br>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 <sup>[45]</sup> |
|-----------------|---|

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 <sup>[46]</sup> |
|-----------------|--|

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.

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | 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 <sup>[47]</sup> |
|-----------------|---|

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 <sup>[48]</sup> |
|-----------------|---|

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<br>Solution 50 U -<br>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

### 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<br>Gastrointestinal infection<br>alternative dictionary used:<br>MedDRA 19.0<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 64 (1.56%)<br>0 / 1<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Appendicitis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Diverticulitis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Laryngitis bacterial<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Peritoneal abscess<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Peritonsillar abscess<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>0 / 0 |
| Salpingitis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 0 / 126 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 64 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 595 (0.17%)<br>0 / 1<br>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<br>50 U - DB Period | Placebo - DB Period | BTX-A-HAC Solution<br>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<br>occurrences (all)   | 2 / 126 (1.59%)<br>3    | 0 / 64 (0.00%)<br>0   | 14 / 595 (2.35%)<br>16    |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 126 (1.59%)<br>2    | 1 / 64 (1.56%)<br>3   | 25 / 595 (4.20%)<br>29    |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)               | 13 / 126 (10.32%)<br>14 | 8 / 64 (12.50%)<br>10 | 168 / 595 (28.24%)<br>252 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 126 (2.38%)<br>3    | 0 / 64 (0.00%)<br>0   | 7 / 595 (1.18%)<br>7      |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 126 (0.79%)<br>1    | 0 / 64 (0.00%)<br>0   | 20 / 595 (3.36%)<br>21    |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 126 (0.79%)<br>1    | 1 / 64 (1.56%)<br>2   | 19 / 595 (3.19%)<br>22    |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 126 (0.79%)<br>1    | 0 / 64 (0.00%)<br>0   | 18 / 595 (3.03%)<br>19    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)  | 0 / 126 (0.00%)<br>0    | 0 / 64 (0.00%)<br>0   | 16 / 595 (2.69%)<br>17    |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 126 (0.79%)<br>5    | 0 / 64 (0.00%)<br>0   | 15 / 595 (2.52%)<br>20    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported