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Statistical Analysis Plan (SAP)

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LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation	Definition
AE	Adverse Event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BoNT/A	botulinum neurotoxin A
BoNT/A-DP	Croma-Pharma GmbH's BoNT/A drug product registered in Korea under the name "Botulax"
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
FACE-Q	FACE-Q Satisfaction with Outcome
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FWS	Facial Wrinkle Scale
GLS-I	Glabellar Line Scale - Investigator
GLS-S	Glabellar Line Scale - Subject
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event

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SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
VS	Vital Signs
WHO	World Health Organization

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1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol CPH-201-201461 Version 1.0 "A Double-Blinded Randomized Controlled Study to Compare the Efficacy, Time to Onset, and Duration of Effect of Botulinum Type A Toxins in the Treatment of Glabellar Frown Lines" dated 27 Aug 2019 for the final analyses. The table of contents and templates for the tables, figures, and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 guideline and the code of Federal Regulations (CFR) 21, part 11.

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

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2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the efficacy of treatment with BoNT/A-DP as defined by the percentage of responders at Week 4 (Facial Wrinkle Scale [FWS] score of 0 or 1 and a ≥ 1 point reduction in FWS score) in reducing the severity of glabellar frown lines at maximum frown (the worst appearance of upper facial lines with maximum load on the muscle; eyebrows pushed together as far as they can go) compared to treatment with [redacted], based on independent investigator assessment and subject assessment.

2.2 Secondary Objectives

1. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 8, 12 and 16, based on investigator and subject assessments.
2. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 2 point reduction in FWS score at maximum frown) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments.
3. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at rest) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments.
4. To assess time to onset of effect after a single treatment with BoNT/-DP compared to a single treatment of [redacted], as measured at Weeks 1, 2, and 4, based on independent investigator and subject assessments.
5. To assess the duration of effect in subjects who respond after a single treatment with BoNT/A-DP or a single treatment of [redacted], based on independent investigator and subject assessments.
6. To assess treatment satisfaction at Weeks 4, 12, and 16 using FACE-Q Satisfaction with Outcome Scale.
7. To determine the safety and presence of any adverse effects of a single treatment of BoNT/A-DP compared to a single treatment of [redacted] in the treatment of glabellar lines.

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3 STUDY DESIGN

3.1 General Study Design

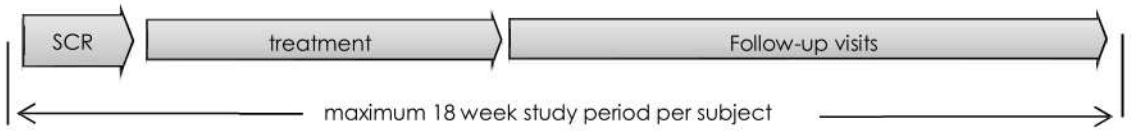
This study is a multi-center, Phase 2, parallel group, randomized, double-blind, comparator-controlled study. Approximately 200 subjects of either gender, between 18 and 75 years of age inclusive, who meet all the inclusion criteria and do not meet any exclusion criteria and who provide written informed consent, will be enrolled in the study.

After a screening period of up to 14 calendar days, eligible subjects will be randomized 1:1 to receive a single treatment of BoNT/A-DP or [redacted] on Day 0. Subjects will attend six follow-up visits for evaluation of efficacy and safety at one, two, and four weeks post-treatment and once every four weeks thereafter until Week 16.

The study will take place in the European Union (EU), United States (US) and Canada.

Investigators and subjects will be blinded to the treatment administered and will evaluate the severity of glabellar lines independently. The subjects must perform their assessment independently and ideally before the investigators, to ensure they are not biased by the investigator. The same investigator must complete the Baseline assessments and FWS at Week 4 (primary endpoint assessments) for a given subject.

The overall study scheme is presented below:



Subjects will participate in this study for a duration of up to 18 weeks, to include screening (maximum of 2 weeks; re-screening is not permitted) and a single treatment (comprised of one injection at five injection points) of BoNT/A-DP or [redacted] followed by six efficacy and safety follow-up visits.

3.2 Randomization and Blinding

3.2.1 Randomization

This is a randomized, double-blind, comparator-controlled efficacy and safety clinical study. Subjects will be randomly assigned at Baseline (Day 0) to receive a single treatment of BoNT/A-DP or [redacted] at a ratio of 1:1.

Randomization will be performed per study site via Interactive Web Response System (IWRS). One

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unique randomization code will be assigned to each subject.

3.2.2 Blinding

BoNT/A-DP will be provided to the sites in glass vials.[redacted] will be provided to the sites as commercially available.

In order to maintain blinding, both BoNT/A-DP and[redacted] will be reconstituted and drawn into the syringes by an unblinded study team member at the site. After the IMPs have been drawn into the syringes, the treatments will look identical (clear solution, comparable volume), thus maintaining the blind.

The unblinded study team member preparing the IMP at the study site must not, by any means, be involved in any other study data collection activities including AE assessment, electronic Case Report Form (eCRF) completion, diary collection, etc. IMP will be assigned to the subjects by IWRS with the lot number and kit number assigned corresponding to the group to which the subjects are assigned. The assigned vial will be reconstituted and the filled syringes for injection will be forwarded to the investigator for injection. Specific Blinding Plans will be created at each study site during the Study Initiation visits. The blind will be maintained.

3.2.3 Unblinding

The decision to unblind lies fully with the investigator. The randomization assignment should not be revealed before the study has been completed and the database has been cleaned and closed. The study will be unblinded using the Study Specific Unblinding Procedure (an unblinding module is standard on all blinded studies; also it is possible to grant access to regulatory unblinding users so that they can monitor the safety of the study, if required).

In case of emergency, the IMP administered to the subjects can be revealed using the unblinding function of the IWRS.

In rare emergencies, unblinding may be necessary for the clinical management of an AE. Investigators should consider unblinding only if knowledge of the administered product will have an influence on the further treatment of the AE. In such events, the investigator should make every attempt to inform the Sponsor before breaking the blind or as soon as possible after unblinding has been performed. The[redacted] or Croma medical team is available to discuss any unblinding need. However, such discussion is not mandatory. The investigator can always unblind per his/her discretion if the actual treatment information is considered relevant for subsequent event treatment. Once unblinding has occurred, the site should immediately contact the[redacted] or Croma medical team. Communication of the unblinding result is considered acceptable. It is at the discretion of the investigator to continue an unblinded subject in the study. The date and time of breaking the code, the reason for breaking the code, study product administered, subject identification number and randomization code will be documented within the IWRS. Subjects for whom the blind had been

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broken may continue in the study as per discretion of the Investigator.

3.3 Study Treatments and Assessments

The duration of study participation for each subject will be up to 18 weeks, to include screening (maximum of 2 weeks; re-screening will not be permitted), and a single treatment (comprised of one injection at five injection points) of BoNT/A-DP (Group A) or [redacted] (Group B) followed by six efficacy and safety follow-up visits.

The subject will receive five injections (4 U per 0.1 mL injection) of BoNT/A-DP or [redacted] on Day 0.

The End of Study visit is planned to take place 16 weeks after treatment.

Subjects will be randomized 1:1 to one of two treatment groups:

Group A (n=100): BoNT/A-DP (20 U, 0.5 mL)
Group B (n=100): [redacted] (20 U, 0.5 mL)

Eligible subjects will be randomized at Baseline (Day 0) to Group A or B in a 1:1 randomization scheme. Investigators and subjects will be blinded to the treatment administered and will evaluate the severity of glabellar lines independently. The subjects should perform their assessment independently and ideally before the investigator, to ensure they are not biased by the investigator. The same investigator must complete the Baseline assessments and FWS at Week 4 (primary endpoint assessments) for a given subject.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 2 below.

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Table 2: Schedule of Study Assessments

Procedures and	Screening[1] (Day -14 to 0)	Randomization[1] (Baseline, Day 0)	Week 1 (± 2 days)	Week 2 (± 5 days)	Week 4 (± 2 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days) End of Study[2]
Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	x							
Inclusion/exclusion criteria	x	x [3]						
Medical history	x							
Demographics	x							
Pregnancy test[4]	x	x			x	x	x	x
Physical	x							x
Vital signs[6]	x	x	x		x		x	x
Concomitant	x	x	x	x	x	x	x	x
GLS-I[7]	x	x	x	x	x	x	x	x
GLS-S[8]	x	x	x	x	x	x	x	x
Photography[9]		x		x	x		x	x
Treatment					x		x	x
IMP administration		x						
Post-treatment obs./AE & AESI assessment[11]		x						
AE and AESI[12]		x	x	x	x	x	x	x
Subject diary		D	R/	R				

1. Screening and Baseline, including randomization and treatment, can be done on the same day. If Screening and Baseline are done on the same day, assessments only need to be performed once.
2. For subjects that are prematurely discontinued from the study (at any time), the End of Study visit will take place within one week of discontinuation.
3. If Screening and Baseline are done on different days, the following inclusion and exclusion criteria are to be re-confirmed at Baseline: investigator and subject assessment of glabellar line severity at maximum frown using GLS-I and GLS-S, respectively, as well as documentation of medical history, concomitant medications and AEs.
4. Pregnancy testing for all women of childbearing potential: Screening, Baseline (if Screening and Baseline are done on different days), and End of Study.
   All pregnancy testing will be urine dip stick testing.
5. Additional pregnancy testing (urine dipstick) for women of childbearing potential in Austrian sites, only.
6. Vital signs include blood pressure (diastolic /systolic) and pulse.
7. Investigator's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point GLS-I: (0 =none, 1=mild, 2=moderate, 3=severe). Results will be recorded in the eCRF.
8. Subject's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point GLS-S: (0 =none, 1=mild, 2=moderate, 3=severe). Results will be recorded in the eCRF.
9. Photographs to be taken of subject's glabellar lines at maximum frown and at rest.
10. Treatment satisfaction will be determined using the FACE-Q Satisfaction with Outcome Scale. Results will be recorded in the eCRF.

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11. Subjects will be monitored for AEs for 30 minutes after administration of the IMP. 30-minute post IMP administration, general, non-leading AE questioning as well as active AESI questioning must be performed.
12. General, non-leading AE questioning as well as active AESI questioning at each indicated visit. The first AESI questioning will be completed at Baseline Visit in order to obtain a full baseline status of any concomitant diseases PRIOR to the first IMP injection.

AESI Questioning: active questioning by guided review of systems per AESI manual. If an AESI is reported, a targeted physical examination around the area of the reported AESI must follow.

AE=adverse event; AESI=adverse event of special interest; D=distribution of subject diary; eCRF=electronic Case Report Form; GLS-I=Glabellar Line Scale- Investigator; GLS-S=Glabellar Line Scale-Subject; IMP=investigational medicinal product; obs=observation; R=return of subject diary

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4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoints

The study comprises co-primary endpoints defined as:

- An FWS score at the Week 4 Visit of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown relative to Baseline, based on investigator assessment.
- An FWS score at the Week 4 Visit of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown relative to Baseline, based on subject assessment.

4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

1. Percentage of responders with an FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown at Weeks 1, 2, 8, 12 and 16, based on independent investigator assessment and subject assessment.
2. Percentage of responders with an FWS score of 0 or 1 and a ≥ 2 point reduction in FWS score at maximum frown at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments.
3. Percentage of responders with an FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at rest at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments.
4. Time to onset of effect, as measured at Weeks 1, 2, and 4, based on independent investigator and subject assessments. Onset of effect is defined as ≥ 1 point improvement in Glabellar Line Scale - Investigator (GLS-I) and Glabellar Line Scale – Subject (GLS-S) score relative to Baseline at maximum frown in glabellar lines. In addition, onset of effect will be assessed by subjects daily during the first 2 weeks after treatment, by recordings in the subject diary.
5. For subjects who respond, duration of effect will be assessed based on independent investigator and subject assessments. Effect will be deemed to be lost when scores return to Baseline values.
6. The FACE-Q assessment at Weeks 4, 12 and 16.

4.3 Safety Endpoints

The safety endpoints of this study are:

1. Frequency, seriousness and severity of TEAEs, SAEs and AESIs, as well as causal relationship to the study medication and the study procedure, during the entire study period.
2. Change in vital signs from Baseline to post-Baseline visits.

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5 SAMPLE SIZE AND POWER

The purpose of the study is to provide preliminary comparative data on BoNT/A-DP versus [redacted]. Subsequently the sample size is primarily based on clinical judgement and practical considerations, rather than formal statistical arguments. However, with a sample size of 100 subjects per group, a two-sided 95% confidence interval (CI) for the difference between BoNT/A-DP and [redacted] will extend 10.8% from expected proportions of 81.5% in both groups based on large sample normal approximation.

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6 ANALYSIS POPULATIONS

6.1 Safety Analysis Set (SAF)

All subjects who received at least one injection with study medication (independent of whether it is BoNT/A-DP or [redacted] will be valid for the SAF. Within the SAF, a subject will be considered for the treatment actually received and not for the treatment assigned by randomization, if different. The SAF will be used for the evaluation of the safety assessments.

6.2 Full Analysis Set (FAS)

The FAS includes all randomized subjects who had a Baseline Visit 1 at Day 0 and at least one post-dose in-clinic assessment with the 4-point scale by either the investigator or the subject on visits at Weeks 1, 2, or 4. Within the FAS a subject will be considered for the treatment assigned by randomization and not for the treatment actually received, if different, i.e., following the intent-to-treat principle. The FAS will be used for the evaluation of the efficacy assessments. The FAS serves as the primary efficacy analysis set.

6.3 Protocol Deviations

Protocol deviations and exclusions of subjects from analysis sets will be identified at the Data Review Meeting (DRM) just prior to study unblinding for the Final Analysis.

Deviations from the protocol will be classified as major or minor.

The following protocol deviations are considered a priori to be major:

- Subject or investigator unblinded to treatment
- Improper storage of IMP and IMP temperature excursion without proper notice to the CRA
- Incorrect treatment allocation or dose
- Wrong injection points used

6.4 Blinded Data Review Meeting (BDRM)

Subjects will be assigned to the SAF and FAS during the BDRM. For the BDRM appropriate listings displaying all relevant data will be provided to the Sponsor and serve as a source for the protocol deviations discussion about the classification into major and minor. No unblinding will be done for the creation of these listings.

Details for and decisions on protocol deviations will also be discussed at the BDRM, taking place between database lock and unblinding. Corresponding documentation should be held outside of the SAP.

Unblinding will be done after the BDRM has been conducted and the minutes have been signed.

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7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

The below table provide the list of derived variables for various duration derivations and Baseline derivations applicable for this study.

Variables	Formula
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study drug, if date of interest is before date of first dose of study drug. Date of interest – date of first dose of study drug + 1, otherwise.
Baseline Derivations	
Baseline	The Baseline value is defined as the last observation before treatment, i.e., pre-treatment values measured on the treatment day (Baseline visit, Day 0), and if missing or not evaluated, the value from the screening visit will be used. Baseline will be missing if no values have been measured before treatment.
Change from Baseline	Post-Baseline value – Baseline value
Relative change from Baseline	[(Post-Baseline value – Baseline value)/Baseline value]*100

7.2 Handling of Missing Data

7.2.1 Missing Data Analysis Methods

Analyses will be performed by visit. The main analysis will be performed based on all available data. That is, no imputation of missing values will be conducted (e.g., no last observation carried forward), except for estimating the response rate at Week 4 for the co-primary endpoints where subjects with missing FWS assessments at Baseline or Week 4 will be considered as non-responders.

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For all other visits and endpoints, summary statistics will be based on observed data.

7.2.2 Handling of Missing or Incomplete Dates

7.2.2.1 Imputation Rules for Missing or Partial AE Start Date:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Otherwise, if the AE start year and month are not the same as that for the first dose date, then impute the AE start day as 1.

Compare the imputed AE start date with the first dose date to determine whether the AE is pre-treatment AE or treatment emergent adverse event (TEAE).

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

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7.2.2.2 Imputation Rules for Missing or Partial Medication Start/Stop Dates

Missing or partial medication start date:

- If only DAY is missing, use the first day of the month.
- If DAY and Month are both missing, use the first day of the year.
- If DAY, Month and Year are all missing, use a date before the first dose date.

Missing or partial medication stop date:

- If only DAY is missing, use the last day of the month.
- If DAY and Month are both missing, use the last day of the year.
- If DAY, Month and year are all missing, assign 'continuing' status to stop date

  If the resultant imputed stop date is later than the death date, revise the imputed stop date as the death date.

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8 STATISTICAL METHODS

8.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

The statistical analysis will be performed after database lock of all data up to the end of the study.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. A two-sided CI using the Newcombe method (using a significance level of 0.05) will be provided for the difference in treatment effects between proportions at week 4. Two-sided 95% confidence intervals (CI) will be provided within individual treatment groups when relevant.

No formal statistical hypothesis testing will be conducted.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum. One additional decimal point for mean and median and two additional decimal points for SD will be used in addition to the number of decimal points used for the measured values.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For statistical analyses, "baseline" refers to the last observation before treatment, i.e. pre-treatment values measured on the treatment day (Baseline visit, Day 0), and if missing or not evaluated, values from screening visit will be used. Baseline will be missing if no values have been measured before treatment.

All summaries will be presented by treatment group, unless otherwise specified.

Analyses will be performed by visit, irrespective of any time window deviations.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by investigational site, patient number, date/time and visit. The treatment group (Test, Reference) will be stated on each listing. Unless otherwise stated, data listings will be based on the SAF. A listing with demographic data for screening failures will be presented.

8.2 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percent of subjects who are randomized, who obtained a dose of study drug, who were randomized and not treated, who were treated and not randomized, who complete the treatment, who complete the study and who withdraw early from the study will be presented.

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The primary reason for early withdrawal will also be tabulated.

Subject disposition will be listed.

The number and percent of subjects in each analysis set will also be tabulated.

Treatment Misallocations:

If a subject was:

- Randomized but not treated, then they will be reported under their randomized treatment group for efficacy analyses. However, they are by definition excluded from the safety analyses as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since they are not randomized but will be included in safety analyses.
- Randomized but got incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analysis, but will be reported under the treatment they actually received for all safety analyses.

8.3 Protocol Deviations

The number of subjects excluded from SAF, and FAS populations and reasons for exclusion will be summarized by treatment group and overall.

Analysis set membership details will be listed, including reason for exclusion from each analysis set.

All major protocol deviations identified will be summarized by treatment group and overall. Minor protocol deviations will be listed only.

A listing will include the inclusion/exclusion criteria violated at Screening and at the Baseline visit as well as other protocol deviations identified based on data recorded on the electronic CRF (eCRF) and/or protocol deviation logs from [redacted] (based on All Subjects).

8.4 Demographics and Baseline Characteristics

8.4.1 Baseline Characteristics

The categorical baseline characteristics such as pregnancy test results at screening will be summarized using frequency counts for the FAS population. Continuous Baseline variables such as systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and pulse rate (beats/min) will be summarised by descriptive statistics in the same way as continuous demographic variables for the FAS population.

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8.4.2 Demographics

Age, age groups, sex, race, ethnicity, height, weight, and Fitzpatrick skin type at Baseline will be summarized descriptively by treatment group and overall using the FAS population. The FDA guideline regarding "Collection of race and ethnicity data in clinical trials" will be followed.

8.4.3 Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities® (MedDRA) Version 22.0 or higher. The table will be based on the SAF population. The previous toxin treatment will be listed only.

8.4.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Standard or Enhanced and categorized as follows:

Prior medications and concomitant medications will be summarized descriptively using frequency tables by anatomical therapeutic chemical (ATC) class and preferred name by treatment group on the FAS population and presented separately for the following groups:

- Medication (recent) discontinued prior to Baseline (Day 0)
- Concomitant medication started at or after Baseline, or started before Baseline and were not discontinued prior to Baseline

Details for imputing missing or partial start and/or stop dates of medication are described in Section 7.2.2.

An individual subject listing will be provided for prior and concomitant medications data.

8.5 Extent of Exposure

8.5.1 Treatment Duration

Duration of study drug (in days) will not be calculated as subjects will receive only one dose on Day 0.

Planned and actual dose as well as injections at all sites per subject will be listed.

8.5.2 Treatment Compliance

All study procedures are to be performed under supervision at the study site, and thus, no separate procedures will be used to monitor subject compliance.

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8.6 Efficacy Analyses

8.6.1 Analysis Methods

The analyses of the primary and secondary outcome measures will be exploratory in nature. Details for each efficacy endpoint will be provided in the following sections. Subgroup analyses will be described in Section 8.8.1.

8.6.1.1 Multiplicity

Since the focus of the statistical analysis is on descriptive statistics and no formal statistical hypothesis testing is planned, no adjustment for controlling the type 1 error rate for the co-primary endpoints is required. Thus, analyses will be considered only exploratory.

8.6.2 Analysis of Primary Efficacy Endpoints

The purpose of the study is to provide preliminary comparative efficacy and safety data of BoNT/A-DP versus[redacted]

The study comprises co-primary endpoints defined as:

- An FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown at the Week 4 Visit relative to Baseline, based on investigator assessment.

  That is, a subject will be considered a responder if they have an FWS score of 0 or 1 and an improvement ≥ 1 point at maximum frown of the glabellar lines at Week 4 relative to Baseline in FWS, based on the investigator assessment.

- An FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown at the Week 4 Visit relative to Baseline, based on subject assessment.

  That is, a subject will be considered a responder if they have an FWS score of 0 or 1 and an improvement ≥ 1 point at maximum frown of the glabellar lines at Week 4 relative to Baseline in FWS, based on the subject assessment.

No formal statistical hypothesis testing will be conducted and no adjustment for controlling the type 1 error rate for the co primary endpoints is required.

The focus of the statistical analysis for the co-primary endpoints will be on descriptive statistics (n and %), and 95% CIs for the difference in treatment effects between BoNT/A-DP and[redacted]

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[redacted]. Two-sided 95% CIs using the Newcombe method will be calculated for the difference between BoNT/A-DP and [redacted] for each co-primary endpoint. Two-sided 95% CIs for the responder rates in the BoNT/A-DP and the [redacted] treatment groups will be calculated using Wilson scores. No formal statistical hypothesis testing will be conducted.

The FAS population will serve as the primary analysis set for the descriptive statistics.

For the investigator assessment, subjects with missing FWS investigator assessment at Baseline or at the Week 4 Visit will be assigned as non-responders.

For the subject assessment, subjects with missing FWS subject assessment at Baseline or at the Week 4 Visit will be assigned as non-responders.

Additional Analyses on the Co-Primary Efficacy Endpoint Variables:

- The co-primary endpoint measures will also be summarized using the observed values only

  For the investigator assessment, subjects with missing FWS investigator assessment at Baseline or at the Week 4 Visit will be excluded from analysis but not assigned as non-responders.

  For the subject assessment, subjects with missing FWS subject assessment at Baseline of at the Week 4 Visit will be excluded from analysis but not assigned as non-responders.

The same analyses as described for the co-primary endpoints above will be conducted for the additional analyses.

In addition, subgroup analyses will be conducted as described in Section 8.8.

8.6.3 Analysis of Secondary Efficacy Endpoints

Since the focus of the statistical analysis is on descriptive statistics and no formal statistical hypothesis testing is planned on secondary endpoints, no adjustment for controlling the type 1 error rate is required.

For the below categorical endpoints,

- Percentage of responders with an FWS score of 0 or 1 and a $\geq$ 1 point reduction in FWS score at maximum frown at Weeks 1, 2, 8, 12 and 16, based separately on independent investigator assessments and subject assessments
- Percentage of responders with an FWS score of 0 or 1 and a $\geq$ 2 point reduction in FWS score at maximum frown at Weeks 1, 2, 4, 8, 12 and 16, based separately on independent investigator assessments and subject assessments
- Percentage of responders with an FWS score of 0 or 1 and a $\geq$ 1 point reduction in FWS score at rest at Weeks 1, 2, 4, 8, 12 and 16, based separately on independent investigator

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assessments and subject assessments

the same analyses will be conducted as described for the co-primary endpoints.

For investigator assessments, subjects with missing FWS investigator assessment at Baseline or at the post-Baseline visit will be assigned as non-responders.

For subject assessments, subjects with missing FWS subject assessment at Baseline or at the post-Baseline visit will be assigned as non-responders.

The analyses of these secondary endpoints will also be conducted on observed values.

For investigator assessments, subjects with missing FWS investigator assessment at Baseline or at the post-Baseline visit will be excluded from the analysis but not assigned as being non-responders.

For subject assessments, subjects with missing FWS subject assessment at Baseline or at the post-Baseline visit will be excluded from the analysis but not assigned as being non-responders.

Appropriate descriptive statistics will be provided for the secondary endpoint analyses.

The following secondary endpoints will be analyzed descriptively using Kaplan-Meier time to event methodology

- Time to onset of effect, as measured at Weeks 1, 2, and 4, based separately on independent investigator assessments and subject assessments. Onset of effect is defined as ≥ 1 point improvement in Glabellar Line Scale - Investigator (GLS-I) and Glabellar Line Scale – Subject (GLS-S) score relative to Baseline at maximum frown in glabellar lines. In addition, onset of effect will be assessed by subjects daily during the first 2 weeks after treatment, by recordings in the subject diary.
- For subjects who respond, duration of effect will be assessed separately based on independent investigator assessments and subject assessments. Effect will be deemed to be lost when scores return to individual Baseline values.

Duration of effect is defined as the date that loss of response occurred – date of IMP Injection +1. Whereas the loss of response is considered when the response returns to the individual "baseline" grade or worse for Week 4 responder (defined as by having achieved FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown at the Week 4 Visit) on FWS at maximum frown. For example, if a subject has a Baseline FWS of 3, the loss of response will be considered when the post-Baseline FWS returns to 3. Duration of effect will be derived separately based on investigator assessments and subject assessments.

For responders that maintain response, censoring will be done at the last visit where FWS grade at maximum frown is assessed.

Survival statistics such as the Kaplan-Meier estimator of the median will be presented.

The FACE-Q assessment at Weeks 4, 12 and 16 will be analyzed descriptively (n and % will be presented).

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The FACE-Q Satisfaction with Outcome Scale will be derived in accordance with the developers' instructions and missing data treated accordingly.

The FAS population will serve as the primary analysis set for the descriptive statistics.

8.7 Safety Analyses

This section describes the safety analyses that will be conducted till the end of the study period. i.e., the safety analyses on all data collected during the treatment period and all data collected in subjects who dropped-out during the study period.

All definitions relative to safety endpoints are detailed in the following sections.

Safety analyses will be conducted on the SAF population and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group.

The safety analyses of changes from Baseline to a specific time point in safety variables (e.g., vital signs) will only include subjects from the SAF population who have data available for both the Baseline and the time point under consideration unless otherwise specified.

No statistical testing methods will be applied to statistically evaluate the differences on safety variables between treatment groups. Safety endpoint variables will be analyzed descriptively only.

8.7.1 Adverse Events

All AEs will be classified by SOC and PT according to MedDRA Version 22.0 or higher.

In summaries by SOC and PT, adverse events will be sorted by decreasing frequency within each SOC and PT. In summaries by PT, AEs will be sorted by decreasing frequency within each PT.

AE summary tables will be presented for TEAEs and AESIs separately by treatment and will include the number and percentage of subjects with any:

- TEAE/AESI
- TEAE/AESI related to study medication (AE will be defined as related if causality is definitely, probably or possibly or if causality assessment is missing)
- TEAE/AESI related to injection procedure (AE will be defined as related if causality is definitely, probably or possibly or if causality assessment is missing)
- Severe TEAE/AESI
- Severe TEAE/AESI related to study medication
- Severe TEAE/AESI related to injection procedure

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- TEAE/AESI leading to discontinuation
- Study medication related TEAE/AESI leading to discontinuation
- Serious TEAE/AESI
- TEAE/AESI leading to death.

All TEAEs as well as all AESIs will be summarized by SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event).

The number of events, as well as the number and rate of affected subjects will be reported by SOC and PT for all TEAEs and for all AESIs separately.

Adverse events will be separated to pre-treatment AEs and TEAEs. TEAEs are defined as all AEs with onset or worsening (increase in severity) after receiving first dose of study medication (independent of whether it is BoNT/A-DP o[redacted]. If it cannot be determined whether an AE is treatment-emergent due to a partial onset date, then it will be counted as such.

TEAEs will be summarized by system organ class (SOC) and preferred term (PT) (MedDRA). The number of events, as well as the number and rate of affected subjects will be reported.

TEAEs and AESIs (per SOC and PT) will also be summarized by seriousness, severity, relationship to study medication, and relationship to procedure using frequency counts and percentages (i.e., number and percentage of subjects with an event).

An individual by-subject listing will be provided for AE data.

8.7.2 Vital Signs

The analyses of variables for vital signs (VS) will focus on the evaluation of the change from Baseline to the scheduled time points after Baseline. Descriptive statistics by visit and of changes from Baseline to each post-Baseline visit by treatment will be presented.

An individual by-subject listing will be provided for VS data.

8.7.3 Physical Examinations

At Screening and the End of Study visit, a full physical examination will be performed by the investigator. A full physical exam will include neurological assessment (including extraocular movements and cranial nerves) as well as assessment for muscle weakness. In addition, if the subject reports an AESI (as detailed in the AESI Manual) a focused physical examination by the physician will also be undertaken to evaluate these symptoms. Any clinically relevant abnormal finding will be documented in the eCRF as AE/medical history.

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All physical examination data and abnormalities will be listed only.

8.8 Other Analysis

8.8.1 Subgroup Analysis

The following subgroup analyses will be performed for the co-primary efficacy endpoints:

a) Subgroup analysis by site
b) Subgroup analysis by Country
c) Subgroup analysis by Geographic Region (Europe and US/Canada)
d) Previous use of Botulinum
e) Subgroup analysis by race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Caucasian (Including Hispanic or Latino and Other))
f) Subgroup analysis of:
   - subjects with previous use of botulinum toxin by site
   - naïve subjects by site
g) Subgroup analysis by Fitzpatrick skin type (TYPE I, TYPE II, TYPE III, TYPE IV, TYPE V, and TYPE VI)
h) Subgroup analysis by sex
i) Subgroup analysis by ethnicity (Hispanic or Latino versus Not Hispanic or Not Latino)
j) Subgroup analysis by age groups (below 65 years, 65-74 years and >= 75 years)
k) Subgroup analysis by additional age groups (below 65 years versus 65 years and older).

Subgroup analyses will be performed on the FAS population. Two-sided 95% CIs using the Newcombe method will be calculated for the difference between BoNT/A-DP and [redacted]. Two-sided 95% CIs for the responder rates in the BoNT/A-DP and the [redacted] treatment groups will be calculated using Wilson scores, when relevant.

8.9 Interim Analysis

No interim analyses are planned.

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9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

- Section 13.1.1 of the protocol incorrectly references the primary efficacy endpoint as the composite endpoint of the investigators' and the subjects' assessments of line severity at maximum frown after treatment with BoNT/A-DP compared to [redacted] at Week 4. No analyses are planned on the composite endpoint.

- Subgroup analyses by country and geographic region will also be performed.

- The Newcombe method, rather than the Clopper-Pearson method as referenced in the protocol, will be used to derive CIs when comparing the two treatment groups.

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10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95 - adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. FDA: Code of Federal Regulations (CFR), part 11 - adopted 15 September 2016.

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11 APPENDICES

Appendix A - Visit Window

Analyses will be performed by nominal visit, irrespective of any time window deviations. For the End of Study (EOS) visit, the following criteria will be applied:

- The nominal visit will be used throughout for all subjects who have not discontinued.
- For discontinued subjects, the EOS data will be assumed to be the preceding visit where no assessments are available.
- For discontinued subjects, the EOS data will be assumed to be the visit following the preceding visit if for the preceding visit an assessment is already available.
- Unless duplicate records are present in the database, there should be no duplicate data per visit.

The following examples illustrate the approach:

Criteria (i):

	Subjid	VISIT	VISITNUM	ADT	ADY
1	xxxx	SCREENING	1	20MAY2020	-11
2	xxxx	BASELINE DAY 0	2	30MAY2020	1
3	xxxx	WEEK 1	3	10JUN2020	11
4	xxxx	WEEK 2	4	14JUN2020	15
5	xxxx	END OF STUDY	8	19JUL2020	50

For this subject, End of Study visit will be assigned to WEEK 4 visit.

Criteria (ii):

	Subjid	VISIT	VISITNUM	ADT	ADY
1	xxxx	SCREENING	1	28JUL2020	-12
2	xxxx	BASELINE DAY 0	2	09AUG2020	1
3	xxxx	WEEK 1	3	18AUG2020	10
4	xxxx	WEEK 2	4	25AUG2020	17
5	xxxx	WEEK 4	5	07SEP2020	30
6	xxxx	WEEK 8	6	08OCT2020	59
7	xxxx	END OF STUDY	8	12JAN2021	119

For this subject, End of Study visit will be assigned to WEEK 12 visit.

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Numbering of Visits

Visit numbers correspond with specific treatment and assessments as outlined in the protocol Schedule of Events, Table 2.

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