CLINICAL STUDY PROTOCOL

Protocol Title: Randomized double blind Phase 3 study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo followed by an open label extension study

Protocol Identifier: CPH-303-201400

Other IDs
EudraCT Number: 2018-003983-30
IND Number: 123178

Botulinum Toxin Treatment of Glabellar **L**ines: **E**fficacy and **S**afety **S**tudy III (BLESS III)

Version Date: 15.07.2019
Version Status: 2.0

Study Sponsor:
Croma-Pharma GmbH
Industriezeile 6
A-2100 Leobendorf
Austria

Randomized double blind Phase 3 study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo followed by an open label extension study

SPONSOR RELATED CONTACT DETAILS

Sponsor:

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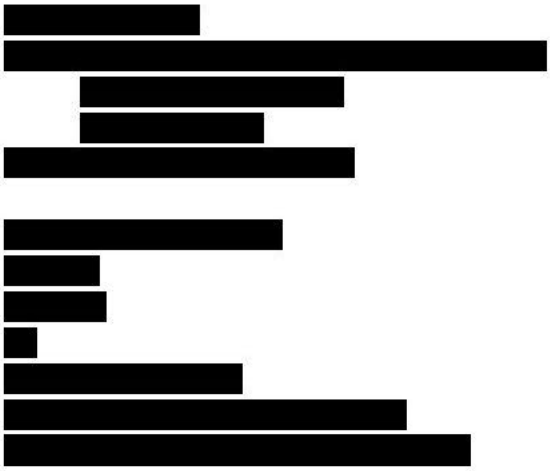
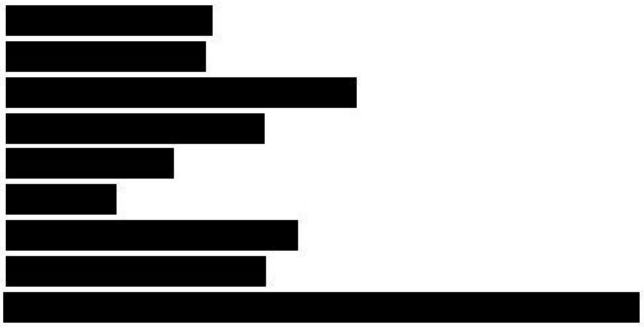
Sponsor's Project Manager:

Sponsor's Medical Experts:





Study Organization, Study Monitoring, Coordinating Investigator, Principal Investigators, Investigation Sites and other study-related information are listed in Section 14.7.

Randomized double blind Phase 3 study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo followed by an open label extension study.

1. SPONSOR SIGNATURE PAGE

I agree to conduct this trial in accordance with the requirements of the Clinical Study Protocol and also in accordance with current versions of the following:

- Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000, Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002)
- The International Conference on Harmonisation (ICH) harmonized tripartite guideline regarding Good Clinical Practice (GCP) (E6 Consolidated Guidance, April 1996)
- Code of Federal Regulation (Title 21, CFR Part 312)
- Local Laws and Regulations

For Sponsor: [redacted]

1.1 Investigator Acknowledgement

PRODUCT: BoNT/A-DP

STUDY TITLE: Randomized double blind Phase 3 study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo followed by an open label extension study.

PROTOCOL IDENTIFIER: CPH-303-201400

IND NUMBER: 123178; EudraCT Number: 2018-003983-30

I have read and understand this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, understand and abide by the requirements for maintenance of source documentation, and provide assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, Code of Federal Regulation (Title 21, CFR Part 312), and all applicable regulatory requirements.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Signature of Principal Investigator Date

Print Name of Principal Investigator

Site name and address

2. SYNOPSIS

INVESTIGATIONAL MEDICINAL PRODUCT	
Name of Investigational Medicinal Product (IMP)	BoNT/A-DP
Name(s) of Active Ingredient(s)	Botulinum toxin A
CLINICAL CONDITION(S)/INDICATION(S)	
Treatment of moderate to severe glabellar frown lines.	
PROTOCOL IDENTIFIER	Study CPH-303-201400, IND No: 123178
PROTOCOL TITLE	Randomized double blind Phase 3 study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, followed by an open label extension study.
Short title	**B**otulinum Toxin Treatment of Glabellar **L**ines: **E**fficacy and **S**afety **S**tudy III (BLESS III)
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	Anticipated April 2019 (FSFV)
Primary Completion	Anticipated January 2021 (LSLV)
Study Completion	Final Clinical Study Report anticipated July 2021
Duration	Up to 62 weeks per subject. Total study duration (FSFV to LSLV) up to 23 months.
STUDY OBJECTIVES AND PURPOSE	
Study purpose	To assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, including efficacy after repeat treatments and long term safety.
Primary Objective	To assess the efficacy of BoNT/A-DP in reducing the severity of glabellar frown lines following treatment (compared with placebo) based on investigator and subject assessment at week 4 (of the first treatment cycle).
Secondary Objective(s)	1. To assess the proportion of responders at maximum frown and at rest at various time points after each treatment, based on investigator and subject assessments. 2. To assess the psychological impact of BoNT/A-DP treatment on subjects (in terms of emotional and social functioning and concerns relating to their glabellar lines) in comparison with placebo after a single treatment.

	3. To assess onset of effect and the duration of effect (at maximum frown) after a single treatment with BoNT/A-DP compared with placebo (first treatment cycle), based on investigator and subject assessments. 4. To provide long term safety data of BoNT/A-DP based on multiple treatment cycles and to establish a sufficient safety database to support regulatory approval. 5. To assess subject perceptions of effect of, and satisfaction with, treatment in comparison with placebo (first treatment cycle), and during the open-label extension phase.
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and safety
Control Type	Concurrent (placebo)
Study Indication Type	Treatment
Intervention model	Parallel for first cycle, followed by an open label extension
Blinding/Masking	Double blind for first cycle, followed by an open label extension
Study Design	The study is a parallel-group, randomized, double blind, placebo-controlled study followed by an open label extension. An interim Analysis will be performed when all subjects finalized the re-evaluation for retreatment visit at week 16 of the first treatment cycle or completed the double blind phase (whichever occurs earlier). The first treatment cycle of the study will comprise two treatment groups as follows: • Group A (active): BoNT/A-DP (20 units, 0.5 mL) • Group B (placebo control): sterile, 0.9% sodium chloride, (0.5 mL). Eligible subjects will be randomized at baseline (day 0) to Group A or B to receive the first treatment in a 3:1 randomization scheme, respectively. Investigators and subjects will be blinded to the treatment administered and will evaluate the severity of glabellar lines independently. The subject should perform their assessment independently and ideally before the investigator, to ensure they are not biased by the investigator. The same investigator should assess the subject at baseline and at the visits at weeks 1, 2 and 4 in the first treatment cycle.

	After a screening period of up to14 calendar days, subjects will receive the first treatment (BoNT/A-DP or placebo) and attend for visits at 1, 2 and 4 weeks after treatment and at 4 weekly intervals thereafter for evaluation of efficacy and safety (primary and key secondary efficacy endpoints are evaluated in the first treatment cycle in comparison with placebo). The first treatment cycle will last at least 12 weeks and will end when the subjects qualify for re-treatment (in accordance with the "eligibility for re-treatment criteria"). After the first treatment cycle is completed, all subjects may enter the open label extension phase and will be dosed with BoNT/A-DP (20 U) for subsequent re-treatments. Evaluation for re-treatment takes place at the earliest at 12 weeks after the first/previous treatment. Subjects who do not qualify for re-treatment at week 12 will have the option (pending eligibility) of re-treatment at a later visit (at 4 weekly intervals thereafter) until they are eligible for re-treatment or until a total of 48 weeks has elapsed since study start. Subjects will attend for visits at 1 and 4 weeks after any re-treatment and at 4 weekly intervals thereafter. At week 2 and week 8 of each open label cycle a telephone call visit will take place. According to the study schedule (Section 2.1 and Section 2.2), a maximum of 4 treatments per subject (4 treatment cycles) is permitted during the study time frame, with treatments separated by a minimum of 12 weeks. The number of treatments administered per subject will depend on the subject's qualification for re-treatment; however, the last opportunity for re-treatment is at week 48.
Planned Duration of Subject Participation	Participation is anticipated to last up to 62 weeks.
Primary Outcome Measure	The primary endpoint is the proportion of subjects among BoNT/A-DP and placebo groups with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥ 2 points in FWS score (at maximum frown) at week 4 visit (of the first treatment cycle) relative to baseline (responders), based on <u>both</u> the investigators' and the subjects' in-clinic assessments. Thus, the primary endpoint is a composite endpoint comprising investigator and subject assessments of treatment effectiveness.

Secondary Outcome Measure(s)	**Key Secondary Efficacy Endpoints (Applicable for first placebo-controlled cycle only)** 1. The extent of change in psychological impact (emotional and social functioning and concerns relating to their glabellar lines) at week 4 after the first treatment, in the BoNT/A-DP group in comparison with placebo, relative to baseline, as assessed by the modified Skindex-16 (Glabellar Line Quality of Life Scale, [GL-QoL]) and the FACE-Q (Appraisal of Lines Between Eyebrows scale and Age Appraisal visual analog scale [VAS]). **Additional Secondary Endpoints** 2. The percentage of responders at maximum frown (as defined above) at week 12 (after the first treatment with BoNT/A-DP or placebo). 3. The percentage of responders at week 16 (after the first treatment). 4. The percentage of responders at week 20 or later (after the first treatment). 5. The proportion of subjects with a ≥ 1 point reduction in FWS score at rest at week 4 in the first treatment cycle, based separately on the investigators' and the subjects' in-clinic assessments (applicable only for subjects who have a FWS score at rest ≥ 1 at baseline). 6. The proportion of responders among BoNT/A-DP and placebo groups with a FWS score at maximum frown of 0 or 1 and an improvement ≥ 2 points in FWS score (at maximum frown) during the first treatment cycle visit relative to baseline, based on both the investigators' and the subjects' in-clinic assessments (composite endpoint, at weeks 1, 2 and 8). 7. The proportion of subjects with ≥ 2-point and ≥ 1 reduction in FWS score (at maximum frown) in the BoNT/A-DP and placebo groups during the first treatment cycle visit relative to baseline, based on the independent rater's assessment of photographs (at baseline and visits 2, 4, 12, 16 and 20 weeks after treatment, within the first treatment cycle). 8. Time to onset of effect in the BoNT/A-DP and placebo groups in the first treatment cycle, as measured at weeks 1, 2 and 4 based separately on subject and investigator assessment. Onset of effect defined as at least a 1 point improvement in FWS score from baseline (at maximum frown).

	In addition, onset of effect will be assessed by subjects daily in the first 2 weeks after treatment, by recordings in the subject diary. 9. The extent of subject perceptions of effect of, and satisfaction with, treatment in the BoNT/A-DP and placebo groups, during each treatment cycle, as assessed by the FACE-Q Satisfaction with Outcome Scale. 10. The proportion of subjects with a ≥ 1 point reduction in FWS score at rest in the BoNT/A-DP and placebo groups, relative to baseline, during the first treatment cycle, based on the independent rater's assessment of photos. 11. The percentage of subjects with a FWS score of 0 or 1 and an improvement ≥ 2 points in FWS score at maximum frown (investigator and subject assessment) at 4 weeks after re-treatment relative to the rating at the preceding end of cycle visit. 12. The proportion of subjects with ≥ 1-point reduction in FWS score (at maximum frown) in the BoNT/A-DP and placebo groups during the first treatment cycle at week 1, 2, 4, 8, 12, 16 and 20 relative to baseline, based on both the investigators' and the subjects' in-clinic assessments. 13. The proportion of subjects with ≥ 1-point reduction in FWS score (at maximum frown) in the BoNT/A-DP group during each re-treatment cycle at week 4 relative to re-treatment-baseline, based on both the investigators' and the subjects' in-clinic assessments. **Secondary Safety Endpoints** 1. Frequency, severity and causal relationship of adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) during the entire study period. 2. Antibody formation, evaluation pre-dose before each treatment, at 4 weeks after each treatment and at the final study visit. 3. Safety assessments by evaluating hematology, clinical chemistry, vital signs and electrocardiogram (ECG) as per study schedule (Section 2.1).
INVESTIGATIONAL MEDICINAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active	BoNT/A-DP **Dosage form:** Injection, lyophilizate for solution for injection

	Dosage frequency: 20 U/treatment comprising a total of five intramuscular (i.m.) injections of BoNT/A-DP (4 U per 0.1 mL injection) administered at a minimum interval of 12 weeks. **Mode of administration:** Two sites in each *corrugator supercilii* muscle and one site in the *procerus* muscle, with an injection volume of 0.1 mL into each site.
Placebo	Sterile, 0.9% Sodium chloride injection **Dosage form:** Injection **Dosage frequency:** A single treatment comprising five injections of 0.1 mL each. **Mode of administration:** Same as for Study IMP. Two sites in each *corrugator supercilii* muscle and one site in the *procerus* muscle, with an injection volume of 0.1 mL into each site.
SUBJECT SELECTION	
Targeted Accrual	353 subjects, with efforts to include a variety of Fitzpatrick skin types. Subject accrual planned as follows: • Approximately 7 sites planned, hence for a 3:1 (BoNT/A-DP: Placebo) randomization scheme, each site should target between 48 and 52 subjects.
Number of Groups/Arms/Cohorts	In the first treatment cycle, two groups. • Group A (active): BoNT/A-DP (20 units, 0.5 mL). • Group B (placebo control): Placebo, 0.5 mL. In the open label extension study (cycles 2-4). • BoNT/A-DP (20 units, 0.5 mL).
Inclusion Criteria	Subjects who meet **ALL** the following criteria are eligible for this study: • Aged ≥ 18 years or older at the time of screening (upper limit 75 years, inclusive). • Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS) as determined by in-clinic assessments by both the investigator and the subject (where: 0= 'none', 1= 'mild', 2= 'moderate', 3= 'severe'). • Subject has a stable medical condition with no uncontrolled systemic disease.

	• Female subjects of childbearing potential must test negative for pregnancy and agree to use highly effective birth control during the course of the study. • Subjects who wear glasses must be able to adequately self-assess the severity of their glabellar lines (according to the FWS), without glasses obstructing the forehead area. • The moderate to severe glabellar lines have an important psychological impact on the subject, as indicated by scores >0 on either the Emotional or the Social Functioning subscale of the modified Skindex-16 (GL-QoL).
Exclusion Criteria	Subjects who meet **ANY** of the following criteria are **NOT** eligible for this study: • Previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening, or any planned treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment). • Known hypersensitivity to the study medication or its excipients. • Any medical condition that may place the subject at increased risk due to exposure to botulinum toxin, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, profound atrophy or weakness in the target muscles, or any other condition (at the investigator's discretion) that might interfere with neuromuscular function or contraindicate botulinum toxin therapy. • Facial laser or light treatment, microdermabrasion, superficial peels or retinoid therapy within the 3 months prior to screening or planned during the study. • Apart from the procedures specified above, previous treatment with any facial aesthetic procedure in the glabellar area (including chemical peeling, injection with biodegradable fillers,) within 12 months prior to screening or planned during the study. • Previous insertion of permanent material in the glabellar area or planned during the study. • Any surgery, or history of surgery, in the glabellar area including surgical removal of the *corrugator*, *procerus* or *depressor supercili* muscles or a

	combination of these, or scars in the glabellar area, or such surgery planned during the study. • Active skin disease/infection or irritation at the treatment area. • Inability to substantially lessen glabellar frown lines even by physically spreading them apart. • Use of a muscle relaxant, within 2 weeks prior to screening or planned during the study. • Marked facial asymmetry or ptosis of eyelid and/or eyebrow, or current facial palsy or neuromuscular junction disorders as judged by the investigator. • Pregnant, breastfeeding or planning to become pregnant during the trial. • Use of prohibited medication including anticholinergic drugs, or drugs which could interfere with neuromuscular function, including aminoglycoside antibiotics and curare-like compounds within 2 weeks prior to screening or planned during the study. • Planned surgery with general anaesthetic (use of local anaesthetic outside the glabellar area is permitted). • Participation in another clinical study within one month of screening and throughout the trial. • Previous participation in another botulinum toxin aesthetic study which involved the treatment of glabellar lines in combination with canthal lines and/or forehead lines in the previous 18 months. • Chronic drug or alcohol abuse (as per investigator discretion).
Eligibility Criteria for re-treatment	The following criteria **MUST** be met for re-treatment: • At time of re-treatment subject does not have relevant changes to their health status from enrollment, which would have prevented subject's entry into the study according to the inclusion and exclusion criteria • The subject must have been randomized to receive treatment and must have received at least one treatment (BoNT/A-DP or placebo). • A minimum of 12 weeks must have elapsed since the previous study treatment.

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The subject's glabellar lines at maximum frown must have relapsed to a FWS score of 2 or 3 as determined by the investigator and the subject.
No relevant infection or inflammation in the planned injection area.
Negative urine pregnancy test, in women of child-bearing potential.
The subject must have received fewer than four study treatments.
The subject must agree and consent to re-treatment.
Re-treatment will be performed at the latest by week 48.

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<tr><td colspan="2">STATISTICAL ANALYSIS</td></tr>
<tr><td>Sample Size Calculation</td><td>
Primary Analysis:

The primary endpoint is a composite endpoint comprising investigators and subject’s assessments of treatment effectiveness using the FWS. Composite endpoint treatment success (CETS) is defined as a ≥2 point reduction in FWS at maximum frown achieving a score of 0 or 1 at the week 4 visit relative to baseline based on investigator assessment and subject assessment. Thus, a subject is a CETS “Responder” only if both investigator- and subject-rated success criteria are satisfied at the week 4 visit after baseline.

The primary analysis of efficacy is the proportion of responders in the BoNT/A-DP treatment group compared with the placebo treatment group. For superiority testing of BoNT/A-DP compared with placebo, the following assumptions for the sample size calculation will be used:

<table>
<tr><th>Item</th><th>Assumption</th><th>Comments</th></tr>
<tr><td>Underlying test</td><td>Fisher’s Exact Test</td><td>Standard test for a response parameter for small numbers</td></tr>
<tr><td>Randomization scheme (BoNT-A/DP:Placebo)</td><td>3:1</td><td>More active treatment subjects to enlarge safety data base</td></tr>
<tr><td>Power 1-β</td><td>90%</td><td>Actual power is 92.3%.</td></tr>
<tr><td>Significance level (α)</td><td>0.025 one-sided</td><td></td></tr>
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	Response Arm BoNT/A-DP	46%	Conservative value based on the results of previous studies (Bless I and Bless II)
	Response Arm Placebo	2%	Conservative value based on the results of previous studies (Bless I and Bless II)
	Software		The sample size calculation was performed using the software nQuery Advisor® 8.2.1.0.

Based on these assumptions, 39 subjects in the BoNT/A-DP arm and 13 subjects in the placebo arm are required, i.e. 52 subjects in total. This is a very small sample size and not sufficient for a detailed evaluation of the data, including subgroup analyses. Furthermore, the response rate could not be estimated with sufficient precision. Assuming a response rate of 46% in the BoNT/A-DG group, a two-sided confidence interval (CI) of 95% with a distance from the response rate to the CI limits of about 5.6% could be achieved with a sample size of 225 subjects in the BoNT/A-DP group. We propose a 3:1 randomization of BoNT/A-DP (225 subjects) to placebo (75 subjects), which we believe is adequate for a precise estimate of response rate and for post-hoc sensitivity analyses (i.e. treatment-by-center and other subgroup analyses), also taking into account a drop-out rate.

In addition sample size is justified in order to fulfill FDA request for additional subjects treated with BoNT/A-DP to provide an adequate Safety database.

In total, 353 subjects will be enrolled. Applying a 15% drop out rate would result in a total number of completing subjects of about 300.

Analysis Data Sets

Safety Analysis Set (SAF):

All subjects who received at least one injection with study medication (independent of whether it is BoNT/A-DP or placebo) 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.

Full Analysis Set (FAS):

	The FAS includes all randomized subjects. 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 (ITT) principle. The FAS will be used for the evaluation of the efficacy assessments. The FAS serves as the primary efficacy analysis set. Modified Full Analysis Set (MFAS): The MFAS includes all randomized subjects who received at least one injection with study medication who had a baseline visit 1 at day 0 and at least one post-dose in-clinic assessment with the FWS by either the investigator or the subject on visits at weeks 1, 2 or 4. Within the MFAS 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 (ITT) principle. The MFAS will be used for the evaluation of the efficacy assessments. Per-protocol Analysis Set (PP): The PP includes all randomized subjects who received at least one injection with study medication who had no significant protocol deviations and an in-clinic assessment with the FWS by the investigator and the subject at baseline (day 0) and at the week 4 visit. For the PP, all subjects will be assigned to the randomized treatment. The PP will only be analyzed for the main efficacy outcome measures.
General Statistical Considerations	Continuous variables will be summarized with means, standard deviations, medians, minimums and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. Analyses will be performed by visit. For responder analyses on the week 4 and week 12 visits, missing in-clinic assessments (by investigator or the subject) with the FWS at baseline or at week 4 and week 12 visits will be assigned as being non-responders. Additionally, missing values will be analyzed using observed values only, last observation carried forward method, and a tipping point analysis approach.

	For patient reported outcome (PRO) instruments, missing data will be imputed per developer guidelines, where these are available. Treatment emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT) (using current version of Medical Dictionary for Regulatory Activities [MedDRA]). The number of events, as well as the number and rate of affected subjects, will be reported. TEAEs (SOC and PT) will also be summarized by seriousness, severity, relationship to study medication, and relationship to procedure. TEAEs will be separately analyzed as events observed on or after first treatment up to before the open label extension (first cycle), and events starting on or after re-treatment until end of study (open label phase). Events in subjects who started the first treatment with placebo but then entered the open label extension for re-treatment with BoNT/A-DP, will be considered to placebo for the first cycle and to BoNT/A-DP for the open label phase. Further aspects of statistical analyses will be detailed within a statistical analysis plan (SAP).
Planned Statistical Analysis	Primary Analysis: The proportion of subjects (responders) meeting the primary endpoint with a FWS score of 0 or 1 and an improvement ≥ 2 points in FWS (at maximum frown) at visit week 4 relative to baseline, based on <u>both</u> the investigator and the subject in-clinic assessments will be analyzed using Cochran-Mantel-Haenszel test (with stratification variable site) using a significance level (α) of 0.025. The hypothesis to be tested is: H_0: $p_{BoNT/A\text{-}DP} \leq p_{Placebo}$ H_1: $p_{BoNT/A\text{-}DP} > p_{Placebo}$ The FAS will serve as the primary analysis set. Subjects with missing investigators' or subjects' in-clinic assessments with the FWS at baseline or week 4 visits will be assigned as being non-responders. Additional Analyses on the Primary Endpoint Variable: Further analyses on the primary endpoint variable are exploratory. A one-sided Pearson χ^2-test will be applied.

	Two-sided CI of 95% for the responder rates in the BoNT/A-DP and the placebo treatment groups will be calculated using Wilson scores. Treatment-by-center interaction will be tested using the Breslow-Day test for homogeneity of the odds ratios. The CIs will also be calculated for the additional analyses as listed in the following: • The primary endpoint measure using the observed values only, i.e. missing investigator or the subject in-clinic assessments with the FWS at baseline or week 4 visit will be excluded from analysis, but not assigned as being non-responder. • The primary endpoint measure using the MFAS and PP. • The primary endpoint measure applying the LOCF for week 4 visit. • Subgroup analysis by site, country and geographic region (US versus EU) o Subgroup analyses will be conducted for sites, country and geographic region (US versus EU). Sites with less than 3 placebo subjects will be combined. The χ^2-test will be applied for each subgroup. In case of a total number of observations below 30, or in case of at least one cell frequency below 5, Fisher's exact test will be used instead of the χ^2-test. Stratified analyses applying the Cochran-Mantel-Haenszel test will also be conducted using factor geographic region. • Subgroup analysis by subjects with previous use of botulinum toxin versus naïve subjects. o Subgroup analyses will be conducted for subjects with treatment with any serotype of botulinum toxin for any indication versus naïve subjects. The χ^2-test or Fisher's exact test (see above corresponding criteria to use Fisher) will be applied for each subgroup. No stratified analysis using factor pre-treated/ naïve subjects is currently planned.

	• In addition the following subgroups will be used for the primary efficacy endpoint: o Race o Subjects with previous use of botulinum toxin by site o Naïve subjects by site o Fitzpatrick skin type o Sex o Ethnicity o Age groups (below 65 years, 65-74 years and 75-84 years; below 65 years versus 65 years and older) Key Secondary Analysis: The testing of the key secondary endpoint will be performed with appropriate multiplicity control based on the FAS population. The results of each test result will only be considered confirmative, if the previous test in the order showed a confirmatory result at a one-sided significance level of 0.025. If the one-sided p-value is larger than 0.025 for any of the tests, the results of the subsequent tests will only be considered exploratory, and not confirmatory. The application of this hierarchical approach keeps the global significance level to 0.025 one-sided and requires no further adjustment of the significance level. The following order of tests will be defined: • Primary endpoint (composite endpoint) • Key secondary endpoint 1 1.1 The modified Skindex-16 (GL-QoL) Emotional domain 1.2 The modified Skindex-16 (GL-QoL) Social Functioning domain 1.3 The modified Skindex-16 (GL-QoL) Overall score 1.4 The FACE-Q Appraisal of Lines Between Eyebrows scale 1.5 The FACE-Q Age Appraisal VAS score The same analyses, inclusive the additional exploratory analyses, as described for the primary endpoint, will be conducted. Subgroup analysis for the key secondary endpoint will be conducted by site, country, geographic region (US

	versus EU), and by subjects with previous use of botulinum toxin versus naïve subjects. Additional Secondary Analyses: The additional secondary efficacy endpoints will be analyzed applying the appropriate statistical method for the comparison of both treatment arms. For proportions, the Cochran-Mantel-Haenszel test (with stratification variable site) as well as the χ^2-test will be applied. In case of a total number of observations below 30, or in case of at least one cell frequency below 5, Fisher's exact test will be used instead of the χ^2-test. The modified Skindex-16 (GL-QoL) and FACE-Q scales will be analyzed according to the foreseen analysis approach of these tools. Besides the FAS population for the analysis with multiplicity control, the analyses of these endpoints will also be based on the MFAS and the PP population. For all analyses, a one-sided significance level of 0.025 will be used, if not stated otherwise.

2.1 Schedule of Study Procedures and Assessments

		Double-blind phase							Open label phase																						
		Cycle 1 (C1)							Cycle 2 (C2)[1]							Cycle 3 (C3)[1]								Cycle 4 (C4)[1]						
Procedures and assessments	Screening (Day -14 to -1)	C1Randomization and 1st treatment (Baseline, Day 0)	C1 Week 1	C1 Week 2	C1 Week 4	C1 Week 8	C1Evaluation for Re-treatment [2,3] (C1 Weeks 12, 16, 20, ...)	C1 End of Cycle Visit [2]	C2 Re-treatment [3]	C2 Week 1	C2 Week 2 (TC)	C2 Week 4	C2 Week 8 (TC)	C2 Evaluation for Re-treatment [2,3] (C2 Weeks 12, 16, 20, ...)	C2 End of Cycle Visit [2]	C3 Re-treatment [3]	C3 Week 1	C3 Week 2 (TC)	C3 Week 4	C3 Week 8 (TC)	C3 Evaluation for Re-treatment [2,3] (C3 Weeks 12, 16, 20, ...)	C3 End of Cycle Visit [2]	C4 Re-treatment [3]	C4 Week 1	C4Week 2 (TC)	C4 Week 4	C4 Week 8 (TC)	End of Study [4]
Visit No*/**	1	2	3	4	5	6	7	7	7	8	9	10	11	12	12	12	13	14	15	16	17	17	17	18	19	20	21	22
Informed consent	x																											
Consent for re-treatment									x							x							x					
Eligibility: Inclusion/Exclusion	x	x																										
Eligibility for re-treatment							x							x							x						
Medical history	x																											
Demographics	x																											
Physical exam***		x	x	x	x			x		x		x			x		x		x			x		x		x		x
Pregnancy test [5]	x	x						x							x							x						x
Vital signs[6]	x	x	x		x			x				x			x				x			x			x			x
Clinical laboratory assessments[7]	x§				x			x				x			x				x			x			x			x
ECG	x§				x			x																				
Concomitant medication	x	x	x	x	x	x	x			x	x	x	x	x			x	x	x	x	x			x	x	x	x	x
FWS Investigator[8]	x	x	x	x	x	x	x					x		x					x		x					x		x
FWS Subject self-assessment[9]	x	x	x	x	x	x	x					x		x					x		x					x		x
Photography[10]		x		x	x		x																					
Psychological impact[11]	x				x			x				x			x				x			x			x			x
Treatment satisfaction[12]					x			x				x			x				x			x			x			x
IMP administration		x							x							x							x					

Post treatment obs./AE and AESI assessment[13]		x							x							x							x						
AE and AESI assessment[15]		x	x	x	x	x	x			x	x	x	x	x			x	x	x	x	x			x	x	x	x	x	
Antibody test[14]	x[§]				x			x				x			x				x			x				x		x	
Subject diary		D	R/ D	R																									

TC = telephone contact: including assessment of concomitant medication, AEs and AESIs[15] (as per AESI manual) on weeks 2 and 8 of each open-label cycle (visits 9, 11, 14, 16, 19 and 21). If an AESI is reported during a telephone contact, subjects will be asked to come to the site for further assessment including a targeted physical examination as soon as possible) * Visit numbers correspond with specific treatment and assessments. If subjects are not eligible for re-treatment at the "Evaluation for Re-treatment" visit, they will return at 4 weekly intervals thereafter, until they are eligible for treatment. The subsequent visit number for the cycle will remain the same, but will be amended with "a, b, c"etc., corresponding to the time extended (at 4 weekly intervals) in that treatment cycle. For example, the first evaluation for re-treatment is at visit 7, week 12, however for subjects who are not eligible at week 12, but at week 16, this visit will be denoted “visit 7a", while "visit 7b" will denote week 20 in the first cycle and "visit 7c" will denote week 24 etc., with each additional letter corresponding to a time point 4 weeks later in that cycle.

** Time differences are measured from the previous treatment administered. A time deviation of ± 5 days is allowed for each visit, except for the week 1 and week 4 visit in each treatment cycle where a time deviation of ± 2 day is permitted. Sites must adhere to the schedule of events and visit windows and subjects must ensure they are available for those visits. Any deviation from the visit schedule and its associated time windows will still be documented as a protocol deviation.

*** Full physical examination will include neurological assessment (including extraocular movements and cranial nerves) as well as assessment for muscle weakness. In addition, if the subject reports any symptoms related to Adverse Events of Special Interest (as detailed in the AESI Manual) a focused physical examination, to evaluate these symptoms will also be undertaken.

§ The ECG performed at screening is the baseline ECG. Laboratory and Anti-drug-antibody (ADA) test samples from screening are considered baseline values.

1 Depending on the duration of treatment effect, a maximum of 4 treatments is permitted.

2 Evaluation for re-treatment takes place at the earliest at 12 weeks after the first/previous treatment. Subjects who do not qualify for re-treatment at week 12 will have the option (pending eligibility) for re-treatment at 4-weekly intervals thereafter, until they are eligible for re-treatment. Once the subject is eligible for re-treatment, the end of cycle procedures will take place and the subject can receive re-treatment (i.e. the end of cycle visit and the re-treatment visit will be conducted on the same day as the Evaluation for Re-treatment visit).

3 The latest time for re-treatment is study week 48; if a subject is not eligible for re-treatment at study week48, the End of Study visit will be completed.

4 The End of Study visit can take place in four-weekly intervals from study-week 48 until study-week 60. For subjects receiving re-treatment at week 48, the last cycle will end 12 weeks later at week 60 (=End of Study visit). End of Study visit will take place at week 48 if week 48 visit is an Evaluation for Re-treatment visit and the subject is not meeting the criteria for re-treatment. For subjects having received their last injection 8 weeks or less prior to week 48, the End of Study visit will take place 12 weeks after the last study drug treatment was given, e.g. week 52 if subject was retreated at week 40. For subjects that get prematurely discontinued from the study (at any time) the End of Study visit will take place within 1 week of discontinuation.

5 Only in women of child-bearing potential; blood serum test at screening and End of Study visit; otherwise urine dip stick.

6 Vital signs include blood pressure (diastolic /systolic) and pulse.

7 Laboratory Assessments: Hematology and Serum Chemistry, details in Section 11.15.

8 Investigator's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point FWS [GLS-I] (0 =none, 1=mild, 2=moderate, 3=severe) and will be recorded in the CRF.

9 Subject's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point FWS [GLS-S] (0 =none, 1=mild, 2=moderate, 3=severe). Subject Assessment will be performed before (ideally) and always independently of investigator assessment and will be recorded in the CRF)

10 Photographs of subject's glabellar lines (at maximum frown and at rest) will be taken at C1 Randomization, C1 week 2, C1 week 4 and each C1 Evaluation for Re-Treatment visit in Cycle 1 until the subject qualifies for re-treatment in order to provide evidence of effect and confirm that the subject did not qualify for re-treatment on the preceding evaluation for re-treatment visit. Although a photograph will be taken at each Evaluation for Re-treatment visit, only the photo of the visit preceding the re-treatment visit will be reviewed by the independent reviewers.

11 Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows and Age Appraisal VAS scales will be used to measure psychological impact and concerns relating to their glabellar lines, respectively (and will be recorded in the CRF).

12 Treatment satisfaction will be determined using the FACE-Q Satisfaction with Outcome Scale (and will be recorded in the CRF).

13 Subjects will be monitored 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.

14 Anti-drug-antibody (ADA) test. If positive, serum samples will be tested for the presence of neutralizing antibodies.

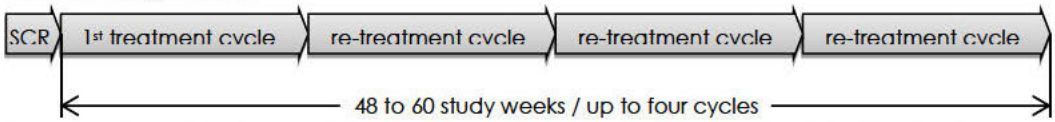
15 General, non-leading AE questioning as well as active AESI questioning at each indicated visit. The first AESI questioning will be completed at Baseline visit in order to obtain a full baseline status of any concomitant diseases prior to the first IMP injection.

AESI Questioning: active questioning by guided review of systems (ROS) as 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; C: Cycle; CRF :Case report form; D:Distribution of subject diary; ECG: Electrocardiogram; FWS: Facial Wrinkle Scale; GL-QoL: Glabellar Line Quality of Life Scale; IMP: Investigational medicinal product; R:Return of subject diary; TC: Telephone call; VAS: Visual Analog Scale

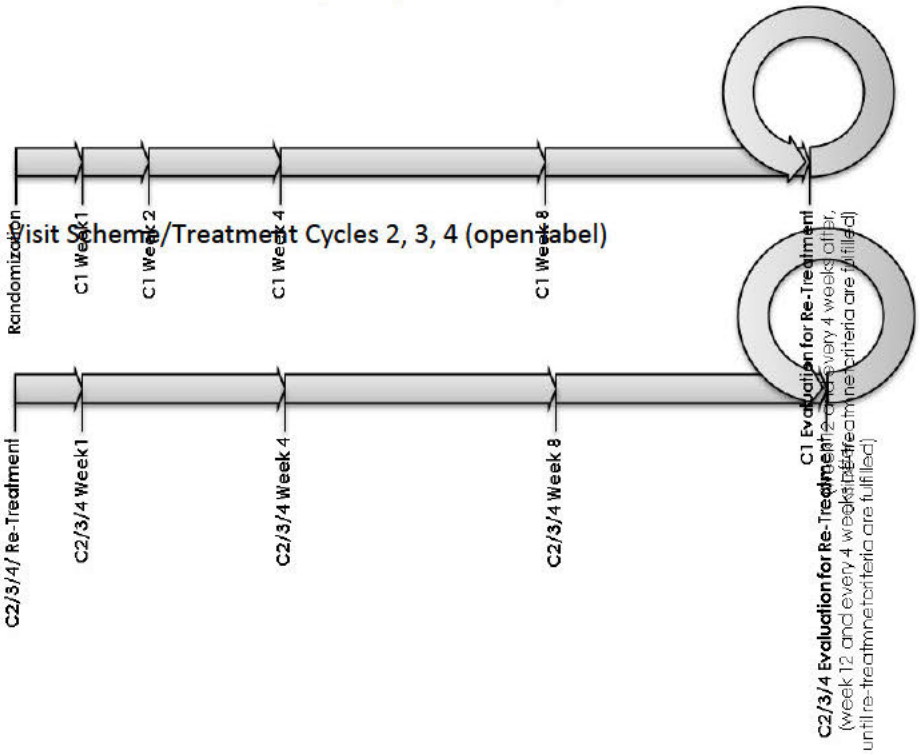
2.2 Study Scheme

Overall study scheme



The duration of study participation for each subject will be up to 14 calendar days of screening followed by 48 to 60 weeks of treatment (re-screening will not be permitted). The first treatment cycle will be a double blinded cycle followed by up to three open label treatment cycles. Each cycle will be at least 12 weeks and can be prolonged in 4-week increments, depending on treatment effect. Re-treatment is possible until study-week48.

Visit Scheme/Treatment Cycle 1 (double blind)



Visit Scheme/Treatment Cycles 2, 3, 4 (open label)

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (ALAT, GPT)
AST	Aspartate aminotransferase (ASAT, GOT)
BoNT/A	Botulinum neurotoxin A
BoNT/A-DP	CROMA Pharma GmbH's BoNT/A Drug Product registered in Korea under the name “Botulax”
CBC	Complete blood count
CETS	Composite endpoint treatment success
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CS	Clinically significant
DAS	Disability Assessment Scale
DF	Dorsifelxion
DRM	Data review meeting
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FSFV	First Subject First Visit
FWS	Facial Wrinkle Scale
GCP	Good Clinical Practice
GL-QoL	Glabellar Line Quality of Life Scale
GLP	Good Laboratory Practice
GLS-I	Glabellar Line Scale for Investigators
GLS-S	Glabellar Line Scale for Subjects
IB	Investigators Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
i.m.	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to treat
IWRS	Interactive Web Response System

Abbreviation	Definition
kDa	Kilo Dalton
LD_{50}	Lethal dose 50 (Median Lethal Dose)
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MAA	Market Access Approval
MAS	Modified Ashworth Scale
MedDRA	Medical Dictionary for Regulatory Activities
MW	Molecular weight
MFAS	Modified Full Analysis Set
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
PRO	Patient reported outcome(s)
PRS	Physician's Rating Scale
PP	Per protocol
PT	Preferred term
ROS	Review of systems
SAE	Serious adverse event
SAF	Safety analysis data set
SAP	Statistical analysis plan
SD	Sprague Dawley
SIC	Subject identification code
SIS	Subject Information Sheet
SOC	System organ class
SOPs	Standard Operating Procedures
TEAE	Treatment Emergent Adverse Event
U	Unit (s)
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization

TABLE OF CONTENTS

4. BACKGROUND INFORMATION

4.1 Background to Botulinum Toxin

Botulinum toxin is produced by anaerobic fermentation of the bacterium *Clostridium botulinum*. A number of different strains of *C. botulinum* have been identified, which produce eight immunologically distinct serotypes (types A - H), all of which interfere with neural transmission by blocking the release of acetylcholine, causing muscle paralysis, however only serotypes A and B are used clinically[1] [2]. The toxins are released from the bacteria as part of a noncovalent multimeric complex, associated with up to six auxiliary proteins, including haemagglutinins and a nontoxin, nonhematuglitin[3].Botulinum neurotoxin A is synthesized as a single-chain polypeptide with a molecular weight of approximately 150 kDa, comprising a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain[4]. The heavy chain targets the toxin to specific types of axon terminals, after which the toxin can be taken into neurons by endocytosis[5,6]. The light chain of the toxin, which has zinc-dependent endoprotease activity, is then released from the endocytotic vesicles and reaches the cytoplasm. The light chain blocks the release of the neurotransmitter acetylcholine, causing dose-dependent weakening of the target muscle. The type A toxin proteolytically degrades its target SNAP-25 protein, which is essential for exocytosis of acetylcholine vesicles located in the peripheral motor neurons3[,7,8]. By preventing neurosecretory vesicles from docking/fusing with the nerve synapse plasma membrane and inhibiting acetylcholine release, the toxin interferes with nerve impulses and causes muscle paralysis3[9] .

The ability of botulinum toxin to inhibit acetylcholine release at the neuromuscular junction has been exploited for use in medical conditions characterized by muscle hyperactivity[10].The broad range of medical indications for botulinum toxin includes treatment of movement disorders (e.g. spasticity, cervical dystonia), urological disorders (e.g. overactive bladder), dermatological conditions (e.g. axillary hyperhidrosis),chronic migraine, as well as cosmetic applications (glabellar lines, canthal lines).

Glabellar lines, which appear as vertical lines between the eyebrows, are caused by contraction of the *corrugator* muscles above the eyebrows. These glabellar frown lines often become more prominent with age and can project negative emotions unintentionally[11,12,13]. In addition, the persistent presence of glabellar frown lines can be suggestive of an older than actual age, affecting an individual's self-perception, emotional well-being, and perception by others, in some cases contributing to depression[14,15].

The first authorised botulinum toxin product on the market was [redacted]®, which received Food and Drug Administration (FDA) approval for therapeutic treatment of strabismus and blepharospasm in 1989 and was first licensed for neuromuscular disorders (via intramuscular [i.m.] route) in the European Union (EU) in 1994. The first report in medical literature on the use of botulinum preparations in the treatment of glabellar lines was published in 1992[16]. Since then, several botulinum toxin type A containing products have been licensed for use worldwide. The major commercially available preparations of botulinum type A toxin are [redacted] all of which are licensed for the treatment of glabellar lines. [redacted], a botulinum toxin type B product, is produced by [redacted]. The cosmetic use of botulinum toxin type A is now widespread[17], with reported aesthetic sales revenue in the United States (US) exceeding $5.7 billion[18].

In the three major licensed type A products, the neurotoxin is derived from the identical Hall strain of Clostridium botulinum type A (strain Hall A, ATCC 3502[19]), although the products have unique properties. The molecular weight (MW) of [redacted] is 500 kDa and the MW of [redacted]® is 150 kDa. CROMA Pharma GmbH's botulinum neurotoxin A drug product (BoNT/A-DP) (900 kDa) is most similar to [redacted] (900 kDa), with a similar molecular weight and similar active moiety and subunits. BoNT/A-DP differs from other BoNT/A containing products, in that it is derived from a new *Clostridium* strain "CBFC26" isolated from canned soy beans in 2001; the isolation and purification procedures also differ. The products have unique properties, hence serotype A botulinum toxins are defined as new biological entities (and not as biosimilars).

Clinical Phase 3 development of BoNT/A-DP was performed in Korea (using doses of20 U or above per treatment), which demonstrated that BoNT/A-DP is not inferior to [redacted][20]. BoNT/A-DP is marketed and approved as "Botulax" in Peru, Uruguay, Paraguay, Bolivia, Chile, Colombia, Ecuador, Ukraine, Honduras, El Salvador, Costa Rica, Guatemala, Thailand, Vietnam, Philippines, India, Azerbaijan, Georgia, Kuwait, Australia and New Zealand. The study Sponsor, CROMA Pharma GmbH, has a focus on aesthetics and obtained the rights (in 2014) to develop the drug further for the EU, US and other markets with a focus on "cosmetic" indications. Two Phase 3 studies (BLESS I and BLESS II) have been conducted for the treatment of glabellar lines. .Both studies, BLESS I (CPH-301-201030) and BLESS II (CPH-302-201030), had an identical study design, but BLESS I had a larger study population of 708 subjects and took place in the US and the EU, BLESS II had a study population of 213 subjects and took place in the US only. The Sponsor is currently using the name BoNT/A-DP for clinical development, with plans to introduce a new name for the product in the EU and US after approval.

The indicated clinical condition (glabellar lines) is chronic in nature and the botulinum toxin effect typically lasts only a few months (function is typically recovered by the sprouting of nerve terminals and formation of new synaptic contacts, which usually takes two to three months), hence subjects need to be injected repeatedly to maintain the effect[21,22].The aim of the current study is to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo for one treatment cycle and to evaluate long term safety and efficacy following repeated injections in the subsequent open label extension phase.

4.2 Clinical Condition/Indication

Hyperfunctional facial lines (mimic wrinkles) are common aesthetic deformities involving the glabellar area, forehead and perorbital area. Glabellar lines occur as a result of the pull on the skin on the underlying facial musculature, predominantly the *procerus* muscle and the *corrugator supercilli*[23]; the latter muscle has no essential function other than to express emotion. Although fine wrinkling on the upper lip and cheeks, and crow's feet, as well as the deeper lines in the nasolabial area are a sign of aging, wrinkling in the glabellar area is associated with the expression of frowning. Excessively prominent lines in this area (which appear as vertical lines between the eyebrows) are often misinterpreted as anger, anxiety, fear, fatigue and melancholia, causing the subject considerable distress[24]. As a result, glabellar lines can negatively influence self-perception, perception by others and emotional wellbeing[25,26]. Although treatments are available for such lines (including topical preparations or surgical procedures), there are several disadvantages to currently available treatments and most facial rejuvenation procedures do not address the underlying musculature responsible for facial lines.

Studies with botulinum toxin have shown that the toxin weakens the overactive underlying muscle contraction, causing a flattening of the facial skin and improved appearance. The effect of the neurotoxin on facial lines was first reported in the early 90's. Subsequent widespread use has supported its efficacy and safety for several therapeutic indications including facial aesthetics [10,27]. Lewis and Bowler (2009)[14] have reported that people who received botulinum toxin treatment for frown lines were significantly happier than those who had received other kinds of cosmetic treatment and high rates of subject satisfaction with treatment have been reported[13,20,28].

4.3 Description of Investigational Medicinal Products

4.3.1 Description of the Investigational Medicinal Product BoNT/A-DP

CROMA Pharma GmbH's botulinum toxin BoNT/A-DP is a 900 kDa multimeric complex, which is composed of a 150 kDa neurotoxin, a 130 kDa non-toxic non-haemagglutinating protein and various haemagglutinins ranging between 17 and 48 kDa in size. The IMP is the *Clostridium botulinum* toxin type A purified from anaerobic culture of *C. botulinum* type A CBFC 26 strain. The genomic DNA sequence encoding the toxin in strain CBFC26 is identical to that for the Hall strain A ATCC 3502. CROMA Pharma GmbH's BoNT/A is supplied as a freeze-dried powder that is reconstituted with sterile diluent (preservative-free saline) prior to injection. The excipients of the IMP (BoNT/A-DP) are human serum albumin and sodium chloride (Table 4-1). Human serum albumin is used as a stabilizing agent and sodium chloride is added to provide isotonicity of the formulation. The labeled potency is 50 units (U)/vial, where one unit corresponds to the median intraperitoneal lethal dose (LD_{50}) when the reconstituted product is injected intraperitoneally into female Swiss-Webster mice under defined conditions[29].

Reconstitution with 1.25 mL sterile diluent (0.9% saline) is performed prior to i.m. injection, to obtain a solution of 4 U/0.1 mL.

Table 4-1 Composition of BoNT/A-DP and Placebo

Name	Components per vial (50 U)	Function	Dose	Appearance
BoNT/A-DP	Clostridium botulinum type A (50 units)* Human serum albumin (0.25 mg) 0.9% Sodium chloride	Active ingredient Excipient Excipient	20 U total (0.5mL) 4U (0.1mL) per injection point	Lyophilizate for solution for injection, which becomes a colorless transparent liquid when saline diluent is added.
Placebo	0.9% sodium chloride (diluent)	Control	0.1 mL per injection point	Colorless transparent liquid

*Reconstitute with 1.25 mL sterile saline, yielding 4 U per 0.1 mL dose

4.3.2 Description of the Placebo Control

Sterile normal saline (0.9% sodium chloride), which is also used as the diluent for reconstitution, will be used as the placebo control in this study.

4.4 Non-clinical and Clinical Summaries

4.4.1 Non-clinical Summary

The efficacy and safety of CROMA Pharma GmbH's BoNT/A have been thoroughly assessed in non-clinical studies.

Efficacy studies to evaluate the paralysis induction potential of CROMA Pharma GmbH's BoNT/A-DP compared to [redacted]) after i.m. injection were performed in Sprague Dawley (SD) rats. Both toxins showed a concentration dependent reduction of amplitude (dY) and response time delay (tC) following administration, which is attributable to the expected pharmacological action of BoNT/A. The extent of CROMA Pharma GmbH's BoNT/A-DP paralysis potential was comparable to that of [redacted]) at all time points (3, 7, 14, 21, 28 days post dose) and concentrations (2, 4, 8 U/animal) tested.

The safety profile of BoNT/A-DP has been demonstrated in single- and repeated-dose toxicity studies in rats and dogs, fertility and reproductive and developmental studies in rats.

Single dose toxicity studies with CROMA Pharma GmbH's BoNT/A-DP have been performed in SD rats (up to 150 U/Kg) and Beagle dogs (up to 200 U/Kg) using the i.m. route. No significant pathology findings were observed. A significant decrease in body weight was observed in animals treated at 30 U/Kg, which is seen as an indirect effect related to paralysis. The LD_{50} value was calculated to be 129.5 U/Kg in rats, while in dogs no LD_{50} was calculated and no toxicity was observed at or above the highest dose tested (200 U/Kg).

Repeat dose toxicity studies were conducted in SD rats and Beagle dogs. In rats, paralysis of the hind legs was observed at 1.5 U/Kg and the no observed adverse effect level (NOAEL) defined as 1.5 U/Kg. In Beagle dogs, no muscle paralysis and no toxicological changes were seen up to 30 U/Kg, hence the NOAEL in Beagle dogs was defined at or above 30 U/Kg. Selected safety pharmacology (electrocardiogram [ECG]) and local tolerance examinations were performed as part of the repeat-dose toxicity studies. The route of administration for all studies was i.m. injection. No histological changes of muscles were observed at the administration site in either species. No systemic toxicity was observed in single or repeated-dose toxicity studies and no compound-related lesions of the muscle groups distant to the injection sites of the peripheral or central nervous system were observed. Further long-term studies have not been conducted with the Investigational Medicinal Product (IMP) since there is no need for continuous application and presence of BoNT/A-DP at the application site to induce and maintain the clinical effect. The maximum number of applications of CROMA-Pharma GmbH's BoNT/A-DP for the treatment of glabellar lines is limited to 3-4 applications per year (minimum interval between treatments is defined at 3 months) and thus identical to the application scheme of other FDA approved BoNT/A containing products (e.g. [redacted]®). In support of CROMA-Pharma GmbH's BoNT/A-DP safety evaluation, it is mentioned that the Food and Drug Administration (FDA) did not see evidence for local or systemic adverse effects after long-term use, when evaluating the safety data package of [redacted] (6 injections, 4 week intervals)[30]. In addition, the mechanism behind the recovery of nerve function is well known and described in detail in peer-reviewed scientific literature available in the public domain. Nerve function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; this usually takes two to three months. Accordingly, a long-term toxicity study >28 days is not considered to add value to the non-clinical development program of CROMA-

Pharma GmbH's BoNT/A-DP, and thus local and systemic toxicity following long-term treatment has not been evaluated for the IMP.

Reproductive toxicity was investigated in an embryo-foetal development toxicity study in the SD rat model, where animals were dosed at 1 to 8 U/kg for 12 days. Clinical signs included paralytic gait in all treatment groups, which is considered to be due to exaggerated pharmacologic effects of BoNT/A-DP. The NOAEL was less than 1 U/Kg.

A repeated dose toxicity study in Sprague-Dawley rats was conducted (Study No. 167857). The purpose of this study was to obtain information on the toxicity of BoNT-A DP in rats after repeated intramuscular administration over a period of six months. Rats initially received doses of 0, 0.67, 2.0 and 6.0 U/kg (first application). Since animals did not show any signs of paralysis after the first administration, dose levels were increased from the second administration onwards to 3.75, 7.5, and 15 U/kg, respectively. At the end of the study neurotoxic action of BoNT/A-DP 50U was demonstrated by clinical symptoms (altered locomotion) occurring at all dose levels and atrophy of the injected muscle. This was confirmed histopathologically by diameter and number of myofibers in all dose groups. Moreover, fatty infiltration was also seen at all dose groups. Often, there was an inflammatory infiltrate at the injection sites and a minor fibrosis. At the end of the 6-months treatment-free recovery period in absence of inflammation and fibrosis a partial recovery was seen in fiber number and diameter and fatty infiltration at the dose level of 0.67/3.75 U/kg body weight once monthly.
At a dose level of 6/15 U/kg body weight BoNT/A-DP 50U showed a clear effect on body weight development in both genders. Body weights were significantly lower than controls throughout the treatment period and not completely reversible in the recovery period. This coincided with lower food consumption during the treatment but not recovery period and was not associated with any clinical symptoms or other signs of systemic toxicity. Thus, this effect is considered secondary to the local effects described above preventing normal movement of the animal.
A target organ other than the injected quadriceps muscle was not identified. Based on the results of this study that affect the skeletal muscle focally only, and considering the relatively small diameter and lengths of the muscle in rats compared to larger species and human, the high frequency of injections and the absence of further findings, the systemic NOAEL was established at 15 U/kg body weight BoNT/A-DP, when administered once monthly over 6 months.

No standard pharmacokinetic or toxicokinetic studies were performed with CROMA Pharma GmbH's BoNT/A-DP, since the chemical nature of the drug is a protein and the expected consequence of metabolism of proteins is the degradation to small peptides and individual amino acids.

All pivotal studies were performed under Good Laboratory Practice (GLP) conditions and according to International Conference on Harmonisation (ICH) guidance.

For further details please refer to the Investigators Brochure (IB).

4.4.2 Clinical Summary

To date, the clinical development of BoNT/A-DP, including clinical two Phase 3 studies (BLESS I and BLESS II) have been performed in the US and Europe by the Sponsor.

The multicenter Phase 3 studies were comprised of two parts. The first part of the studies were a randomized, double blind, placebo-controlled, phase which aimed to demonstrate efficacy and

safety of BoNT/A-DP compared with placebo. The second part was an open label extension phase to evaluate efficacy after repeat treatments and long term safety. Each product was administered at a dose of 20 U (0.5 mL).

The primary efficacy endpoint of these studies was the proportion of subjects among BoNT/A-DP and placebo groups with a FWS score of 0 or 1 and an improvement ≥2 points in FWS score (at maximum frown) at the week 4 visit (of the first treatment cycle) relative to baseline (responders), based on both the investigator's and the subject's in-clinic assessments. Thus, the primary endpoint is a composite endpoint comprising investigator and subject assessments of treatment effectiveness.

In addition Phase 3 and Phase 4 trials, has been performed in Korea using the IMP name "Botulax". The Sponsor is currently using the name BoNT/A-DP for clinical development.

In clinical trials to date, more than 1,400 subjects have been exposed to BoNT/A-DP for cosmetic and other indications, with doses ranging from 20 U for glabellar lines up to 360 U for the treatment of post stroke upper limb spasticity (Table 4-2). A brief summary of the results is provided below, for further details please refer to the IB.

4.4.2.1 Phase 3: BLESS I: Indication; Glabellar Lines

A total of 708 subjects were randomized; 531 subjects were allocated to BoNT/A-DP and 177 subjects to placebo. The double-blind phase was completed by 500 (94.2%) and 160 (94.4%) subjects in the BoNT/A-DP and placebo groups, respectively; and the study was completed by 456 (85.9%) and 145 (81.9%) subjects, respectively.

The composite responder rate (reduction in FWS of ≥ 2 points and FWS score of 0 or 1 at maximum frown) at Week 4 from baseline was 46.5% for the BoNT/A-DP group and 0.0% for the placebo group; the difference in responder rates between the BoNT/A-DP and placebo groups was 46.50% (95% confidence interval [CI]: 41.78, 50.76) ($p < 0.001$, CMH test) in favor of BoNT/A-DP (FAS); thus this study confirmed the superior efficacy of BoNT/A-DP compared to placebo in the treatment of glabellar lines. Findings were robust. The results for the Modified Full Analysis Set (MFAS) and Per Protocol Set (PPS) are consistent with the FAS results. There was no statistically significant treatment-by-center interaction difference in the odds ratios between the centers in the responder rates as determined by the investigator (Breslow-Day test p-value = 0.363) (FAS). Sensitivity analyses with missing values handled with LOCF and observed values showed results that were consistent with the primary results. Results were similar by Fitzpatrick skin type, by demographic factors, and by whether the subject had received previous treatment with botulinum toxin. The responder rate was 66.5% and 0.6% of subjects for the BoNT/A-DP and placebo group, respectively, as assessed by investigators; and 55.6% and 0.0%, respectively, as assessed by subjects ($p < 0.001$, CMH test in both instances) (FAS); thus confirming the conclusions from the composite (concordant) primary endpoint.

The results for the ad hoc analyses for ≥ 1 point improvement in FWS at maximum frown are consistent with the primary efficacy endpoint and clearly demonstrate a clinically meaningful effect of the BoNT/A-DP on the targeted hyperdynamic lines. During the double-blind phase, the composite rate of ≥ 1 point improvement in FWS at maximum frown at Week 4 was 81.5% for the BoNT/A-DP group and 1.7% for the placebo group; with rates of 90.9% and 9.7% of subjects for the

BoNT/A-DP and placebo group, respectively, as assessed by investigators; and 84.5% and 7.4%, respectively, as assessed by subjects ($p < 0.001$, CMH test in all instances) (FAS).

This benefit was maintained up to Week 16 post-injection for approximately 20% of subjects. Composite rates of ≥ 1 point improvement in FWS at maximum frown were 45.1% and 1.2%, respectively, in the BoNT/A-DP and placebo groups, at Week 12, 20.8% and 0.6%, respectively, at Week 16, and 9.9% and 0.0%, respectively, at Week 20 ($p < 0.001$ in each instance).

Consistent with the primary endpoint, efficacy was maintained with up to 3 retreatments, with 81.5%, 74.4% and 70.3% of subjects in the BoNT/A-DP group at Week 4 after the first, second and third retreatment cycles, respectively, having shown composite rates of ≥ 1 point improvement in FWS at maximum frown (with rates of 93.1%, 91.1% and 87.4% of subjects as assessed by investigators; and 84.4%, 76.7% and 73.4% of subjects, as assessed by subjects after the first, second and third retreatment cycles, respectively).

No deaths and no study drug-related SAEs were reported during the study. One (0.1%) subject during the study reported a BoNT/A-DP-related AE that led to discontinuation (headache; during the open-label phase). Pregnancy led to discontinuation from the study for 3 subjects.

During the double-blind phase of the study, 19 (3.6%) subjects experienced TEAEs considered to be at least possibly related to BoNT/A-DP and 4 (2.3%) subjects experienced TEAEs considered to be at least possibly related to placebo. Study drug-related TEAEs in the BoNT/A-DP and placebo groups, respectively included headache: 10 (1.9%) subjects and 1 (0.6%) subject; injection site pain: 2 (0.4%) subjects and 1 (0.6%) subject; and head discomfort: 2 (0.4%) subjects in the BoNT/A-DP group and none in the placebo group. The rate of headache was higher in the BoNT/A-DP group compared to the placebo group. All other events were experienced by no more than 1 (0.1%) subject.

One AESI was reported for 1 (0.1%) subject each in the BoNT/A DP and placebo groups during the double-blind phase and 3 (0.4%) subjects in the open-label phase. A total of 3 (0.4%) subjects had AESIs related to BoNT/A-DP and 2 (0.3%) subjects had AESIs related to injection procedure. No subjects had AESIs related to placebo or injection procedure.

A secondary objective of the study was to provide long term safety data of BoNT/A-DP based on multiple treatment cycles. This study showed no increases in TEAE rates or TEAE severity with up to 4 cycles of treatment, thus confirming safety after repeated treatments and over prolonged period of use.

There was no development of ADA during the study.

4.4.2.2 Phase 3: BLESS II: Indication; Glabellar Lines

The composite responder rate (at maximum frown) at Week 4 was 48.8% for the BoNT/A-DP group and 1.9% for the placebo group (FAS); the difference in responder rates between the BoNT/A-DP and placebo groups at Week 4 was 46.86% (95% confidence interval [CI]: 35.77, 54.70, $p < 0.001$, CMH test) in favor of BoNT/A-DP (FAS); thus, this study confirmed the superior efficacy of BoNT/A-DP compared to placebo in the treatment of glabellar lines. Findings were robust. The results for the Modified FAS (MFAS) and Per Protocol Set (PPS) were consistent with the FAS results. There was no statistically significant treatment-by-center difference in the odds ratios between the centers in the composite responder rate (Breslow-Day test p-value = 0.193; FAS). Sensitivity

analyses with missing values handled with LOCF and observed values showed results that were consistent with the primary results. Results were similar according to Fitzpatrick skin type, demographic factors (most subjects were white and female), and whether the subject had received previous treatment with botulinum toxin. The responder rates were 75.0% for the BoNT/A-DP group, and 1.9% for the placebo group as assessed by investigators; and 51.9% and 1.9% for the BoNT/A-D and placebo group, respectively as assessed by subjects ($p < 0.001$, CMH test in both instances, FAS), which was consistent with the results obtained from the composite (concordant) primary endpoint analyses.

The results for the ad hoc analyses for rates of ≥ 1 point improvement in FWS at maximum frown were consistent with the primary efficacy endpoint and clearly demonstrate a clinically meaningful effect of the BoNT/A-DP on the targeted hyperdynamic lines. During the double-blind phase, the composite rates of ≥ 1 point improvement in FWS at maximum frown at week 4 were 83.1% for the BoNT/A-DP group and 1.9% for the placebo group; with rates of 90.0% and 3.8% of subjects for the BoNT/A-DP and placebo group, respectively, as assessed by investigators; and 85.0% and 9.4% respectively, as assessed by subjects ($p < 0.001$, CMH test in all instances) (FAS).

Composite rates of ≥ 1 point improvement in FWS at maximum frown were 40.5% and 2.1%, respectively in the BoNT/A DP and placebo groups, at Week 12 ($p < 0.001$), 12.1% and 0.0%, respectively at Week 16 ($p = 0.006$), and 4.7% and 0.0%, respectively at Week 20 ($p = 0.068$). The benefit was maintained up to Week 12 post-injection for approximately 40% of subjects and up to Week 16 for approximately 12% of subjects.

Consistent with the primary endpoint, efficacy was maintained with up to 3 retreatments, with 82.4%, 78.9% and 71.1% of subjects at Week 4 after the first, second and third retreatment cycles, respectively having shown composite rates of improvement of ≥ 1 point in FWS at maximum frown.

Overall, 213 subjects were randomized and received at least 1 treatment and were included in the SAF, 160 subjects in the BoNT/A-DP group, and 53 subjects in the placebo group. No deaths were reported during the study. There were no SAEs that were related to study medication, and no TEAEs that led to discontinuation.

TEAEs with an incidence ≥ 1% of subjects in any BoNT/A-DP stratum which were reported more frequently in the BoNT/A DP group than in the placebo group and included upper respiratory tract infection (6 [3.8%] subjects in the BoNT/A DP group and 1 [1.9%] subject in the placebo group); and urinary tract infection (4 [2.5%] subjects), eyelid ptosis (3 [1.9%] subjects), gastroenteritis (2 [1.3%] subjects), and concussion (2 [1.3%] subjects), all in the BoNT/A-DP group; no subjects in the placebo group experienced these events. TEAEs considered to be at least possibly related to treatment with BoNT/A-DP during the double-blind, and open-label parts of the study (N = 208) included 6 (2.9%) subjects with headache, 2 (1.0%) subjects with eyelid ptosis, and 1 (0.5%) subject each with blepharospasm, injection site nodule, and dry skin.

A total of 2 (1.0%) subjects who received BoNT/A-DP (N = 208) reported a severe TEAE; these included 1 (0.5%) subject each with vitreous detachment and asthma, both unrelated to study drug.

AESIs during treatment with BoNT/A-DP during the double-blind, included eyelid ptosis, constipation and dysarthria reported for 1 (0.6%) subject each. During the open-label phase, AESIs included eyelid ptosis reported for 1 (0.5%) subject. All AESIs were of mild severity. None of the AESIs was considered to be related to study drug.

A secondary objective of the study was to provide long term safety data of BoNT/A-DP based on multiple treatment cycles. This study showed no increases in TEAE rates or TEAE severity with up to 4 cycles of treatment, thus confirming safety after repeated treatments and over prolonged period of use.

There was no development of ADA during the study.

4.4.2.3 Phase 3 Study HG-11-01: Indication; Glabellar Lines

Phase 3 study HG-11-01 was a comparative non-inferiority trial to evaluate the safety and efficacy for improvement of glabellar lines of BoNT/A-DP compared to® in subjects with moderate to severe glabellar lines. Study HG-11-01 was performed in Korea with 134 subjects receiving BoNT/A-DP and 137 subjects receiving[20]. Each product was administered at a dose of 20 U (0.5 mL).

The primary endpoint was the response rate of physicians' assessment using the Facial Wrinkle Scale (FWS) at week 4. Secondary endpoints included the response rate according to investigator at weeks 8, 12 and 16, photographic assessment (3 independent blinded raters) at weeks 4, 8, 12 and 16, subjects' improvement assessment and subjective self-satisfaction levels.

Response rates for maximum frown at week 4 were comparable between the groups, at 89.3% in the BoNT/A-DP group and 81.9% in the group. On the basis of secondary endpoints for photographic assessment, the response rates were significantly higher for BoNT/A-DP than at 4weeks (p=0.02) and 8weeks (p< 0.005) after treatment. Thirty eight subjects (28.4%) reported 63 cases of adverse events (AEs) in the BoNT/A-DP group, and 45 subjects (32.8%) reported 62 cases of AEs in the group, thus the incidence of AEs was low and similarly distributed between treatment groups. No AE occurred within 30 minutes after administration of the IMP and no subjects died during the study. Thirty three treatment-related adverse events (TEAEs) were reported in 28 subjects (10.3%) and the incidence rate of TEAEs was lower in the BoNT/A-DP group than in the group (9.0% vs. 11.7%). Among TEAEs, injection site reaction was reported in four subjects in the BoNT/A-DP group and 11 subjects in the B group; eyelid ptosis was reported in six subjects in the BoNT/A-DP group and three subjects in the group. No TEAE was evaluated to be severe in intensity. Among TEAEs, six cases of moderate severity were reported in the BoNT/A-DP group and one in the group.

One serious adverse event (SAE) was reported in each group (cellulitis in the BoNT/A-DP group and sudden hearing loss in the® group); however, neither case was treatment-related. Antibody formation test results pre- and post-dose were negative for all subjects.

BoNT/A-DP therefore demonstrated the expected safety and efficacy profile of botulinum toxin A products, with no noticeable difference in the assessment of safety and efficacy between the groups administered BoNT/A-DP and®.

4.4.2.4 Phase 3 Study HG-06-01: Indication; Blepharospasm

Study HG-06-01 was a double blind, randomized, active control comparative, parallel-designed, Phase 3 clinical trial to evaluate the safety and efficacy of BoNT/A-DP in essential blepharospasm.

Study HG-06-01 was performed in Korea with 121subjects receiving BoNT/A-DP and 104subjects receiving [redacted]®. The total dose administered varied from 12.5 to 60 U.

The primary endpoint was "efficacy rate after administration of test product" and the efficacy rate was defined as an elevation of more than one grade (Scott method) at the fourth week after administration. Secondary endpoints included the effectiveness duration period, the degree of spasm, eyelid closure force, and vision function at predefined visit points, percentages of improvement (to grade 0 or 1) at the fourth week after administration of test product (Scott method), and percentages of cases where more than two grades are elevated at the fourth week after administration of test product (Scott method). The efficacy rates were comparable (98.91% in the BoNT/A-DP group vs. 100% in the [redacted] group) and BoNT/A-DP was not inferior to [redacted] (the lower limit of confidence interval [CI] for test group - control group was -2.87%, which exceeded the non-inferiority boundary of -10%). With regard to secondary endpoints, there was no statistical difference between the test group and control group with respect to the duration of effect.

A total of 73 AEs was reported in 47 subjects in the BoNT/A-DP group and 77 AEs were reported in 42 subjects in the [redacted] group, with no statistically significant difference (p=0.8136). The frequency of TEAEs was low and similarly distributed between treatment groups (27.56% in the BoNT/A-DP group vs. 39.56% in the [redacted] group).

Three cases of SAEs requiring hospitalization were reported in two subjects in the BoNT/A-DP group. One subject had moderate arrhythmia, and the other two subjects experienced severe headache and anxiety. The arrhythmia was considered ‘definitely not related’ to the treatment. The cases of headache and anxiety were considered ‘probably not related’ to treatment and the subjects completed the study without any further AEs. Other safety endpoints were also investigated, including vital signs, laboratory tests, and antibody formation. No clinically significant finding was observed, no antibody formation was reported and there was no significant difference between treatment groups.

Long-term safety of BoNT/A-DP was evaluated through the extension study HG-08-01 (up to 48 weeks) and there was no significant difference in the incidence of AEs between groups (p=0.5293, chi-square test). Antibody formation test results pre- and post-dose were negative for all subjects.

As a result, there was no noticeable difference in the assessment of safety and efficacy between the groups administered BoNT/A-DP or [redacted].

4.4.2.5 Phase 3 Study HG-11-02: Indication; Equinus Foot Deformity in Children with Cerebral Palsy

Study HG-11-02 was a double blind, randomized, active control comparative, multicenter-designed, Phase 3 clinical trial to evaluate the safety and efficacy of BoNT/A-DP versus [redacted] for the treatment of dynamic equinus foot deformity in children with cerebral palsy. Study HG-11-02 was performed in Korea with 72 subjects receiving BoNT/A-DP and 72 subjects receiving [redacted] control. The total dose administered was 6 U/Kg body weight for bilateral palsy and 4 U/Kg for unilateral palsy, with a maximum dose/injection limit not exceeding 200 U.

The primary endpoint was the responder rate determined by the Physician’s Rating Scale (PRS) score at week 12, with a responder defined as an increase in the PRS score by 2 points or more for each leg. Secondary endpoints included safety assessment, comparison of the test and control

groups at 6 and 24 weeks after administration and comparison of changes in PRS, Passive Range of Motion Scale (ankle dorsifelxion [DF], knee flexion), Gross Motor Function Measure-88, Gross Motor Function Measure-66 and Modified Tardieu Scale (ankle DF) between the test and control groups at 6, 12 and 24 weeks after administration.

The responder rate was 60.27% (44/73 subjects) in the BoNT/A-DP group compared to 61.43% (43/70 subjects) in the [redacted]® group. Moreover, the lower limit of 95% CI for the between-group difference in responder rates (-1.15%) was 17.16%, which was higher than the non-inferiority margin of-24.00%, demonstrating that BoNT/A-DP was not inferior to [redacted] Among the secondary endpoints, no statistically significant difference was noted between the BoNT/A-DP group and the [redacted] group.

A total of 152 AEs were reported in 54 subjects (73.97%) in the BoNT/A-DP group and 128 AEs were reported in 45 subjects (64.29%) in the [redacted] group, with no statistically significant difference between groups.

A total of five SAEs were reported in four subjects in the BoNT/A-DP group (including 1 case of severe intussusception and moderate cases of tonsillar hypertrophy, asthma, bronchitis and pharyngotonsillitis), all of which were unrelated to BoNT/A-DP and recovered without sequelae. In the [redacted] group, nine SAEs were reported in six subjects, (including one case of acute tonsillitis, osteochondrosis and meningitis and six cases of moderate pneumonia), all of which were unrelated to [redacted]® and recovered without sequelae. Antibody formation test results pre- and post-dose were negative.

Therefore, for the treatment of equinus foot deformity in children with cerebral palsy, the responder rate in the BoNT/A-DP group was comparable to that of the [redacted]® group; BoNT/A-DP was not inferior to [redacted] and there were no statistically significant differences in AE frequency between both treatment groups.

4.4.2.6 Phase 3 Study HG-13-01: Indication; Post Stroke Upper Limb Spasticity

Study HG-13-01 was a randomized, double blind, multi-center, active drug controlled, Phase 3 clinical trial to compare the efficacy and safety of BoNT/A-DP versus [redacted] in the treatment of post-stroke upper limb spasticity. Study HG-13-01 was performed in Korea with 94 subjects receiving BoNT/A-DP and 92 subjects receiving [redacted]®. The total dose administered varied from 10 to 200 U, with a maximum i.m. administration across injection sites of 360 U.

The primary endpoint was the variation in the muscle tone value of wrist flexor measured by Modified Ashworth Scale (MAS) at week 4 post-dose compared to baseline as evaluated by the investigator. Secondary endpoints included the change in elbow flexor, finger flexor and thumb flexor muscle tone as measured by MAS at weeks 4, 8 and 12 compared to baseline, change in the Disability Assessment Scale (DAS), global assessment evaluated by the investigator and the subject at weeks 4, 8 and 12 and the change in the Caregiver Burden Scale at weeks 4, 8 and 12 post-treatment.

The change in wrist flexor muscle tone as measured by MAS at week 4 compared to baseline was -1.45±0.61 (median -1.00) in the test group and -1.40±0.57 (median -1.00) in the control group. The difference in variation between treatment groups was -0.06 (95% 2-sided CI [-0.23, 0.12], hence the upper limit of the 95% 2-sided CI (0.12) was below the non-inferiority margin set for this study (0.5),

thus verifying that BoNT/A-DP was not inferior to the comparator, [redacted] The inter-group difference in MAS variation at all time points (all p>0.05) was not statistically significant. Also, there was no statistically significant difference in the distribution of global assessment of improvement between treatment groups at each time point (p>0.05). In both groups, the Caregiver Burden Scale score decreased significantly from baseline after treatment ($p \leq 0.01$).

The proportion of subjects who experienced an AE after IMP administration was 20.00% (19/95 subjects, 23 events) in the test group and 25.00% (23/92 subjects, 28 events) in the [redacted] control group, while adverse drug reactions were reported at a frequency of 2.11% (2/95 subjects, two events) in the test group and 1.09% (1/92 subjects, one event) in the control group. A total of six SAEs were reported in six subjects, three in the BoNT/A-DP group (branchial cyst, oedema peripheral and back pain) and three in the [redacted] group (tuberculous pleurisy, facial injury and muscle spasticity), which were mild or moderate in severity and were considered unrelated to the IMP. No clinically significant differences were observed between treatment groups with respect to laboratory tests, vital signs or physical examination and no antibody formation was reported.

The study therefore demonstrated that BoNT/A-DP was not inferior to [redacted] for muscle tone improvement efficacy in subjects with post-stroke upper limb spasticity. Comparative equivalence in safety was also demonstrated, indicating that BoNT/A-DP is safe and effective for the treatment of post-stroke upper limb spasticity.

4.4.2.7 Phase 4 Study HG-BTBPS-12102: Indication; Blepharospasm

Study HG-BTBPS-12102 was a Phase 4 open-label, single-group, multi-center trial which was conducted after the approval of BoNT/A-DP (Botulax) in Korea. Subjects were included who were diagnosed with essential blepharospasm and had a spasm severity of 2~4 (according to Scott's method). The full analysis set comprised 102 subjects. The total dose varied between 12.5 and 60 units maximally per subject and was adapted based on the severity of spasms and symptoms.

The primary endpoint was the rate of subjects with an improvement of one grade in severity of spasm (Scott's method) at week 4 post-treatment. Secondary endpoints were also assessed 4 weeks post treatment and included the following: the duration of treatment effect, changes of severity of spasms, rate of subjects with grade 0 or 1 severity and the rate of subjects with more than 2 grades improvement.

The primary endpoint, which was the rate of subjects with an improvement of one grade in severity of spasm (Scott's method) at week4 post-treatment was met by 87 of 91 (95.6%) subjects in the per protocol data set. Response to BoNT/A-DP treatment was non-inferior to results from other botulinum toxin A products, assuming a reference value of 92.28%, a non-inferiority margin of -10% and a 95% CI. Of the 91 subjects included in the per protocol (PP) analysis, 81 subjects (89.01%) were retreated with the IMP. The mean duration of drug effect was 108.53 (±1.65) days. A total of 69 subjects (75.82%) showed an improvement to grade 0 or 1 and an improvement in severity of spasm of up to two grades.

Among the full analysis set (FAS), which included 101 subjects, 61 AEs were observed in 41 subjects (40.59%). Among these, 30 AEs in 23 subjects (22.77%) were classified as related to the study drug. Only 1 AE (1.64%) was evaluated as grade 2 in severity, while the remaining 60 AEs (98.36%) were judged as grade 1. Physical examination showed 3 single findings at one visit. One SAE, judged

unrelated to study drug, was reported in 1 subject, which comprised a case of leukaemia, where the subject suffered abdominal pain and was hospitalized due to sepsis.

The results of this Phase 4 study confirm the efficacy and safety of BoNT/A-DP in treatment of subjects with blepharospasm, consistent with the results of the Phase 3 study (HG-06-01) and the extension study (HG-01-08).

Table 4-2 Description of Clinical Safety and Efficacy Studies Performed with BoNT/A-DP

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
Glabellar Line										
HG-11-01 Phase 3 Glabellar lines	Korea Multi-center	Status: Completed Start Date: 01.08.2011 Completion Date: 05.06.2012 LPO: 08.03.2012	R, DB, AC, P	BoNT/A-DP20U; o[redacted] 20U, i.m.	To evaluate safety and efficacy of BoNT/A-DP compared with [redacted] for treatment of moderate to severe glabellar lines	134 verum 137 control	One admin. 16 weeks follow up	224 female, 44 male Age: 48 +/- 9.6(21 to 65)	Male/ female adults aged between 18 and 65. Subjects with moderate to severe glabellar lines rated grade 2-3 by physician's rating line severity at maximum frown.	Responder rate at Week 4 by physician's rating line severity at maximum frown. Two-sided 95% confidence interval for the difference of Responder rate calculated by method of Chow.

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-13-02 Botulax Inj. Post-Marketing Surveillance in patients with moderate to severe Glabellar Lines.	Multi-center Korea	Status: Completed Start date: 26.11.2013 Completion date: 01 Nov 2016	Post-Marketing Surveillance	BoNT/A-DP 20U; i.m.	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators muscle and/or procerus muscle activity in adults	815 subjects	One admin. 4 weeks follow up	Male or female subject 18 to 65 years	Male/female adults between 18 and 65. Patients with moderate to severe glabellar lines associated with corrugator muscle and procerus activity.	Responder rate at Week 4 by physician's rating line severity at maximum frown

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
CPH-301-201030 Phase 3 study in subjects with glabellar lines	Centers in Europe and US	Status: Completed Start Date: 21.3.2016 LPO: 16.11.2017	1st cycle R, DB, PC, 2nd to 4th cycle OL, S	BoNT/A-DP 20U or placebo i.m.	To compare the safety and efficacy of BoNT/A-DP with placebo in reducing the severity of glabellar lines based on investigator and subject assessment. Also to assess safety and efficacy after repeat treatments.	529 subjects active treatment, 175 subjects per placebo arm	Administration of first dose in comparison with placebo, followed by an open label extension with possibility to receive three additional doses over a period of up to 62 weeks per subject (FSI - LSLV 23 months)	Male or female subject 18 to 75 years	Moderate to severe glabellar lines as assessed by the investigator and the subject. Glabellar lines have a psychological impact on the subject	Responder rate by investigator- and subject assessment at maximum frown at week 4 after treatment by injection (composite endpoint).

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
CPH-302-201030 Phase 3 study in subjects with glabellar lines	Centers in US	Status: Completed Start Date: 12.4.2016 LPO: 10.10.2017	1st cycle R, DB, PC, 2nd to 4th cycle OL, S	BoNT/A-DP 20U or placebo i.m.	To compare the safety and efficacy of BoNT/A-DP with placebo in reducing the severity of glabellar lines based on investigator and subject assessment. Also to assess safety and efficacy after repeat treatments.	160 subjects active treatment, 53subjects per placebo arm	Administration of first dose in comparison with placebo, followed by an open label extension with possibility to receive three additional doses over a period of up to 62 weeks per subject (FSI - LSLV 23 months)	Male or female subject 18 to 75 years	Moderate to severe glabellar Lines as assessed by the investigator and the subject.	Responder rate by investigator- and subject assessment at maximum frown at week 4 after treatment by injection (composite endpoint).

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
CPH-303-201400 Phase 3 study in subjects with glabellar lines	Centers in US and EU	Status: to be started	1st cycle R, DB, PC, 2nd to 4th cycle OL, S	BoNT/A-DP 20U or placebo i.m.	To compare the safety and efficacy of BoNT/A-DP with placebo in reducing the severity of glabellar lines based on investigator and subject assessment. Also to assess safety and efficacy after repeat treatments.	353 planned	Administration of first dose in comparison with placebo, followed by an open label extension with possibility to receive three additional doses over a period of up to 62 weeks per subject (FSI - LSLV 23 months)	Male or female subject 18 to 75 years	Moderate to severe glabellar Lines as assessed by the investigator and the subject.	Responder rate by investigator- and subject assessment at maximum frown at week 4 after treatment by injection (composite endpoint).

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
Blepharospasm										
HG-06-01 Phase 1 and 3 Blepharospasm	Multi-center Korea	Status: Completed Phase 1 Start Date: 4.12.2007 Phase 3 start date: 21.04.2008 Completion Date: Phase1: 23.12.2009 LPO: 14.08.2008 Phase 3: - 23.12.2009 LPO - 24.07.2008	R, DB, AC, P	12.5 to 60U per subject (BoNT/A-DP or [redacted]®) i.m.	To evaluate the efficacy of the study drug in subjects with essential blepharospasm.	Verum: 121, active control:104	One administration 24 weeks follow up	54 male and 171 female Age 61.4 +/- 9.03(21 to 81)	Adults of above age 18 and below age 75 Subjects with essential blepharospasm of which degree of spasm is Grade 2 ~ 4 (Scott method)	Safety &Efficacy rate after administration.The drug was consider effective when symptoms were improved by more than 1 Grade when evaluated at 4 weeks after drug administration using Scott's scale.

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-08-01 Extension to study (HG-06-01) **Phase 3** Blepharospasm	Multi-center Korea	Status: Completed Start Date: 04.08.2008 Completion Date: -08.03.2011 LPO 22.12.2009	R, DB, AC, P	12.5 to 60U per subject(BoNT/A-DP or [redacted]) i.m.	To evaluate the duration of the effect of the study drug after the second dose in subjects with essential blepharospasm.	77 verum and 82 control	Subjects received a single dose of the study (2nd dosing) and were observed for up to 24 weeks.	41 male 118 female Age 61.8±8.7 (22 to 75)	Subjects who have entered HG-06-01, received the study drug (either the test drug or comparator), and completed the study according to the protocol	The number of days elapsed between the 2nd dosing of the study drug (test drug or comparator) and the administration of [redacted] or other comparable surgical intervention due to recurrence of blepharospasm symptoms
HG-BTBPS-12102 Phase 4 Blepharospasm	Multi-center Korea	Status: Completed Start Date: 07.03. 2013 Completion Date: 28.08.2014	Phase IV OL, S	12.5-60 U per patient BoNT/A-DP	Efficacy and safety showing that BoNT/A-DP is not inferior to [redacted]	102	1 admin. 16 weeks follow up	Both gender (24-78)	Adults of above age 18 and below age 75 Patients with essential blepharospasm, degree of spasm is Grade 2 ~ 4 (Scott method)	Response rate of subjects with an improvement of more than one grade ar 4 weeks post-injection

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-10-01	Multi-center Korea	Status: Completed Start Date: 05.02.2011 Completion date: 06.03.2017	Post-Marketing Surveillance	12.5-60 U per patient BoNT/A-DP	(1)Serious adverse events/adverse drug reactions (2)Unexpected adverse events/ adverse drug reactions not reflected in the precautions for use (3)Known adverse drug reactions (4)Non-serious adverse drug reactions (5) Other safety and efficacy information	243	1 admin. 4 weeks follow up	Both gender	Adults aged 18 and older with benign essential belpharospam	Efficacy will be assessed based on the symptom treatment rate, that is, the percentage of subjects with alleviated symptoms at Week 4 of treatment by at least 1 grade of Scott`s scale.

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-13-03 Phase 4 Blepharospasm	Multi-center Korea	Status: Completed Start Date: 17.04.2014 Completion date: 03.05.2016 LPO: 10.2015	OL, S	12.5-60 U per patient BoNT/A-DP	Efficacy and safety showing that BoNT/A-DP is not inferior to [redacted]	102	1 admin. 16 weeks follow up	Both gender	Adults aged 18 and older with benign essential belpharospam	The result was determined as Effective or Ineffective (determined as Effective in case of improvement of ≥1 grade by Scott's Description at Post-treatment Week 4) and this study was declared successful if the lower limit of the 95% confidence interval of the difference between the reference value (92.28%) and the study group effective rate was ≥-10%, i.e., a non-inferiority margin.

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-BOT-IV3 Phase 4 Blepharospasm	Multi-center Korea	Status: Completed Start Date: 17.06.2015 Completion date: 23.06.-2016 LPO: 01.2016	OL, S	12.5-60 U per patient BoNT/A-DP	Efficacy and safety showing that BoNT/A-DP is not inferior to [redacted]	232	1 admin. 16 weeks follow up	Both gender	Adults aged 18 and older with benign essential belpharospam	Change in JRS total score at Week 4 after treatment from baseline
Pediatric cerebral palsy										

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-11-02 Phase 3 Pediatric cerebral palsy	Multi-center Korea	Status: Completed Start Date: 26.03.2012 Completion Date: 24.11.2014 LPO 02.06.2014	R, DB, AC, P	1. bilateral palsy, the investigational products are administered to both legs at a dose of 6U/kg body weight (3U/kg for each leg). 2. unilateral palsy, the investigational products are administered to the rigid leg at a dose of 4U/kg body weight. 3.maximal exposure 200 U i.m.	This study aims to evaluate the safety and efficacy of "Botulax Inj. (study drug)" versus [redacted] Inj. (control drug)" for improving equinus deformity in children with cerebral palsy.	144 cases (study group: 72, control group: 72)	One administration and 24 week follow-up	Both genders, Planned age range 2-10 years	1.Subject diagnosed with spastic cerebral palsy 2.Subject with dynamic equinus foot deformity 3.Subject with GMFCS Level I, II or III	Responder rate of subjects whose PRS score increased by two or more points 12 weeks after administration of the Investigational Medicinal Products compared to that at Baseline.

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HGPV-16-02 Botulax Inj. Post-Marketing Surveillance (pediatric cerebral palsy patient aged 2 or above with dynamic equinus foot deformity by spasticity)	Multi-center Korea	Status: Ongoing Start date: 24.06.2016	Post-Marketing Surveillance	Up to 6U per kg BoNT/A-DP, maximal exposure 200 U i.m.	1)Serious adverse events/adverse drug reactions (2)Unexpected adverse events/ adverse drug reactions not reflected in the precautions for use (3)Known adverse drug reactions (4)Non-serious adverse drug reactions (5) Other safety and efficacy information(Distance spreading of Toxin)	600 subjects planned	One administration and 12 week follow-up	Both genders, ≥2 years old	pediatric cerebral palsy patient aged 2 or above with dynamic equinus foot deformity by spasticity	Change in PRS score at Week 12 after treatment from baseline

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
Post stroke upper limb spasticity										

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-13-01 Phase 3 Post stroke upper limb spasticity	Multi-center Korea Prof. Min-Ho Jeon and others	Status: Completed Start Date: 26.08.2013 Completion Date: 15.11.2014 LPO 05.2014	R, DB, AC	Maximum of 360 U BoNT/A-DP or [redacted]®. i.m	To evaluate efficacy, safety and non-inferiority of BoNT/A-DP compared to [redacted] for improvement of muscle tone pre-dose versus post - dose in subjects with Post - stroke upper limb spasticity	94 verum and 92 control	One administration and 12 week follow-up	Male or female subject (35 - 75 years)	≥ 6 weeks since last stroke, ≥ 2 points in focal spasticity of wrist flexor, ≥ 1 points at least 1of elbow flexor and finger flexor as measured on MAS(0 to 4) Targeted functional disability item with a rating of 2 or greater on disability assess. scale) (0 to 3)	Change from Baseline at Week4 for wrist flexor muscle tone as measured on the MAS (Modified Ashworth Scale)

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HGPV-16-01 Botulax Inj. Post-Marketting Surveillance (Muscle spasticity: For adult patients aged 20 or above with post stroke upper limb spasticity)	Multi-center Korea	Status: Ongoing Start date: 29.04.2016	Post-Marketing Surveillance	Maximum of 360 U BoNT/A-DP	1)Serious adverse events/adverse drug reactions (2)Unexpected adverse events/ adverse drug reactions not reflected in the precautions for use (3)Known adverse drug reactions (4)Non-serious adverse drug reactions (5) Other safety and efficacy information	600 subjects planned	One administration and 12 week follow-up	Male or female subject >20 years old	Muscle spasticity: For adult patients aged 20 or above with post stroke upper limb spasticity	Change in MAS score at Week 4, 12 after treatment from baseline
Crow`s Feet Lines										

Protocol No. / Phase / Indication	Number/ Location of Centers	Study Status: Start Date: Completed. Date:	Design Control Type	Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Random/ Total	Treat-ment Duration (Max)	Gender Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Endpoints
HG-BOTCFL-III1 Phase 1 and 3 Crow`s Feet Lines	Multi-center Korea	Status: Ongoing	DB, R, AC	Maximum of 24 U BoNT/A-DP or [redacted] i.m	To assess safety and efficacy of Botulax as compared with [redacted] in subjects with Moderate to Severe Crow`s Feet Lines	240 planned	One administration and 16 week follow-up	Male or female subject	1. Male or female of at least 19 to 65 years old 2. Bilaterally symmetrical moderator-to-severe CFL at maximum smile on the FWS as rated by the investigator	After 4 weeks of administration, percentage of participants achieving None or Mild on the investigator's assessment of the severity of crow's Feet lines (CFL) at maximum smile using the facial wrinkle scale (FWS).

DB=double blind; PB=Subject blinded; P=parallel group; PC=placebo-controlled; R=randomized; AC=Active control; i.m=intramuscular; OL=open label; S=single arm, LPO: last patient out
*PMS for essential blepahrospm: recruiting plan were 600 cases according protocol, however due to recruitment problems additional three Phase IV studies (HG-BTBPS-12102, HG-13-03, HG-BOT-IV3) have been conducted. The reaming 243 cases were obtained via post marketing surveillance.

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4.4.2.8 Post Marketing Safety Data

BoNT/A-DP (Botulax®) was first authorized to Hugel at a dose of 100 U in the Republic of Korea on 13 Mar 2009 and is also authorized at doses of 50 U, 150 U, and 200 U. BoNT/A-DP is also authorized in 24 other countries (Azerbaijan, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Georgia, Guatemala, Honduras, India, Kuwait, Mongolia, Panama, Paraguay, Dominican Republic, Peru, Philippines, Russia, Thailand, Ukraine, Uruguay and Vietnam).

According to information by the Korean manufacturer overall 9,054,819 vials (50 U, 100 U, 150U or 200 U) of BoNT/A-DP have been distributed during the period between March 13, 2009 to September 2018, (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Approval was obtained in Korea (on April 29, 2016) for 150 U Botulax® for the treatment of muscle spasticity in adult patients aged 20 or above with post stroke upper limb spasticity and (on June 24, 2016) for the treatment of equinus foot deformity in children with cerebral palsy.

Table 4 3 Cumulative and Interval Post-Marketing Exposure to BoNT/A DP

*Export to Japan for use on named patient basis

*Export to Japan for use on named patient basis

Year/ U per vial	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018 (until Q3)
100	4,515*	59,091	139,057	160,989	286,513	314,909	566,655	1,072,020	1,939,778	1,265,831
50				33,877	90,510	152,789	115,069	137,374	159,686	139,965
200		7,325	4,031	47,899	119,114	284,061	208,572	427,536	631,669	662,088
150								43	10,488	13,365

*Export to Japan for use on named patient basis

Table 4-3 Cumulative and Interval Post−Marketing Exposure to BoNT/A-DP

Hugel, the marketing authorization holder (MAH) in the Republic of Korea for BoNT/A-DP (Botulax®), prepared a PSUR for the reporting period 14 Mar 2017 to 13 Mar 2018. No SAEs were reported in the post-marketing glabellar lines study HG-13-02 in the reporting interval or cumulatively.

The PSUR reported that no new risk minimization activities were considered necessary.

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In conclusion, on the basis of spontaneous reports, post-marketing drug use investigations and phase 4 clinical trials, the product's efficacy and safety have been confirmed and no particular safety signal was observed. Collection of information on adverse events, adverse drug reactions and efficacy will be continued to identify factors potentially affecting safety and efficacy and to assure safety of the product. Currently further clinical studies are ongoing in Korea for the indications of Crow`s feet (lateral canthal lines; Phase I/III), muscle spasticity (post market surveillance) and cerebral palsy (post market surveillance), in accordance with Korean regulations.

Overall drug safety is similar to that reported for other BoNT/A products.

4.5 Study Rationale

As outlined in the Clinical Summary (Section 4.4.2), BoNT/A-DP should be a valuable option for the treatment of glabellar lines and other indications. BoNT/A-DP has been shown to be safe and well tolerated when administered at doses up to 360 U, which is well above the 20 U dose planned for use in this study. The current Phase 3 study is designed as a randomized double blind study to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, followed by an open label extension study to evaluate efficacy after repeat treatments and long term safety. Data obtained from this study (and from BLESS I and BLESS II) will provide evidence of efficacy and subject safety in controlled clinical trial setting and will be used for registration purposes. The dose rationale for this study is described in Section 4.5.1.3.

4.5.1.1 Study Design Justification

This will be a multicenter, double blind, placebo-controlled study, followed by an open label extension. The study will take place in the US and EU.

To allow all subjects to profit from treatment and to obtain adequate safety data for BoNT/A-DP treatment, the study will be comprised of two parts. The first part will comprise a double blinded treatment cycle comparing BoNT/A-DP with placebo (ratio 3: 1 respectively) and will be used for the determination of primary and key secondary efficacy endpoints. The 3:1 ratio was selected to increase the number of subjects on active IMP, thus extending the safety database and still providing a sufficient number of placebo subjects for relevant comparisons in efficacy and safety. The second part of the study will be an open label safety extension, in which all subjects (regardless of initial treatment group assignment) will receive BoNT/A-DP, to assess long term safety of the treatment and efficacy after repeat treatments.

A total of 353 subjects will be enrolled, which should allow for a precise estimate of response rate and for post-hoc sensitivity analyses.

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4.5.1.2 Justification for Schedule

The study schedule includes a maximum of four permitted treatments per subject(four treatment cycles), separated by a minimum interval of 12 weeks, during the study time frame of up to 60 weeks in treatment phase. A minimum interval of 12 weeks between treatments was selected, since the median duration of effect has been reported to be 85 days (12.1 weeks) [31] and this treatment interval has been evaluated in several repeat treatment studies[32,33].

However, since treatment duration of 120 days [34], 17.1± 6.5 weeks [35] or four to six months[36]have been reported and re-treatment intervals have been estimated at a mean of 3.9 months[36], the schedule has been devised flexibly such that subjects can obtain re-treatment when they qualify (according to the "Eligibility Criteria for Re-treatment" Section 7.3), which can be at week 12 at the earliest or at four weekly intervals thereafter. Hence, the duration of effect of BoNT/-DP will be evaluated in the first treatment cycle compared with placebo. The duration of effect of BoNT/-DP after repeat treatment will be assessed in the open label extension study. The duration of effect has been reported to increase with repeat treatment[37].

4.5.1.3 Dose Justification

The dose selected is 20 U, where 1U is defined as "the calculated median intraperitoneal lethal dose (LD_{50}) in mice". Study HG-11-01 performed in South Korea demonstrated that a dose of 20 U BoNT/A-DP per treatment was safe and highly efficacious in the treatment of glabellar lines, with reported responder rates similar to those of the [redacted] comparator product administered at the same dose (20 U). The potency units of botulinum toxins for injection are specific to the preparation and assay methods utilized and are not interchangeable with other preparations[38](historical data with similar products have confirmed the efficacy of a 20 U dose and current safety recommendations favour the use of such small doses[39];FDA Guidance for Upper Facial Lines).

4.6 Evaluation of Anticipated Risks and Benefits of the Investigational Medicinal Product to Human Subjects

4.6.1 Possible Benefits for the Subject

The benefit of participation in this study is the expected reduction in the severity of glabellar frown lines after treatment with BoNT/A-DP. Since the subjects recruited are also negatively impacted psychologically by their glabellar lines, it is anticipated that treated subjects will benefit in terms of quality of life (emotional and social functioning; improved self-perception). Subjects receiving placebo for the first treatment cycle will benefit from free medical screenings and follow-up provided to all study subjects and will benefit from treatment when they enter the open label study.

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4.6.2 Possible Risks/Inconveniences for the Subject

Botulinum toxin drug products present a unique set of safety concerns related to the potential for local and distant spread of toxin effect. Therefore, an active evaluation of subjects for signs and symptoms of local and distant spread of toxin effect will be performed throughout the study at each study visit. Subjects will be warned about signs of the spread of toxin effects including asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, breathing difficulties and possible adverse events of special interest (AESIs, please see Section 11.1). Respiratory, speech or swallowing difficulties can also result, which could be life threatening, however no definitive SAE reports of distant spread of toxin effect associated with cosmetic or dermatologic use of botulinum toxin at the labeled dose of 20 U (for glabellar lines) or 100 U (for severe primary axillary hyperhidrosis) have been reported to date. Baseline physical examinations will also be conducted to rule out pre-existing neurological or muscular deficiencies. In addition, key safety measures such as vital signs and pregnancy tests (where appropriate) will be conducted at suitable intervals to ensure no participating subjects are pregnant.

As is the case with all injected products, injection site reactions such as pain, tenderness, redness, induration and/or swelling may occur after administration. In addition, a number of other symptoms have been experienced by single subjects including pruritus, hypertonia, ptosis, headache, diplopia, edema and blurred vision. The most frequently observed injection site reactions were injection site pain and swelling. The vast majority of AEs were rated as mild.

In addition, as with any IMP, there may be unforeseeable risks associated with the use of BoNT/A-DP or placebo control. As a side effect of drawing blood, pain, hematoma, and in very rare cases an infection at the venipuncture site may occur.

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5. STUDY PURPOSE AND OBJECTIVES

5.1 Study Purpose

The purpose of the study is to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, including efficacy after repeat treatments and long term safety.

5.2 Primary Objective

To assess the efficacy of BoNT/A-DP in reducing the severity of glabellar frown lines following treatment (compared with placebo) based on investigator and subject assessment at week 4 (of the first treatment cycle).

5.3 Secondary Objectives

1. To assess the proportion of responders at maximum frown and at rest at various time points after each treatment, based on investigator and subject assessments.
2. To assess the psychological impact of BoNT/A-DP treatment on subjects (in terms of emotional and social functioning and concerns relating to their glabellar lines) in comparison with placebo after a single treatment.
3. To assess onset of effect and the duration of effect (at maximum frown) after a single treatment with BoNT/A-DP compared with placebo (first treatment cycle), based on investigator and subject assessments.
4. To provide long term safety data of BoNT/A-DP based on multiple treatment cycles and to establish a sufficient safety database to support regulatory approval.
5. To assess subject perceptions of effect of, and satisfaction with, treatment in comparison with placebo (first treatment cycle) and during the open-label extension phase.

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6. STUDY DESIGN

6.1 Brief Summary

This multicenter Phase 3 study is comprised of two parts. The first part of the study is a randomized, double blind, placebo-controlled, phase which aims to demonstrate efficacy and safety of BoNT/A-DP compared with placebo. The second part is an open label extension phase to evaluate efficacy after repeat treatments and long term safety.

Subjects can receive a maximum of four treatment cycles over the duration of the study, a single treatment in the first cycle compared with placebo, and up to three subsequent treatments in the open label extension study.

Based on historical data with similar products, it is anticipated that there will be a significant difference in responder rates between BoNT/A-DP and placebo in the first treatment cycle[11,40,41] and it is anticipated that the duration of effect in subjects administered the active treatment will last approximately 12 weeks[36].

6.2 Overall Study Design

The study is a parallel-group, randomized, double blind, placebo-controlled study followed by an open label extension.

6.3 Population to be studied

A total of approximately 353 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.

6.3.1 First Treatment Cycle

The first treatment cycle of the study will comprise two treatment groups as follows:

- Group A (active): BoNT/A-DP (20 units, 0.5 mL).
- Group B (placebo control): sterile, 0.9% sodium chloride (0.5 mL).

An interim Analysis will be performed when all subjects finalized the double blind phase re-evaluation for retreatment visit at week 16 of the first treatment cycle or completed the double blind phase (whichever occurs earlier).

Eligible subjects will be randomized at baseline (day 0) to Group A or B to receive the first treatment in a 3:1 randomization scheme, respectively. 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 should assess the subject at baseline and at the visits at weeks 1, 2 and 4 in the first treatment cycle.

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After a screening period of up to 14 calendar days, subjects will receive the first treatment (BoNT/A-DP or placebo) and attend for visits at 1, 2 and 4 weeks after treatment and at 4-weekly intervals thereafter for evaluation of efficacy and safety (primary and key secondary efficacy endpoints will only be evaluated in the first treatment cycle in comparison with placebo). Re-screening will not be permitted.

The effect of botulinum toxin typically lasts a few months, hence the first treatment cycle will last at least 12 weeks and will end when the subjects qualify for re-treatment (in accordance with the "eligibility for re-treatment criteria" as outlined in Section 7.3). Efficacy duration of four to six months[36] or 17.1 ± 6.5 weeks[35] have been reported from other studies, hence the study is designed flexibly to adequately assess the duration of effect compared with placebo in the first treatment cycle.

6.3.2 Open Label Extension

After the first treatment cycle is completed, all subjects may enter the open label extension phase and will be dosed with BoNT/A-DP (20 U) for subsequent re-treatments.

Subjects will attend for visits at 1 and 4 weeks after re-treatment and at 4-weekly intervals thereafter. Additional telephone call follow-ups will take place in the open label extension phase two and eight weeks after each re-treatment. Each re-treatment cycle will last at least 12 weeks and will end when the subject qualifies for re-treatment (in accordance with the "eligibility for re-treatment criteria" as outlined in Section 7.3) or with the End of Study visit (see below). According to the study schedule (Section 2.2), a maximum of 4 treatments per subject (4 treatment cycles) is permitted during the study time frame, with treatments separated by a minimum of 12 weeks.

A subject may move to the next treatment cycle if more than 12 weeks have passed since the previous treatment. Starting at week 12 and at 4-weekly intervals thereafter, subjects will attend the site for the Evaluation for Re-treatment visit. If the subject has a FWS score (at maximum frown) of ≥ 2, as determined by both the subject and the investigator, this visit on the same day at the same site visit will then be considered the End of Cycle visit and all other criteria required to determine eligibility for re-injection will be assessed e.g. negative urine pregnancy test (in women of child-bearing potential), lack of infection or inflammation in the planned injection area etc. Furthermore, all additional tests e.g. laboratory tests required for final cycle assessment will be performed (as outlined in the Schedule of events, Section 2.1). If the subject qualifies for re-treatment, on the same day at the same site visit, the subject will then enter the next treatment cycle and will receive the next study drug treatment as part of the Re-Treatment visit (i.e. day 0 of the next treatment cycle).

If the FWS score (at maximum frown) is assessed as ≥2 by both the investigator and the subject, but the additional criteria for reinjection are not met, e.g. relevant infection or inflammation at the injection site, the subject may attend for a visit 4 weeks thereafter. Subjects with a positive pregnancy test, or subjects who do not agree to re-treatment, will be withdrawn from the study and the End of Study visit will be conducted at the earliest opportunity.

If at an Evaluation for Re-treatment visit the subject wants to get re-treated, but the investigator does not agree or vice versa (i.e. the FWS score is not ≥ 2 by both assessments), the subject will return to the site 4 weeks thereafter for another Evaluation for Re-treatment visit. There is no limit to the number of Evaluation for Re-treatment visits. In order to consider a visit as the End of Cycle visit, there must always be agreement between investigator and subject on a FWS score (at maximum frown) of ≥2.

6.3.3 End of Study Visit

The End of Study visit can take place in four-weekly intervals from study-week 48 until study-week 60. The last study drug re-treatment will be administered no later than week 48. For subjects receiving a re-treatment at week 48, the last cycle will end 12 weeks later at week 60 (i.e. End of Study visit).

The End of Study visit will take place at week 48, if the week 48 visit is an Evaluation for Re-treatment visit and the subject does not meet the criteria for re-treatment i.e. this visit is 12 or more weeks after the last treatment. As week 48 is the last possible time point for re-treatment, such subjects will continue with all additional assessments of the End of Study visit on the same day. For subjects having received their last injection 8 weeks or less prior to week 48, the End of Study visit will take place 12 weeks after the last study drug treatment was given, e.g. week 52 if the subject was re-treated at week 40.

For subjects who are prematurely discontinued from the study (at any time), the End of Study visit will take place within 1 week of discontinuation.

The number of treatments administered per subject will depend on the subject's qualification for re-treatment. A maximum of four study treatments may be administered per subject, with the last opportunity for re-treatment being week 48. A subject will be followed-up until he/she would qualify for re-treatment (if below 48 weeks), since there is no maximum time frame for re-treatment.

6.3.4 Numbering of Visits

Visit numbers correspond with specific treatment and assessments as outlined in the Schedule of Events, Section 2.1. If subjects are not eligible for re-treatment at the "Evaluation for Re-treatment" visit, they will return at 4-weekly intervals thereafter, until they are eligible for treatment. The subsequent visit number for the cycle will remain the same, but will be amended with "a, b, c" etc., corresponding to the time extended (at 4-weekly intervals) in that treatment cycle. For example, the first evaluation for re-treatment is at visit 7, week 12; however for subjects who are not eligible at week 12, but at week 16, this visit will be denoted visit "7a", while "visit 7b" will denote week 20 in the first cycle and "visit 7c" will denote week 24 etc., with each additional letter corresponding to a time point 4 weeks later in that cycle. This approach will enable the visit numbers to be standardized, while allowing flexibility to assess the duration of efficacy in the first treatment cycle and in the open label extension.

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6.3.5 Allowed Time Deviations per Visit

A time deviation of ± 5 days is allowed for each visit (including telephone visits), except for the week 1 and week 4 visit in each treatment cycle, where a time deviation of ± 2 day is permitted. Sites must adhere to the schedule of events and visit windows and subjects must ensure they are available for those visits. Any deviation from the visit schedule and its associated time windows will still be documented as a protocol deviation.

6.3.6 Duration of Study Period and Subject Participation

Subjects will participate in this study for a duration of 50 to 62 weeks from signing the informed consent form (ICF) to the End of Study visit (i.e. up to 14 calendar days for screening, followed by 48 to 60 weeks study participation).
Subjects will receive a maximum of four permitted rounds of treatment, with a minimum interval between treatments of 12 weeks.

6.4 Outcome Measures

6.4.1 Primary Outcome Measure

6.4.1.1 Efficacy

The primary efficacy endpoint is the proportion of subjects among BoNT/A-DP and placebo groups with a FWS score of 0 or 1 and an improvement ≥2 points in FWS score (at maximum frown) at the week 4 visit (of the first treatment cycle) relative to baseline (responders), based on both the investigator's and the subject's in-clinic assessments. Thus, the primary endpoint is a composite endpoint comprising investigator and subject assessments of treatment effectiveness.

6.4.2 Secondary Outcome Measures

6.4.2.1 Key Secondary Efficacy Endpoint

1. The extent of change in psychological impact (emotional and social functioning and concerns relating to their glabellar lines) at week 4 after the first treatment, in the BoNT/A-DP group in comparison with placebo, relative to baseline, as assessed by the modified Skindex-16 (Glabellar Line Quality of Life Scale [GL-QoL]) and the FACE-Q (Appraisal of Lines Between Eyebrows scale and Age Appraisal Visual Analog Scale (VAS)), respectively.

6.4.2.2 Additional Secondary Endpoints

2. The percentage of responders at maximum frown (as defined in 6.4.1.1) at week 12 (after the first treatment with BoNT/A-DP or placebo).
3. The percentage of responders at week 16 (after the first treatment).
4. The percentage of responders at week 20 or later (after the first treatment).

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5. The proportion of subjects with a ≥ 1 point reduction in FWS score at rest at week 4 in the first treatment cycle, based separately on the investigators' and the subjects' in-clinic assessments (applicable only for subjects who have a FWS score at rest ≥ 1 at baseline).
6. The proportion of responders among BoNT/A-DP and placebo groups with a FWS score of 0 or 1 and an improvement ≥ 2 points in FWS score (at maximum frown) during the first treatment cycle visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments (composite endpoint, at weeks 1, 2 and 8).
7. The proportion of subjects with ≥ 2 point and ≥ 1 point reduction in FWS score (at maximum frown) in the BoNT/A-DP and placebo groups during the first treatment cycle visit relative to baseline, based on the independent rater's assessment of photographs (at baseline and visits 2, 4, 12, 16 and 20 weeks after treatment, within the first treatment cycle).
8. Time to onset of effect in the BoNT/A-DP and placebo groups in the first treatment cycle, as measured at weeks 1, 2 and 4 based separately on subject and investigator assessments. Onset of effect defined as at least a 1 point improvement in FWS score from baseline (at maximum frown). In addition, onset of effect will be assessed by subjects daily in the first 2 weeks after treatment, by recordings in the subject diary.
9. The extent of subject perceptions of effect of, and satisfaction with, treatment, in the BoNT/A-DP and placebo groups, during each treatment cycle, as assessed by the FACE-Q Satisfaction with Outcome Scale.
10. The proportion of subjects with a ≥ 1 point reduction in FWS score at rest in the BoNT/A-DP and placebo groups, relative to baseline, during the first treatment cycle, based on the independent rater's assessment of photos.
11. The percentage of subjects with a FWS score of 0 or 1 and an improvement of ≥ 2 points in FWS score at maximum frown (investigator and subject assessment) at 4 weeks after re-treatment relative to the rating at the preceding end of cycle visit.
12. The proportion of subjects with ≥ 1-point reduction in FWS score (at maximum frown) in the BoNT/A-DP and placebo groups during the first treatment cycle at week 1, 2, 4, 8, 12, 16 and 20 relative to baseline, based on both the investigators'and the subjects'in-clinic assessments.
13. The proportion of subjects with ≥ 1-point reduction in FWS score (at maximum frown) in the BoNT/A-DP group during each re-treatment cycle at week 4 relative to re-treatment-baseline, based on both the investigators'and the subjects'in-clinic assessments.

6.4.2.3 Safety

The secondary safety endpoints include:

1. Frequency, severity and causal relationship of AEs, SAEs and AESIs during the entire study period.
2. Antibody formation, evaluation pre-dose before each treatment, at 4 weeks after each treatment and at the final study visit.
3. Safety assessments by evaluating hematology, clinical chemistry, vital signs and ECGs as per study schedule (Section 2.1).

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6.5 Randomization and Blinding

6.5.1 Randomization

This is a randomized, double blind, placebo-controlled efficacy and safety clinical study followed by an open label extension. Subjects will be randomly assigned to receive either BoNT/A-DP or placebo at a ratio of 3:1 respectively in the first treatment cycle. The 3:1 ratio in favor of active treatment versus placebo has been selected to increase the safety data base.

Randomization will be performed per study site via interactive web response system (IWRS). One unique randomization code will be assigned to each subject.

6.5.2 Blinding

For the first placebo controlled treatment cycle (the double-blind cycle of this trial), BoNT/A-DP and placebo will be provided to the sites in glass vials. Since BoNT/A-DP-vials contain a pellet of lyophilized BoNT/A-DP, they can be discerned from placebo-vials (empty vials). However, after reconstitution by an unblinded study team member at the site, both 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, case report form (CRF) 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 (blinded medication number and batch/lot number during the double-blind phase of the study at the given site). The assigned vial will be reconstituted and will be forwarded to the investigator for injection. Specific Blinding Plans will be created at each study site during the Study Initiation visits. .

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

6.6 Study Stopping Rules

In a case of critical non-compliance of site to the Code of Federal Regulation (Title 21, CFR Part 312), the study protocol, the Declaration of Helsinki, or any applicable regulation, the Sponsor may stop the entire study or participation of a study site at any time. In addition, the Sponsor may stop the entire study, or terminate participation of a study site for any medical reason at any time.

In the event of individual subject's premature study termination resulting from an AE, refer to Section 9.5.

Premature termination of a subject

A subject -must be terminated from the study if any of the following occur:

- Withdrawal of informed consent.
- Treatment with any other investigational product in another clinical study.
- Treatment with any BoNT other than study medication.
- Pregnancy (with follow-up until the end of the current treatment cycle).
- Any significant treatment-related side effects where treatment continuation would constitute an unacceptably high risk for the subject.

Premature termination of a site or of the entire study

A site or the entire study may be terminated if any of the following occur:

- Critical non-compliance to Code of Federal Regulation (Title 21, CFR Part 312), the study protocol, the Declaration of Helsinki, or any applicable regulation.
- The positive benefit/risk ratio is no longer maintained.
- The Sponsor may stop the entire study for any medical reason at any time.
- The Sponsor can terminate the study or a study site at any time for any other reason.

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7. SUBJECT SELECTION, WITHDRAWAL AND DISCONTINUATION

7.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

- Aged ≥ 18 years or older at time of screening (upper limit 75 years, inclusive).
- Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS) as determined by in-clinic assessments by both the investigator and the subject (where: 0= 'none', 1= 'mild', 2= 'moderate', 3= 'severe').[i]
- Subject has a stable medical condition with no uncontrolled systemic disease.
- Female subjects of childbearing potential must test negative for pregnancy and agree to use highly effective birth control during the course of the study.
- Subjects who wear glasses must be able to adequately self-assess the severity of their glabellar lines (according to the FWS), without glasses obstructing the forehead area.
- The moderate to severe glabellar lines have an important psychological impact on the subject as indicated by scores > 0 on either the Emotional or the Social Functioning subscale of the modified Skindex-16 (GL-QoL).

7.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are **NOT** eligible for this study:

- Previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening, or any planned treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment).
- Known hypersensitivity to the study medication or its excipients.
- Any medical condition that may place the subject at increased risk due to exposure to botulinum toxin, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, profound atrophy or weakness in the target muscles, or any other condition (at the investigator's discretion) that might interfere with neuromuscular function or contraindicate botulinum toxin therapy. Facial laser or light treatment, microdermabrasion, superficial peels or retinoid therapy within the 3 months prior to screening or planned during the study.
- Apart from the procedures specified above, previous treatment with any facial aesthetic procedure in the glabellar area (including chemical peeling, injection with biodegradable fillers) within 12 months prior to screening or planned during the study.
- Previous insertion of permanent material in the glabellar area or planned during the study.
- Any surgery, or history of surgery, in the glabellar area including surgical removal of the *corrugator*, *procerus* or *depressor supercilii* muscles or a combination of these or scars in the glabellar area or such surgery planned during the study.
- Active skin disease/infection or irritation at the treatment area.
- Inability to substantially lessen glabellar frown lines even by physically spreading them apart.

[i]Will be assessed at screening and at baseline visits.

- Use of a muscle relaxant within 2 weeks prior to screening, or planned during the study.[ii]
- Marked facial asymmetry or ptosis of eyelid and/or eyebrow, or current facial palsy or neuromuscular junction disorders as judged by the investigator.
- Pregnant, breastfeeding or planning to become pregnant during the trial.
- Use of prohibited medication including anticholinergic drugs, or drugs which could interfere with neuromuscular function, including aminoglycoside antibiotics and curare-like compounds within 2 weeks prior to screening or planned during the study.[iii]
- Planned surgery with general anaesthetic (use of local anaesthetic outside the glabellar area is permitted).
- Participation in another clinical study within 1 month of screening and throughout the trial.
- Previous participation in another botulinum toxin aesthetic study which involved the treatment of glabellar lines in combination with canthal lines and/or forehead lines, within the previous 18 months.
- Chronic drug or alcohol abuse (as per investigator discretion).

7.3 Eligibility Criteria for Re-treatment

The following criteria **MUST** be met for re-treatment:

- At time of re-treatment subject does not have relevant changes to their health status from enrollment, which would have prevented subject's entry into the study according to the inclusion and exclusion criteria.
- The subject must have been randomized to receive treatment and must have received at least one treatment (BoNT/A-DP or placebo).
- A minimum of 12 weeks must have elapsed since the previous study treatment.
- The subject's glabellar lines at maximum frown must have relapsed to a FWS score of 2 or 3 as determined by both the investigator and the subject.
- No relevant infection or inflammation in the planned injection area.
- Negative urine pregnancy test, in women of child-bearing potential.
- The subject must have received fewer than four study treatments.
- The subject must agree and consent to re-treatment.
- Re-treatment will be performed at the latest by week 48.

7.4 Withdrawal and Discontinuation

A subject may voluntarily withdraw from study participation and data collection for any reason at any time (withdraw consent). A subject will be considered lost to follow-up when at least three unsuccessful attempts to contact the subject have been documented.

[ii] Will be assessed at screening and baseline visits.

[iii] Will be assessed at screening and baseline visits.

Every effort will be made to have the withdrawn/discontinued subject complete the End of Study visit (see Section 6.3.3). The reason for withdrawal/discontinuation will be recorded on the CRF (see Section 9.5).

In the event of an AE/AESI/SAE, clinical and/or laboratory investigations that are beyond the scope of the required study procedures may be performed as part of the evaluation of the event. Any subject with an AE, AESI, SAE or clinically significant abnormal laboratory, ECG, or other clinical test values will be evaluated by the investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the investigator, or until values are stable, a plausible explanation has been provided, or the subject has received another injection with botulinum toxin outside the study.

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8. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

8.1 Packaging

The dosage form of BoNT/A-DP is lyophilizate for solution for injection. BoNT/A-DP is provided in single use vials containing50 U/vial. BoNT/A-DP will be reconstituted with a volume of 1.25 mL sterile physiological saline (diluent, as outlined in Section 8.3).

The dosage form of the placebo control is a solution for injection. Empty vials will be provided for placebo but identical in appearance to the BoNT/A-DP vials. At the study site, 1.25 mL of sterile physiological saline will be added to a vial.

8.2 Labeling

In accordance with the valid regulatory requirements for blinded clinical trials, the active drug and placebo control will be labeled similarly for the double blinded part of the study. A different label will be used for the open label extension part of the study. The content of the labels will be in accordance with the applicable regulatory authority requirements.

8.3 Storage and Handling

Unopened BoNT/A-DP must be stored at +2 to +8°C in a refrigerator with a calibrated minimum-maximum thermometer. After reconstitution, the product (in the vial) can be stored under refrigerated conditions (+2 to +8 °C) for up to 24 hours.

Storage at lower or higher temperatures should be avoided. In order to guarantee proper storage conditions, the current temperature and the minimum and maximum temperature since the last reading in the storage refrigerator shall be monitored and documented ideally five times per week, but no less than three times per week. The temperature log will be included in the Trial Master File after study completion. The investigator should immediately report any temperature deviations. In case of any temperature deviation, the IMP must be quarantined and the Sponsor must be contacted immediately for resupply.

After administration to subjects, residual drug in the vial or syringe, together with used vial and syringes must be inactivated by autoclaving, treatment with hypochlorite or be discarded in appropriate containers and disposed of as medical biohazardous waste in accordance with local requirements. Product accountability is addressed in Section 8.3.7.

8.3.1 Administration

8.3.2 Foreign Body Inspection

Prior to use, the vial should be visually inspected by the person responsible for reconstitution, to ensure the product is not discolored and that it is free from foreign particulate matter. In such a case, the product must be replaced via replacement function in IWRS.

In the double blind phase of the study, the person responsible for reconstituting the IMP for administration will be unblinded and must not disclose unblinding information to the investigator or any other blinded member of the study team.

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8.3.3 Dilution

Sterile physiological saline (0.9% sodium chloride solution for injection) will be used as the diluent for reconstitution of BoNT/A-DP and will be added at a volume of 1.25 mL for 50 U. For the placebo control, 1.25 mL of sterile saline will be added to each vial prior to filling syringes. Diluent will be injected slowly into the vial, to avoid foam/bubble formation or vigorous agitation which may cause denaturation. If a vacuum does not pull the diluent into the vial, the vial will be discarded. The date and time of reconstitution will be recorded in the CRF. Reconstituted IMP should be colorless and transparent with no visible particulate matter. The reconstituted drug must be administered within 24 hours, during this time the product will be stored in a refrigerator (+2 to +8°C). A volume of 0.5 mL will be taken from the vial for treatment. **The use of product from one vial or syringe is restricted to one single subject treatment during a single session**.

8.3.4 Dose for Administration

The injection sites should be prepared according to standard clinical procedures.

A volume of 0.5 mL of the properly reconstituted IMP should be drawn into the sterile syringe and any air bubbles in the syringe barrel expelled. The needle used to reconstitute the product should be removed and replaced with a sterile insulin or tuberculin-type syringe of 1 mL volume with 0.01 mL graduation and with the gauge range of 30 to 31G, which the investigator routinely uses for toxin administration. The diluted BoNT/A-DP or placebo will be applied to the injection sites using a sterile 30 to 31 G gauge needle. Each subject will receive a total of five i.m. injections at each injection visit of 4 U/0.1 mL per injection site (i.e. a total of 20 U, 0.5mLactive BoNT/-DP or placebo control), that is, two injections in each *corrugator supercilii* muscle and one injection in the *procerus* muscle with an injection volume of 4U (0.1mL) into each site as shown in Figure 1.

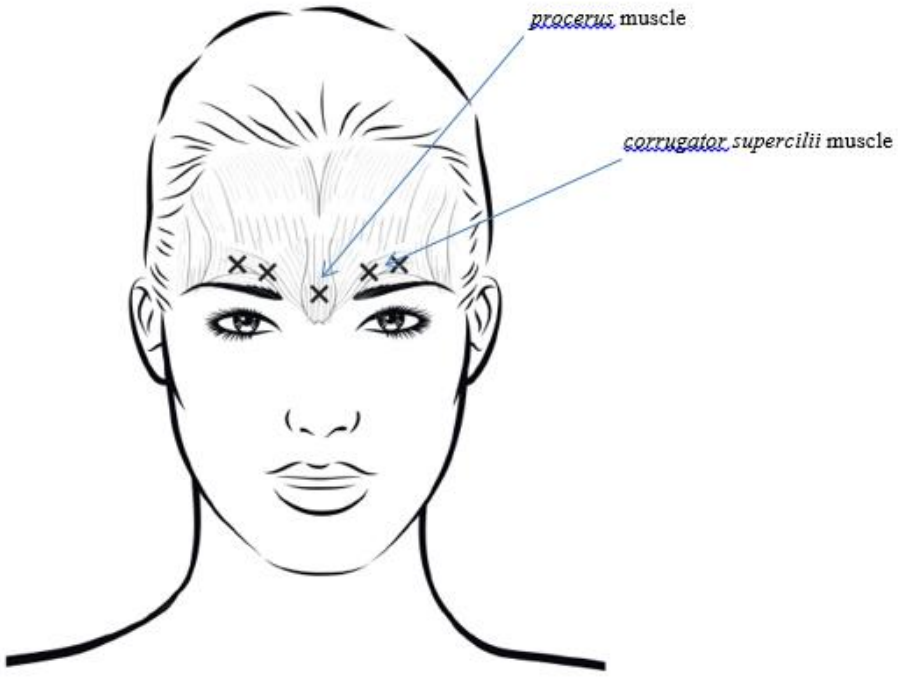

Figure 1 Illustration of proposed injection sites

8.3.5 Method of Administration

The selected injection sites include two sites in each *corrugator supercilii* muscle and one site in the *procerus* muscle. In order to reduce the complication of blepharoptosis, injections near the *levatorpalpebrae superioris* must be avoided, particularly in subjects with large brow depressor complexes. When injecting into two sites of each *corrugator supercilii* muscle, the first injection will be made right above the medial margin of eyebrows. The second injection will be made ca. 1cm above the supraorbital ridge (rigid bony boundaries palpable above the upper part of the upper eyelid) where midlines of the eyebrows meet. The injection site of the *procerus* muscle will be just above the midline of the nasal bridge where horizontal wrinkles are made between the medial end of eyebrows. When injecting into the medial ends of *corrugator supercilii* muscles and on the midlines of the eyebrows, the injection sites will be at least 1 cm away from the supraorbital ridge (rigid bony boundaries palpable above the upper part of the upper eyelid).

Injections will be made with caution to avoid intravascular injection. Before injecting the test drug or placebo control, a thumb or an index finger will be placed firmly below the orbital rim to prevent drug effusion to this area. The needle will be oriented superiorly and medially and

the exact amount of drug will be injected. Additional information regarding administration can be found in the Study Reference Manual/Operational Manual.

8.3.6 Description of Treatment

The subject will receive five injections (4U per 0.1 mL injection) per treatment visit (total dose of 20 U, 0.5 mL) at a minimum interval of 12 weeks, for a maximum of four treatments during the study. Subjects randomized to receive placebo will receive placebo for their first treatment and may enter the open label extension after the first treatment cycle and receive BoNT/A-DP for the subsequent treatments. The treatment schedule is illustrated in Section 2.2.

8.3.7 Investigational Medicinal Product Accountability

The investigator will ensure that the required storage conditions as specified in the Section 8.3 are guaranteed at the investigational site, as described in the Site Specific Blinding Plan. Authorized unblinded study personnel will maintain accurate records of the receipt of all blinded IMP shipped by the Sponsor (for the double blind portion of the study), including date received, drug identity code, date of manufacture or expiration date, amount received and disposition. In the open label extension phase of the study, IMP can be handled by any study team member delegated this task. IMP must be dispensed only at the study site as specified in the protocol (see Section 8.3). Records will be maintained that include the subject identification code (SIC), the dispensation date and amount of IMP dispensed. The IMP must be dispensed only at the institution specified for each site. After reconciliation by the clinical monitor, all remaining unused unreconstituted IMP will be returned to the Sponsor, or destroyed at site with the permission of the Sponsor, in accordance with applicable law and study site procedures. Partially used reconstituted IMP will be destroyed after use (e.g. autoclaved, treated with hypochlorite or discarded in appropriate containers and disposed of as medical biohazardous waste). If unused unreconstituted IMP is to be destroyed by the site, the investigator will provide documentation in accordance with Sponsor's specifications.

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9. STUDY PROCEDURES

9.1 Informed Consent and Enrollment

Any subject who provides informed consent (i.e. signs and dates the ICF) and has been proven eligible during screening will be considered enrolled in the study. Study procedures cannot commence until the subject has undergone the informed consent process and signed the ICF.

Efforts will be made to include subjects with a diversity of Fitzpatrick skin types.

9.2 Subject Identification Codes

A SIC will automatically be assigned by the IWRS system at screening, which will comprise B3 (denoting the BLESS III study), followed by a single digit country identification, a two digit site identification and a three digit subject identification number. All study documents (e.g. CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. An abbreviated SIC containing only the 3-digit subject number is acceptable, when the country identifier and site number are clearly assigned to the document.

9.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects screened. The log will also serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

The overall study design is illustrated in Section 2.2. Details on the procedures to be performed at each study visit, including screening are listed in

Table 9-1 below and are listed in Section 2.1 Schedule of Study Procedures and Assessments and in Section 11.15 Clinical Laboratory Tests.

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Table 9-1 BLESS III Study Visit Schedule: List of Activities and Parameters to be assessed at Each Study Visit

VISIT [1]	TIME [2]	ACTION	COMMENT
Visit 1 Screening	Up to 14 days	Informed consent (Section 9.1) Inclusion and exclusion criteria (Section 7) FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FWS Investigator (GLS-I, Section 10.1.1) Demographic data (Section 11.14) Medical history (Section 11.11) Concomitant medication (Section 11.10.1) Vital signs (Section 11.13) ECG (Section 11.16) Serum pregnancy test (if applicable, Section 11.12) Clinical laboratory assessments (Section 11.15) Antibody test (Section 11.15.2)	
Visit 2 Baseline First treatment	Baseline Day 0	Inclusion and exclusion criteria[3] (Section 7) Full physical examination (Section 11.11) FWS Subject self-assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section 10.1.1) Photography (Section 10.1.2) Urine pregnancy test (if applicable) (Section 11.12) Concomitant medication (Section 11.10.1) AE assessment (Section 11) AESI questioning (Section 11.2) Vital signs (Section 11.13) **FIRST TREATMENT** (Section 8.3) Post-treatment observation and AE assessment over 30 minutes. AESI questioning after 30 min Distribute Subject Diary (Section 9.4)	
Visit 3 C1 Week 1	7 days ± 2 day after Baseline (Day 0)	Collect/ Review/Distribute Subject Diary (Section 9.4) FWS Subject self-assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment (Section 11)[13] Vital signs (Section 11.13) Concomitant medication (Section 11.10.1)	
Visit 4 C1	14 days ± 5 days after	Collect Subject Diary (Section 9.4) FWS Subject self-assessment (GLS-S, Section 10.1.1)	

Week 2	Baseline (Day 0)	FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1) Photography (Section 10.1.2)[12]	
Visit 5 C1 Week 4	4 weeks ± 2 days after Baseline (Day 0)	FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1) Photography (Section 10.1.2) Vital signs (Section 11.13) ECG (Section 11.16) Antibody test (Section 11.15.2) Clinical laboratory assessments (Section 11.15)	
Visit 6 C1 Week 8	8 weeks ± 5 days after Baseline (Day 0)	FWS Subject Self assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section 10.1.1) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1)	
Visit 7 (or 7a, 7b, 7c) Evaluation for re-treatment Visit[4] End Of Cycle[5] Second treatment - entry to open label extension	12 weeks ± 5 days after Baseline (Day 0), with possible extension at 4-weekly (± 5 days) intervals until subject is eligible for re-treatment	FWS Subject self-assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section10.1.1) AE and AESI assessment (Section11)[13] Concomitant medication (Section11.10.1) Confirmation of eligibility for re-treatment (Section 7.3) Photography (Section 10.1.2)	
		Urine pregnancy test (if applicable, Section 11.12) Vital signs (Section 11.13) ECG (Section 11.16) Clinical laboratory assessments (Section 11.15) Full physical examination (Section 11.11) Antibody test (Section 11.15.2) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FACE-Q Satisfaction with Outcome Scale (Section20.6)	

		Eligibility for re-treatment (Section 7.3) [6] Consent for re-treatment **SECOND TREATMENT - OPEN LABEL** (Section 8.3) Post-treatment observation and AE assessment over 30 minutes AESI questioning after 30 min	
Visit 8 C2 Week 1	1 week ± 2 days after second treatment	AE and AESI assessment (Section11)[13] Concomitant medication (Section11.10.1) Full physical examination (Section 11.11)	
Visit 9 C2 Week 2	14 days ± 5 days after second treatment	AE and AESI assessment(Section11)[13] Concomitant medication (Section11.10.1)	Telephone call[7]
Visit 10 C2 Week 4	4 weeks ± 2 days after second treatment	FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section20) FACE-Q Satisfaction with Outcome Scale (Section20.6) FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment(Section11)[13] Concomitant medication (Section11.10.1) Vital signs (Section11.13) Clinical laboratory assessments (Section 11.15) Antibody test (Section11.15.2)	
Visit 11 C2 Week 8	8 weeks ± 5 days after second treatment	AE and AESI assessment (Section 11)[13]Concomitant medication (Section 11.10.1)	Telephone call[7]
Visit 12 (or 12a, 12b, 12c) Evaluation for re-treatment Visit [4] End Of Cycle[5]	12 weeks ± 5 days after second treatment, with possible extension at 4-weekly(± 5 days) intervals until subject	FWS Subject self-assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section 10.1.1) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1) Confirmation of eligibility for re-treatment (Section 7.3) Urine pregnancy test (if applicable, Section 11.12)	

Third treatment	is eligible for re-treatment	Vital signs (Section 11.13) Clinical laboratory assessments (Section 11.15) Full physical examination (Section 11.11) Antibody test (Section 11.15.2) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows and Age Appraisal VAS scales (Section 20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) Eligibility for re-treatment (Section 7.3)[5] Consent for re-treatment **THIRD TREATMENT** (Section 8.3) Post-treatment observation and AE assessment over 30 min AESI questioning after 30 min	
Visit 13 C3 Week 1	1 week ± 2 days after third treatment	Full physical examination (Section 11.11) AE and AESI documentation (Section 11)[13] Concomitant medication (Section 11.10.1)	
Visit 14	14 days ± 5days after third treatment	AE and AESI assessment (Section11)[13] Concomitant medication (Section11.10.1)	Telephone call[7]
Visit 15 C3 Week 4	4 weeks ± 2 days after third treatment	FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment(Section 11)[13] Concomitant medication (Section11.10.1) Vital signs (Section 11.13) Antibody test (Section 11.15.2) Clinical laboratory assessments (Section 11.15)	
Visit 16 C3 Week 8	8 weeks ± 5 days after third treatment	AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1)	Telephone call[7]
Visit 17 (or 17a, 17b, 17c)	12 weeks ± 5 days after third treatment,	FWS Subject self-assessment (GLS-S, Section 10.1.1) FWS Investigator (GLS-I, Section10.1.1)	

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Evaluation for re-treatment Visit End Of Cycle Fourth treatment	with possible extension at 4-weekly (± 5 days) intervals until subject is eligible for re-treatment	AE and AESI assessment(Section 11)[13] Concomitant medication (Section11.10.1) Confirmation of eligibility for re-treatment (Section 7.3) Urine pregnancy test (if applicable, Section 11.12) Vital signs (Section 11.13) Clinical laboratory assessments (Section 11.15) Full physical examination (Section 11.11) Antibody test (Section 11.15.2) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) Eligibility for re-treatment (Section7.3)[6] Consent for re-treatment **FOURTH TREATMENT** (Section 8.3) [8] Post-treatment observation and AE assessment over 30 min AESI questioning after 30 min	
Visit 18 C4 Week 1	1 week ± 2 days after fourth treatment	Full physical examination (Section 11.11) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1)	
Visit 19 C4 Week 2	14 days ± 5 days after fourth treatment	AE and AESI assessment (Section11)[13] Concomitant medication (Section11.10.1)	Telephone call[7]
Visit 20 C4 Week 4	4 weeks ± 2 days after fourth treatment	FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) FWS Investigator (GLS-I, Section 10.1.1) Full physical examination (Section 11.11) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1) Vital signs (Section 11.13) Clinical laboratory assessments (Section 11.15) Antibody test (Section 11.15.2)	

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Visit 21 C4 Week 8	8 weeks ± 5 days after fourth treatment	AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1)	Telephone call[7]
Visit 22 End of Study Visit [9]	12 weeks ± 5 days after fourth treatment or on the same day when no further treatment can be given[10, 11]	FWS Subject self-assessment (GLS-S, Section 10.1.1) Modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS (Section 20) FACE-Q Satisfaction with Outcome Scale (Section 20.6) FWS Investigator (GLS-I, Section 10.1.1) AE and AESI assessment (Section 11)[13] Concomitant medication (Section 11.10.1) Serum pregnancy test (if applicable, Section 11.12) Vital signs (Section 11.13) Full Physical examination (Section 11.11) Clinical laboratory assessments (Section 11.15) Antibody test (Section 11.15.2)	

[1]An unscheduled visit is permitted, if necessary. Assessments performed at an unscheduled visit will be at the investigator's discretion, but should include AE assessment, AESI query, concomitant medication and possibly FWS.

[2] A time deviation of ± 5 days is allowed for each visit, except for the week 1 and week 4 visit in each treatment cycle where a time deviation of ± 2 day is permitted. Sites must adhere to the schedule of events and visit windows and subjects must ensure they are available for those visits. Any deviation from the visit schedule and its associated time windows will still be documented as a protocol deviation.

[3]Inclusion and exclusion criteria to be re-confirmed at baseline include FWS for subject and investigator and concomitant medication.

[4] At an Evaluation for Re-treatment visit (visits 7, 12 and 17), if the FWS score (at maximum frown) is not ≥ 2, as determined by both the subject and the investigator, the subject will return at 4-weekly intervals thereafter until this criteria is met. The subsequent visit number for the cycle will remain the same, but will be amended with "a, b, c" etc., corresponding to the time extended (at 4 weekly intervals) in that treatment cycle, with each additional letter corresponding to a time point 4 weeks later in that cycle. For example, the first evaluation for re-treatment is at visit 7, week 12, however for subjects who are not eligible for re-treatment at week 12, but at week 16, this visit will be denoted “visit 7a", while "visit 7b" and "visit 7c" will denote visits at week 20 and week 24 in the first treatment cycle, respectively.

If the subject wants to get re-treated, but the investigator does not agree or vice versa (i.e. the FWS score is not ≥ 2 by both assessments), the subject will return to the site 4weeks thereafter for another Evaluation for Re-treatment visit.

[5] Each treatment/re-treatment cycle will last at least 12 weeks. If more than 12 weeks have passed since the previous treatment and the subject has a FWS score (at maximum frown) of ≥ 2, as determined by

both the subject and the investigator, this visit will then be considered the End of Cycle visit and all other criteria required to determine eligibility for re-injection will be assessed.

[6] If the subject qualifies for re-treatment (in accordance with the eligibility for re-treatment criteria) at the End of Cycle visit, the subject may then enter the next treatment cycle and will receive the next study drug treatment. If the FWS score (at maximum frown) is assessed as ≥ 2 by both the investigator and the subject, but the additional criteria for reinjection are not met, e.g. presence of relevant infection or inflammation at the injection site, the subject will be allowed to return 4 weeks later for re-assessment .

[7] Visits 9, 11, 14, 16, 19 and 21 will be telephone calls and will not require the subject to visit the site. If an AESI is reported, subjects must come to the site as soon as possible for an unscheduled visit, including a targeted physical examination to evaluate the AESI.[8] A maximum of four treatments per subject (four treatment cycles) is permitted during the study time frame, with treatments separated by a minimum of 12 weeks. There is no limit to the number of Evaluation for Re-treatment visits.

[9] The End of Study visit can take place in four-weekly intervals from study-week 48 until study-week 60. For subjects receiving re-treatment at week 48, the last cycle will end 12 weeks later at week 60 (=End of Study visit). End of Study visit will take place at week 48 if week 48 visit is an Evaluation for Re-treatment visit and the subject is not meeting criteria for re-injection. For subjects having received their last injection 8 weeks or less prior to week 48, the End of Study visit will take place 12 weeks after the last study drug treatment was given, e.g. week 52 if the subject was retreated at week 40. A ± 2 day time window is always applied for conducting the End of Study visit.

[10]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. For subjects terminating the study early as per decision made at a site visit, the study procedures required at the End of Study visit should be performed at the visit during which the subject was terminated from the study.

[11]In subjects who do not receive any additional treatments, assessments already performed that day do not need to be repeated if both visits take place on the same day.

[12]Photographs of subject's glabellar lines will be taken at C1 Randomization, C1 Week 2, C1 Week 4 and each C1 Evaluation for Re-Treatment visit in Cycle 1 until the subject qualifies for re-treatment in order to provide evidence of effect and confirm that the subject did not qualify for re-treatment on the preceding Evaluation for Re-treatment visit. Although a photograph will be taken at each Evaluation for Re-treatment visit, only the photo of the visit preceding the re-treatment visit will be reviewed by the independent reviewers

[13]AESI Questioning: active questioning by guided review of systems (ROS) as per AESI manual. If an AESI is reported, a targeted physical examination around the area of the reported AESI must follow.

9.3.1 Unscheduled Visit

An unscheduled visit can be held at any time during the study, if deemed necessary by the investigator. In addition, an unscheduled visit must be scheduled to occur as soon as possible if an AESI is reported during any telephone contact. An unscheduled visit will not replace any of the above visits as per schedule of events. Assessments performed at an unscheduled visit

will be at the investigator's discretion, but should include AE assessment, AESI query, concomitant medication and possibly FWS.

In case of an unscheduled visit, the investigator should complete the "Unscheduled Visit Form" in the CRF.

9.4 Subject Diary and Patient Reported Outcomes

9.4.1 Subject Diary

A paper subject diary will be provided to each subject at the baseline visit (day 0) and one week after the first treatment visit to record the following information:

- Daily documentation of FWS score at maximum frown.

The subject diary will be collected at the visit one week after the first treatment and the subject will be given a second diary to be returned at the visit two weeks after the first treatment. Subjects will be trained on use of the diary during the baseline visit (training will be recorded in the source).

Treatment onset will be evaluated by the subject and the investigator (using FWS) at study visits one, two and four weeks after the first treatment and documented accordingly. In addition, for further determining onset of treatment, the subject will record the FWS score in diaries daily for the first two weeks after treatment (in the first treatment cycle).

The subject diary will serve as a source record and remain at the study site. Entries in the subject diary will be transcribed into the electronic data capture (EDC) system by the blinded member of the site study team.

9.4.2 Patient Reported Outcomes

A patient-reported outcome (PRO) instrument (i.e. a questionnaire plus the information and documentation that support its use) is a means to capture patient, or subject views of outcomes used to measure treatment benefit or risk in IMP clinical trials. Three PRO instruments will be used in this study to support claims in the product label, comprising:

- The FWS, which will be used to evaluate the severity of glabellar lines (Section20.1 and Section 10.1) which will be completed by the subject (PRO; Glabellar Line Scale for Subjects, GLS-S) and the investigator (clinician reported outcome; Glabellar Line Scale for Investigators, GLS-I).

- The modified Skindex-16 (GL-QoL) and FACE-Q scales (Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS), which will be used to measure the psychological impact of glabellar lines and concerns relating to their glabellar lines, respectively (Section 20.3 and Section20.4, Section 20.5).

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- The FACE-Q Satisfaction with Outcome Scale which will be used to measure subject satisfaction with treatment (Section 20.6).

Entries in the questionnaires will be transcribed into the EDC system by a blinded member of the site study team.

9.5 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, followed all appropriate conditions of a protocol (with or without protocol deviations). Completion of the first cycle and the open label cycles will be documented on two different CRF pages.

Subjects will be considered to be "per protocol completers" of Cycle 1 if they had no major protocol deviations **in the first cycle** and an in-clinic assessment with the FWS by the investigator and the subject at baseline (day 0) and at the week 4 visit were performed.

Subjects will be considered to be "per protocol completers" of the study if they have completed the final cycle within week 48-60, without major protocol deviation.

Reasons for completion or non-completion will be reported on the Completion/Termination CRF, including: completed, screen failure, premature termination due to AE (including death), discontinuation by subject(e.g.dropout, lost to follow-up, withdrawn informed consent), physician decision (e.g.non-compliance with protocol, or for safety reasons), study terminated by Sponsor, or other reason to be specified by the investigator. Regardless of the reason for subject withdrawal, all data available for the subject up to the time of completion/discontinuation should be transferred from the subject records on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the End of Study visit. All procedure and assessment results performed at such visits will be recorded under the Termination visit assessments. If a subject terminates participation in the study during or after a visit and does not return for a Completion/Termination visit, or is lost to follow up their last recorded assessments shall remain under the last visit they attended (i.e. no assessment data shall be recorded under/transferred to the Completion/Termination visit assessments). The reason for discontinuation will be recorded on the CRF.

9.6 Procedures for Monitoring Subject 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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10. ASSESSMENT OF EFFICACY

10.1 Assessment of Glabellar Line Severity: Facial Wrinkle Scale

In accordance with FDA Guidelines for Upper Facial Lines, efficacy will be determined using well defined, valid and reliable clinician-reported and subject-reported assessments, capable of measuring the critical outcomes that contribute to a conclusion of overall success or failure. For both investigator and subject assessment, measurements will be made at maximum frown (which represents the worst appearance of upper facial lines with maximum load on the muscle) and at rest (which represents the best appearance of upper facial lines with the least load on the muscle), which allows one to impute benefit when the face is in dynamic motion (variable load on the muscle).

The scale used most frequently in clinical studies is the FWS, which is a four-point rating scale as follows: 0 = no facial wrinkles; 1 = mild facial wrinkles; 2 = moderate facial wrinkles; and 3 = severe facial wrinkles. The scale has been validated and shown to be reproducible[42]. However, this scale includes pictures at rest and at maximum frown within the one scale, meaning that the sensitivity of the scale at rest is low. The instrument proposed for use in this study is the FWS, which is named Glabellar Line Scale for Investigators [GLS-I] and Glabellar Line Scale for Subjects [GLS-S], as described in Section 20.1. The scale and the proposed instructions for its use by investigators and subjects are described in Section 20.1 and in the completion manuals: 'Glabellar Line Scale– Subject: Completion Manual', 'Glabellar Line Scale - Subject: Completion Manual for Investigator', and 'Glabellar Line Scale – Investigator: Completion Manual'.

10.1.1 Subject and Investigator In-clinic Assessment

Subjects will be trained extensively in accurate self-assessment of their glabellar line severity by the investigator at the baseline visit, as outlined in FWS completion manuals 'Glabellar Line Scale – Subject: Completion Manual' and 'Glabellar Line Scale - Subject: Completion Manual for Investigator'. Investigators will complete training before trial initiation and will receive training certification. Investigators will also have an FWS completion manual: 'Glabellar Line Scale – Investigator: Completion Manual'. Subject FWS assessment must be performed independently of the investigator and ideally before the investigator FWS assessment, to rule out any influence or bias from the investigator. The date and time of assessment will be recorded for each visit in the double blind cycle and for the week 4 visits during the open label cycles.

Subjects and investigators will assess the severity of the subject's glabellar lines at maximum frown and at rest using the FWS instrument (Section20.1), i.e. the GLS-S (for subjects) and the GLS-I (for investigators).

In the first treatment cycle, the severity of the subjects' glabellar lines will be evaluated by the subject and the investigator at baseline and at study visits 1, 2, 4, 8, 12 weeks and at 4 weekly intervals thereafter (week 16, week 20, etc.) until the subject qualifies for re-treatment with glabellar line severity returning to a score of 2 or 3 on the FWS. The same investigator must assess the subjects at baseline and at the visits at weeks 1, 2 and 4 in the first treatment cycle,

although every effort shall be made to have the same investigator assess subjects at all time points.

The primary efficacy endpoint will be a composite endpoint of the investigators' and the subjects' assessments of line severity at maximum frown in comparison with placebo at week 4. A subject will be considered a responder if they have a FWS score of 0 or 1 and an improvement ≥ 2 points in FWS score (at maximum frown) at the week 4 visit (of the first treatment cycle) relative to baseline, based on both the investigator's and the subject's in-clinic assessments. Responder rates at other time points in the first treatment cycle will be evaluated as secondary endpoints.

In the open label extension phase, the percentage of responders (FWS score of 0 or 1 and an improvement ≥ 2 points in FWS score at maximum frown) at week 4 after re-treatment relative to the rating at the preceding end of cycle visit will be determined as a secondary efficacy endpoint.

10.1.2 Photo-evaluator Assessment

Photography will be performed by specifically trained personnel in accordance with the relevant imaging manual. Photographs of subjects at maximum frown and at rest will be taken in the first treatment cycle at the following visits: baseline before the first treatment, study visits 2and 4weeks after the first treatment and at the Evaluation for Re-treatment visits, i.e. week 12 after baseline and 4 weekly thereafter until the subject qualifies for re-treatment. Selected photographs will subsequently be assessed by independent blinded raters. Although a photograph will be taken at each evaluation for the re-treatment visit, only the photograph of the visit preceding the re-treatment visit will be reviewed by the independent raters (in addition to the photographs at baseline, week 2 and week 4) and the data will be included in the analysis of additional secondary efficacy endpoints.

10.2 Psychological Impact

The psychological impact of glabellar lines and concerns relating to glabellar lines will be measured using the modified Skindex-16 (GL-QoL) Scale[43] (Section 20.3) and the FACE-Q Appraisal of Lines Between Eyebrows scale and Age Appraisal VAS [44] (Section 20.4), respectively, at screening, 4weeks after each treatment and the end of each treatment cycle.

10.3 Subject Satisfaction with Treatment

Treatment satisfaction will be measured using the FACE-Q Satisfaction with Outcome Scale[45] (Section20.6) at 4 weeks after each treatment administration and at the end of each treatment cycle.

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11. ASSESSMENT OF SAFETY

11.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered an IMP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. AEs will be recorded from signing the ICF until the End of Study visit. SAEs and AESIs are subgroups of AEs as defined below. Any remark for AEs in general also applies to AESIs and SAEs.

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. before informed consent) should be recorded as Medical History; however any increase in severity, frequency or duration of a pre-existing disease during the course of the study will be recorded as an AE. Clinically significant test results at screening will be recorded as Medical History. Any untoward medical occurrence in a subject between ICF and first dose will be recorded as a Pre-treatment Event on the Medical History page. Any untoward medical occurrence in a subject after first dose until End of Study visit will be recorded as an AE. All AEs, AESIs, and SAEs must be recorded, irrespective of whether they are considered study drug related.

The investigator may contact the Sponsor's Medical Expert if additional information is needed for the assessment of AEs.

11.1.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs, AESIs, and SAEs

Newly detected abnormal clinical laboratory findings (e.g. clinical chemistry, hematology) or other abnormal assessments (e.g. ECGs, physical examination, vital signs) that are judged by the investigator as clinically significant must be recorded as AEs, AESIs, or SAEs. Clinically significant abnormal clinical laboratory findings or other abnormal assessments present at the Screening visit will be documented as Medical History. If there is worsening during the study this will be documented as an AE, AESI, or SAE.

The investigator will exercise medical and scientific judgment in deciding whether an abnormal clinical laboratory finding or other abnormal assessment is clinically significant.

11.2 Adverse Events of Special Interest

A specific concern in treatment with botulinum toxin products is the potential for local and distant spread of toxin effect, a unique set of safety concerns related to use of botulinum toxin drug products (draft guidance for industry *Upper Facial Lines: Developing Botulinum Toxin Drug Products*). Therefore, subjects will be instructed and educated on possible warning signs and precautions and on rare AESIs through the Subject Information Sheet (SIS). Safety data related to this specific potential effect should be obtained through directed query at each study visit and if an AESI as below is reported a targeted physical examination should be

conducted to evaluate for signs and symptoms of local and distant spread of toxin effect. AESI assessment and documentation is mandatory based upon the event term. An AESI must also be reported even if e.g. duration of the event is to considered unusual for an AESI or if the event is considered as being not related to the study drug. Adverse events of special interest potentially suggestive of distant spread of toxin, include:

accommodation disorder	*dyspnea*	*Paresis*
areflexia	*extraocular muscle paresis*	*peripheral nerve palsy*
aspiration	*eyelid function disorder*	*peripheral paralysis*
blurred vision	*eyelid ptosis*	*pelvic floor muscle*
botulism	*facial palsy*	*weakness*
bradycardia	*facial paresis*	*pneumonia aspiration*
bulbar palsy	*fourth cranial nerve paresis*	*pupillary reflex impaired*
constipation	*hemiparesis*	*quadriparesis*
cranial nerve palsies	*hypoglossal nerve paresis*	*respiratory arrest*
cranial nerve paresis	*hyporeflexia*	*respiratory depression*
cranial nerve paralysis	*hypotonia*	*respiratory failure*
diaphragmatic paralysis	*monoparesis*	*speech disorder*
diplopia	*muscular weakness*	*third cranial nerve paresis*
dry mouth	*paralysis*	*trigeminal nerve paresis*
dysarthria	*paralysis flaccid*	*urinary retention*
dysphagia	*paralytic ileus*	*vocal cord paralysis*
dysphonia	*paraparesis*	*vocal cord paresis*

The first AESI questioning will be undertaken (in accordance with the AESI Manual) prior to the first injection, in order to obtain a full baseline status of any concomitant diseases. If an AESI is reported, a targeted physical examination must be conducted. If reported during a telephone contact, subjects must come to the site for further assessment as soon as possible.

11.3 Serious Adverse Events

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Results in death.
- Is life threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires subject hospitalization or results in prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

Note: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are: invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse. Hospitalization is defined as at least 1 overnight stay. Pre-planned hospitalizations (known already prior to signing the ICF) will not be considered an SAE, unless any of above criteria are fulfilled over the course of the hospitalization due to unplanned complications.

11.4 Treatment-Emergent Adverse Events (TEAEs)

A TEAE is defined as any event not present prior to the initiation of the treatment, or any event already present that worsens in terms of severity, duration, or frequency following exposure to the treatment.

11.5 Evaluation of AEs, AESIs, SAEs, TEAEs

11.5.1 Assessment of Causality

The investigator is obliged to assess the relationship between the IMP as well as study procedure and the occurrence of each AE/AESI/SAE. This relationship will be classed as not related, unlikely, possibly, probably or definitely related as follows:

- Not related (both circumstances must be met):
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs.
    - Is not associated with the IMP or study procedure (i.e. does not follow a reasonable temporal relationship to the administration of IMP or has a much more likely alternative etiology).
- Unlikely related (either one or both circumstances are met):
    - Has little or no temporal relationship to the IMP or study procedure.
    - A more likely alternative etiology exists.
- Possibly related (both circumstances must be met):
    - Follows a reasonable temporal relationship to the administration of IMP.
    - An alternative etiology is equally or less likely compared to the potential relationship to the IMP or study procedure.
- Probably related (both circumstances must be met):

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- Follows a reasonable temporal relationship to the administration of IMP, which may include but is not limited to the following:
  - Reappearance of a similar reaction upon re-administration (positive re-challenge).
  - Positive results in a drug sensitivity test (skin test, etc.).
  - Toxic level of the IMP as evidenced by measurement of the IMP concentrations in the blood or other bodily fluid.
- Another etiology is unlikely or significantly less likely

- Definitely related:
  - Has clear and undoubted relationship to the administration of IMP.

The investigator will use his/her clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to IMP administration will be considered and investigated. The investigator will also consult the IB in the determination of his/her assessment.

For the purpose of expedited regulatory reporting, events assessed as possibly, probably, or definitely related to IMP or study procedure will be considered as drug related.

11.5.2 Assessment of Severity

The following definitions for rating severity will be used:

- Mild:
  - The AE is easily tolerated and does not interfere with daily activity.
- Moderate:
  - The AE interferes with daily activity but the subject is still able to function.
- Severe:
  - The AE is incapacitating and/or requires medical intervention.

11.5.3 Outcome

The outcome options that can be utilized include:

- Ongoing
- Resolved
- Resolved with Sequelae
- Death

- Unknown

11.5.4 Action Taken with Study Drug

Action taken with study drug includes:

- None
- Discontinued

11.6 Adverse Event Monitoring and Assessment

Subjects will be monitored for AEs throughout the study from signing the ICF until the End of Study visit. Should an SAE occur after the End of Study visit, which is considered as at least possibly related to study drug or procedure, such events should always be reported to CROMA Pharma GmbH or its representative, even after the end of the study. Such events would generally not be entered into the clinical database but will be entered into the safety database.

Subjects will be questioned concerning their well-being at all study visits from screening through to the End of Study visit. Questions for evaluation of AEs will be posed in a non-leading manner, so as not to bias the response. In addition to questioning at specific time points, subjects will be encouraged to spontaneously report any AEs, AESIs, or SAEs. In addition, as per Section 11.2, AESIs will be questioned in an active manner. Any subject with an AE, AESI, SAE or clinically significant abnormal test result will be evaluated by the investigator and will be treated and/or followed up as per local clinical practice. A physician, either at the investigative site or at a nearby hospital emergency room, will administer treatment for any SAEs. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved. AEs, AESIs, and SAEs ongoing at End of Study will be followed up until the event is resolved or stable. Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Whenever possible, a specific disease or syndrome, rather than individual associated signs and symptoms, should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

When documenting AEs, standard medical terminology should be used in order to avoid the use of vague, ambiguous, or colloquial expressions (see Section 11.1). Each AE will be evaluated by the investigator for:

- Seriousness, as defined in Section11.3.
- Severity, as defined in Section 11.5.2.
- Causal relationship to IMP exposure, as defined in Section 11.5.1.
- Causal relationship to procedure.

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- Outcome.
- Action taken with study drug.

If the severity rating for an ongoing AE changes before the event resolves, the AE will be reported in an additional row in the AE log (or additional AE page) with complete information (i.e. start and stop date, severity, relationship, outcome etc.).

11.6.1 Reporting Serious Adverse Events and Adverse Events of Special Interest

All SAEs and AESIs for all subjects occurring from the time of informed consent until the End of Study visit must be reported to CROMA Pharma GmbH or their representative **within 24 hours** of the knowledge of the occurrence. If considered at least possibly related to study treatment, SAEs observed after the End of Study visit must also be reported.

Paper SAE/AESI forms should be completed at the site and faxed to the Medical & Safety Services Department [redacted] Clinical Research **within 24 hrs** of awareness of the event.

[redacted]

The preferred way of submitting the safety reports is via the above email address. Fax numbers have been provided as back up.

If the report is sent via email then the completed and signed SAE/AESI or Pregnancy report form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

There may be situations when an SAE/AESI has occurred and the investigator has minimal information to include in the initial SAE/AESI report to CROMA Pharma GmbH, or their representative. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE/AESI report form. Minimum criteria are identifiable subject (number), a suspect product (i.e. IMP or concomitant medication), an identifiable reporting source (investigator/study-site identification) and an event or outcome that can be identified as serious or as an AESI. The investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE/AESI report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements for SAEs.

11.6.2 Exposure *In Utero* During Clinical Trials

The Sponsor or representative must be notified of any subject that becomes pregnant while participating in this clinical trial. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator or designee to report any pregnancy in a subject that occurs during the trial to [redacted] Clinical Research, as specified above (Section 11.6.1) **within 24 hours** of awareness of the pregnancy, using the pregnancy reporting form.

Once a pregnancy has been detected/reported, no further study drug injections must be administered. Pregnant subjects will be followed-up until the end of the current injection cycle and will then be withdrawn from the study. At the end of the injection cycle, an End of Study visit will be conducted. Following detection of pregnancy, no invasive assessments must be conducted in pregnant women including no blood sampling for e.g. safety laboratory assessments or antibodies. The treatment code for pregnant women will be unblinded.

11.6.3 Overdose

Overdose is defined as any dose above the total body dose per injection session (i.e. 20 U/treatment). Single treatment doses of up to 50 U of [redacted], a botulinum toxin with similar potency units to the study drug, are frequently used for cosmetic/aesthetic indications[31,46,47,48,49] and it is generally recognized that doses greater than 20 U may be required for larger muscles[50]. The treatment dose in this study is 20 U and the treatment vials contain only 50 U, hence there is virtually no risk of overdose.

11.7 Urgent Safety Measures

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from CROMA Pharma GmbH. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The Sponsor (CROMA Pharma GmbH) will also ensure the responsible ethics committee (EC) is notified of the urgent measures taken in such cases, according to local regulations.

11.8 Pre-existing Diseases

Pre-existing diseases that are present before entry into the study and described in the medical history and that manifest with the same severity, frequency, or duration subsequent to IMP administration, need not be recorded as AEs. However, if there is an increase in severity, frequency or duration of a pre-existing disease, the event shall be documented as an AE.

11.9 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (IB). “Unexpected” also refers to the AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Each unexpected AE experienced by a subject will be recorded on the AE CRF.

11.10 Medical, Medication and Non-Drug Therapy History

11.10.1 Medication and Non-Drug Therapies

All medication taken for up to eight weeks prior to ICF signature, and all concomitant medications taken or administered during the study, will be documented in the subject’s clinic/hospital and study records using the guidelines set forth by the Sponsor. The prior and concomitant medication information will be documented on the Concomitant Medication CRF.

In addition to product name (preferably generic name), the dose, indication, route of administration and frequency, as well as the start and end date of treatment, will be documented. In the context of this study, information on non-drug therapies will only be collected in relation to SAEs.

Prohibited Medication and Excluded Non-drug Therapies

The medication listed below must not be taken during the conduct of the study:

- Treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment).
- Use of a muscle relaxant.
- Use of anticholinergic drugs, or drugs which could interfere with neuromuscular function, including aminoglycoside antibiotics and curare-like compounds.

- Surgery with general anaesthetic.

The following non-drug therapies are excluded during the study:

- Facial laser or light treatment, microdermabrasion, superficial peels or retinoid therapy.
- Treatment with any facial aesthetic procedure in the glabellar area (including chemical peeling, injection with biodegradable fillers,).
- Insertion of permanent material in the glabellar area.
- Surgery in the glabellar area including surgical removal of the c*orrugator, procerus* or *depressor supercili* muscles or a combination of these, or scars in the glabellar area.

11.11 Medical History and Physical Examinations

Medical history will be taken at screening, including a record of previous treatment with botulinum toxin. At baseline and subsequent study visits (as listed in Section 2.1 and Section 9.3), a full physical examination will be performed by the investigator. 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 Adverse Event of Special Interest (as detailed in the AESI Manual) a focused physical examination by the physician, to evaluate these symptoms will also be undertaken. Any clinically relevant abnormal finding will be documented in the CRF as AE/medical history.

11.12 Pregnancy test

For women of child-bearing potential (i.e. being pre-menopausal with no 12 consecutive months without a menstrual period or not surgically sterilized), a blood serum pregnancy test will be performed at screening and at the end of the study and urine dip-stick pregnancy tests will be performed before re-treatment.

Pregnancy tests may be performed at more regular intervals per local regulatory requirements.

11.13 Vital Signs

Vital signs will include pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Vital signs will be measured at screening, at each visit involving IMP administration (to be recorded before IMP administration, i.e. baseline for the first treatment cycle and end of cycle visit before re-treatment), at the visit 4 weeks after treatment and at the end of the study. Vital sign values will be recorded on the CRF.

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11.14 Demographic Data

Demographic data will only be collected at visit 1 (screening). These data include age(at time ICF signed),year of birth, height (cm), weight (kg), gender, race and ethnicity (including Fitzpatrick Skin Type). Height and weight data will be used for the calculation of body mass index.

11.15 Clinical Laboratory Tests (Safety)

A full list of the parameters that will be analyzed can be found below.

Any safety laboratory results outside the normal range will be evaluated by the investigator or his designee as “clinically significant” or “not clinically significant”. Any test assessed as being clinical significant must be documented as pre-treatment event (if obtained at Screening) or as AE. Sites will conduct re-tests for blood samples which could not be analyzed at the central lab due to e.g. haemolysis etc. Repeat of lab tests for clinically significant test results are at the discretion of the investigator.

11.15.1 Hematology and Clinical Chemistry

Blood will be obtained for assessment of complete blood count (CBC) and clinical chemistry parameters in accordance with the schedule, i.e. at screening, 4 weeks after each treatment and at the end of cycle visit. Please refer to the laboratory manual for collection and processing of samples. CBC and clinical chemistry tests will be performed on ethylenediaminetetraacetic acid -anticoagulated whole blood and serum, respectively in the central laboratory. The CBC will include hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, red blood cell count, and white blood cell count, as well as differential and platelet count.

The clinical chemistry panel will consist of sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen, gamma glutamyltranspeptidase, creatinine, cholesterol and glucose (random). Testing of the blood samples will be performed at the central laboratory.

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11.15.2 Antibody Test

Serum samples will be tested for the presence of antibodies to botulinum toxin using an Anti Drug Antibody (ADA) ELISA assay; initially only the last sample obtained from each study subject will be analyzed together with the pre-dose baseline sample. If a sample tests positive for anti-drug antibodies, the other samples from the subject will be analyzed to determine when antibodies developed. Serum samples which test positive for binding antibodies will subsequently be tested for neutralizing activity. Blood serum for ADA tests will be collected at screening, at the visit 4 weeks after treatment and at the end of cycle visit for each treatment cycle and will be stored for future analysis should the need arise, based upon the presence of ADA at the end of the study. Sample storage at -80°C is preferable, but samples can be stored at -20°C at sites if -80°C storage is not available. Samples will be stored (at [redacted].) until completion of the trial and will be destroyed thereafter.

11.16 Electrocardiograms

A 12-lead ECG will be performed on each subject at screening (which will be taken as baseline), at week 4 after the first treatment (presumed steady state) and at the end of cycle for the first treatment cycle. Any observation assessed as being clinical significant must be documented as pre-treatment event (if obtained at Screening) or as AE.

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12. STATISTICS

12.1 Sample Size and Power Calculations

Primary Analysis:

The primary endpoint is a composite endpoint comprising investigator and subject assessments of treatment effectiveness using the FWS. Composite endpoint treatment success (CETS) is defined as ≥2 point reduction in FWS score at maximum frown achieving a score of 0 or 1 at the visit week 4 relative to baseline based on investigator assessment and subject assessment. Thus, a subject is a CETS "Responder" only if both investigator- and subject-rated success criteria are satisfied at the visit 4 weeks after baseline.

The primary analysis of efficacy is the proportion of responders in the BoNT/A-DP treatment group compared with the placebo treatment group. For superiority testing of BoNT/A-DP compared with placebo, the following assumptions for the sample size calculation will be used:

Item	***Assumption***	***Comments***
Underlying test	Fisher's Exact Test	Standard test for a response parameter for small numbers
Randomization scheme	3:1	More active treatment subjects to enlarge safety data base
Power 1-β	90%	Actual power is 92.3%.
Significance level (α)	0.025 one-sided	
Response Arm BoNT/A-DP	46%	Conservative value based on the results of previous studies (Bless I and Bless II)
Response Arm Placebo	2%	Conservative value based on the results of previous studies (Bless I and Bless II)
Software		The sample size calculation was performed using the software nQuery Advisor® 8.2.1.0.

Based on these assumptions, 39 subjects in the BoNT/A-DP arm and 13 subjects in the placebo arm are required, i.e. 52 subjects in total. This is a very small sample size and not sufficient for a detailed evaluation of the data, including subgroup analyses. Furthermore, the response rate could not be estimated with sufficient precision. Assuming a response rate of 60% in the BoNT/A-DG group, a two-sided CI of 95% with a distance from the response rate to the CI limits of about 5.6% could be achieved with a sample size of 225 subjects in the BoNT/A-DP group. We propose a 3:1 randomization of BoNT/A-DP (225 subjects) to placebo (75 subjects), which we believe is adequate for a precise estimate of response rate and for post-hoc

sensitivity analyses (i.e. treatment-by-center and other subgroup analyses), also taking into account a drop-out rate.

In addition sample size is justified in order to fulfill FDA request for additional subjects treated with BoNT/A-DP to provide an adequate Safety database.

In total, 353 evaluable subjects will be enrolled. Applying a 15% drop out rate would result in a total number of about 300 subjects.

12.2 Data Sets and Analysis Cohorts

Safety Analysis Set (SAF):

All subjects who received at least one injection with study medication (independent of whether it is BoNT/A-DP or placebo) 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.

Full Analysis Set (FAS):

The FAS includes all randomized subjects, regardless of whether they received study medication. 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 (ITT) principle. The FAS will be used for the evaluation of the efficacy assessments. The FAS serves as the primary efficacy analysis set.

Modified Full Analysis Set (MFAS):

The MFAS includes all randomized subjects who received at least one injection with study medication who had a baseline (visit 1 at day 0) and at least one post-dose in-clinic assessment with the FWS by either the investigator or the subject on visits at weeks 1, 2 or 4. Within the MFAS, 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 (ITT) principle. The MFAS will be used for the evaluation of the efficacy assessments.

Per-protocol Analysis Set (PP):

The PP includes all randomized subjects who received at least one injection with study medication who had no significant protocol deviations and an in-clinic assessment with the FWS by the investigator and the subject at baseline (day 0) and at the week 4 visit. For the PP, all subjects will be assigned to the randomized treatment. The PP will only be analyzed for main efficacy outcome measures.

Data Review Meeting:

Subjects will be assigned to the SAF, FAS, MFAS and PP during a data review meeting (DRM). Further details on the analysis sets, criteria for the PP, and the DRM will be specified within the statistical analysis plan (SAP). Details for and decisions on protocol deviations will be specified in a classification meeting taking place between database lock and unblinding. Corresponding documentation should be held outside of the SAP.

12.3 Procedure for Accounting for Missing, Unused, and Spurious Data

Analyses will be performed by visit. For responder analyses on visits at week 4 and week 12, missing in-clinic assessments (investigator or the subject) with the FWS at baseline or week 4 and week 12 visits will be assigned as being non-responders.

As sensitivity analyses, the following additional approaches for handling of missing values will be applied:

- Analysis on observed values only, i.e. missing values will be excluded from analysis.
- Last observation carried forward (LOCF)

Tipping point analysis: each missing value will be assigned to either a response or non-response, so that all possible combinations of replacing 1 or more missing values within each treatment group will be analyzed. p-values will be calculated for each combination and graphically displayed using a scatter plot.

12.4 Methods of Analysis

12.4.1 Primary Outcome Measure

Primary Analysis:

The proportion of subjects (responders) meeting the primary endpoint with a FWS score of 0 or 1 and an improvement ≥ 2 points in FWS score (at maximum frown) at week 4 visit relative to baseline, based on both the investigator and the subject in-clinic assessments will be analyzed using the Cochran-Mantel-Haenszel test (with stratification variable site; small sites with less than 3 placebo subjects will be combined) using a significance level (α) of 0.025. The hypothesis to be tested is:

H_0: $p_{BoNT/A\text{-}DP} \leq p_{Placebo}$

H_1: $p_{BoNT/A\text{-}DP} > p_{Placebo}$

The Cochran-Mantel-Haenszel test will be applied using SAS procedure Proc Freq (using the General Association Statistic). The one-sided p-value will be derived by halving the two-sided p-value delivered by the SAS procedure. Superiority of BoNT/A-DP over placebo will only be concluded if, besides statistical significance (one-sided p-value ≤0.025), the proportion of responders in the BoNT/A-DP treatment group is higher than for the placebo treatment group.

The FAS will serve as the primary analysis set.

Subjects with missing investigator or subject in-clinic assessments with the FWS at baseline or visit week 4 will be assigned as being non-responders.

Additional Analyses on the Primary Endpoint Variable:

Further analyses on the primary endpoint variable are exploratory. A one-sided Pearson χ^2-test will be applied. Two-sided CI of 95% for the responder rates in the BoNT/A-DP and the placebo treatment groups will be calculated using Wilson scores. Treatment-by-center interaction will be tested using the Breslow-Day test for homogeneity of the odds ratios. The CIs will also be calculated for the additional analyses as listed in the following:

- The primary endpoint measure using the observed values only, i.e. missing investigator or the subject in-clinic assessments with the FWS at baseline or week 4 visit will be excluded from analysis but not assigned as being non-responders.
- The primary endpoint measure using the MFAS and the PP.
- The primary endpoint measure applying the LOCF for week 4 visit.
- Subgroup analysis by site, country and geographic region (US versus EU).
    - Subgroup analyses will be conducted for sites, , country and geographic region (US versus EU). Sites with less than 3 placebo subjects will be combined. The χ^2-test will be applied for each subgroup. In case of a total number of observations below 30, or in case of at least one cell frequency below 5, Fisher's exact test will be used instead of the χ^2-test. Stratified analyses applying the Cochran-Mantel-Haenszel test will also be conducted using factor geographic region.
- Subgroup analysis by subjects with previous use of botulinum toxin versus naïve subjects.
    - Subgroup analyses will be conducted for subjects with treatment with any serotype of botulinum toxin for any indication versus naïve subjects. The χ^2-test or Fisher's exact test (see above corresponding criteria to use Fisher) will be applied for each subgroup. No stratified analysis using factor pre-treated/naïve subjects is currently planned.

- In addition, the following subgroups will be used for the primary efficacy endpoint:

    - Race

    - Subjects with previous use of botulinum toxin by site

    - Naïve subjects by site

    - Fitzpatrick skin type

    - Sex

- Ethnicity
- Age groups (below 65 years, 65-74 years and 75-84 years; below 65 years versus 65 years and older)

12.4.2 Secondary Outcome Measures

Key Secondary Analyses:

The testing of the key secondary endpoint will be performed with appropriate multiplicity control based on the FAS population. The results of each test result will only be considered confirmative if the previous test in the order showed a confirmatory result at a one-sided significance level of 0.025. If the one-sided p-value is larger than 0.025 for any of the tests, the results of the subsequent tests will only be considered exploratory, and not confirmatory. The application of this hierarchical approach keeps the global significance level to 0.025 one-sided and requires no further adjustment of the significance level.

The following order of tests will be defined:

- Primary endpoint (composite endpoint)
- Key secondary endpoint 1

1.1: The modified Skindex-16 (GL-QoL) Emotional domain
1.2: The modified Skindex-16 (GL-QoL) Social Functioning domain
1.3: The modified Skindex-16 (GL-QoL) Overall score
1.4: The FACE-Q Appraisal of Lines Between Eyebrows scale
1.5: The FACE-Q Age Appraisal VAS score

Analysis of key secondary endpoint 1: The extent of change in psychological impact (emotional and social functioning, and concerns relating to glabellar lines) at week 4 after the first treatment, in the BoNT/A-DP group in comparison with placebo, relative to baseline, as assessed by the modified Skindex-16 (GL-QoL) and the FACE-Q Appraisal of Lines Between Eyebrows and FACE-Q Age Appraisal VAS.

The modified Skindex-16 (GL-QoL) and FACE-Q Appraisal of Lines Between Eyebrows scale and FACE-Q Age Appraisal VAS will be analyzed according to the foreseen analysis approach of these tools, as described below.

Emotional and Social Functioning

The modified Skindex-16 (GL-QoL) Emotional and Social Functioning domains and overall scores will be derived in accordance with the Skindex-16 manual, adapted for the GL-QoL. The scores will be standardized on a scale from 0 (no impact) to 100 (maximal impact); a scale score is the average of responses to items addressing a construct. Domain and overall scores will be calculated if at least two of three social and of at least two of four emotional domain items are present. The absolute change from baseline (measured on the screening visit) will be calculated for the domain and overall scores and statistically compared between the treatment groups using the Wilcoxon Rank Sum test (or t-test). Estimates of ‘mild’,

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'moderate', and 'severe' psychological impact, and of the minimal clinical important difference, will be used to aid interpretation of scores and will be considered exploratory.

The analysis will be conducted with respect to the hierarchical order of key secondary endpoints; the analysis using the Emotional domain first, the Social Functioning domain second, and the overall score third. All analyses will be conducted on observed values only, i.e. missing domain and overall scores will be excluded from analysis; no imputation of missing domain and overall scores will be performed.

Concerns Relating to Glabellar Lines

The FACE-Q Appraisal of Lines Between Eyebrows scale and FACE-Q Age Appraisal VAS scores will be derived in accordance with the developers' instructions and missing data treated accordingly. The absolute change from baseline (measured on the screening visit) will be calculated for each scale and statistically compared between the treatment groups using the Wilcoxon Rank Sum test. All analyses will be conducted on observed values only, i.e. missing scale scores will be excluded from analysis; no imputation of missing scores will be performed. This analysis will be conducted with respect to the hierarchical order of key secondary endpoints as well; the analysis of FACE-Q Appraisal of Lines Between Eyebrows scale first, followed by the analysis of FACE-Q Age Appraisal VAS scores.

Exploratory Analyses

Exploratory analyses of modified Skindex-16 (GL-QoL) domain and overall score and FACE-Q Appraisal of Lines Between Eyebrows scale and FACE-Q Age Appraisal VAS will also be conducted using the MFAS and the PP population. Subgroup analysis by site, by geographic region, by country and by subjects with previous use of botulinum toxin versus naïve subjects will be conducted.

Additional Secondary Analyses:

Analysis of additional secondary endpoint 1: The percentage of responders at maximum frown (as defined above) at week 12 (after the first treatment with BoNT/A-DP or placebo).

The same analyses, inclusive of the additional exploratory analyses, as described for the primary endpoint will be conducted.

Analysis of additional secondary endpoint 2: The percentage of responders at week 16 (after the first treatment).

The analysis of the week 16 visit will be conducted on observed values only, i.e. missing investigator or the subject in-clinic assessments with the FWS at baseline or week 16 visit will be excluded from analysis but not assigned as being non-responders. Subjects who were re-treated before visit week 16 are considered to be non-responders.

In addition, the same analyses, inclusive of the additional exploratory analyses, as described for the primary endpoint will be conducted.

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Analysis of additional secondary endpoint 3: The percentage of responders at week 20 or later (after the first treatment).

The analysis of percentage of responders at week 20 (after the first treatment) will be conducted on observed values only, i.e. missing investigator or the subject in-clinic assessments on FWS at baseline or visit week 20 will be excluded from the analysis but not assigned as being non-responders. Subjects who were re-treated before visit week 20 are considered to be non-responders.

In addition, the same analyses, inclusive the additional exploratory analyses as described for the primary endpoint, will be conducted (for subgroups also).

Analysis of additional secondary endpoint 4: The proportion of subjects with a ≥ 1 point reduction in FWS score at rest at week 4 in the first treatment cycle, based separately on the investigator and the subject in-clinic assessments

In general, the same statistical analyses, inclusive of the additional exploratory analyses as described for the primary endpoint, will be conducted.

The analysis on the investigator's in-clinic assessment will be conducted only for subjects who have an investigator's in-clinic assessment of a FWS score at rest ≥ 1 at baseline. This will similarly be applied for the analysis of the subject's in-clinic assessment.

Subjects with missing investigator in-clinic assessments at baseline or week 4 visit will be assigned as being non-responders for this endpoint. This will similarly be applied for the subject's in-clinic assessment.

In general, the additional secondary efficacy endpoints will be analyzed applying the appropriate statistical method for the comparison of both treatment arms. For proportions, the Cochran-Mantel-Haenszel test (with stratification variable site) and the Pearson χ^2-test will be applied. In case of a total number of observations below 30, or in case of at least one cell frequency below 5, Fisher's exact test will be used instead of the χ^2-test. Two-sided 95% CIs for response rates will be calculated, where appropriate. Additionally the cumulative proportions of effects at weeks 1, 2, and 4 will be calculated. Time to onset of effect in the first treatment cycle will be analyzed descriptively and by using the Kaplan-Meier method. Moreover, the daily assessments of the line severity when frowning will be analyzed descriptively. The FACE-Q satisfaction with outcome scale will be analyzed descriptively.

All endpoints, with exception of "responder" 4 weeks after re-treatment, will be analyzed for the first treatment cycle only. The analysis of "responder" 4 weeks after re-treatment will be conducted on observed values only, i.e. subjects with missing investigator or the subject in-clinic assessments on FWS week 4 or at the preceding end of the cycle visit will be excluded from analysis. Subjects who were treated with placebo during the first treatment cycle are excluded from the analysis of this endpoint, but not assigned as being non-responders. A two-sided McNemar test (using a significance level of 0.05) will be used to compare the response

proportions between week 4 re-treatment visit and at the preceding end of the cycle visit. This endpoint will be separately analyzed for each open label extension cycle.

Analyses of percentage of responders at other visits after first treatment but before re-treatment are exploratory only. Additional exploratory analyses, as described for the primary endpoint, will not be conducted, with the exception of the calculation of 95% CIs.

Besides the FAS population for the analysis with multiplicity control, the analyses of these endpoints will also be based on the MFAS and the PP population. For all analyses, a one-sided significance level of 0.025 will be used, if not stated otherwise. Additional exploratory subgroup analyses by site, or by subjects with previous use of botulinum toxin versus naïve subjects, will be conducted for additional secondary analyses. For secondary endpoint 4 all subgroup analyses as described for the primary endpoint will be conducted. For the proportion of subjects with ≥ 1 point reduction in FWS score during the first treatment cycle at week 12, 16 and 20 relative to baseline subgroup analyses by site, by country, by geographic region and by subjects with previous use of botulinum toxin versus naïve subjects will be conducted.

Secondary Safety Endpoints:

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.

Analysis of secondary safety endpoint 1 (adverse events):

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 or placebo). 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 analyzed overall (for BoNT/A-DP or placebo), and for BoNT/A-DP treatment group additionally separately per first treatment cycle or open label extension phase: events starting on or after first treatment up to before open label extension (first cycle), and events starting on or after re-treatment until end of study (open label phase). If it cannot be determined whether an AE started during the first treatment cycle or the open label extension phase due to a partial onset date, then it will be counted as having started during first treatment cycle.

Events of subjects who started the first treatment with placebo but then entered the open label extension for re-treatment with BoNT/A-DP will be considered to placebo for the first cycle and to BoNT/A-DP for the open label phase.

Treatment-emergent adverse events 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 (SOC and PT) will also be summarized by seriousness,

severity, relationship to study medication, and relationship to procedure. Treatment-emergent AESIs will be tabulated separately.

Analysis of secondary safety endpoint 2 (antibody formation):

The presence of antibodies will be summarized by counts and percentages of subjects by treatment group and time point. For the subgroup of subjects with a sample test positive for anti-drug antibodies, all analyzed samples will be analyzed descriptively by counts over time as well.

Analysis of secondary safety endpoint 3 (laboratory data, vital signs, ECG):

All laboratory values will be classified as normal or abnormal according to the central laboratory normal ranges and indicated as clinically significant (CS) or not clinically significant (NCS) by the investigator. Quantitative laboratory values will be summarized with means, standard deviations, medians, minima and maxima at baseline and over time and of absolute changes from baseline. Categorical variables will be summarized by counts and percentages of subjects in corresponding categories. Shift tables illustrating changes with respect to the central laboratory normal ranges and the investigator assessment between baseline and post-baseline visits will be created: Number and percentage of subjects with normal, CS and NCS laboratory values.

The analyses of variables for vital signs will focus on the evaluation of the change from baseline to the scheduled time points after baseline. Descriptive analysis with means, standard deviations, medians, minima and maxima of the time course and of changes from baseline to each post-baseline visit will be presented.

Normal/abnormal shift tables will be created for the overall ECG interpretation by treatment group for all applicable time points.

An additional safety evaluation will be performed by defining cycle 2 day 0 as baseline for subjects who switched from placebo to BoNT/A-DP.

12.4.3 Further Analyses

Baseline data, including demographic data will be analyzed descriptively. Subject disposition, including discontinuation and reasons for discontinuation, and subject exposure will be tabulated in detail. Concomitant medication, including application site concomitant medication, will be coded according to the World Health Organization (WHO) drug dictionary and tabulated accordingly.

12.5 General Statistical Considerations

The statistical analysis of the first treatment cycle and the open label extension phase (cycles 2-4) will be performed after database lock of all data up to the end of study (can take place in four-weekly intervals from study week 48 until study week 60 [see schedule of study procedures and assessments Section 2.1]) and final unblinding.

Further aspects of statistical analyses will be detailed within a SAP. This plan will be finalized prior to the database lock and/or study unblinding.

Continuous variables will be summarized with means, standard deviations, medians, minima and maxima. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories.

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.

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

12.5.1 Demographic and Baseline Characteristics

Summary statistics will be provided by treatment group for demographics (e.g., age, gender, race, ethnicity, Fitzpatrick skin type) and for baseline characteristics.

For all efficacy endpoints, baseline will be defined as the measurement prior to receipt of the first dose of study medication.

12.5.2 Interim Analysis

An interim analysis will be performed after all subjects finalized the re-evaluation for retreatment visit at week 16 of the first treatment cycle or completed the double blind phase (whichever occurs earlier). A data base closure for all data belonging to the double blind phase up to and including the C1 re-evaluation for retreatment visit at week 16 will be performed prior to this interim analysis. All data belonging to the double blind phase up to and including the C1 re-evaluation for retreatment visit at week 16 will be checked and all queries resolved before data base closure. A blind data review will be conducted prior to unblinding based on all data of the double blind phase up to and including the C1 re-evaluation for retreatment visit at week 16 to check for protocol deviations and to allocate the subjects to the analysis sets. After data base closure, data unblinding and analysis for the double blind phase up to and including the C1 re-evaluation for retreatment visit at week 16 will be done.

Since the primary and the key secondary efficacy endpoints belong to the first 16 weeks of the double blind phase, the final analysis of these endpoints will be conducted during this interim analysis (which is based on the final data of the double blind phase up to and including the C1 re-evaluation for retreatment visit at week 16) and no alpha adjustment needs to be done.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study-related records and data, including source documentation for monitoring by the study monitor or authorized representatives of the Sponsor, audits by the Sponsor or authorized representatives of the Sponsor, EC review, and applicable regulatory authority inspections. If contacted by applicable regulatory authorities, or during an inspection, the investigator will notify the Sponsor of contact, cooperate with the authorities, provide the Sponsor with copies of all documents received from the authorities, and allow the Sponsor to comment on any responses. In the event of an inspection, the investigator agrees to allow the inspector direct access to all relevant documents and to allocate his/her time and that of the study site personnel to the inspector to discuss findings in any relevant issues. The investigator will allow Croma-Pharma GmbH personnel to be present as an observer during a regulatory inspection, if requested.

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14. QUALITY CONTROL AND QUALITY ASSURANCE

Standard Operating Procedures (SOPs) belonging to [redacted] will be adhered to for all activities relevant to the quality of the study, and performed by [redacted] employees, and are routinely monitored by the [redacted]. Vendors sub-contracted by [redacted] or Croma-Pharma GmbH will adhere to their own relevant SOPs.

A Sponsor-designated, monitor (independent to the site) will be responsible for the monitoring of the study and its data within the CRFs. The monitoring of the study will be performed according to [redacted] monitoring SOPs.

14.1 Investigator's Responsibility

The investigator will comply with the protocol, Code of Federal Regulation (Title 21, CFR Part 312) and applicable regulatory requirements and local laws and regulations. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site. The investigator verifies by signature the integrity of all data transmitted to the Sponsor. Except where the investigator's signature is specifically required, it is understood that the term "investigator", as used in this protocol, and in study-related documents refers to the investigator or authorized study personnel that the investigator has designated to perform a certain duty. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

14.2 Study Organization

The name and contact information of all of the individuals involved with the study (e.g. investigator(s), medical director, authorized representative(s) of the Sponsor, laboratories, steering committees, and oversight committees, if applicable) will be maintained by the Sponsor and provided to the investigator.

14.3 Training

The study monitor or authorized representatives of the Sponsor will ensure that the investigator and study site personnel understand all requirements of the protocol, the study status of the IMP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor or authorized representatives of the Sponsor will be available for consultation with the investigator, and will serve as the liaison between the study site and the Sponsor.

14.4 Monitoring

The study monitor and/or other authorized representatives of the Sponsor is/are responsible for monitoring that each study site conducts the study according to the protocol, SOPs, other written instructions, Code of Federal Regulation (Title 21, CFR Part 312) and applicable regulatory guidelines. The investigator will permit the study monitor or other authorized representatives to visit the study site at appropriate intervals to observe the progress of the study, review study records/documentation, and ensure that informed consent has been

obtained for each subject prior to performing any study procedure. Monitoring processes specific to the study will be described in the clinical monitoring plan.

14.5 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits (quality assurance) to evaluate study conduct and compliance with the protocol, SOPs, other written instructions/agreements, Code of Federal Regulation (Title 21, CFR Part 312) and applicable regulatory guidelines/requirements.

The investigator will permit auditors to visit the study site. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and information in the informed consent documentation of this clinical trial.

14.6 Non-compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject or when the change(s) involves only logistical or administrative aspects of the study (e.g. change of phone number). In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The Sponsor, or authorized designee, will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the investigator's participation. The Sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

14.7 Facilities

The study management will be performed by:

[redacted]

The following certified **clinical laboratory** will perform clinical laboratory tests required by this protocol:

[redacted]

The **statistical analysis** will be performed by:

[redacted]

The **photographic** procedures performed by the clinical study sites and the independent photo assessment will be provided and supported by:

[redacted]

[redacted]

Principal Investigators and Investigation Sites

A list of investigation sites including names, addresses and professions of the principal Investigators (PIs), names and addresses of investigation sites and names and addresses of involved institutions if applicable will be kept in the Trial Master File (TMF) and will be updated accordingly.

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15. ETHICS

15.1 Basic Principles

This research will be carried out in accordance with the current versions of the Declaration of Helsinki; the Code of Federal Regulation (Title 21, CFR Part 312), and local regulatory requirements.

15.2 Ethics Committee and Regulatory Authorities

Before enrollment of subjects into this study, the protocol, ICF and any promotional material or advertisements will be reviewed and approved by the appropriate EC and regulatory authorities, where applicable. The IB will be provided for review. The study will commence only when the committee has approved the protocol or a modification thereof and a copy of the approval letter is received by CROMA Pharma GmbH.

If a protocol is substantially amended, the protocol amendment, revised ICF (if applicable), and any revised promotional material or advertisements will be reviewed and approved by the appropriate EC and regulatory authorities, where applicable. A substantial protocol amendment will only be implemented upon the Sponsor's receipt of approval and, if required, upon the Sponsor's notification of Regulatory Authority(ies) approval.

It is the investigator's responsibility to obtain EC approval for the protocol and all subsequent major changes, in compliance with local law.

15.3 Informed Consent

Investigators will choose subjects in accordance with the eligibility criteria.

It is the investigator's or designee's (where applicable) responsibility to explain the trial to each potential subject and obtain written informed consent (stating clearly that the study includes the possibility of up to three repeat treatments depending on a number of factors)before any trial procedures are performed.

The purpose of the study, procedures to be carried out, and potential risks will be described to the subjects in non-technical terms in the SIS. Subjects will be required to read, sign, and date the ICF, summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will sign and date one copy of the ICF, the investigator/designee providing the information and obtaining the consent will also sign. The copy will be retained by the subject and the original will be retained on file by the investigator. The copy of the SIS will also be given to the subject.

By signing the ICF, subjects agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The Sponsor will provide to the investigator in written form any new information that significantly impacts the subjects' risks associated with IMP exposure. The SIS and ICF will be updated, if necessary.

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16. DATA HANDLING AND RECORD KEEPING

All raw data generated in connection with this study (and site files), together with the original copy of the final report, will be retained in the archives of [redacted] until at least five years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least five years have elapsed since the formal discontinuation of clinical development of BoNT/A-DP. These documents will be retained for a longer period if required by the applicable regulatory requirements, or by an agreement with the Sponsor. The trial master file (TMF) will be archived by the Sponsor.

The study site should maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and the Sponsor (or designee), and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all CRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities.

The investigator should retain records required to be maintained for a period of five years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least five years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the investigator must make provision for the subjects' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of Croma-Pharma GmbH. Should the investigator wish to assign the study records to another party or move them to another location, Croma-Pharma GmbH must be notified in writing of the new responsible person and/or the new location.

Subjects' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

16.1 Confidentiality Policy

The investigator and all personnel involved in the trial will maintain a policy of confidentiality.

16.2 Source Documentation and Case Report Forms

Data will be recorded at sites using CRFs and reviewed during monitoring visits. The recorded data in the EDC system will be verified with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. CRFs will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for. Data collected at screening will be reported in CRFs, regardless of screening outcome.

Source data (e.g. clinical laboratory reports, ECG printouts) should bear the study number, subject number, date of data generation, and, if reviewed, dated signature of the investigator or designee. Adverse events, concomitant medication data and clinical observations will be in the subjects' hospital notes, or recorded on source data forms, and will be transferred into the CRF after assessment by the investigator or designee.

Other data of medical measurement without print-outs (date and time of study activities, i.e. time of blood sampling, administration of study medication) performed during the study will be captured on the respective laboratory requisition forms or dispensing/administration log, which will serve as source documentation for the respective activities. Data produced by automatic devices with original print-outs (e.g. clinical laboratory test results, ECG traces, blood pressure measurements) will be included in the source documentation. Clinical laboratory parameters will be provided in laboratory print-outs which are to be reviewed, signed and dated by the investigator or designee. Any results outside the normal range should be assessed for clinical significance. The investigator will maintain complete and accurate study documentation in the Investigator Site File.

The investigator will comply with the procedures for data recording and reporting. Any corrections to source documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; 2) if not self-evident a reason for the change must be given; and 3) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

16.2.1 Case Report Forms

The investigator is responsible for the procurement and the quality of source data.

Authorized study site personnel will transcribe source data and source data changes to the CRF. All data should preferably be entered into the CRF on the day of the study visit, but no later than 2 working days thereafter. Changes to a CRF, if not self-evident, will require documentation of the reason for each change. After completion of the study, an electronic (or if necessary paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 16.3).

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines (e.g.Code of Federal Regulation (Title 21, CFR Part 312)). All data management activities will be conducted by the Sponsor's representative who will follow their SOPs. Data management and control processes specific to the study will be described in the Data Management Plan.

Once all the Data Quality Control steps have been performed, the database will be locked and the records will be released for reporting and statistical analysis. Data will be transferred to the study sites via CDs and transferred to the study Sponsor via an external hard drive. The media will contain subject PDF files of the electronic CRFs.

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16.2.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

16.2.3 Data Entry

Data must be recorded using the EDC system. All study site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with the Title 21 Code of Federal Regulations (21 CFR Part 11). All passwords will be strictly confidential.

16.2.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for medical history and AEs.
- WHO drug information for concomitant medications.

16.3 Document and Data Retention

The investigator will retain study documentation and data (paper and/or electronic forms) in accordance with applicable regulatory requirements and the data retention policy, as described in the Clinical Study Agreement.

The medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

16.3.1 Data Base Lock

Two data base locks will be performed, one after all subjects finalized the double blind phase (see section 12.5.2) and one after all data of the first treatment cycle and of the open label extension phase are entered into the CRF. In both cases the data base will be locked as soon as the respective data base is confirmed as 'clean'. Before the data base lock for the double blind phase, a data review meeting will take place. Further details will be described in the Data Management Plan.

17. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/Sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

18. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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19. REVISION HISTORY

Version	Date	Reason for Revision
Final Version	17.12.2018	N/A (original document)
Final Version 2.0	15.07.2019	- Reordering of secondary study objectives - Key secondary endpoints "percentage of responders at maximum frown at week 12 (after the first treatment)", "percentage of responders at week 16 (after the first treatment)", and "proportion of subjects with a ≥ 1 point reduction in FWS score at rest at week 4 in the first treatment cycle" are now set as additional secondary endpoints, but not as key secondary. - Clarification on Analysis sets: -The FAS will contain all randomized patients, no injection with study medication needed. -The MFAS includes all randomized subjects who received at least one injection with study medication who had a baseline visit 1 at day 0 and at least one post-dose in-clinic assessment with the FWS by either the investigator or the subject on visits at weeks 1, 2 or 4. - The PP includes all randomized subjects who received at least one injection with study medication who had no significant protocol deviations and an in-clinic assessment with the FWS by the investigator and the subject at baseline (day 0) and at the week 4 visit. For the PP, all subjects will be assigned to the randomized treatment actually received. -Subgroup analysis by site, country and geographic region (US versus EU) was added - Addition of Subgroup analysis for the primary efficacy endpoint - For secondary endpoint 4 all subgroup analyses as described for the primary endpoint will be conducted. For the proportion of subjects with ≥ 1 point reduction in FWS score during the first treatment cycle at week 12, 16 and 20 relative to baseline subgroup analyses by site, by country, by geographic region and by subjects with previous use of botulinum toxin versus naïve subjects will be conducted. - Physical examination assessment will also be done on each End of Cycle Visit - Addition of the following clarification regarding AESI questioning: 30-minute post IMP administration, general, non-leading AE questioning as well as active AESI questioning must be performed - Clarification on subject Identification code: A SIC will automatically be assigned by the IWRS system at screening, which will comprise B3 (denoting the BLESS III study), followed by a single digit

Version	Date	Reason for Revision
		country identification, a two digit site identification and a three digit subject identification number -Update of emotional and Social functioning: Domain and overall scores will be calculated if at least two of three social and of at least two of four emotional domain items are present.

20. SUPPLEMENTS

20.1 Glabellar Line Scale - Subject (GLS-S)

- Glabellar lines, also known as frown lines, are the vertical wrinkles between your eyebrows that may appear worse when you frown.
- In this questionnaire you will be asked to rate the severity of your glabellar lines (how deep they are) when your face is relaxed (at rest) and then when you are frowning.
- Please use the accompanying drawings and the photo atlas to help you make your ratings.
- Not everyone's lines are the same on both sides of their face. Please use your most severe line to score the questionnaire.

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1) Line severity at rest

- Please look directly in a mirror in a well-lit room with nothing obstructing your face (for example, tie back your hair or use a hairband, remove any make up and ensure your glasses do not obstruct the area between your eyebrows) and rate the lines between your eyebrows as they appear **when your face is relaxed** (at rest).
- Check the most appropriate scale score in the table below:

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[redacted]

2) Line severity when frowning

- **Now please frown** (push your eyebrows together as far as they will go, as if you are feeling angry, using your facial muscles not your fingers) and look in the mirror. How would you rate the lines between your eyebrows now?
- Check the most appropriate scale score in the table below:

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[redacted]

20.2 Glabellar Line Scale – Investigator (GLS-I)

- In this questionnaire you will be asked to rate the severity of the patient's glabellar lines when their face is at rest and when they are at maximum frown.
- Please use the accompanying drawings and the photo atlas to help you make your ratings.
- If the patient has any asymmetry in their glabellar lines, please use the most severe line to score the questionnaire.

1) Line severity at rest

Ask the patient to remove anything obstructing their forehead area (for example glasses and make-up, and tie back their hair or use a headband if necessary). In a well-lit room, and when the patient is looking directly at you, please rate the severity of the patient's glabellar lines **at rest**:

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2) Line severity at maximum frown

Please now rate the severity of the patient's glabellar lines **at maximum frown** (asking the patient to push their eyebrows together as far as they will go):

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[redacted]

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20.3 GL-QoL (Modified Skindex-16)

During the past week how much have your glabellar lines bothered you? Glabellar lines are the vertical lines between your eyebrows that are more noticeable when you frown.

For each question please check the box from 0 (Never bothered) to 4 (Always bothered) that best represents how much the lines between your eyebrows have bothered you. If the question is not relevant to you, please check 'Never bothered'.

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[redacted]

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20.4 FACE-Q Appraisal of Lines Between Eyebrows Scale

FACE-Q APPRAISAL OF LINES-BETWEEN EYEBROWS

These questions ask about how you look right now. For each question, circle only one answer. With the area between your eyebrows in mind, in the past week, how much have you been bothered by:

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20.5 FACE-Q Age Appraisal VAS Scale[44]

FACE-Q AGE APPRAISAL-VAS

We would like to know how old you think you look. How many years younger or older do you think you look compared with your actual age? Please circle one number below:

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20.6 FACE-Q Satisfaction with Outcome Scale[45]

FACE-Q SATISFACTION WITH OUTCOME

20.7 Subject BMI Formula and Calculation

Table 20-1 BMI Formula and Calculation	
Measurement Units	**BMI Formula and Calculation**
Kilograms and meters	Formula: weight (kg) / [height (m)]^2 Calculate BMI by dividing weight in kilograms (kg) by height in meters (m) squared
Pounds and inches	Formula: weight (lb) / [height (in)]^2 × 703 Calculate BMI by dividing weight in pounds (lb) by height in inches (in) squared and multiplying by a conversion factor of 703.

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21. REFERENCES

[1]Aoki KR. Pharmacology and immunology of botulinum toxin serotypes.*Journal of neurology* 2001; **248 Suppl 1**: 3-10.
[2]Carruthers A, Carruthers J. Botulinum toxin products overview. *Skin therapy letter* 2008; **13**(6): 1-4.
[3]Said S, Meshkinpour A, Carruthers A, Carruthers J. Botulinum toxin A: its expanding role in dermatology and esthetics.*American journal of clinical dermatology* 2003; **4**(9): 609-16.
[4]Brin M. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl*1997; **6**: S146-68.
[5]Bandyopadhyay S CA, DasGupta BR, Sathyamoorthy V. Role of the heavy and light chains of botulinum neurotoxin in neuromuscular paralysis. *The Journal of biological chemistry* 1987; **262**(6): 2660-3.
[6]BR D, H. S. A common subunit structure in Clostridium botulinum type A, B and E toxins. *BiochemBiophys Res Commun*1972; **48**(1): 108-12.
[7]Coffield JA, Considine RV, Jeyapaul J, Maksymowych AB, Zhang RD, Simpson LL. The role of transglutaminase in the mechanism of action of tetanus toxin.*The Journal of biological chemistry* 1994; **269**(39): 24454-8.
[8] Lebeda FJ, Olson MA. Secondary structural predictions for the clostridial neurotoxins.*Proteins* 1994; **20**(4): 293-300.
[9]Simpson LL. Identification of the major steps in botulinum toxin action. *Annual review of pharmacology and toxicology* 2004; **44**: 167-93.
[10]Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. *Drugs in R&D* 2015; **15**(1): 1-9.
[11]Carruthers A, Kiene K, Carruthers J. Botulinum A exotoxin use in clinical dermatology. *Journal of the American Academy of Dermatology* 1996; **34**(5 Pt 1): 788-97.
[12] Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines.*Journal of the American Academy of Dermatology* 2002; 46(6): 840-9.
[13] Cox SE, Finn JC. Social implications of hyperdynamic facial lines and patient satisfaction outcomes.*International ophthalmology clinics* 2005; **45**(3): 13-24.
[14]Lewis MB, Bowler PJ. Botulinum toxin cosmetic therapy correlates with a more positive mood. *Journal of cosmetic dermatology* 2009; **8**(1): 24-6.
[15]Wollmer MA, de Boer C, Kalak N, et al. Facing depression with botulinum toxin: a randomized controlled trial. *Journal of psychiatric research* 2012; **46**(5): 574-81.
[16]Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *The Journal of dermatologic surgery and oncology* 1992; **18**(1): 17-21.

croma
est. 1976

[17]Carruthers A, Carruthers J. You want to inject what? *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2015; **41 Suppl 1**: S2-8.
[18]Wilson SC, Soares MA, Reavey PL, Saadeh PB.Trends and drivers of the aesthetic market during a turbulent economy.*Plastic and reconstructive surgery* 2014; **133**(6): 783e-9e.
[19] Frevert J. Content of botulinum neurotoxin in Botox(R)/Vistabel(R), Dysport(R)/Azzalure(R), and Xeomin(R)/Bocouture(R).*Drugs in R&D* 2010; **10**(2): 67-73.
[20]Kim BJ, Kwon HH, Park SY, et al. Double-blind, randomized non-inferiority trial of a novel botulinum toxin A processed from the strain CBFC26, compared with onabotulinumtoxin A in the treatment of glabellar lines. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2014.
[21]de Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proceedings of the National Academy of Sciences of the United States of America* 1999; **96**(6): 3200-5.
[22]Lebeda FJ, Cer RZ, Stephens RM, Mudunuri U. Temporal characteristics of botulinum neurotoxin therapy.*Expert review of neurotherapeutics* 2010; **10**(1): 93-103.
[23] Blitzer A, Brin MF, Keen MS, Aviv JE. Botulinum toxin for the treatment of hyperfunctional lines of the face. *Archives of otolaryngology--head & neck surgery* 1993; **119**(9): 1018-22.
[24]Carruthers A, Carruthers J. A single-center dose-comparison study of botulinum neurotoxin type A in females with upper facial rhytids: assessing patients' perception of treatment outcomes. *Journal of drugs in dermatology : JDD* 2009; **8**(10): 924-9.
[25] Dayan SH, Arkins JP, Patel AB, Gal TJ. A double-blind, randomized, placebo-controlled health-outcomes survey of the effect of botulinum toxin type a injections on quality of life and self-esteem. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2010; **36 Suppl 4**: 2088-97.
[26]Fagien S, Cox SE, Finn JC, Werschler WP, Kowalski JW. Patient-reported outcomes with botulinum toxin type A treatment of glabellarrhytids: a double-blind, randomized, placebo-controlled study. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2007; **33**(1 Spec No.): S2-9.
[27]De Boulle K, Fagien S, Sommer B, Glogau R. Treating glabellar lines with botulinum toxin type A-hemagglutinin complex: a review of the science, the clinical data, and patient satisfaction. *Clinical interventions in aging* 2010; **5**: 101-18.
[28]Fagien S, Carruthers JD. A comprehensive review of patient-reported satisfaction with botulinum toxin type a for aesthetic procedures. *Plastic and reconstructive surgery* 2008; **122**(6): 1915-25.
[29] Hoffman RO, Helveston EM. Botulinum in the treatment of adult motility disorders.*International ophthalmologyclinics* 1986; **26**(4): 241-50.
[30]FDA 125274.Dysport - Pharmacology/Toxicology Review and Evaluation.*FDA* 2008.

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est. 1976

[31]Baumann L, Brandt FS, Kane MA, Donofrio LM. An analysis of efficacy data from four phase III studies of botulinum neurotoxin type A-ABO for the treatment of glabellar lines.*Aesthetic surgery journal / the American Society for Aesthetic Plastic surgery* 2009; **29**(6 Suppl): S57-65.
[32]Monheit GD, Cohen JL, Reloxin Investigational G. Long-term safety of repeated administrations of a new formulation of botulinum toxin type A in the treatment of glabellar lines: interim analysis from an open-label extension study. *Journal of the American Academy of Dermatology* 2009; **61**(3): 421-5.
[33] Rzany B, Flynn TC, Schlobe A, Heinz M, Harrington L. Long-term results for incobotulinumtoxinA in the treatment of glabellar frown lines. *Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]* 2013; **39**(1 Pt 1): 95-103.
[34]Jones D, Carruthers J, Narins RS, et al. Efficacy of incobotulinumtoxinA for treatment of glabellar frown lines: a post hoc pooled analysis of 2 randomized, placebo-controlled, phase 3 trials. *Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]* 2014; **40**(7): 776-85.
[35]Kawashima M, Harii K. An open-label, randomized, 64-week study repeating 10- and 20-U doses of botulinum toxin type A for treatment of glabellar lines in Japanese subjects.*International journal of dermatology* 2009; **48**(7): 768-76.
[36] Flynn TC. Botulinum toxin: examining duration of effect in facial aesthetic applications. *American journal of clinical dermatology* 2010; **11**(3): 183-99.
[37]Ascher B, Klap P, Marion MH, Chanteloub F. [Botulinum toxin in the treatment of frontoglabellar and periorbital wrinkles.An initial study]. *Annales de chirurgieplastiqueetesthetique* 1995; **40**(1): 67-76.
[38] Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. *Biologics: targets & therapy* 2014; **8**: 227-41.
[39]Benecke R. Clinical relevance of botulinum toxin immunogenicity. *BioDrugs: clinical immunotherapeutics, biopharmaceuticals and gene therapy* 2012; **26**(2): e1-9.
[40]Carruthers A, Carruthers J, Coleman WP, 3rd, et al. Multicenter, randomized, phase III study of a single dose of incobotulinumtoxinA, free from complexing proteins, in the treatment of glabellar frown lines. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2013; **39**(4): 551-8.
[41]Hanke CW, Narins RS, Brandt F, et al. A randomized, placebo-controlled, double-blind phase III trial investigating the efficacy and safety of incobotulinumtoxinA in the treatment of glabellar frown lines using a stringent composite endpoint. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2013; **39**(6): 891-9.
[42]Honeck P, Weiss C, Sterry W, Rzany B, Gladys study g. Reproducibility of a four-point clinical severity score for glabellar frown lines. *The British journal of dermatology* 2003; **149**(2): 306-10.

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est. 1976

[43]Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. *Dermatologic clinics* 2012; **30**(2): 231-6, xiii.
[44] Panchapakesan V, Klassen AF, Cano SJ, Scott AM, Pusic AL. Development and psychometric evaluation of the FACE-Q Aging Appraisal Scale and Patient-Perceived Age Visual Analog Scale. *Aesthetic surgery journal / the American Society for Aesthetic Plastic surgery* 2013; **33**(8): 1099-109.

[45]Klassen AF, Cano SJ, Schwitzer JA, Scott AM, Pusic AL. FACE-Q scales for health-related quality of life, early life impact, satisfaction with outcomes, and decision to have treatment: development and validation. *Plastic and reconstructive surgery* 2015; **135**(2): 375-86.
[46]Rubin M, Dover J, Maas C, Nestor M.An analysis of safety data from five phase III clinical trials on the use of botulinum neurotoxin type A-ABO for the treatment of glabellar lines.*Aesthetic surgery journal / the American Society for Aesthetic Plastic surgery* 2009; **29**(6 Suppl): S50-6.
[47]Rzany B, Ascher B, Monheit G. Treatment of glabellar lines with botulinum toxin type A (Speywood Unit): a clinical overview. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2010; **24 Suppl 1**: 1-14.
[48]Kane MA, Brandt F, Rohrich RJ, et al. Evaluation of variable-dose treatment with a new U.S. Botulinum Toxin Type A (Dysport) for correction of moderate to severe glabellar lines: results from a phase III, randomized, double-blind, placebo-controlled study. *Plastic and reconstructive surgery* 2009; **124**(5): 1619-29.
[49]Carruthers J, Rivkin A, Donofrio L, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Repeated OnabotulinumtoxinA Treatments in Subjects With Crow's Feet Lines and Glabellar Lines. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2015; **41**(6): 702-11.
[50] Carruthers J, Fagien S, Matarasso SL, Botox Consensus G. Consensus recommendations on the use of botulinum toxin type a in facial aesthetics. *Plastic and reconstructive surgery* 2004; **114**(6 Suppl): 1S-22S.