CLINICAL STUDY PROTOCOL

A Double-Blinded Randomized Controlled Study to Compare the Efficacy, Time to Onset, and Duration of Effect of Botulinum Type A Toxins in the Treatment of Glabellar Frown Lines

Protocol Identifier: Study CPH-201-201461

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Head 2 Head BLESS

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Study Sponsor:
Croma-Pharma GmbH
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A Double-Blinded Randomized Controlled Study to Compare the Efficacy, Time to Onset, and Duration of Effect of Botulinum Type A Toxins in the Treatment of Glabellar Frown Lines

1. SPONSOR RELATED CONTACT DETAILS

Sponsor: Croma-Pharma GmbH
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Sponsor's Project Manager:

Sponsor's Medical Experts:

Responsibilities for study organization, study monitoring, statistical analysis and photographic procedures are listed in Section 17.7. A list of investigators and investigation sites will be kept in the Trial Master File.

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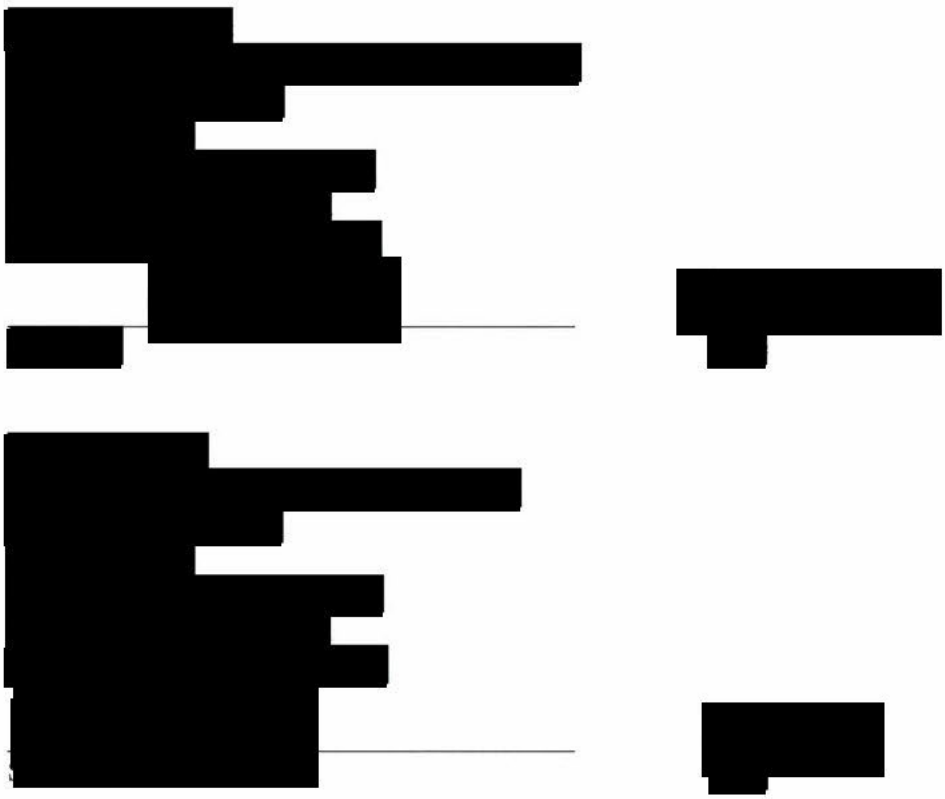
2. SPONSOR SIGNATURE PAGE

I agree to conduct this study 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 Harmonization (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:



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3. INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BoNT/A-DP

STUDY TITLE: A Double-Blinded Randomized Controlled Study to Compare the Efficacy, Time to Onset, and Duration of Effect of Botulinum Type A Toxins in the Treatment of Glabellar Frown Lines

PROTOCOL IDENTIFIER: CPH-201-201461

IND NUMBER: 123178; EudraCT Number: 2019-003481-41

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 Institutional Review Board/Independent Ethics Committee. 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

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4. SYNOPSIS

INVESTIGATIONAL MEDICINAL PRODUCT	
Name of Investigational Medicinal Products (IMPs)	BoNT/A-DP [redacted]
Name of Active Ingredient	Botulinum toxin A
CLINICAL CONDITION/INDICATION	
Treatment of moderate to severe glabellar frown lines	
PROTOCOL IDENTIFIER	Study CPH-201-201461
PROTOCOL TITLE	A Double-Blinded Randomized Controlled Study to Compare the Efficacy, Time to Onset, and Duration of Effect of Botulinum Type A Toxins in the Treatment of Glabellar Frown Lines
Short title	Head 2 Head BLESS (H2H)
STUDY PHASE	Phase 2
PLANNED STUDY PERIOD	
Initiation	First subject is planned for Q4 2019
Primary Completion	Anticipated October 2020
Study Completion	Final Clinical Study Report anticipated January 2021
Duration	Up to 18 weeks per subject. Total study duration (first subject first visit to last subject last visit) up to 30 weeks.
End of Study	A subject is considered to have completed the study if they have completed the End of Study Visit. The end of the study is defined as the date of last subject last visit.
STUDY OBJECTIVES AND PURPOSE	
Study purpose	To provide preliminary comparative efficacy and safety data of BoNT/A-DP versus [redacted]
Primary Objective	To assess the efficacy of treatment with BoNT/A-DP as defined by the percentage of responders at Week 4 (Facial Wrinkle Scale [FWS] score of 0 or 1 and a ≥ 1 point reduction in FWS score) in reducing the severity of glabellar frown lines at maximum frown (the worst appearance of upper facial lines with maximum load on the muscle; eyebrows pushed together as far as they can go) compared to treatment with [redacted] based on independent investigator assessment and subject assessment.

Secondary Objectives	1. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 8, 12 and 16, based on investigator and subject assessments. 2. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 2 point reduction in FWS score at maximum frown) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments. 3. To assess the percentage of responders (FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at rest) after a single treatment with BoNT/A-DP compared to a single treatment of [redacted] at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments. 4. To assess time to onset of effect after a single treatment with BoNT/-DP compared to a single treatment of [redacted] as measured at Weeks 1, 2, and 4, based on independent investigator and subject assessments. 5. To assess the duration of effect in subjects who respond after a single treatment with BoNT/A-DP or a single treatment of [redacted] based on independent investigator and subject assessments. 6. To assess treatment satisfaction at Weeks 4, 12, and 16 using FACE-Q Satisfaction with Outcome Scale. 7. To determine the safety and presence of any adverse effects of a single treatment of BoNT/A-DP compared to a single treatment of [redacted] in the treatment of glabellar lines.
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and safety
Control Type	Concurrent
Study Indication Type	Treatment
Intervention model	Parallel design
Blinding/Masking	Double-blind
Study Design	The study is a parallel group, randomized, double-blind, active-controlled study. The study will comprise 200 subjects randomized 1:1 to one of two treatment groups as follows: • Group A: 100 subjects treated with BoNT/A-DP (20 units [U], 0.5 mL) • Group B: 100 subjects treated with [redacted] (20 U, 0.5 mL) After a Screening period of 0 to 14 calendar days, eligible subjects will be randomized 1:1 at Baseline (Day 0) to Group A or Group B. Subjects will receive a single treatment comprising 5 injections of BoNT/A-DP or [redacted] on Day 0 and will attend follow-up visits for evaluation of

	efficacy and safety at one, two, and four weeks post-treatment and once every four weeks thereafter until Week 16. Investigators and subjects will be blinded to the treatment administered and will evaluate the severity of glabellar lines independently. The subjects must perform their assessment independently and ideally before the investigators, to ensure they are not biased by the investigator. The same investigator must complete the Baseline assessments and FWS at Week 4 (primary endpoint assessments) for a given subject.
Planned Duration of Subject Participation	18 weeks per subject, to include a maximum of two weeks of Screening, one day of treatment and 16 weeks of follow-up.
Primary Outcome Measure	The study comprises co-primary endpoints defined as: • An FWS score at the Week 4 Visit of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown relative to Baseline, based on investigator assessment. • An FWS score at the Week 4 Visit of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown relative to Baseline, based on subject assessment.
Secondary Outcome Measures	**Secondary Efficacy Endpoints** The following are considered key secondary endpoints: 1. Percentage of responders with an FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at maximum frown at Weeks 1, 2, 8, 12 and 16, based on independent investigator assessment and subject assessment. 2. Percentage of responders with an FWS score of 0 or 1 and a ≥ 2 point reduction in FWS score at maximum frown at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments. 3. Percentage of responders with an FWS score of 0 or 1 and a ≥ 1 point reduction in FWS score at rest at Weeks 1, 2, 4, 8, 12 and 16, based on independent investigator and subject assessments. 4. Time to onset of effect, as measured at Weeks 1, 2, and 4, based on independent investigator and subject assessments. Onset of effect is defined as ≥ 1 point improvement in Glabellar Line Scale - Investigator (GLS-I) and Glabellar Line Scale – Subject (GLS-S) score relative to Baseline at maximum frown in glabellar lines. In addition, onset of effect will be assessed by subjects daily during the first 2 weeks after treatment, by recordings in the subject diary. 5. For subjects who respond, duration of effect will be assessed based on independent investigator and subject assessments. Effect will be deemed to be lost when scores return to Baseline values. 6. The FACE-Q assessment at Weeks 4, 12 and 16. **Secondary Safety Endpoint** 1. Frequency, seriousness and severity of treatment-emergent adverse events (TEAEs), serious AEs (SAEs) and AEs of special interest (AESIs), as well as causal relationship to the study medication and the study procedure, during the entire study period. 2. Change in vital signs from Baseline to post-Baseline visits.

INVESTIGATIONAL MEDICINAL PRODUCTS: DOSE AND MODE OF ADMINISTRATION	
BoNT/A-DP	**Dosage form:** Injection, lyophilizate for solution for injection **Dosage frequency for glabellar line:** one 20 U treatment of BoNT/A-DP (administered as 4 U per 0.1 mL, at each of five injection points) **Mode of administration for glabellar line:** Intramuscular injection at 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.
[redacted]	**Dosage form:** Injection, lyophilizate for solution for injection **Dosage frequency for glabellar line:** one 20 U treatment of [redacted] (administered as 4 U per 0.1 mL, at each of five injection points) **Mode of administration for glabellar line:** Intramuscular injection at 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	Total of 200 subjects. Subject accrual planned as follows: • 100 subjects per treatment group • Approximately six sites planned in European Union, United States and Canada
Number of Groups	Two groups are planned: • Group A, n=100: BoNT/A-DP (20 U, 0.5 mL) • Group B, n=100: [redacted] (20 U, 0.5 mL)
Inclusion Criteria	Subjects who meet **ALL** the following criteria are eligible for this study: • 18 - 75 years of age, inclusive, at the time of Screening. • Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on GLS-I/GLS-S) 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 GLS-S), without glasses obstructing the forehead area.

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 study (other than the investigational treatment). • Known hypersensitivity to either 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 three months prior to Screening or planned during the study. o Apart from the procedures specified above, previous treatment with any facial aesthetic procedure in the glabellar area (including chemical peeling, injection with biodegradable fillers, photo-rejuvenation) within 12 months prior to Screening or planned during the study. • Previous insertion of permanent material in the glabellar area, or planned insertion during the study. • Any planned or history of surgery in the glabellar area and/or canthal line area, or scars in the glabellar and/or canthal line. • Active skin disease/infection or irritation at the treatment area. • Inability to substantially lessen glabellar frown lines and or lateral canthal lines even by physically spreading them apart. • Use of a muscle relaxant within 2 weeks prior to Screening, or planned use 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 study. • 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 anesthetic (use of local anesthetic outside the glabellar area is permitted). • Participation in another clinical study within one month of Screening and throughout the study. • 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).

STATISTICAL ANALYSIS	
Sample Size Calculation	The purpose of the study is to provide preliminary comparative data on BoNT/A-DP versus [redacted] Subsequently the sample size is primarily based on clinical judgement and practical considerations, rather than formal statistical arguments. However, with a sample size of 100 subjects per group, a two-sided 95% confidence interval (CI) for the difference between BoNT/A-DP and [redacted] will extend 10.8% from expected proportions of 81.5% in both groups based on large sample normal approximation.
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 [redacted]) will be valid for the SAF. Within the SAF, a subject will be considered for the treatment actually received and not for the treatment assigned by randomization, if different. The SAF will be used for the evaluation of the safety assessments. Full Analysis Set (FAS): The FAS includes all randomized subjects who had a Baseline Visit 1 at Day 0 and at least one post-dose in-clinic assessment with the 4-point scale by either the investigator or the subject on visits at Weeks 1, 2, or 4. Within the FAS a subject will be considered for the treatment assigned by randomization and not for the treatment actually received, if different, i.e., following the intent-to-treat principle. The FAS population will be the primary population for efficacy parameters.
General Statistical Considerations	The primary objective of the study is to provide preliminary comparative data of BoNT/A-DP versus [redacted] The study comprises co-primary responder endpoints defined as: • An FWS score of 0 or 1 and ≥ 1 point reduction in FWS score at maximum frown at the Week 4 Visit relative to Baseline based on investigator assessment • An FWS score of 0 or 1 and ≥ 1 point reduction in FWS score at maximum frown at the Week 4 Visit relative to Baseline based on subject assessment That is, responders are defined as having an FWS score of 0 or 1 and an improvement ≥ 1 point at maximum frown of the glabellar lines at Week 4 relative to Baseline in FWS, based on the investigators' and the subjects' in-clinic assessments. The focus of the statistical analysis for the co-primary endpoints will be on descriptive statistics (n and %), and 95% CIs for the difference in treatment effects between BoNT/A-DP and [redacted] 95% Clopper-Pearson CIs will be calculated for the difference between BoNT/A-DP and [redacted] for each co-primary endpoint. No formal statistical hypothesis testing will be conducted. For other endpoints, categorical variables will be summarized by presenting absolute and relative frequencies (n and %) of subjects for each endpoint. Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum. Time-to-response and duration of response will be analyzed using Kaplan-Meier methodology.

	Analyses will be performed by visit. The main analysis will be performed based on all available data. That is, no imputation of missing values will be conducted (e.g., no last observation carried forward) except for the co-primary endpoints where missing data will be assumed to be non-responders. Treatment-emergent AEs 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 percentage of affected subjects, will be reported. Treatment-emergent AEs (SOC and PT) will also be summarized by seriousness, severity, relationship to study medication, and relationship to procedure.

4.1 Schedule of Study Procedures and Assessments

Procedures and assessments	Screening[1] (Day -14 to 0)	Randomization[1] (Baseline, Day 0)	Week 1 (± 2 days)	Week 2 (± 5 days)	Week 4 (± 2 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days) End of Study[2]
Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	x							
Inclusion/exclusion criteria	x	x[3]						
Medical history	x							
Demographics	x							
Pregnancy test[4]	x	x			x[5]	x[5]	x[5]	x
Physical examination	x							x
Vital signs[6]	x	x	x		x		x	x
Concomitant medication	x	x	x	x	x	x	x	x
GLS-I[7]	x	x	x	x	x	x	x	x
GLS-S[8]	x	x	x	x	x	x	x	x
Photography[9]		x		x	x		x	x
Treatment satisfaction[10]					x		x	x
IMP administration		x						
Post-treatment obs./AE & AESI assessment[11]		x						
AE and AESI[12] assessment		x	x	x	x	x	x	x
Subject diary		D	R/D	R				

1. Screening and Baseline, including randomization and treatment, can be done on the same day. If Screening and Baseline are done on the same day, assessments only need to be performed once.
2. For subjects that are prematurely discontinued from the study (at any time), the End of Study visit will take place within one week of discontinuation.
3. If Screening and Baseline are done on different days, the following inclusion and exclusion criteria are to be re-confirmed at Baseline: investigator and subject assessment of glabellar line severity at maximum frown using GLS-I and GLS-S, respectively, as well as documentation of medical history, concomitant medications and AEs.
4. Pregnancy testing for all women of childbearing potential: Screening, Baseline (if Screening and Baseline are done on different days), and End of Study. All pregnancy testing will be urine dip stick testing.
5. Additional pregnancy testing (urine dipstick) for women of childbearing potential in Austrian sites, only.
6. Vital signs include blood pressure (diastolic /systolic) and pulse.
7. Investigator's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point GLS-I: (0 =none, 1=mild, 2=moderate, 3=severe). Results will be recorded in the eCRF.
8. Subject's assessment of glabellar line severity at maximum frown and at rest. Assessment will be made using the 4-point GLS-S: (0 =none, 1=mild, 2=moderate, 3=severe). Results will be recorded in the eCRF.
9. Photographs to be taken of subject's glabellar lines at maximum frown and at rest.
10. Treatment satisfaction will be determined using the FACE-Q Satisfaction with Outcome Scale. Results will be recorded in the eCRF.
11. Subjects will be monitored for AEs for 30 minutes after administration of the IMP. 30-minute post IMP administration, general, non-leading AE questioning as well as active AESI questioning must be performed.
12. General, non-leading AE questioning as well as active AESI questioning at each indicated visit. The first AESI questioning will be completed at Baseline Visit in order to obtain a full baseline status of any concomitant diseases PRIOR to the first IMP injection.
    AESI Questioning: active questioning by guided review of systems per AESI manual. If an AESI is reported, a targeted physical examination around the area of the reported AESI must follow.

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

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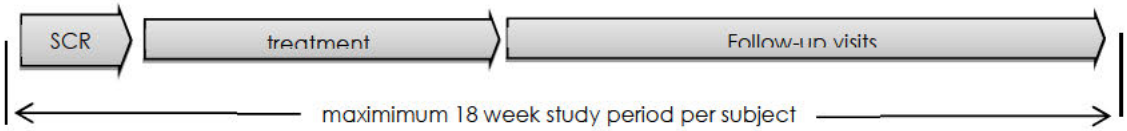
4.2 Study Scheme

Overall study scheme



The duration of study participation for each subject will be up to 18 weeks, to include screening (maximum of 2 weeks; re-screening will not be permitted), and a single treatment (comprised of one injection at five injection points) of BoNT/A-DP (Group A) or Botox Cosmetic (Group B) followed by six efficacy and safety follow-up visits. A total of 200 subjects will be randomized 1:1 to Group A or Group B at Baseline. Both investigators and subjects will be blinded to treatment. Investigators and subjects will evaluate the severity of glabellar lines independently.

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BoNT/A	botulinum neurotoxin A
BoNT/A-DP	Croma-Pharma GmbH's BoNT/A drug product registered in Korea under the name “Botulax”
CFR	Code of Federal Regulations
CI	confidence interval
Croma	Croma-Pharma GmbH
DRM	Data Review Meeting
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FWS	Facial Wrinkle Scale
GLS-I	Glabellar Line Scale - Investigator
GLS-S	Glabellar Line Scale - Subject
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
i.m.	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kDa	kilo Dalton
LD_{50}	lethal dose, 50% (median lethal dose)
MedDRA	Medical Dictionary for Regulatory Activities
MW	molecular weight
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event

Abbreviation	Definition
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Sprague Dawley
SIC	Subject Identification Code
SIS	Subject Information Sheet
SmPC	Summary of Product Characteristics
SOC	system organ class
SOPs	Standard Operating Procedures
TEAE	treatment-emergent adverse event
TMF	Trial Master File
U	Unit
US	United States
WHO	World Health Organization

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7. BACKGROUND INFORMATION

7.1 Background to Botulinum Toxin

Botulinum toxin is produced by anaerobic fermentation of the bacterium *Clostridium botulinum* (*C. 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 hemagglutinins and a nontoxin, nonhematuglitin[3]. Botulinum neurotoxin A (BoNT/A) is synthesized as a single-chain polypeptide with a molecular weight (MW) of approximately 150 kilo Dalton (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 neurons[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 paralysis[3,9.]

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 authorized 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] and [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 MW of [redacted] is 500 kDa and the MW of [redacted] is 150 kDa. Croma-Pharma GmbH's BoNT/A drug product (BoNT/A-DP) (900 kDa) is most similar to [redacted] (900 kDa), with a similar MW 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 soybeans 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 of 20 units (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 (hereafter referred to as Croma), 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) for the treatment of glabellar lines have been completed; one Phase 3 study (BLESS III) is underway. BLESS I (CPH-301-201030) and BLESS II (CPH-302-201030) had identical study designs, and used placebo controls. 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. BLESS III, also placebo controlled, is currently ongoing in the US and EU, and has a targeted accrual of 353 subjects.

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 [redacted].

7.2 Clinical Condition/Indication

Hyperfunctional facial lines (mimic wrinkles) are common aesthetic deformities involving the glabellar area, forehead and periorbital 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].

7.3 Description of Investigational Medicinal Products

An overview of the investigational and comparator products is provided in Table 7-1.

Table 7-1 Composition of BoNT/A-DP and Comparator ([redacted])

Components	BoNT/A-DP	[redacted]
Active ingredient	*Clostridium botulinum* type A (50 U)*	*Clostridium botulinum* type A neurotoxin complex (50 U)
Excipients	human serum albumin (0.25 mg)	human albumin (0.25 mg)
	preservative-free sodium chloride (0.9%)	preservative-free sodium chloride (0.45 mg)
Dose	20 U total (0.5 mL) 4 U (0.1 mL) per five injection points	20 U total (0.5 mL) 4 U (0.1 mL) per five injection points
Appearance	Lyophilizate for solution for injection, which becomes a colorless transparent liquid when preservative-free sodium chloride is added	Sterile, vacuum-dried powder that becomes clear, colorless, and free of particulate matter when preservative-free sodium chloride is added

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

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

Croma`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-hemagglutinating protein and various hemagglutinins ranging between 17 and 48 kDa in size. The investigational medicinal product (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´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 7-1). 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 (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.

7.3.2 Description of the Comparator ([redacted])

[redacted] is a commercially available product, and will be stored, reconstituted and administered per product specifications.

The Summary of Product Characteristics (SmPC) for [redacted] will be provided.

7.3.3 Handling of the Investigational Medicinal Products

Both BoNT/A-DP and [redacted] will be reconstituted and drawn into the injection syringe by unblinded study personnel prior to provision to the investigator to maintain blinding (Section 9.6.2).

Handling of both products (reconstitution; storage; temperature control checks; product accountability) will be done by unblinded members of the study team.

7.4 Non-clinical and Clinical Summaries

7.4.1 Non-clinical Summary

The efficacy and safety of Croma´s BoNT/A have been thoroughly assessed in multiple non-clinical studies in Sprague Dawley (SD) rats and Beagle dogs treated up to 28 days; fertility and reproductive and developmental studies have been carried out in SD rats; and selected safety pharmacology (electrocardiogram) and local tolerance examinations have performed as part of repeat-dose toxicity studies in both species.

Across these studies, no significant or unexpected pathology or toxicity findings have been observed in single or multiple dose toxicity studies using the i.m. route; no histological changes of muscles were observed at the administration site; and no compound-related lesions of the muscle groups distant to the injection sites of the peripheral or central nervous system were observed. In both SD rats and Beagle dogs, significant decreases in body weight, considered an indirect effect related to paralysis, have been observed at doses of BoNT/A-DP ranging from 6-30 U/kg of body. Paralytic gait has been seen in reproductive toxicity testing, and was considered to be due to exaggerated pharmacologic effects of BoNT/A-DP. The no observed adverse effect level (NOAEL) in rats ranged from 1-15 U/kg and in Beagle dogs at or above 30 U/kg. The LD_{50} value has been calculated to be 129.5 U/kg in rats; in dogs, no LD_{50} has been calculated.

In a comparison efficacy study in SD rats, the extent of Croma´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.

Because the mechanism behind the recovery of nerve function is well known and well described in peer-reviewed scientific literature, and because the FDA noted no evidence

for local or systemic adverse effects after long-term use when evaluating the safety data package of Dysport® (six injections, four week intervals)[30], Croma has not evaluated local and systemic toxicity following long-term treatment with BoNT/A-DP. No standard pharmacokinetic or toxicokinetic studies have been performed with Croma´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 conditions and according to International Conference on Harmonization (ICH) guidance. For further details, please refer to the Investigators Brochure (IB).

7.4.2 Clinical Summary

To date, the clinical development of BoNT/A-DP has included multiple Phase 3 studies and one Phase 3 study; one Phase 3 study is ongoing.

Two multi-center Phase 3 studies (BLESS I and BLESS II) were performed in the US and Europe. Both studies were comprised of two parts. The first parts of the studies were randomized, double-blind, placebo-controlled, phases 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 on-going BLESS III study continues with this study design.

In all three studies, the primary efficacy endpoint was 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 ≥ 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 was a composite endpoint comprising investigator and subject assessments of treatment effectiveness.

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

In clinical studies 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.

There have been no deaths reported during the studies, no serious adverse events (SAEs) related to study medication, no treatment-emergent AEs (TEAEs) that led to discontinuation and no development of anti-drug antibody during the studies.

For further details, please refer to the IB.

7.5 Study Rationale

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. This current Phase 2 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 [redacted] Data obtained from this study (and from BLESS I, BLESS II and BLESS III) will provide evidence of efficacy and subject safety in controlled clinical study setting. The dose rationale for this study is described in Section 7.5.1.2.

7.5.1.1 Study Design Justification

This will be a multi-center, randomized, double-blind, comparator-controlled study. The study will take place in the EU, US and Canada.

To allow all subjects to profit from treatment and to obtain adequate data for BoNT/A-DP treatment, the study will be comprised of a double-blinded treatment comparing BoNT/A-DP with [redacted] (ratio 1:1). Primary and secondary endpoints will compare efficacy, safety and subject satisfaction after a single treatment of the investigational BoNT/A-DP to an existing commercially available product [redacted]

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

7.5.1.2 Dose Justification

The dose selected is 20 U, where 1 U is defined as "the calculated median intraperitoneal 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. The potency units of botulinum toxins for injection are specific to the preparation and assay methods utilized and are not interchangeable with other preparations[31] (historical data with similar products have confirmed the efficacy of a 20 U dose and current safety recommendations favor the use of such small doses[32]; FDA Guidance for Upper Facial Lines).

Both BoNT/A-DP and [redacted] will be administered at a dose of 20 U, allowing a comparison of equivalent doses.

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

7.6.1 Possible Benefits for the Subject

The benefit of participation in this study is the expected reduction in the severity of glabellar frown lines. All subjects will benefit from free medical screenings and follow-up.

7.6.2 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 AEs of special interest (AESIs; Section 14.1). 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. BoNT/A-DP will be administered at a dose of 20 U; [redacted] will be administered per product label (20 U).

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. As a side effect of drawing blood, pain, hematoma, and in very rare cases an infection at the venipuncture site may occur.

In addition, as with any IMP, there may be unforeseeable risks associated with the use of BoNT/A-DP.

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8. STUDY PURPOSE AND OBJECTIVES

8.1 Study Purpose

To provide preliminary comparative efficacy and safety data of BoNT/A-DP versus [redacted]

8.2 Primary Objective

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

8.3 Secondary Objectives

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

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9. STUDY DESIGN

9.1 Brief Summary

This is a multi-center Phase 2 study.

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

9.2 Overall Study Design

The study is a parallel group, randomized, double-blind, comparator-controlled study.

9.3 Population to be Studied

Approximately 200 subjects of either gender, between 18 and 75 years of age inclusive, who meet all the inclusion criteria and do not meet any exclusion criteria and who provide written informed consent, will be enrolled in the study.

9.3.1 Treatment and Follow-up

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

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

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

After a Screening period of up to 14 calendar days, subjects will receive a single treatment, comprised of five injections, of BoNT/A-DP or [redacted] on Day 0, and attend follow-up visits at one, two, and four weeks after treatment and once every four weeks thereafter through Week 16, for evaluation of efficacy and safety. Re-screening will not be permitted.

9.3.2 End of Study Visit

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

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

9.3.3 Numbering of Visits

Visit numbers correspond with specific treatment and assessments as outlined in the Schedule of Study Procedures and Assessments, Section 4.1 and in the details of the Screening and Study Visits, Table 12-1.

9.3.4 Allowed Time Deviations per Visit

A time deviation of ± 5 days is allowed for each visit, except for the Week 1 and Week 4 visits, 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 be documented as a protocol deviation.

9.3.5 Duration of Study Period and Subject Participation

Subjects will participate in this study for a duration of 18 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 16 weeks study participation).

Subjects will receive a single treatment of BoNT/A-DP or [redacted] on Day 0.

9.4 End of Study Definition

A subject is considered to have completed the study if they have completed the End of Study Visit.

The end of the study is defined as the date of last subject last visit.

9.5 Outcome Measures

9.5.1 Primary Efficacy Endpoints

The study comprises co-primary endpoints defined as:

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

Details on subgroup analyses on the primary endpoint variable are provided in Section 15.4.1.

9.5.2 Secondary Efficacy Endpoints

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

9.5.3 Secondary Safety Endpoints

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

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9.6 Randomization and Blinding

9.6.1 Randomization

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

Randomization will be performed per study site via Interactive Web Response System (IWRS). One unique randomization code will be assigned to each subject.

9.6.2 Blinding

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

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

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

9.6.3 Unblinding

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

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

In rare emergencies, unblinding may be necessary for the clinical management of an AE. Investigators should consider unblinding only if knowledge of the administered product will have an influence on the further treatment of the AE. In such events, the

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

9.7 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 12.6.

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 detected at Screening or Baseline.
- Any significant treatment-related side effects where study 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 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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10. SUBJECT SELECTION, WITHDRAWAL AND DISCONTINUATION

10.1 Inclusion Criteria

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

- 18 - 75 years of age, inclusive, at the time of Screening.
- Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on GLS-I/GLS-S) as determined in-clinic assessments by both the investigator and 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 GLS-S), without glasses obstructing the forehead area.

10.2 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 study (other than the investigational treatment).
- Known hypersensitivity to either 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 three 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, photo-rejuvenation) within 12 months prior to Screening or planned during the study.
- Previous insertion of permanent material in the glabellar area, or planned insertion during the study.
- Any planned or history of surgery in the glabellar area and/or canthal line area, or scars in the glabellar and/or canthal line.
- Active skin disease/infection or irritation at the treatment area.

- Inability to substantially lessen glabellar frown lines and or lateral canthal lines even by physically spreading them apart.
- Use of a muscle relaxant within two weeks prior to Screening, or planned use 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 study.
- Use of prohibited medication including anticholinergic drugs, or drugs which could interfere with neuromuscular function, including aminoglycoside antibiotics and curare-like compounds within two weeks prior to Screening or planned during the study.
- Planned surgery with general anesthetic (use of local anesthetic outside the glabellar area is permitted).
- Participation in another clinical study within one month of Screening and throughout the study.
- 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).

10.3 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 after at least three unsuccessful phone calls have been made and one certified letter has been sent, in an attempt to contact the subject. All efforts to contact the subject must be documented.

Every effort will be made to have the withdrawn/discontinued subject complete the End of Study visit (Section 9.3.2). The reason for withdrawal/discontinuation will be recorded on the eCRF (Section 12.6).

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, or SAE will be evaluated by the investigator and will be treated and/or followed up until the symptoms return to normal or acceptable levels, as judged by the investigator.

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11. INVESTIGATIONAL MEDICINAL PRODUCT AND COMPARATOR

[redacted]

Only unblinded personnel will be involved in any handling of the IMP prior to provision to the investigator. Unblinded personnel must not disclose unblinding information to the investigator or any other blinded member of the study team.

The SmPC for [redacted] will be provided.

11.1 Packaging

BoNT/A-DP is provided in single use vials containing 50 U/vial. BoNT/A-DP will be reconstituted with a volume of 1.25 mL sterile physiological saline (diluent, as outlined in Section 11.3.3).

[redacted] will be provided as commercially available, in single use 50 U vials, and will be reconstituted per product instructions.

11.2 Labeling

In accordance with the valid regulatory requirements for blinded clinical studies, syringes containing the reconstituted active drug and comparator control will be labeled similarly. The content of the labels will be in accordance with the applicable regulatory authority requirements.

11.3 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.

[redacted] will be stored and handled per the product guidelines.

In order to guarantee proper storage conditions, the current temperature and the minimum and maximum temperature since the last reading in the storage refrigerator must be monitored and documented five times per week. Monitoring of the storage refrigerator and completion of the temperature log are to be done only by unblinded study personnel. The temperature log will be included in the Trial Master File (TMF) 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 11.3.7.

11.3.1 Administration

11.3.2 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.

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.

11.3.3 Dilution

Sterile physiological saline (0.9% preservative-free 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. 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. Reconstituted BoNT/A-DP should be colorless and transparent with no visible particulate matter. The reconstituted BoNT/A-DP 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.

[redacted] will be reconstituted per product instructions.

The date and time of reconstitution will be recorded in the eCRF.

The use of product from one vial or syringe is restricted to one single subject treatment.

11.3.4 Dose for Administration

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

A volume of 0.5 mL of the properly reconstituted BoNT/A-DP or[redacted] 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 33 G, which the investigator routinely uses for toxin administration.

Each subject will receive a total of five i.m. injections of 4 U/0.1 mL (total of 20 U) of BoNT/A-DP or[redacted]: two injections in each *corrugator supercilii* muscle and one injection in the *procerus* muscle, as shown in Figure 1.

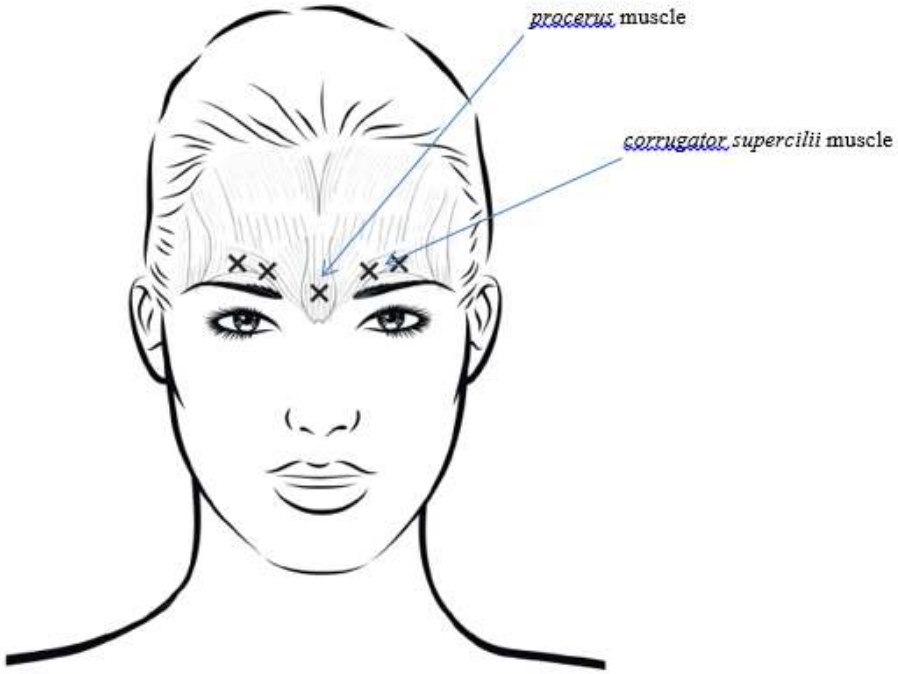

Figure 1 Illustration of proposed injection sites

11.3.5 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. 1 cm 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 ends 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 BoNT/A-DP or [redacted], 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 of BoNT/A-DP can be found in the Study Reference Manual/Operational Manual; additional information regarding administration of [redacted] can be found in the SmPC.

11.3.6 Description of Treatment

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

11.3.7 Investigational Medicinal Product Accountability

The investigator will ensure that the required storage conditions as specified in the Section 11.3 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, including date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IMP must be dispensed only at the study site as specified in the protocol (see Section 11.3). 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.

12. STUDY PROCEDURES

12.1 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.

12.2 Subject Identification Codes

An SIC will automatically be assigned by the IWRS system at Screening, which will comprise H2H (denoting "Head 2 Head BLESS") followed by a single digit country identification, a two-digit site identification and a three-digit subject identification number. All study documents (e.g., eCRFs, 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.

12.3 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 eCRFs, regardless of Screening outcome.

The overall study design is summarized in Section 4.2 and detailed in Section 9. Details on the procedures to be performed at each study visit, including Screening, are listed in Table 12-1 below and are detailed in Section 4.1 Schedule of Study Procedures and Assessments.

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Table 12-1 BLESS III Study Visit Schedule: List of Activities and Parameters to be assessed at Each Study Visit

VISIT [1]	TIME [2]	ACTION
Visit 1[3] Screening	0 to 14 days	Informed consent (Section 12.1) Inclusion and exclusion criteria (Section 10) Medical history (Section 14.11) Demographic data (Section 14.14) Urine dip stick pregnancy test (all applicable subjects, Section 14.12) Physical examination (Section 14.11) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2)
Visit 2[3] Treatment	Baseline Day 0	Urine dip stick pregnancy test (all applicable subjects, Section 14.12) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Photography (Section 13.1.2) Inclusion and exclusion criteria[4] (Section 10) AE assessment (Section 14) AESI questioning pre-dose[5] (Section 14.2) **TREATMENT** (Section 11.3) Post-treatment observation as well as AE and AESI assessment after 30 minutes[6] Distribute Subject Diary (Section 12.5)
Visit 3 Week 1	7 days ± 2 days after Baseline	Collect/Review/Distribute Subject Diary (Section 12.5) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) AE and AESI assessment (Section 14)
Visit 4 Week 2	14 days ± 5 days after Baseline (Day 0)	Collect Subject Diary (Section 12.5) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Photography (Section 13.1.2) AE and AESI assessment (Section 14)

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Visit 5 Week 4	4 weeks ± 2 days after Baseline (Day 0)	Urine dip stick pregnancy test (applicable subjects in Austria only , Section 14.12) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Photography (Section 13.1.2) FACE-Q Satisfaction with Outcome Scale (Sections 13.2 and 23.3) AE and AESI assessment (Section 14)
Visit 6 Week 8	8 weeks ± 5 days after Baseline (Day 0)	Urine dip stick pregnancy test (applicable subjects in Austria only, Section 14.12) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Concomitant medication (Section 14.10) AE and AESI assessment (Section 14)
Visit 7 Week 12	12 weeks ± 5 days after Baseline (Day 0)	Urine dip stick pregnancy test (applicable subjects in Austria only, Section 14.12) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Photography (Section 13.1.2) FACE-Q Satisfaction with Outcome Scale (Sections 13.2 and Section 23.3) AE and AESI assessment (Section 14)
Visit 8[7] Week 16 End of Study	16 weeks ± 5 days after Baseline (Day 0)	Urine dip stick pregnancy test (all applicable subjects, Section 14.12) Physical examination (Section 14.11) Vital signs (Section 14.13) Concomitant medication (Section 14.10) GLS-I (Sections 13.1.1 and 23.1) GLS-S (Section 13.1.1 and 23.2) Photography (Section 13.1.2) FACE-Q Satisfaction with Outcome Scale (Sections 13.2 and 23.3) AE and AESI assessment (Section 14)

[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 GLS-I/GLS-S.

[2] A time deviation of ± 5 days is allowed for each visit, except for the Week 1/Visit 3, and Week 4/Visit 5 visits, where deviations of ± 2 day are 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] Screening and Baseline, including randomization and treatment, can be done on the same day. If Screening and Baseline are done on the same day, assessments only need to be performed once.

Pregnancy testing on all applicable subjects must be repeated at the Baseline Visit if Screening and Baseline assessments are not done on the same day.

[4] If Screening and Baseline are done on different days, the following inclusion and exclusion criteria are to be re-confirmed at Baseline: GLS-I and GLS-S for investigator and subject, respectively, and concomitant medications.

[5] AESI assessment at Visit 2, Day 0 to be done prior to treatment. AESI Questioning: active questioning by guided review of systems as per AESI manual. If an AESI is reported, a targeted physical examination around the area of the reported AESI must follow.

[6] Subjects will be monitored for AEs 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.

[7] 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.

12.4 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 the GLS-I and GLS-S.

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

12.5 Subject Diary and Patient Reported Outcomes

12.5.1 Subject Diary

A paper subject diary will be provided to each subject at Visit 2, Baseline (Day 0) and at Visit 3 (Week 1) for daily documentation of GLS-S score at maximum frown. Subjects will be trained on use of the diary during the Baseline visit and the training will be recorded in the source.

The first subject diary will be collected at Visit 3 (Week 1) one week after treatment; the second diary will be collected at Visit 4 (Week 2), two weeks after treatment. The diary shall be checked for completeness at both visits to ensure all required data has been entered.

The subject will record the GLS-S score in diaries daily for the first two weeks after treatment.

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

12.5.2 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 subject views of outcomes used to measure treatment benefit or risk in IMP clinical studies. Two PRO instruments will be used in this study to support claims in the product label, comprising:

- The GLS-S (Section 13.1.1, Section 23.2).
- The FACE-Q Satisfaction with Outcome Scale which will be used to measure subject satisfaction with treatment (Section 13.2, Section 23.3).

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

12.6 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). Study completion will be documented in the eCRF.

Reasons for completion or non-completion will be reported on the Completion/Termination eCRF, 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 eCRF.

Every effort will be made to have discontinued subjects complete the End of Study visit. All procedure and assessment results performed at the End of Study visit 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 eCRF.

12.7 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.

13. ASSESSMENT OF EFFICACY

13.1 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 (the worst appearance of upper facial lines with maximum load on the muscle; eyebrows pushed together as far as they can go) and at rest (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[33]. 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 FWS proposed for use in this study is comprised of the GLS-I and GLS-S. The scales and the instructions for use for the investigator and subject are provided in Section 23.1 and Section 23.2, respectively; additional information for the investigator is provided in the completion manuals: 'Glabellar Line Scale - Subject: Completion Manual for Investigator', and 'Glabellar Line Scale - Investigator: Completion Manual'.

13.1.1 Investigator and Subject In-clinic Assessment

Investigators and subjects will assess the severity of the subject's glabellar lines at maximum frown and at rest using the GLS-I and the GLS-S, respectively.

Subjects will be trained extensively in accurate self-assessment of their glabellar line severity by the investigator at the Screening Visit, as outlined in the completion manuals (Glabellar Line Scale - Subject: Completion Manual for Investigator and Glabellar Line Scale – Investigator: Completion Manual). Investigators will complete training before study initiation. Subject assessment must be performed independently of the investigator and ideally before the investigator assessment, to rule out any influence or bias from the investigator. The date and time of assessment will be recorded for each visit.

The same investigator must complete Baseline assessments and FWS at Week 4 (primary endpoint assessments) for a given subject.

The primary efficacy endpoint will be a composite endpoint of the investigators' and the subjects' assessments of line severity at maximum frown after treatment with

BoNT/A-DP compared to [redacted] at Week 4. A subject will be considered a responder if they have a FWS score of 0 or 1 and an improvement ≥ 1 point in FWS at maximum frown at the Week 4 Visit relative to Baseline, based on both the investigator's and the subject's in-clinic assessments of the GLS-I and GLS-S, respectively.

13.1.2 Photography

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 at the following visits: Baseline before treatment; at study Visits 4, 5, and 7 (2, 4, and 12 weeks post-treatment, respectively); and at Visit 8, End of Study (16 weeks post-treatment).

13.2 Subject Satisfaction with Treatment

Treatment satisfaction will be measured using the FACE-Q Satisfaction with Outcome Scale[34] (Section 23.3) at Visits 5 and 7, and at Visit 8, End of Study (4, 12, and 16 weeks post-treatment, respectively).

14. ASSESSMENT OF SAFETY

14.1 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 administration of the study treatment will be recorded as a Pre-treatment Event on the Medical History page. Any untoward medical occurrence in a subject that occurs after treatment until the 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.

14.2 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 listed 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., the duration of the event is considered unusual for an AESI or if the event is considered as being not related to the study drug. AESIs 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*	*pupillary reflex impaired*
constipation	*paresis*	*quadriparesis*
cranial nerve palsies	*hemiparesis*	*respiratory arrest*
cranial nerve paresis	*hypoglossal nerve paresis*	*respiratory depression*
cranial nerve paralysis	*hyporeflexia*	*respiratory failure*
diaphragmatic paralysis	*hypotonia*	*speech disorder*
diplopia	*monoparesis*	*third cranial nerve paresis*
dry mouth	*muscular weakness*	*trigeminal nerve paresis*
dysarthria	*paralysis*	*urinary retention*
dysphagia	*paralysis flaccid*	*vocal cord paralysis*
dysphonia	*paralytic ileus*	*vocal cord paresis*
	paraparesis	

The first AESI questioning will be undertaken (in accordance with the AESI Manual) prior to treatment, in order to obtain a full Baseline status of any concomitant diseases. If an AESI is reported, a targeted physical examination of the relevant area must be conducted.

14.3 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 one 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.

14.4 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.

14.5 Evaluation of AEs, AESIs, SAEs, TEAEs

14.5.1 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):
  - 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.

14.5.2 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.

14.5.3 Outcome

The outcome options that can be utilized include:

- Ongoing
- Resolved
- Resolved with Sequelae
- Death
- Unknown

14.5.4 Action Taken with Study Drug

Action taken with study drug includes:

- None
- Discontinued

14.6 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 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 14.2, 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 eCRF. 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 eCRF.

When documenting AEs, standard medical terminology should be used in order to avoid the use of vague, ambiguous, or colloquial expressions (see Section 14.1). Each AE will be evaluated by the investigator for:

- Seriousness, as defined in Section 14.3.
- Causal relationship to IMP exposure, as defined in Section 14.5.1.
- Causal relationship to procedure, as defined in Section 14.5.1.
- Severity, as defined in Section 14.5.2.
- Outcome, as defined in Section 14.5.3.
- Action taken with study drug, as defined in Section 14.5.4.

If the severity rating for an ongoing AE worsens 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.).

14.6.1 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 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 emailed or faxed to the [redacted] **within 24 hours** of awareness of the event:

[redacted]

The preferred way of submitting safety reports is via email; fax numbers are provided for backup.

If a report is sent via email the completed and signed SAE/AESI or Pregnancy report form must be attached to the email; describing an event 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, 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), 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.

14.6.2 Exposure *In Utero* during Clinical Studies

The Sponsor or representative must be notified of any subject that becomes pregnant while participating in this clinical study. 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 study to [redacted] Clinical Research, as specified above (Section 14.6.1) **within 24 hours** of awareness of the pregnancy, using the pregnancy reporting form.

Pregnant subjects will be withdrawn from the study if pregnancy is detected at the Screening or Baseline Visit. Following detection of pregnancy, no invasive assessments may be conducted in pregnant women. The treatment code for pregnant women will be unblinded.

14.6.3 Overdose

Overdose is defined as any dose above the total body dose per injection (i.e., 20 U/treatment of either BoNT/A-DP or [redacted]). 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[35,36,37,38] and it is generally recognized that doses greater than 20 U may be required for larger muscles[39]. The treatment dose for both products in this study is 20 U and the treatment vials for both products contain only 50 U, hence there is virtually no risk of overdose.

14.7 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. In the event 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 one calendar day after the change is implemented. The Sponsor (Croma-Pharma GmbH) will also ensure the responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC) is notified of the urgent measures taken in such cases, according to local regulations.

14.8 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.

14.9 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 of the IB/SmPC. “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 eCRF.

14.10 Medication and Non-Drug Therapy History

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 eCRF.

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 study, other than BoNT/A-DP or [redacted] administered as part of this study.
- 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 anesthetic.

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 supercilii* muscles or a combination of these.

14.11 Medical History and Physical Examinations

Medical history will be taken at Screening, including a record of previous treatment with botulinum toxin. At Screening and the End of Study visit, a full physical examination will be performed by the investigator. A full physical exam will include

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

14.12 Pregnancy Test

For all women of childbearing potential (i.e., pre-menopausal with no more than 12 consecutive months without a menstrual period or not surgically sterilized), a pregnancy test will be performed at Screening, Baseline, and at the End of Study visit. Additional pregnancy tests will be performed for women of childbearing potential at all sites in Austria, at Visits 5, 6 and 7 (4, 8 and 12 weeks post-treatment, respectively).

All pregnancy tests will be urine dipstick tests.

14.13 Vital Signs

Vital signs will include pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Vital signs will be measured at Screening; Baseline (to be recorded before IMP administration); Visits 3, 5, and 7; and at Visit 8, End of Study. Vital sign values will be recorded on the eCRF.

14.14 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).

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15. STATISTICS

15.1 Sample Size and Power Calculations

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

15.2 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 [redacted]) will be valid for the SAF. Within the SAF, a subject will be considered for the treatment actually received and not for the treatment assigned by randomization, if different. The SAF will be used for the evaluation of the safety assessments.

Full Analysis Set (FAS):

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

Data Review Meeting:

Subjects will be assigned to the SAF and FAS during a Data Review Meeting (DRM). Further details on the DRM will be specified within the Statistical Analysis Plan (SAP). Details for and decisions on protocol deviations will also be discussed at the DRM, taking place between database lock and unblinding. Corresponding documentation should be held outside of the SAP.

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

Analyses will be performed by visit. When estimating the response rate at Week 4 for the co-primary endpoints, missing assessments with the FWS at Baseline or Week 4

will be assigned as being non-responders. For all other visits and endpoints, summary statistics will be based on observed data.

15.4 Methods of Analysis

15.4.1 Primary Outcome Measure

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

The study comprises co-primary endpoints defined as:

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

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

The focus of the statistical analysis for the co-primary endpoints will be on descriptive statistics (n and %), and 95% CIs for the difference in treatment effects between BoNT/A-DP and [redacted]. 95% Clopper-Pearson CIs will be calculated for the difference between BoNT/A-DP and [redacted] for each co-primary endpoint. No formal statistical hypothesis testing will be conducted.

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

Subjects with missing investigator or subject in-clinic assessments with the FWS at Baseline or Week 4 Visit will be assigned as being non-responders.

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

Additional Analyses on the Primary Endpoint Variable

- The primary endpoint measure will also be summarized using the observed values only, i.e., missing investigator or subject in-clinic assessments with the FWS at Baseline or Week 4 Visits will be excluded from analysis but not assigned as being non-responders.

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- The following subgroup analysis will be conducted:
  - site
  - previous use of Botulinum
  - 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)

15.4.2 Secondary Outcome Measures

Key Secondary Analyses:

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

The following are considered key secondary endpoints:

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

For categorical endpoints, the same analyses will be conducted as described for the co-primary endpoints. Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum. 95% confidence of the difference in treatment effects will be calculated. Time-to-response and duration of response will be analyzed using Kaplan-Meier methodology.

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

Secondary Safety Endpoints:

Safety endpoint variables will be analysed descriptively only.

Analysis of secondary safety endpoint 1 (AEs):

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 [redacted]). If it cannot be determined whether an AE is treatment-emergent due to a partial onset date, then it will be counted as such.

Treatment-emergent AEs 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. Treatment-emergent AEs (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 (vital signs):

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.

15.4.3 Further Analyses

Baseline data, including demographic data, will be analysed 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.

15.5 General Statistical Considerations

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

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 the Screening Visit will be used.

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

15.5.1 Interim Analysis

No interim analyses are planned.

16. 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, IRB/IEC 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 personnel to be present as an observer during a regulatory inspection, if requested.

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17. 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] Quality Assurance Division. Vendors sub-contracted by [redacted] or Croma 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 eCRFs. The monitoring of the study will be performed according to [redacted] monitoring SOPs.

17.1 Investigator's Responsibility

The investigator will comply with the protocol; Title 21, CFR Part 312; applicable regulatory requirements; 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.

17.2 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) will be maintained by the Sponsor and provided to the investigator.

17.3 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.

17.4 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; 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.

17.5 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; 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 study-related files and correspondence, and information in the informed consent documentation of this clinical study.

17.6 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 one calendar day after the change is implemented. The Sponsor, or authorized designee, will also ensure the responsible IRB/IEC 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 IRB/IEC and applicable regulatory authorities of any investigator termination.

17.7 Facilities

The **study management and monitoring** will be performed by:

[redacted]

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

[redacted]

The **photographic** procedures performed by the clinical study sites will be supported by:

[redacted]

[redacted]

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[redacted]

Principal Investigators and Investigation Sites

A list of investigation sites including names, addresses and professions of the principal investigators, names and addresses of investigation sites and names and addresses of involved institutions if applicable will be kept in the TMF and will be updated accordingly.

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18. ETHICS

18.1 Basic Principles

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

18.2 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 IRB/IEC 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.

If the 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 IRB/IEC 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 IRB/IEC approval for the protocol and all subsequent major changes, in compliance with local law.

18.3 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 study to each potential subject and obtain written informed consent before any study 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, and 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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19. 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 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 IRB/IEC 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 eCRFs, 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. Should the investigator wish to assign the study records to another party or move them to another location, Croma 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.

19.1 Confidentiality Policy

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

19.2 Source Documentation and Electronic Case Report Forms

Data will be recorded at sites using eCRFs 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. Electronic 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 eCRFs, regardless of Screening outcome.

Source data (Subject Diary, etc.) 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 eCRF after assessment by the investigator or designee.

Other data of medical measurement without print-outs (date and time of study activities, i.e., administration of study medication, completion of PROs) performed during the study will be captured on the respective requisition forms or dispensing/administration log, which will serve as source documentation for the respective activities. 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.

19.2.1 Electronic 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 eCRF. All data should preferably be entered into the eCRF on the day of the study visit, but no later than two working days thereafter. Changes to an eCRF, 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 eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (Section 19.3).

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., 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 eCRFs.

19.2.2 Computer Systems

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

19.2.3 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 CFR Part 11. All passwords will be strictly confidential.

19.2.4 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.

19.3 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.

19.4 Data Base Lock

The database will be locked as soon as the database is confirmed as ‘clean’. Before the database is locked, a blinded DRM will take place. Further details will be described in the Data Management Plan.

20. 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.

21. PUBLICATION POLICY

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

22. REVISION HISTORY

Version	Date	Reason for Revision
Final Version		N/A (original document)

23. SUPPLEMENTS

23.1 Glabellar Line Scale – Investigator (GLS-I)

- In this questionnaire you will be asked to rate the severity of the subject's glabellar lines when their face is at rest and when they are at maximum frown (the worst appearance of upper facial lines with maximum load on the muscle; eyebrows pushed together as far as they can go).
- Please use the accompanying drawings and the photo atlas to help you make your ratings.
- If the subject has any asymmetry in their glabellar lines, please use the most severe line to score the questionnaire.

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1) Line severity at rest

Ask the subject 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 subject is looking directly at you, please rate the severity of the subject's glabellar lines **at rest**:

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2) Line severity at maximum frown

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

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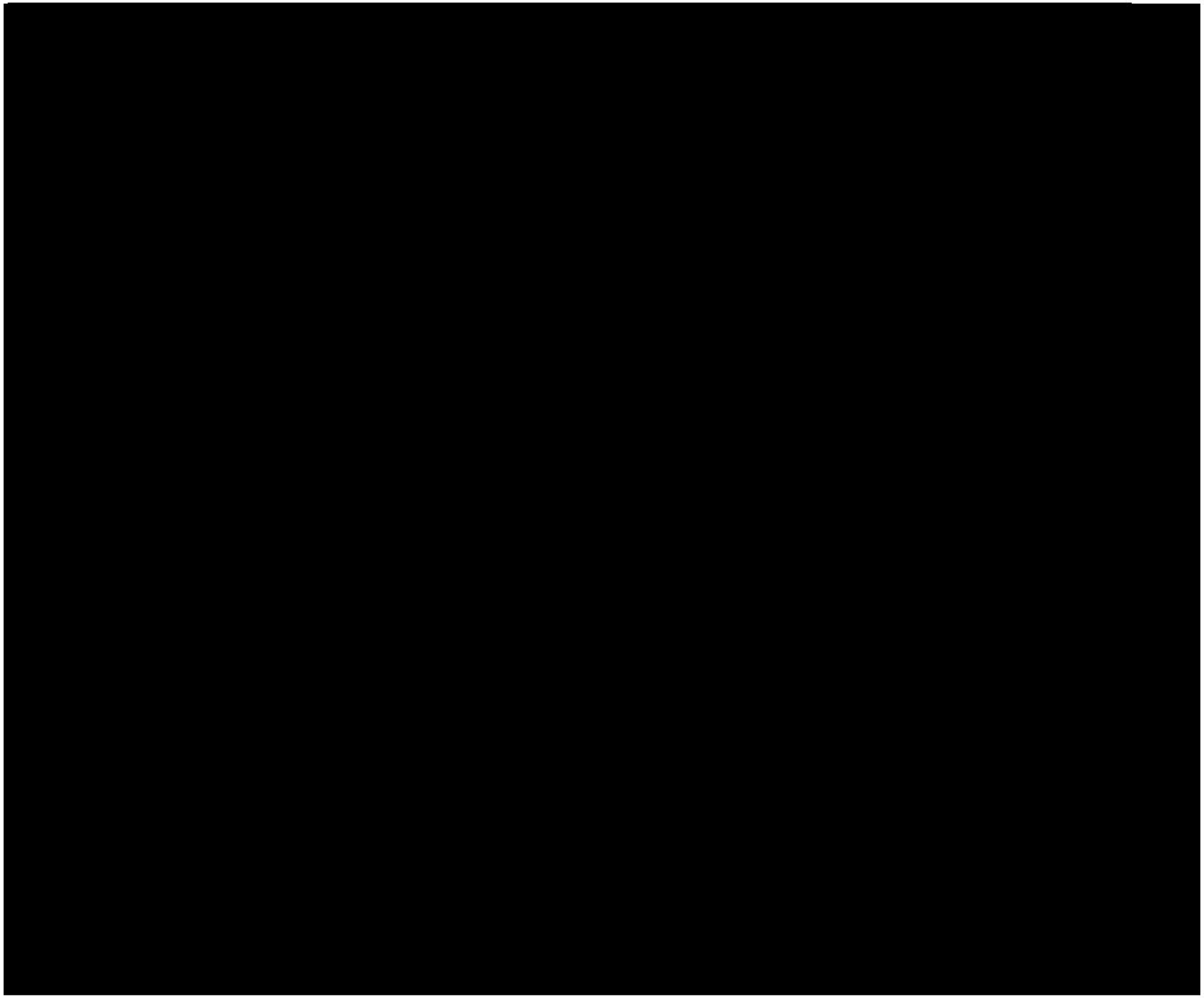

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23.2 Glabellar Line Scale - Subject (GLS-S)

- 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 (eyebrows pushed together as far as they can go).
- 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:

2) Line severity when frowning

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- **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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23.3 FACE-Q Satisfaction with Outcome Scale[34]

FACE-Q SATISFACTION WITH OUTCOME

We would like to know how you feel about your most recent procedure. For each statement, circle only one answer. Please indicate how much you agree or disagree with each statement.

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