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CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 43QM1902

CONFIDENTIAL

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Version: 4.0

TITLE PAGE

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of QM1114-DP for the Treatment of Moderate to Severe Lateral Canthal Lines and Glabellar Lines Alone or in Combination

(READY – 3)

Clinical Trial Number (CTN): 43QM1902

IND Number: 110196

SPONSOR:

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SAFETY:
For safety questions, please contact the Safety e-mail or Medical Monitor using the details provided in Section 11.9. Serious adverse events (SAEs) and pregnancy report forms should be submitted as described in Sections 7.2.6.2.2 and 7.2.6.2.3.

MEDICAL MONITOR:
For any medical questions related to the clinical study protocol, please contact the Medical Monitor using the details provided in Section 11.9.

This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), ICH-Good Clinical Practice (GCP),[1] and applicable regional and national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

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Clinical Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of QM1114-DP for the Treatment of Moderate to Severe Lateral Canthal Lines (LCL) and Glabellar Lines (GL) Alone or in Combination (READY – 3)	
Short Title: QM1114-DP Lateral Canthal Lines and Glabellar Lines	
Clinical Study Population:	Male and female subjects, 18 years of age and older, with moderate to severe lateral lateral canthal lines (LCL) at maximum smile and moderate to severe glabellar lines (GL) at maximum frown.
Clinical Study Design:	This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, US study with treatment of QM1114-DP in the LCL and GL, alone or in combination. Following the informed consent and the screening process, eligible subjects will be randomly assigned to treatment in a 2:2:2:1 ratio. Subjects will receive a single treatment at baseline (Day 0) of either: • 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects), • 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects), • 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or • Placebo in both the LCL and GL (59 subjects). Randomization will be stratified by study center. Subjects eligible for the treatment must meet the severity criteria for LCL and GL at baseline (i.e. moderate to severe LCL and GL at maximum smile and maximum frown, respectively). LCL should be bilaterally symmetrical. Baseline wrinkle severity determination will be based on both investigator and subject ratings using the 4-point photographic scale of LCL severity (LCL-ILA; LCL-SLA) and the 4-point photographic scale of GL severity (GL-ILA) and the subject 4-point categorical scale (GL-SLA). Following treatment at baseline, subjects will be monitored for efficacy and safety over a period of 6 months.
Target Indication:	This study is designed to evaluate the safety and efficacy of QM1114-DP for the treatment of moderate to severe LCL and moderate to severe GL, alone or in combination.
Total Number of Subjects (Planned):	Approximately 413 subjects will be enrolled.
Number of Clinical Study Centers (Planned):	Up to 15 centers
Region(s) / Country(ies) Involved (Planned):	US and Canada
Clinical Study Duration:	The planned duration of recruitment (from first subject first visit [FSFV] to last subject first visit [LSFV]) is approximately 3 months. The planned clinical study duration from FSFV to last subject last visit (LSLV) is approximately 9.5 months.
Duration of Subject Participation:	Clinical study participation for each subject is approximately 6.5 months.

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Key Inclusion Criteria:	1. Male or female 18 years of age or older. 2. Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum smile as assessed by the Investigator live assessment (LCL-ILA). 3. Bilaterally symmetrical LCL graded as Level 2 or Level 3 on the 4-point Photographic Scale (ranging from Level 0 to Level 3) at maximum smile as assessed by the subject live assessment (LCL-SLA). 4. Moderate to severe GL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum frown as assessed by the Investigator (GL-ILA). 5. Moderate to severe GL (grade 2 or 3 on the Static 4-Point Categorical Scale ranging from 0 [no wrinkles] to 3 [severe wrinkles]) at maximum frown as assessed by the subject (GL-SLA). 6. Female of non-childbearing potential (i.e., post-menopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], or has undergone hysterectomy or bilateral oophorectomy). OR Female of childbearing potential with a negative urine pregnancy test at screening and baseline and agrees to use a highly effective and approved contraceptive method for the duration of the study. A highly effective method of contraception is defined as: • Bilateral tubal ligation; • Combined (estrogen and progesterone containing) oral, intravaginal or transdermal contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit; • Intra uterine device (IUD) inserted at least 28 days prior to screening visit; • Intrauterine hormone-releasing system; • Partner vasectomized for at least three months prior to screening visit; • Progestogen-only oral, injectable or implantable contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit; or • Strict abstinence (i.e., refraining from heterosexual intercourse for the entire duration of the subject's participation in the study). 7. Time and ability to complete the study and comply with instructions. 8. Understands the study requirements and signed the informed consent form (ICF).

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Key Exclusion Criteria:	1. Previous use of any Botulinum toxin in facial areas within 9 months prior to study treatment. 2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product). 3. Female who is pregnant, breast feeding, or intends to conceive a child during the study. 4. Known allergy or hypersensitivity to any component of the investigational product (QM1114-DP). 5. Inability to substantially reduce the appearance of facial rhytides in the treatment area by physically spreading them apart, as determined by the Investigator. 6. Clinically significant abnormal focused physical examination finding(s) at screening or baseline visits, in the investigator's opinion. 7. Excessive skin laxity in the treatment area or periorbital area. 8. Previous use of any hyaluronic acid soft tissue augmentation therapy in the lateral canthal or glabella area within 6 months before baseline. 9. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc.) or semi-permanent (e.g., calcium hydroxylapatite, Poly-L-Lactic acid or polymethyl-methacrylate) product; lifting threads, or autologous fat in the treatment area. 10. History, presence, or predisposition of eyelid or eyebrow ptosis (heavy eyebrows), amblyopia (i.e., lazy eye), or previous surgery around the eye that may lead to the above events, as determined by the Investigator. 11. Marked facial asymmetry, excessive dermatochalasis (i.e., excess of skin in eyelids), or marked periocular or eyebrow asymmetry. 12. Presence of scar(s), piercing(s), or tattoos (including microblading of eyebrow or eyeliner) in the treatment area or around the treatment area, that in the Investigator's opinion, may interfere with study evaluations. 13. Presence of inflammation, active infection or skin disorder, such as eczema, rosacea, facial psoriasis, herpes zoster etc., near or in the treatment area. 14. Presence of cancerous or pre-cancerous lesions in the treatment area. 15. History of other facial treatment, surgery, or other aesthetic procedures (e.g. ablative skin resurfacing, laser treatment, microneedling, or chemical peel) in the previous 12 months that, in the Investigator's opinion, could interfere with study injections and/or assessments or expose the subject to undue risk by study participation. 16. Planned facial surgery, eye surgery (including LASIK procedure) or aesthetic procedures (e.g. ablative skin resurfacing, laser

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	treatment, microneedling, or chemical peel in the upper or midfacial area) during the study period. 17. History or presence of facial nerve palsy, or any medical condition that may put the subject at increased risk with exposure to botulinum toxin including diagnosed myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function. 18. Use of medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases, and aminoglycoside antibiotics. 19. Subject with bleeding disorder or subject currently using anticoagulants. 20. Subject has any prior or current psychiatric illness (e.g. psychosis, depression, anxiety), alcohol or drug abuse, or is taking antidepressant, anxiolytic, or antipsychotic medication that, in the Investigator's opinion, could affect the subject's safety and/or the conduct or outcome of the study. 21. Other concurrent medical conditions, therapy or other condition that in the Investigator's opinion would interfere with the evaluation of the study medication safety or efficacy and/or put the subject at risk if he/she participates to the study. 22. Participation in an investigational device or drug study within 30 days prior to study treatment or plans to enroll in any other investigational study during participation in this study. 23. Study center personnel, close relatives of the study center personnel (e.g. parents, children, siblings, or spouse), employees or close relatives of employees at the Sponsor company.
Investigational Product:	QM1114-DP, buffered solution for injection
Strength/Concentration:	100 U/mL
Dosage (total dose):	The maximum total dose is 110 U (1.10 mL) of QM1114-DP, administered as: • 60 U total (0.6 mL total/0.3 mL per treatment side) 10 U per LCL injection point (0.1 mL per LCL injection point) AND/OR • 50 U total (0.5 mL total) 10 U per GL injection point (0.1 mL per GL injection point)
Route:	Intramuscular injection
Dose regimen:	Single treatment at baseline visit
Location of treated area:	Lateral canthus and glabellar areas
Placebo Product:	Placebo, buffered solution for injection
Strength/Concentration:	N/A
Dosage (total dose):	The maximum total dose is 1.10 mL of placebo, administered as: • 0.6 mL total (0.3 mL per treatment side) 0.1 mL per LCL injection point AND/OR • 0.5 mL total 0.1 mL per GL injection point
Route:	Intramuscular injection
Dose regimen:	Single treatment at baseline visit

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Location of treated area:	Lateral canthus and glabellar areas
Efficacy Assessments:	• Investigator 4-point Photographic Scale of LCL Severity at CCI [redacted] maximum smile (Investigator assessment [LCL-ILA]) • Subject 4-point Photographic Scale of LCL Severity at CCI [redacted] maximum smile (subject assessment [LCL-SLA]) • Investigator 4-point Photographic Scale of GL Severity at CCI [redacted] maximum frown (Investigator assessment [GL-ILA]) • Subject Static 4-point Categorical Scale of GL Severity at maximum frown (subject assessment [GL-SLA]) CCI [redacted]
Study Objective:	The objective of the study is to evaluate the efficacy and safety of a single dose of QM1114-DP for the treatment of moderate to severe LCL and GL, alone or in combination.
Primary Efficacy Objective and Endpoint:	The primary objective of this study is to evaluate the efficacy of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, compared to placebo for the treatment of moderate to severe LCL and GL. <u>GL</u> For the primary endpoint, the composite responder rate will be evaluated at Month 1 using the GL-ILA and the GL-SLA at maximum frown. A composite responder is defined as a subject who achieves a grade of 0 or 1 in GL severity and at least 2 grades improvement from baseline on both the GL-ILA and GL-SLA scales concurrently. <u>LCL</u> For the primary endpoint, the composite responder rate will be evaluated at Month 1 using the LCL-ILA and the LCL-SLA at maximum smile. A composite responder is defined as a subject who achieves grade/level 0 or 1 in LCL severity and at least 2 grades improvement from baseline on both the LCL-ILA and LCL-SLA scales concurrently.

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Secondary Efficacy Objectives and Endpoints:	To evaluate the efficacy of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, and placebo for the treatment of moderate to severe LCL and GL. Endpoints: Percentage of subjects who achieve grade 0 or 1 at: CCI • Each post-treatment visit (excluding Month 1) using the GL-ILA at maximum frown • Each post-treatment visit (excluding Month 1) using the LCL-ILA at maximum smile

CCI

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CCI [redacted]	
Safety Assessments:	• Adverse events (AEs) • Focused physical examination (FPE) • Vital signs • Electrocardiogram (ECG) • Laboratory safety tests (chemistry and hematology) • Production of neutralizing antibodies against QM1114-DP
Safety Objectives and Endpoints:	To evaluate the safety of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, compared to placebo for the treatment of moderate to severe LCL and GL. Endpoints: • Incidence and severity of treatment emergent AEs (TEAEs) • FPE findings • Vital signs • ECG • Laboratory parameters (clinical chemistry and hematology) • Neutralizing antibody production

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Other Assessments:	• Photography • Pregnancy test
Blinding:	This is a double-blind study in which neither the Investigator, sub-Investigator, study staff, nor the subject will know the subject's study product assignment (i.e., QM1114-DP and/or placebo). Placebo is identical in appearance to QM1114-DP but contains no active drug substance. Subjects will be randomized at baseline to either treatment with QM1114-DP, QM1114-DP and placebo, or placebo. In order to maintain the blind, the study products, will be supplied in identical vials, each with a unique number on the vial label. Both study products will be administered in exactly the same way.
Principal Statistical Method:	The primary efficacy endpoints will be a composite responder rate at Month 1 based on the ILA and SLA of LCL severity at maximum smile, and ILA and SLA of GL severity at maximum frown. A responder is defined as a subject who achieves grade/level 0 or 1 and at least 2 grades improvement from baseline, on both the Investigator and subject scales concurrently. The responder rates of QM1114-DP and placebo will be compared using Cochran-Mantel-Haenszel test (stratified by center) at 5% significance level (2-sided). The group treated in one rhytid area (LCL or GL) alone, and the group with concurrent LCL and GL treatment will be analyzed separately. To control the type I error rate among the 4 primary efficacy comparisons, the fixed sequence procedure will be used which requires no adjustment to the level of significance. The comparisons will be done in the following order: 1. GL alone group vs placebo on the GL scale 2. GL + LCL group vs placebo on the GL scale 3. LCL alone group vs placebo on the LCL scale 4. GL + LCL group vs placebo on the LCL scale All other endpoints will be analyzed descriptively. For efficacy, percentages of subjects over time will be presented in graphs. Duration of treatment effect and time to onset will be analyzed with Kaplan-Meier methods.
Sample Size:	The study was initially planned to enroll approximately 350 subjects who will be treated with either: • 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 100 subjects), • 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 100 subjects), • 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 100 subjects), or • Placebo in both the LCL and GL (50 subjects). The sample size is determined by the number of subjects exposed to QM1114-DP in the LCL and GL, and amount of long-term safety data. Further, during the study the sample size was increased due to the public health emergency related to the COVID-19 pandemic to ensure a sufficient number of subjects in the mITT efficacy population.

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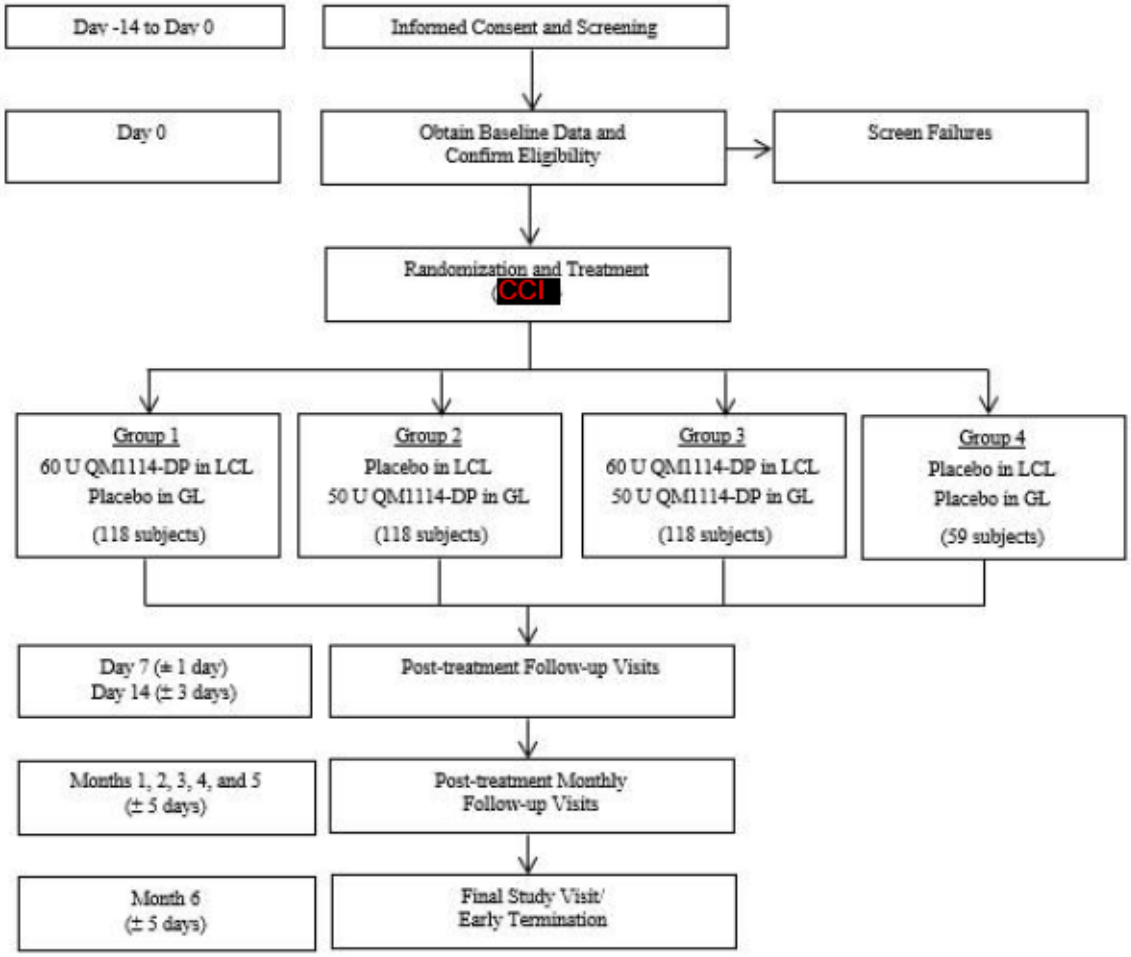
	The study is planned to enroll approximately 413 subjects who will be treated with either: • 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects), • 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects), • 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or • Placebo in both the LCL and GL (59 subjects). CCI [redacted]
Interim Analysis (IA):	Not applicable. An interim analysis is not planned for this study.

CLINICAL STUDY SCHEMATIC AND FLOW CHART

Table 1 Clinical Study Schematic

Screening ↓ Baseline/Randomization to Treatment ↓				
	Group 1	Group 2	Group 3	Group 4
	n=118	n=118	n=118	n=59
Treatment	LCL Treatment 60 U of QM1114-DP in LCL Placebo in GL	GL Treatment 50 U of QM1114-DP in GL Placebo in LCL	LCL and GL Treatment 60 U of QM1114-DP in LCL 50 U of QM1114-DP in GL	Placebo Placebo in LCL Placebo in GL
Treatment Frequency	Treatment at baseline	Treatment at baseline	Treatment at baseline	Treatment at baseline
↓ Follow up Visits Days 7 and 14, and Months 1, 2, 3, 4, 5, and 6/ET				

Figure 1 Study Flow Chart



SCHEDULE OF ASSESSMENTS

Table 2 Schedule of Assessments

Definition 1 month = 4 weeks/28 days All visit windows are calculated from Baseline/Day 0	Visit 1 Screening[1]	Visit 2 Baseline/Day 0[1] (within 2 weeks after screening)	Visit 3 Day 7 (±1 day)	Visit 4 Day 14 (± 3 days)	Visit 5 Month 1 (±5 days)	Visit 6 Month 2 (±5 days)	Visit 7 Month 3 (±5 days)	Visit 8 Month 4 (±5 days)	Visit 9 Month 5 (±5 days)	Visit 10 Month 6/ET[2] (±5 days)
Informed Consent	X									
Demographic Data[3] including, Fitzpatrick skin type, medical history & concurrent diseases, previous facial treatments/procedures (toxin naïve/non-toxin naïve)	X									
Inclusion /Exclusion Criteria	X	X[4]								
Concomitant Therapies/ Procedures	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X[5]	X	X	X	X	X	X	X	X
Urine Pregnancy Test[6]	X	X[4]								X
Vital Signs (blood pressure, heart rate, and respiratory rate)[7]		X[5]	X	X	X					X
ECG		X[4]			X					X
Blood sample clinical chemistry and hematology		X[4]								X
Blood sample for serum antibody testing		X[4]			X					X
Lateral Canthal Lines Severity (LCL-ILA)	X	X[4]	X	X	X	X	X	X	X	X
Glabellar Line Severity (GL-ILA)	X	X[4]	X	X	X	X	X	X	X	X
Focused Physical Examination (face, head, neck)[8]	X	X[4]	X	X	X					X
Photography		X[4]	X	X	X	X	X	X	X	X
Randomization		X[4]								
Treatment		X[9]								
CCI										
Subject assessments										
Lateral Canthal Lines Severity (LCL-SLA)[10]	X	X[4]	X	X	X	X	X	X	X	X
Glabellar Line Severity (GL-SLA)[10]	X	X[4]	X	X	X	X	X	X	X	X
CCI										

1. *Screening and baseline visits may be on the same day. If completed on the same day, only perform study assessments once (i.e., PE, UPT, SLA, ILA, AE, concomitant therapies/procedures, inclusion/exclusion review)*
2. *If the subject withdraws before the final visit the assessments at Month 6/ET should be completed, if possible.*
3. *Includes date of birth, gender, race, ethnicity, height, and weight.*
4. *To be performed before treatment.*
5. *To be performed before treatment and post-treatment.*
6. *Females of childbearing potential.*
7. *Vital signs are taken seated after 10 minutes rest. Vital signs are taken prior to any blood draw (excluding post-treatment measurements on Day 0).*
8. *Post-baseline, events suggestive of remote spread of toxin are also considered while doing clinical evaluations based on the subject's symptoms and signs. Directed questioning and examination will then be performed as appropriate.*
9. *Following treatment administration, subjects will be monitored at the study center for 30 minutes.*
10. *Subjects will make their Lateral Canthal Line and/or Glabellar Line assessments independently of the Investigator's assessment.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	*Definition*
°C	Degrees Celsius
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
AST/ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BoNT	Botulinum Toxin
BoNT-A	Botulinum Toxin Type A
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CTN	Clinical Trial Number
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
CCI [redacted]	
FSFV	First Subject First Visit (first subject screened, i.e. who signs the informed consent form)
FSLV	First Subject Last Visit
CCI [redacted]	
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GL	Glabellar Lines

Abbreviation/Term	*Definition*
GLP	Good Laboratory Practices
Hb	Haemoglobin
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
i.e.	That is (Latin: id est)
ILA	Investigator Live Assessment
IM	Intramuscular
IND	Investigational New Drug
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-Investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator File	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
Investigational Product	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine Device
kDa	Kilodalton
KM	Kaplan-Meier
LCL	Lateral Canthal Lines
LSFV	Last Subject First Visit (last subject screened, i.e. who signs the informed consent form)
LSLV	Last Subject Last Visit (last subject who completed its last clinical study visit)
MAS	Merz Aesthetics Scale™
MD	Medical Doctor

Abbreviation/Term	*Definition*
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-treat
mL	Milliliter
MTD	Maximum tolerated dose
N or n	Number
N/A	Not Applicable
NAB	Neutralizing Antibody
OTC	Over-the-Counter
PE	Physical Examination
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
Plt	Platelet count
PP	Per-Protocol
PQC	Product Quality Complaint
PT	Preferred Term
QA	Quality Assurance
RA	Regulatory Authority
RBC	Red blood cell
Reference product	An investigational or marketed product (i.e. active control), or placebo, used as a comparator in a clinical study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
Sponsor File	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
SLA	Subject Live Assessment
Study Files	The Investigator file and the Sponsor file
Study Products	The investigational product and the reference product under study
Study Site	The location(s) where the study-related activities are actually conducted
TEAE	Treatment Emergent Adverse Event

Abbreviation/Term	*Definition*
UPT	Urine Pregnancy Test
US	United States
v/v	Volume/volume
WBC	White blood cell
WFI	Water for injection
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Medical Background and Short Rationale for the Clinical Study

Botulinum toxin (BoNT) is a potent neurotoxic protein produced by the Gram-positive anaerobic bacterium, *Clostridium botulinum*. The molecule is produced naturally by these bacteria together with a series of accessory proteins, forming what is termed the "toxin complex". The neurotoxin is the cause of the severe and potentially fatal disease of botulism. In addition, the protein is used in very small quantities as a treatment modality for aesthetic and medical indications, many of which are characterized by increased muscle activity. Botulinum toxins occur in seven known serotypes (A-G) that are produced by different strains of *Clostridium botulinum*. Clinically-important biologic activity is limited primarily to the A and B serotypes, of which the type A serotype (BoNT-A) is used widely throughout the world for the treatment of a range of clinical conditions.

BoNT-A blocks the release of acetylcholine into the neuromuscular junction (synapse) cleft, thereby prohibiting the activation of acetylcholine receptors. Paresis by chemical denervation thus occurs in the target muscle, leading to inhibition of muscular contraction. The active neurotoxin is 150 kDa molecular weight and QM1114-DP only contains this part of the toxin complex: there are none of the other accessory proteins which are normally associated with the 150 kDa active moiety.

Since the 1970s, BoNT-A has been investigated and subsequently approved for the treatment of multiple indications around the world.[2,3] Treatment of strabismus by relaxation of overactive extraocular muscles was the first reported medical use.[4] Clinical studies for aesthetic indications were first performed in the late 1980s.[5] Since then, many other clinical indications have been investigated,[6-8] although the number of approved indications is much smaller. BoNT-A products have been licensed in the US for the aesthetic indications of glabellar lines (GL), lateral canthal lines (LCL) and forehead lines (FL), together with therapeutic indications such as strabismus, blepharospasm, hemifacial spasm, cervical dystonia, focal spasticity, prophylactic treatment of chronic migraine, overactive bladder and hyperhidrosis.

In the early 1990s, patients treated with BoNT-A for blepharospasm were observed to lose their frown lines and,[5,9] since publishing these observations, the use of BoNT-A in the aesthetic setting has accelerated. Injectable BoNT-A products have been investigated for multiple aesthetic indications in attempts to reverse the appearance of aging, especially in the facial region.[2] In the treatment of facial lines, the effect of BoNT-A injections usually persists for approximately 4-6 months. Facial muscle activity and severity of the facial wrinkles then returns to baseline. Full functionality of facial muscles is usually restored by approximately 6 months post-treatment.[10]

There are four BoNT-A products currently licensed in the United States (US) for the treatment of GL (Botox Cosmetic®, Dysport®, Xeomin®, and Jeuveau™), and one licensed for the treatment of LCL (Botox Cosmetic®). QM1114-DP is a novel botulinum toxin type-A1 which is presented as a liquid formulation. Unlike the main commercially available botulinum toxins in the US, QM1114-DP is manufactured and formulated without any animal or human proteins. As a novel BoNT-A with a differentiated formulation, QM1114-DP is being developed for the treatment of moderate to severe GL and LCL in adults over 18 years.

1.2 Study Product Profile

1.2.1 Drug Profile

QM1114 is a protein dimer of 150 kilodalton (kDa) CCI [redacted] Unlike other commercially available BoNTs, QM1114 is manufactured and formulated without any animal or human proteins, thereby reducing the potential risk of viral contamination in the product.

CCI [redacted]

1.2.2 Pre-Clinical Documentation

The pre-clinical pharmacology-toxicology program has included appropriate toxicology studies to support safety for administration of QM1114-DP at the proposed dose of 50 unit (U), 60 U, and combined total dose of 110 U which will be evaluated in this study.

CCI [redacted]

No safety pharmacology or pharmacokinetic studies were conducted for QM1114-DP since no systemic exposure to the product is expected with a single IM administration to specific facial muscles using the dose proposed. Additionally, BoNT-A binds with high affinity at the neuronal synapses at the local injection site.[11] Therefore, any metabolism and elimination of the product would occur at the local site of injection.

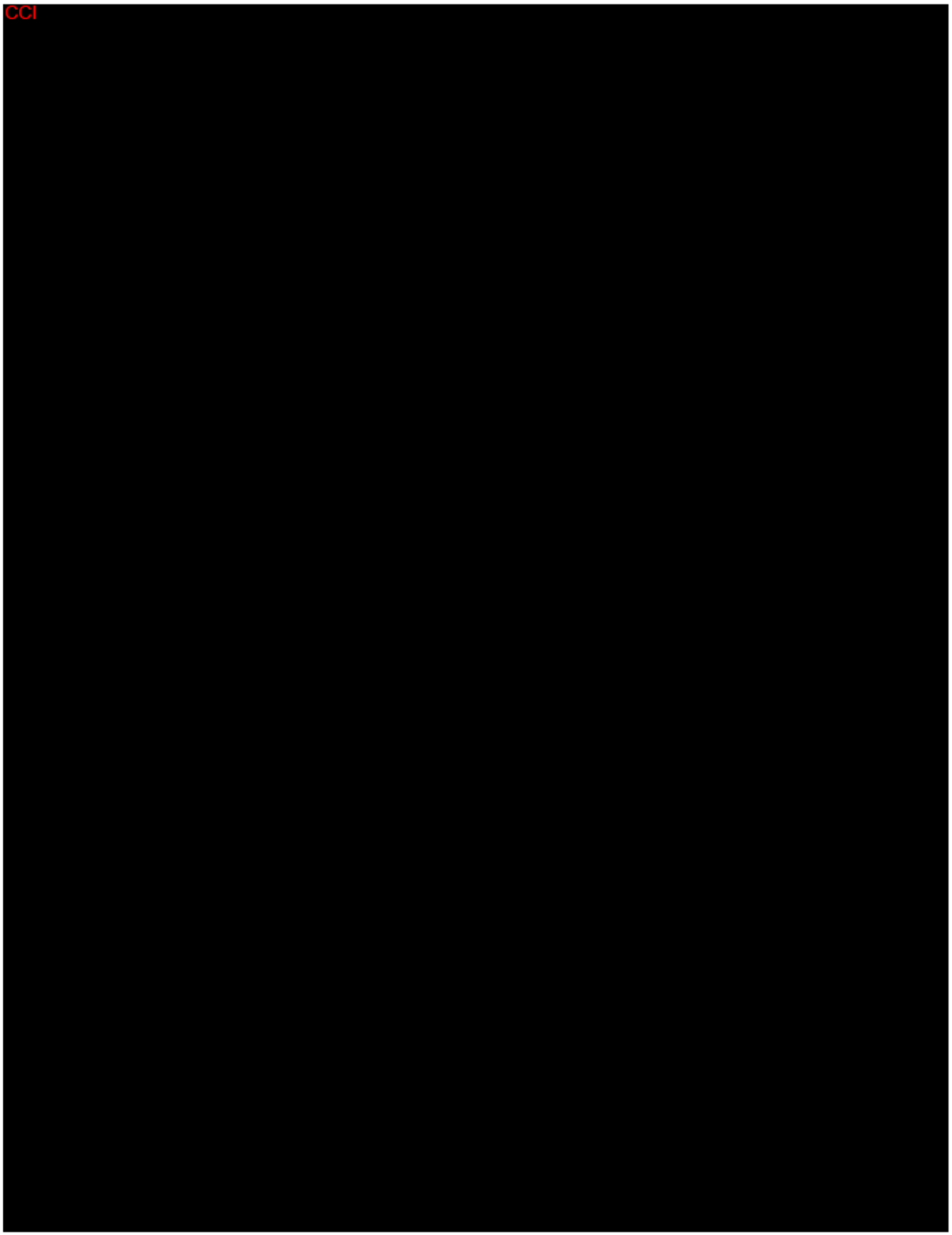
CCI [redacted]

CCI

1.2.3 Clinical Documentation

CCI

CCI



CCI

CTN 43QM1313

Following successful completion of clinical study CCI, a randomized, double-blind, placebo controlled, dose finding study of QM1114-DP using three different single doses of QM1114-DP (30, 45, 60 U) in male or female subjects aged over 18 years with moderate to very severe GL was performed.

Efficacy in reduction of GL severity was evaluated using the 5-point MAS scale. Efficacy assessments were made for up to and including six months post-treatment.

CCI

CCI [redacted]

1.2.4 Dose Rationale

Non-clinical studies have shown a similarity between QM1114-DP potency units and Speywood units (i.e., the Dysport®/Azzalure® product). In the treatment of the LCL with Speywood units the recommended dose is 60 U. In the treatment of the GL with Speywood units the recommended dose is 50 U.

For treatment of the LCL and GL, alone or in combination, both the safety and efficacy of QM1114-DP was established in the phase 1 study (CCI [redacted]). For treatment in the LCL the 60 U dose has been selected for further clinical development, and for treatment in the GL the 50 U dose has been selected. For the combined LCL and GL treatment, QM1114-DP was evaluated at two ascending dose levels (i.e., 110 U [50 U in the GL and 60 U in the LCL], and 140 U [50 U in the GL and 90 U in the LCL). The 110 U dose has been selected for further clinical development in the treatment of LCL and GL. This is consistent with the combined recommended Speywood unit doses in each treatment area as well as clinical experience, as specified above.

1.3 Risk/Benefit Assessment

CCI [redacted]

In the phase 2 study (CTN 43QM1313; GL treatment area only), QM1114-DP was well tolerated at all dose levels. The treatment-related TEAEs reported in the study were of similar type as those reported for other toxins in GL treatment. CCI [redacted]

The risk of AEs occurring may be reduced by using physicians who are experienced in the botulinum toxin injection technique. All treating Investigators will be trained in the administration technique of QM1114-DP prior to the study start.

The benefit to subjects receiving QM1114-DP in this study will be a temporary reduction in the appearance of their LCL and/or GL. The subjects in the placebo group are not expected to gain any clinical benefit from their participation in the study; however, as this is an aesthetic indication there are no sequelae to lack of efficacy beyond a disappointment in the reduction of severity of their LCL and/or GL. In addition, only one subject out of seven will receive placebo only in the study; most subjects (6/7 subjects) will receive QM1114-DP in one or both treatment areas (i.e., LCL and/or GL).

No additional risks specific to the QM1114-DP 50 U, 60 U, and 110 U doses are anticipated, and sufficient clinical experience with BoNT-A products with similar mode of action for facial aesthetic use at dose levels corresponding to the dose levels in this study demonstrate the potential benefit of the proposed treatments. Adverse events will be recorded at each study visit, and subjects will also be queried for any potential signs and symptoms of local and distant spread of the toxin effect.

In conclusion, given the anticipated low level of transient and acceptable risks, the risk/benefit assessment of the use of QM1114-DP for the treatment of moderate to severe LCL and GL, and appears to offer a substantial clinical benefit at reasonable risk.

2. CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS

2.1 Clinical Study Objectives

The objective of the study is to evaluate the efficacy and safety of a single dose of QM1114-DP for the treatment of moderate to severe LCL and GL, alone or in combination.

2.1.1 Primary Efficacy Objectives and Endpoints

The primary objective of this study is to evaluate the efficacy of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, compared to placebo for the treatment of moderate to severe LCL and GL.

GL

For the primary endpoint, the composite responder rate will be evaluated at Month 1 using the GL-ILA and the GL-SLA at maximum frown. A composite responder is defined as a subject who achieves grade/level 0 or 1 in GL severity and at least 2 grades improvement from baseline on both the GL-ILA and GL-SLA scales concurrently.

LCL

For the primary endpoint, the composite responder rate will be evaluated at Month 1 using the LCL-ILA and the LCL-SLA at maximum smile. A composite responder is defined as a subject who achieves grade/level 0 or 1 in LCL severity and at least 2 grades improvement from baseline on both the LCL-ILA and LCL-SLA scales concurrently.

2.1.2 Secondary Efficacy Objectives and Endpoints

The secondary efficacy objectives and endpoints of the study are:

Objective: To evaluate the efficacy of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, and placebo for the treatment of moderate to severe LCL and GL.

Endpoint: Percentage of subjects who achieve a score or 0 or 1 at:

CCI [redacted]

- Each post-treatment visit (excluding month 1) using the GL-ILA at maximum frown
- Each post-treatment visit (excluding month 1) using the LCL-ILA at maximum smile

CCI [redacted]

CCI

2.1.4 Safety Objectives and Endpoints

To evaluate the safety of a single dose of 60 U of QM1114-DP in the LCL and 50 U of QM1114-DP in the GL, alone or in combination, compared to placebo for the treatment of moderate to severe LCL and GL.

Safety endpoints include:

- Incidence and severity of TEAEs
- Focused physical examination (FPE) findings
- Vital signs
- Electrocardiogram (ECG)
- Laboratory parameters (clinical chemistry and hematology)
- Neutralizing antibody production

2.2 Clinical Hypothesis

The clinical hypothesis of the study is that QM1114-DP is more effective than placebo for the treatment of moderate to severe LCL and GL, and has an acceptable safety profile.

3. OVERALL CLINICAL STUDY DESCRIPTION

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with treatment of QM1114-DP in the LCL and GL, alone or in combination.

Following the informed consent and the screening process, eligible subjects will be randomly assigned to treatment in a 2:2:2:1 ratio. Subjects will receive a single treatment at baseline (Day 0) of either:

- 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects),
- 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects),
- 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or
- Placebo in both the LCL and GL (59 subjects).

Randomization will be stratified by study center.

Subjects eligible for the treatment must meet the severity criteria for LCL and GL at baseline (i.e. moderate to severe LCL and GL at maximum smile and maximum frown, respectively). LCL should be bilaterally symmetrical. Baseline wrinkle severity determination will be based on both investigator and subject ratings using the 4-point photographic scale of LCL severity (LCL-ILA; LCL-SLA) and the 4-point photographic scale of GL severity (GL-ILA) and the subject 4-point categorical scale (GL-SLA).

Following treatment at baseline, subjects will be monitored for safety and efficacy according to the Schedule of Assessments (Table 2).

Efficacy assessments will include (Section 7.1):

- Investigator 4-point Photographic Scale of LCL Severity at CCI maximum smile (Investigator assessment [LCL-ILA])
- Subject 4-point Photographic Scale of LCL Severity at CCI maximum smile (subject assessment [LCL-SLA])
- Investigator 4-point Photographic Scale of GL Severity at CCI maximum frown (Investigator assessment [GL-ILA])
- Subject Static 4-point Categorical Scale of GL Severity at maximum frown (subject assessment [GL-SLA])

CCI

Safety assessments will include (Section 7.2):

- AEs
- Focused physical examination (FPE)
- Vital signs
- ECG
- Laboratory safety tests (chemistry and hematology)
- Production of neutralizing antibodies against QM1114-DP

Selection criteria for the study population are described in Section 5. Detailed information about study tasks by treatment visit is outlined in Section 8 and in Table 2. Information regarding clinical supplies and treatment procedure are provided in Section 6 .

4. CLINICAL STUDY DURATION AND TERMINATION

The planned duration of recruitment (from first subject first visit [FSFV] to last subject first visit [LSFV]) is approximately 3 months.

The planned clinical study duration from FSFV to last subject last visit (LSLV) is approximately 9.5 months.

Clinical study participation for each subject is approximately 6.5 months.

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical study center (for example, lack of subject enrollment or non-compliance with clinical study protocol, regulation, or GCP) or prematurely suspend the clinical study (for example, for safety, study product quality, regulatory, efficacy, or logistical reasons) at any time with appropriate notification.

5. SELECTION AND DISPOSITION OF CLINICAL STUDY POPULATION

5.1 Number of Subjects

As a screen failure rate of approximately 10 percent is anticipated, approximately 454 subjects will be screened in order to get 413 subjects enrolled in a 2:2:2:1 ratio to:

- 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects),
- 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects),
- 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or
- Placebo in both the LCL and GL (59 subjects).

It is expected that each center will recruit a similar number of subjects.

5.2 Clinical Study Population Characteristics

In order to be eligible for the clinical study, subjects must fulfill all of the following criteria. These criteria are applicable at both screening and baseline unless otherwise specified.

5.2.1 Inclusion Criteria

1. Male or female 18 years of age or older.

2. Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum smile as assessed by the Investigator live assessment (LCL-ILA).

3. Bilaterally symmetrical LCL graded as Level 2 or Level 3 on the 4-point Photographic Scale (ranging from Level 0 to Level 3) at maximum smile as assessed by the subject live assessment (LCL-SLA).

4. Moderate to severe GL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum frown as assessed by the Investigator (GL-ILA).

5. Moderate to severe GL (grade 2 or 3 on the Static 4-Point Categorical Scale ranging from 0 [no wrinkles] to 3 [severe wrinkles]) at maximum frown as assessed by the subject (GL-SLA).

6. Female of non-childbearing potential (i.e., post-menopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], or has undergone hysterectomy or bilateral oophorectomy).

   OR

   Female of childbearing potential with a negative urine pregnancy test at screening and baseline, and agrees to use a highly effective and approved contraceptive method for the duration of the study. A highly effective method of contraception is defined as:

   - Bilateral tubal ligation;
   - Combined (estrogen and progesterone containing) oral, intravaginal or transdermal contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit;
   - Intra uterine device (IUD) inserted at least 28 days prior to screening visit;
   - Intrauterine hormone-releasing system;
   - Partner vasectomized for at least three months prior to screening visit;
   - Progestogen-only oral, injectable or implantable contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit; or
   - Strict abstinence (i.e., refraining from heterosexual intercourse for the entire duration of the subject's participation in the study).
7. Time and ability to complete the study and comply with instructions.
8. Understands the study requirements and signed the informed consent form (ICF).

5.2.2 Exclusion Criteria

1. Botulinum toxin treatment in facial areas within 9 months prior to study treatment.
2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product).
3. Female who is pregnant, breast feeding, or intends to conceive a child during the study
4. Known allergy or hypersensitivity to any component of the investigational product (QM1114-DP).
5. Inability to substantially reduce the appearance of facial rhytides in the treatment area by physically spreading them apart, as determined by the Investigator.
6. Clinically significant abnormal focused physical examination finding(s) at screening or baseline visits, in the investigator's opinion.
7. Excessive skin laxity in the treatment area or periorbital area.
8. Previous use of any hyaluronic acid soft tissue augmentation therapy in the lateral canthal or glabella area within 6 months before baseline.

9. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc.) or semi-permanent (e.g., calcium hydroxylapatite, Poly-L-Lactic acid or polymethyl-methacrylate) product; lifting threads, or autologous fat in the treatment area.
10. History, presence, or predisposition of eyelid or eyebrow ptosis (heavy eyebrows), amblyopia (i.e., lazy eye), or previous surgery around the eye that may lead to the above events, as determined by the Investigator.
11. Marked facial asymmetry, excessive dermatochalasis (i.e., excess of skin in eyelids), or marked periocular or eyebrow asymmetry.
12. Presence of scar(s), piercing(s), or tattoos (including microblading of eyebrow or eyeliner) in the treatment area or around the treatment area, that in the Investigator's opinion, may interfere with study evaluations.
13. Presence of inflammation, active infection or skin disorder, such as eczema, rosacea, facial psoriasis, herpes zoster etc., near or in the treatment area.
14. Presence of cancerous or pre-cancerous lesions in the treatment area.
15. History of other facial treatment, surgery, or other aesthetic procedures (e.g. ablative skin resurfacing, laser treatment, microneedling, or chemical peel) in the previous 12 months that, in the Investigator's opinion, could interfere with study injections and/or assessments or expose the subject to undue risk by study participation.
16. Planned facial surgery, eye surgery (including LASIK procedure) or aesthetic procedures (e.g. ablative skin resurfacing, laser treatment, microneedling, or chemical peel in the upper or midfacial area) during the study period.
17. History or presence of facial nerve palsy, or any medical condition that may put the subject at increased risk with exposure to botulinum toxin including diagnosed myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function.
18. Use of medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases, and aminoglycoside antibiotics.
19. Subject with bleeding disorder or subject currently using anticoagulants.
20. Subject has any prior or current psychiatric illness (e.g. psychosis, depression, anxiety), alcohol or drug abuse, or is taking antidepressant, anxiolytic, or antipsychotic medication that, in the Investigator's opinion, could affect the subject's safety and/or the conduct or outcome of the study.
21. Other concurrent medical conditions, therapy or other condition that in the Investigator's opinion would interfere with the evaluation of the study medication safety or efficacy and/or put the subject at risk if he/she participates to the study.
22. Participation in an investigational device or drug study within 30 days prior to study treatment or plans to enroll in any other investigational study during participation in this study
23. Study center personnel, close relatives of the study center personnel (e.g. parents, children, siblings, or spouse), employees or close relatives of employees at the Sponsor company.

5.3 Medical History

Relevant history of surgical events and medical conditions shall be documented in the subject's study file and electronic case report form (eCRF) using medical terminology.

5.4 Previous and Concomitant Therapies

5.4.1 Definition

Previous therapies are defined as therapies that have been stopped within the 4 weeks preceding the screening visit or within timeframes specified in the inclusion/exclusion criteria.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical study, or
- any new therapies received by the subject since the screening visit.

5.4.2 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers (area of treatment should be indicated), X-rays, surgeries, tooth extractions.

5.4.3 Recording

Previous and concomitant therapies are to be recorded in the subject's source documents and eCRFs.

Concomitant therapies are to be reviewed at each visit and updated in the source documents and eCRFs as needed.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form should be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

5.4.4 Authorized Concomitant Therapies

Unless listed in prohibited concomitant therapies (see Section 5.4.5), all are authorized.

5.4.5 Prohibited Concomitant Therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety assessment of the study products:

- Botulinum toxin of any serotype.
- Any other investigational new drug or device.
- Any absorbable (temporary) or non-absorbable (permanent) material in the treatment areas.
- Facial aesthetic procedures (e.g., ablative skin resurfacing, laser treatment, micro needling, photodynamic therapy, tattooing or chemical peel) or any other procedures in the treatment area.
- Facial surgery or eye surgery (including LASIK procedure).
- Medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics.

If a prohibited therapy becomes a necessary treatment for best clinical interest of the subject or due to safety reason, the Medical Monitor (Section 11.9) should be notified, if time permits, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives a prohibited therapy during the clinical study, the Medical Monitor (Section 11.9) should be notified to discuss the subject's continuation in the clinical study.

5.5 Procedures/Reasons for Subject Discontinuation

An Investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Month 6/ ET visit should be completed for all subjects discontinuing the clinical study and the appropriate eCRF should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the exit form. For discontinuation due to an AE, the AE form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

Potential reasons for discontinuation are listed below:

- Adverse Event: Complete an AE form.

- Withdrawal by Subject: Includes consent withdrawal, subject relocation, schedule conflicts, etc. Explain the reason for withdrawal in the comment section of the eCRF exit form.
- Lost to Follow-up: Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF exit form.
- Other: This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF exit form.

A subject who has been randomized and assigned a kit number/randomization number cannot be replaced by another subject if he/she discontinues the clinical study for any reason. Additional subjects could be enrolled (randomized/assigned to treatment) in order to attain the number of evaluable subjects.

Pregnancies occurring during the screening period are considered screen failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed. In case of a pregnancy occurring after the baseline visit, follow the procedures described in Section 7.2.6.2.3. The subject may remain in the study, but no invasive procedure should be conducted (e.g. no sample taken for lab test).

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

6. CLINICAL SUPPLIES

Details of the drug composition and excipients are provided in the current QM1114-DP Investigators Brochure.[12]

6.1 Clinical Supply Identification and Use

6.1.1 QM1114-DP

The investigational product (QM1114-DP) will be supplied as a sterile solution for injection containing the drug substance, QM1114-DS. The drug substance is a BoNT Type A. QM1114-DS is diluted in a buffer solution.

At the baseline visit, QM1114-DP will be administered per the blinded randomization assignment as one of the following:

- 6 equal aliquots of 0.1 mL in each of the injection sites in the LCL areas for a total volume of 0.6 mL (0.3 mL per LCL treatment side) of QM114-DP, or
- 5 equal aliquots of 0.1 mL in each of the injection sites in the GL area for a total volume of 0.5 mL of QM1114-DP, or
- 11 equal aliquots of 0.1 mL in each of the injection sites in the GL and LCL areas for a total volume of 1.10 mL of QM1114-DP.

CCI [redacted]

6.1.2 Placebo

Placebo will be supplied as a buffered solution for injection containing only the buffer solution of QM1114-DP; placebo does not contain active drug substance.

At the baseline visit, placebo will be administered per the blinded randomization assignment as one of the following:

- 6 equal aliquots of 0.1 mL in each of the injection sites in the LCL areas for a total volume of 0.6 mL (0.3 mL per LCL treatment side) of placebo, or
- 5 equal aliquots of 0.1 mL in each of the injection sites in the GL area for a total volume of 0.5 mL of placebo, or
- 11 equal aliquots of 0.1 mL in each of the injection sites in the GL and LCL areas for a total volume of 1.10 mL of placebo.

The placebo product should be stored at the recommended temperature (between 2°C and 8°C; 36 °F – 46 °F). The placebo product should not be frozen and should be protected from light.

6.1.3 Study Product Description

Table 3 Description and Usage of the Study Products

	Investigational product	Reference product
Name of drug substance	QM1114-DS	N/A
Internal Code	QM1114-DP	Placebo
Pharmaceutical Form	Solution for injection	Solution for injection
Concentration	100 units/mL, buffered solution	N/A, buffer solution
CCI		
Dosage	60 units 0.6 mL total 0.1 mL per LCL injection point AND/OR 50 units 0.5 mL total 0.1 mL per GL injection point	N/A 0.6 mL total 0.1 mL per LCL injection point AND/OR N/A 0.5 mL total 0.1 mL per GL injection point
Route	Intramuscular injection	Intramuscular injection
Dose regimen	Single treatment at baseline visit	Single treatment at baseline visit
Location of treated area	Lateral canthus and glabellar areas	Lateral canthus and glabellar areas

6.1.4 Subject Identification Number (SIN)

Each study participant who has signed the ICF will be entered into the eCRF system and a subject number will be assigned via the eCRF system. For the duration of the study, the subject will be identified using the subject number for all documentation and discussion.

Subject numbers will consist of the study center number followed by a consecutive number starting with 001 at each center. The subject numbers shall be allocated in ascending sequential order within each center. If a subject is deemed not eligible for the study participation, the reason for screen failure should be specified. A screen failure cannot be re-screened.

A log/listing should be maintained by each site for all subjects who have signed the ICF. There should be sufficient information to link the eCRF to a study subject's source documents and medical records.

6.1.5 Method of Treatment Assignment

Before starting the study, a randomization list stratified by study center will be generated. When the Investigator has confirmed subject eligibility, the subject will be allocated a study product within the Electronic Data Capture (EDC) system.

6.1.6 Kit Number/Randomization Number

A kit number/randomization number, a unique number on the label of the study products, will be assigned to each eligible subject at baseline.

Kit number/randomization number will be allocated in ascending sequential order to each eligible subject.

6.1.7 Instructions for Use and Administration

QM1114-DP will be compared to placebo in this study and administered based on randomization.

Placebo is identical in appearance to the active QM1114-DP but contains no active drug substance.

QM1114-DP and placebo are administered in exactly the same way. All treating Investigators will be trained in the administration technique prior to the study start.

Handling of accidently damaged or spilled study product is described in the Material Safety Data Sheet.

See also QM1114-DP Investigators Brochure.[12]

6.1.7.1 Treatment Procedure

6.1.7.1.1 Lateral Canthus Areas

Prior to injection, the treatment area should be cleaned with a suitable antiseptic solution. An appropriately sized syringe and needle (e.g., 30-33 gauge needle) should be used to administer treatment.

At baseline, subjects will be randomized to receive treatment with QM1114-DP or placebo in the LCL. A total dose volume of 0.6 mL divided into six equal aliquots (0.1 mL per injection site) will be administered intramuscularly in the lateral canthus areas, 0.3 mL per side.

There are two options for the injection sites in the lateral canthus areas; see Figure 2 and Figure 3 below. The injection site option for each subject is based on Investigator discretion and should be consistent for the right and left treatment sides.

Figure 2 Injection Sites for Treating LCL Option 1

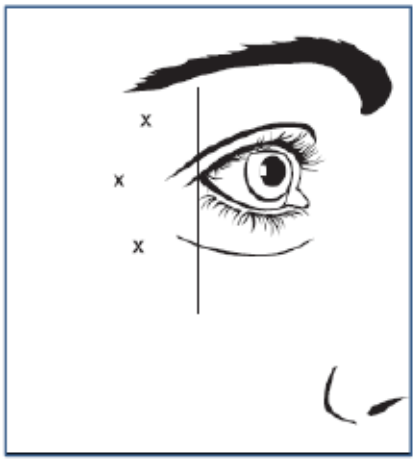
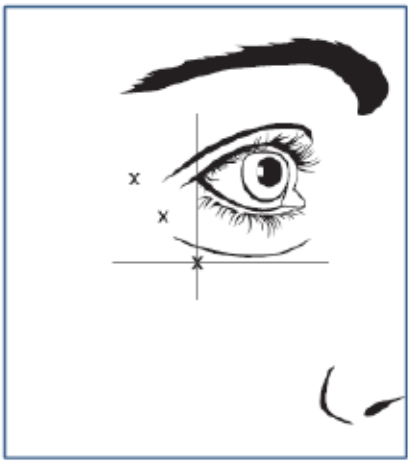


Figure 3 Injection Sites for Treating LCL Option 2



Injections should be performed at a 20-30° angle to the skin, with bevel of needle tip pointed up and away from the eye and very superficial. All injection points, three per side, should be at the external part of the orbicularis oculi muscle and sufficiently far from the orbital rim (at least 1 - 2 cm). The injection points should be separated by 1-1.5 cm distance.

When lines in the lateral canthal region appears both above and below the lateral canthus, inject per figure 2. In case lines in the lateral canthal region are mainly below the lateral cantus, inject per figure 3.

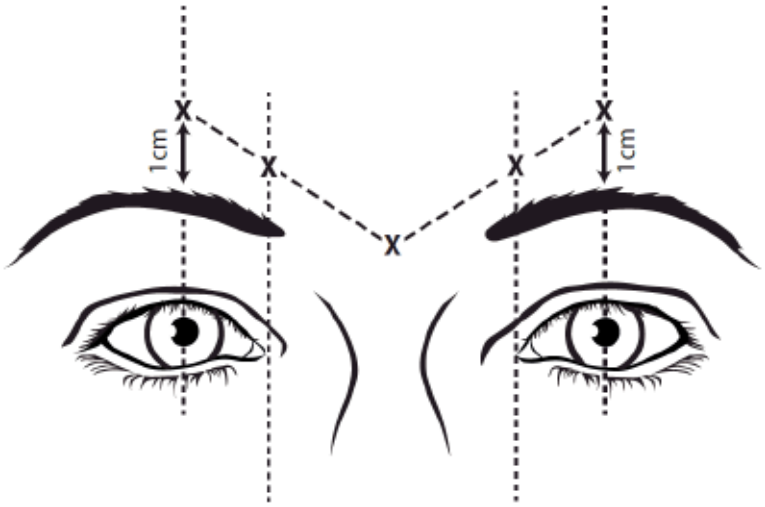
The anatomical landmarks can be more readily identified if observed and palpated at maximum smile. Care must be taken to avoid injecting the zygomaticus major/minor muscles to avoid lateral mouth drop and asymmetrical smile.

6.1.7.1.2 Glabellar Lines

Prior to injection, the treatment area should be cleaned with a suitable antiseptic solution. An appropriately sized syringe and needle (e.g., 30-33 gauge needle) should be used to administer treatment.

At baseline, subjects will be randomized to receive treatment with QM1114-DP or placebo in the GL. Each treatment includes five intramuscular (IM) injections of equal volume (0.1 mL) administered at 5 injection sites in the glabellar region (0.5 mL in total). The injections should commence in the procerus muscle followed by the corrugator supercilii muscles on each side, moving outwards from the median. All injections should be approximately 1 cm above the upper orbital rim and internal to the mid-pupillary lines (Figure 4).

Figure 4 Injection Sites for Treating Glabellar Lines



In order to minimize risks of regional effect of the neurotoxin (e.g., eyelid ptosis), the investigator should use one thumb to apply pressure on the upper orbital rim while injecting. It is recommended that injection is not closer than 1 cm above the central eyebrow or the bony supraorbital ridge. Moreover, the tip and bevel of the needle should always be pointed away from the study subject.

6.1.7.2 Post-treatment Care

Following treatment administration at baseline, subjects will be monitored at the study center for 30 minutes.

Subjects will be instructed to avoid applying pressure, rubbing or massaging the treated areas, or lying face down for 4 hours after treatment.

6.1.7.3 Treatment Regimen

Each subject will receive a single treatment with QM1114-DP and/or placebo at the baseline visit.

The treatments investigated in this study are:

- 60 U of QM1114-DP in the LCL
- 50 U of QM1114-DP in the GL
- Placebo

6.2 Study Product Packaging and Labeling

QM1114-DP and placebo are manufactured under aseptic conditions. CCI [redacted]

The labels will be printed in English. The text of the label will detail the information requested by Good Manufacturing Practice and local regulations, and at a minimum include the protocol number, storage conditions, and an investigational test article disclaimer ("Caution: New Drug - Limited by Federal (or United States) law to investigational use.")

6.3 Supplies Management

6.3.1 Accountability

Upon receipt of the study products, the Investigator or designee will maintain accurate records of the study products delivery to the clinical study center, the inventory at the clinical study center, the use by each subject, the reconciliation of all study products received from the Sponsor's designee, and the return to the Sponsor's designee for disposal of unused study products.

All study products sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted.

6.3.2 Storage of Study Products

Study products must be stored in a safe and secure area with restricted access, under the storage conditions specified by the Sponsor (see Table 3).

6.3.3 Dispensing and Return

All study products must be inventoried and a record of the dispensing for each subject must be appropriately documented. Any dispensing errors must be reported to the Sponsor/CRO and properly documented.

In the event of early termination/suspension of the clinical study, a rapid recall of study products will be initiated.

Unused or expired study product will be returned for destruction to the Sponsor representative at time points approved by the Sponsor.

6.3.4 Treatment Compliance Management and Record

The treatment is an injection administered by the Investigator. Details of the injection procedure will be recorded in the eCRF and subject source documents. No other measurements of treatment compliance will be made.

6.3.5 Dose Modification

Dose modifications are not permitted.

6.3.6 Product Quality Complaints

Product Quality complaints (PQCs) should be reported to the Safety e-mail listed in Section 11.9. A PQC is an external judgement presuming a quality defect of a product; quality issue for a product relating to its presentation or use, identified by a subject, a practitioner or Investigator site personnel, a distributor, or anyone else involved in clinical supplies handling. Examples may include but are not limited to appearance issues, odor, damaged stoppers, low fills, and foreign matter in the product. These complaints may or may not represent a potential risk to the subject. A PQC form must be completed by the study center personnel and forwarded to the Sponsor or designee within 24 hours of awareness. Affected study product should be quarantined, and not used, until further notice by the Sponsor.

Additional contact details are provided in the Investigator's site file.

6.4 Blinding

This is a double-blind study in which neither the Investigator, sub-Investigator, study staff, nor the subject will know the subject's study product assignment (i.e., QM1114-DP and/or placebo). Placebo is identical in appearance to QM1114-DP but contains no active drug substance.

Subjects will be randomized at baseline to either treatment with QM1114-DP, QM1114-DP and placebo, or placebo. In order to maintain the blind, the study products, will be supplied in identical vials, each with a unique number on the vial label. Both study products will be administered in exactly the same way.

An un-blinded statistician will generate the randomization schedule; however, he/she will not be involved in any other aspect of the study prior to database lock.

The Sponsor's staff or designees directly involved in clinical operations management, data management, and statistical evaluation of the study will remain blinded until the database is locked, unless emergency unblinding is required.

6.4.1 Verification of Blinding

The Sponsor's staff or designees will assess and verify maintenance of the study blind during the study through routine monitoring visits.

6.4.2 Unblinding During the Clinical Study

Emergency un-blinding during the clinical study may be required for therapeutic or for regulatory reasons (for expedited safety reporting).

A blind-break system will be available for Investigators. In such an emergency, the Investigator will only break the blind for the subject involved.

The Investigator must notify the Sponsor immediately in the event of such an emergency (see contact details in Section 7.2.6.2.2). If possible, the Investigator should notify the Sponsor before breaking the blind in order to discuss this decision with the Sponsor. The Investigator is required to document each case of emergency unblinding and inform the Sponsor immediately.

7. CLINICAL STUDY ASSESSMENT

7.1 Efficacy Assessments

7.1.1 Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA)

The validated Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Appendix 1), developed by Galderma, includes two grading systems: one for the Investigator live assessments at maximum smile, CCI [redacted]. The scale represents LCL severities from none (grade 0), mild (grade 1), moderate (grade 2), to severe (grade 3). Each grade is also depicted by an individual photograph and descriptive text. The Investigators will be trained on the use of the LCL-ILA.

The Investigators will use the LCL-ILA for direct, live comparison with the subject's face for grading LCL severity at screening, baseline (prior to treatment), and at all post-treatment visits. Left and right LCL should be assessed separately at CCI [redacted] maximum smile.

7.1.2 Subject 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-SLA)

The validated Subject 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-SLA) (Appendix 2), developed by Galderma, includes two grading systems: one for the subject's live assessments at maximum smile, CCI [redacted]. The scale represents LCL severities from Level 0, Level 1, Level 2, to Level 3. Each grade is also depicted by an individual photograph and descriptive text. Subjects will be trained on the use of the LCL-SLA.

Subjects make their assessments independently of the Investigator's assessment. Subjects will evaluate their LCL severity (left and right side separately) at CCI [redacted] maximum smile, respectively, at screening, baseline (prior to treatment), and at all post-treatment visits.

7.1.3 Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA)

The validated Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Appendix 3) includes two grading systems: one for Investigator live assessments at maximum frown, CCI [redacted]. The scale represents the severity of GL from none (grade 0), mild (grade 1), moderate (grade 2) to severe (grade 3). Each grade is also depicted by an individual photograph and a descriptive text. The Investigators will be trained on the use of the 4-point Photographic Scale.

The Investigators will use the 4-point Photographic Scales for direct, live comparison with the subject's face at CCI [redacted] at maximum frown at screening, baseline (prior to treatment), and at all post-treatment visits.

7.1.4 Subject Static 4-point Categorical Scale of Glabellar Line Severity (GL-SLA)

Subjects will make their assessment of glabellar line severity independently of the Investigator's assessment. Subjects will be asked to evaluate their GL at maximum frown at screening, baseline (prior to treatment), and at all post-treatment visits using the following Static 4-Point Categorical Scale.

Grade	Severity of Glabellar Lines	Description
0	No wrinkles	Smooth skin
1	Mild wrinkles	Fairly smooth skin
2	Moderate wrinkles	Frown lines
3	Severe wrinkles	Deep frown lines

CCI [redacted]

CCI

7.2 Safety Assessments

Safety assessment will be conducted for all subjects at the time points indicated in Schedule of Assessments (Table 2). Safety parameters include an evaluation of AEs, CCI vital signs, ECG, laboratory safety tests (chemistry and hematology), and neutralizing antibody production.

7.2.1 Focused Physical Examination (FPE)

At the time points indicated in the Schedule of Assessments (Table 2), the Investigator or designee will perform a physical examination of the subject that includes the face, head, and neck. Further details are provided in Appendix 6.

Post-baseline, the signs and symptoms will also be monitored via physical examination of face, head, and neck to evaluate local effect of toxin. In addition, general physical examination to evaluate the remote spread events will be conducted. The list of remote spread of toxin events is considered while doing clinical evaluations based on subject's symptoms and signs (Appendix 7). Directed questioning and examination will then be performed as appropriate.

The Investigator may choose to investigate any other sign that he/she observes during the physical examination. Abnormalities noted pre-injection, i.e. at the screening/baseline visits, should be recorded as medical history and abnormalities noted post-injection should be recorded as AEs.

7.2.2 Vital Signs

At the time points indicated in the Schedule of Assessments (Table 2), evaluation of vital signs shall be performed after approximately 10 minutes rest in the sitting position. It shall include measurement of systolic and diastolic blood pressure, heart rate, and respiratory rate. Vital signs will be taken prior to any blood draw, excluding post-treatment measurements on Day 0.

All abnormal values at the baseline visit identified, as clinically significant by the Investigator, shall be recorded in the Medical History form.

For any clinically significant changes from the baseline visit, an AE is to be recorded.

7.2.3 Electrocardiogram (ECG)

The 12-lead ECG recordings will be made after the subjects have been resting in a supine position for at least 10 minutes at the time points indicated in Table 2, the baseline ECG should be done prior to treatment. The subjects should avoid postural changes during the ECG recordings. At each time-point, the ECG will be recorded in triplicate. The triplicates will be performed at approximately one-minute intervals.

ECGs will be stored electronically and submitted to a central reviewer for analysis. Paper printouts may also be collected for general cardiac safety monitoring at the clinical research site.

Clinically significant abnormal values at baseline shall be recorded in the Medical History form. For any clinically significant changes from baseline, an AE is to be recorded.

The Investigator and Medical Monitor will be alerted (*eg*, email) for ECGs that are identified as "abnormal, clinically significant" by the central ECG laboratory.

7.2.4 Laboratory Safety Tests

Blood samples will be collected at baseline (prior to treatment) and at Month 6/ET, and sent to a central laboratory for analysis. Instructions for blood sampling are detailed in a separate laboratory manual.

The following laboratory safety tests shall be performed:

- Hematology: White blood cell (WBC) count with differential, red blood cell (RBC) count, haemoglobin (Hb), hematocrit (hct), and platelet count (Plt)
- Blood chemistry: Creatinine, urea nitrogen, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST=SGOT), alanine aminotransferase (ALT=SGPT), and bilirubin (total and conjugated)

The Investigator or a medically qualified sub-Investigator must review and evaluate laboratory values for each subject in a timely manner. The Investigator or designee will initial and date all laboratory reports and note on the report whether or not an out of range laboratory value is clinically significant. An out of range laboratory value should be considered as clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires additional active management, e.g. close observation, more frequent follow-up assessments, or further diagnostic investigation

For each out of range laboratory result, the Investigator or designee will enter directly in the eCRF the Investigator judgment on the presence or the absence of a clinical significance.

All clinically significant out-of-range laboratory values for blood samples collected at baseline will be recorded in the medical history (report a diagnosis rather than an individual laboratory parameter abnormality whenever possible).

All clinically significant out of range laboratory values for blood samples collected after baseline are to be reported as an AE if this abnormality was not present at the baseline visit or is assessed as having worsened since the screening visit (i.e., there is a significant change from baseline).

For AEs, whenever possible, the Investigator is to provide a diagnosis rather than to report individual laboratory abnormalities.

7.2.5 Neutralizing Antibody Testing

Subjects will have blood samples taken at baseline prior to treatment, Month 1, and Month 6/ET for measurement of serum neutralizing antibody testing against QM1114-DP.

Additional information and detailed description of sample volumes, processing, and storage requirement will be included in a Laboratory Manual.

7.2.6 Adverse Events

AEs are to be monitored throughout the course of the clinical study from the time the informed consent form has been signed. All AEs are to be reported on the AE form of the eCRF with complete information as required.

If AEs occur, the main concern shall be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical study center personnel for reporting AEs and medical emergencies.

At each post enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "Have you noticed any change in your health since the last visit?" Additional questioning and examination will then be performed as appropriate.

7.2.6.1 Definitions

7.2.6.1.1 Adverse Events (AE)

According to ICH E2A,[15] an AE is any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus, any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease (including new episodes of a chronic disease [e.g., hay fever, allergy]) compared to the condition at the first visit, should be considered as an AE. Lack of efficacy is not considered as an AE.

Notes:

- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.

- Pregnancy is not to be considered as an AE; however, is an important medical event that must be monitored as described in Section 7.2.6.2.3.

- The effects of all BoNT products may spread from the area of injection to produce symptoms consistent with BoNT effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin that affects swallowing and breathing can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. BoNT is contraindicated in individuals with known hypersensitivity to any BoNT preparation or to any of the components in the formulation.

7.2.6.1.2 Treatment Emergent Adverse Event (TEAE)

A TEAE is an event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pretreatment state.

7.2.6.1.3 Serious Adverse Events (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic test(s) (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical study, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

7.2.6.1.4 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study product information (e.g., Investigator's Brochure for an unapproved investigational product or the medicinal package insert/summary of product characteristics for an approved investigational product).

7.2.6.1.5 Adverse Event Reporting Period

The clinical study period during which AEs must be reported is the period from when the subject signed the ICF to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical study, even after a subject has completed the clinical study.

7.2.6.1.6 Severity

Severity is a clinical determination of the intensity of an AE and not the severity of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according to his/her medical judgment.

Mild	Awareness of signs or symptom, but easily tolerated.
Moderate	Discomfort, enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or perform usual activity.

7.2.6.1.7 Relationship to the Study Product and/or Clinical Study Procedure

The Investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study product and/or clinical study procedure.

Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline:

Reasonable Possibility: According to the reporting Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:

- The study product (active or placebo) and the AE.
- The clinical study protocol procedure (e.g., bruising or marks from blood draws, injection related trauma, etc.) and the AE.

A two-point scale (Yes or No response) shall be used for the causality assessment. The Investigator shall be asked to indicate a response to each of the following questions in the eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

No Reasonable Possibility: No suggestive evidence or arguments can be identified regarding a causal relationship between the study product or the clinical study protocol procedure and the AE.

7.2.6.2 Reporting Procedures

7.2.6.2.1 Procedures for Reporting Adverse Events

The collection of AEs is from the time that a subject signs the ICF to their final visit.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study product or not, will be recorded immediately in the source document, and described on the AE form of the eCRF along with the date of onset, severity, relationship to the study product, and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

At study end, AEs assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The Investigator will maintain all pertinent medical records in the subject's study file. If necessary and approved by the subject or their legal health care representative, the Investigator may contact the subject's personal physician or other health care provider(s) to obtain further details.

For SAEs (see Section 7.2.6.2.2) and pregnancies (see Section 7.2.6.2.3), the Sponsor is to be informed immediately by e-mail. The event must be reported by to the Safety email within 24 hours of receipt of the information (contact details in Section 7.2.6.2.2).

7.2.6.2.2 Procedure for Reporting a Serious Adverse Event

For a SAE occurring during the clinical study, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.

2. Ensure that the event is classified as an SAE (Section 7.2.6.1.3).

3. Complete the AE form provided in the eCRF as fully as possible.

   Print and complete the SAE form. E-mail the completed form, accompanied by any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours of receipt of the information to Safety e-mail listed below. The demographics, medical history, drugs/therapies form, medical and surgical procedures form, and AE pages of the eCRF must be completed and available for review in the EDC system at the time of the report.

4. Immediately send the completed SAE report form to the Safety e-mail and discuss further actions to be taken.

   E-mail: PPD

   Additional contact details are provided in the Investigator's site file.

5. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, send all additional follow-up information on the SAE to the Safety e-mail within 24 hours of receipt of the updated information. SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.

6. Obtain and maintain in his/her files all pertinent medical records and information regarding the SAE.

7. Inform the Sponsor of the final outcome of the event. Send a follow-up SAE form, when appropriate, to the Safety e-mail.

8. Prompt notification of SAEs by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Boards (IRBs), and Investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and the Sponsor policy and are forwarded to Investigators as necessary. An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the Investigator's Brochure (IB) and will notify the IRB, if appropriate according to local requirements.

9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB.

7.2.6.2.3 Procedures for Reporting Pregnancies

Any pregnancy occurring during the clinical study, where the fetus could have been exposed to the study product, must be monitored until its outcome in order to ensure the complete collection of safety data.

Subjects who become pregnant during the screening period are considered as screening failures; they are recorded as such in the eCRF and no pregnancy form is to be completed.

If a subject becomes pregnant after the screening period, the Investigator is to do the following:

1. The subject does not need to be withdrawn from the clinical study, i.e. she may continue to attend the planned study visits, but no invasive procedure should be conducted (e.g. no sample taken for lab test).

2. Complete the Pregnancy Report Part A as fully as possible. Send the form within 24 hours of receipt of the information to the Safety e-mail listed above (and in Section 11.9).

3. Monitor and record the progress of the pregnancy until its outcome. If necessary and approved by the subject or their legal health care representative, contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow up information.

4. At the outcome of the pregnancy, complete the Pregnancy Report Part B. For all the additional evaluations, send the follow-up information to the Safety e-mail within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.

5. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.6.2.2).

7.3 Other Assessments

7.3.1 Photography

Standardized digital photographs will be taken of the subject's lateral canthus region, glabellar region, and the full face at baseline (prior to treatment) and at each post-treatment visit.

Each Investigator (or designee) will take photographs using identical camera equipment, conditions, and settings. Detailed instructions for photography will be provided in a separate photography manual.

7.3.2 Pregnancy Test

For females of childbearing potential, a urine pregnancy test will be performed prior to treatment at screening, baseline (prior to treatment) and Month 6/ET. A negative pregnancy test is required for study inclusion. The result will be documented.

7.4 Appropriateness of Measurements

The efficacy and safety measurements used in this study are considered standard measurements, and are generally recognized as reliable, accurate, and relevant. The validated 4-point Photographic Scale of Glabellar Line Severity has been chosen in agreement with the FDA. A similar scale has been developed for LCL in accordance with FDA guidance.

8. CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of Clinical Study Visits

Please refer to the Schedule of Assessments Table 2.

A written, signed ICF (inclusive of HIPAA and photo consent) must be obtained prior to performing any clinical study-related evaluations and/or procedures. The subject must be provided with a fully completed, dated and signed copy.

8.1.1 Screening/Visit 1 (-14 days to Day 0)

The screening and baseline visits may be performed on the same day; however, a maximum of 14 days is allowed between the screening and baseline visits.

At the screening visit, the Investigator or designee will:

1. Review and explain the nature of the study to the subject, particularly the prohibited activities and constraints (e.g., restrictions for other aesthetic treatments and the use of topical and systemic medications, see Section 5.4.5).
2. Obtain the signed and dated ICF (inclusive of HIPAA and photo consent); provide a fully completed dated and signed copy to the subject.
3. Collect information regarding demographics (i.e., date of birth, gender, race, ethnicity, height, and weight), Fitzpatrick skin type, relevant medical history and concurrent diseases, previous facial treatments/procedures (including toxin naïve/non-toxin naïve), previous medications and procedures, and concomitant medications and procedures (see Table 2 Schedule of Assessments).
4. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessments using the 4-point Photographic Scales (LCL-SLA). LCL severity of Level 2 or Level 3 on the LCL-SLA at maximum smile, as assessed by the subject, is required for study inclusion. (Section 7.1.2 and Appendix 2)
5. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete self-assessment using the Static 4-point Categorical Scales (GL-SLA). Moderate to severe GL (score of 2 or 3 on the Static 4-point Categorical Scale)) at maximum frown, as assessed by the subject, is required for study inclusion. (Section 7.1.4)
6. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scales (LCL-ILA). Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the LCL-ILA) at maximum smile, as assessed by the Investigator, is required for study inclusion. (Section 7.1.1 and Appendix 1)
7. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scales (GL-ILA). Moderate to severe GL (grade 2 or 3 on the 4-point Photographic Scale) at maximum frown, as assessed by the investigator, is required for study inclusion. (Section 7.1.3 and Appendix 3)
8. Investigator to perform a focused PE. (Appendix 6). Record abnormal findings as medical history. Clinically significant abnormal findings are exclusionary; document as screen fail and do not enrolled the subject in the study.
9. If the subject is a female of childbearing potential, collect urine for UPT and complete pregnancy test (see laboratory manual for additional procedures). Document the result. A negative result is required for study inclusion.
10. Record any AEs on the eCRF. AEs will be collected starting from the time of Informed Consent signature.
11. Review the inclusion/exclusion criteria, and confirm if subject meets study eligibility requirements.
    - If yes, schedule the baseline visit.
    - If no, document the subject as a screen failure.

12. For all subjects, enter the subject information into the eCRF; a SIN will be assigned via the eCRF system.

8.1.2 Baseline/Visit 2 [Day 0]

If the screening and baseline visits are performed as on same day, only perform study assessments once (i.e., AE, concomitant therapies/procedures, UPT, PE, SLA, ILA, inclusion/exclusion review). A maximum of 14 days is allowed between the screening and baseline visits.

At the baseline visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. CCI [redacted]
4. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete the self-assessments using the 4-point Photographic Scales (LCL-SLA). LCL severity of level 2 or 3 on the 4-point Photographic Scale at maximum smile, as assessed by the subject, is required for study inclusion. (Section 7.1.2 and Appendix 2)
5. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete the self-assessment using the Static 4-point Categorical Scale (GL-SLA). Moderate to severe GL (grade of 2 or 3 on the Static 4-point Categorical Scale) at maximum frown, as assessed by the subject, is required for study inclusion. (Section 7.1.4)
6. Investigator to complete assessment of the subject's LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scales (LCL-ILA). Moderate to severe LCL (grade 2 or 3 on the 4-point Photographic Scale) at maximum smile, as assessed by the Investigator, is required for study inclusion.
7. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scales (GL-ILA). Moderate to severe GL (grade of 2 or 3 on the 4-point Photographic Scale) at maximum frown, as assessed by the investigator, is required for study inclusion. (Section 7.1.3 and Appendix 3)
8. CCI [redacted]
9. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
10. Obtain 12-lead ECG recording after the subject has been resting in a supine position for at least 10 minutes (Section 7.2.3).
11. If the subject is a female of childbearing potential, collect urine for UPT and complete pregnancy test (see laboratory manual for additional procedures). Document the result. A negative result is required for study inclusion.

12. Collect blood sample (chemistry and hematology) for analysis at the central laboratory (Section 7.2.4).
13. Collect blood sample for neutralizing antibody testing (Section 7.2.5).
14. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
15. Investigator to perform a focused PE. (Appendix 6). Clinically significant abnormal findings are exclusionary; document as screen fail and do not enroll the subject in the study.
16. Review the inclusion/exclusion criteria, and confirm if subject meets study eligibility requirements.
    - If yes, enroll/randomize the subject in the clinical study. Proceed to next steps.
    - If no, document the subject as a screen failure.
17. For all subjects, enter appropriate data into the eCRF; the SIN should have been assigned via the eCRF system at the screening visit
18. For subjects who meet all eligibility requirements, the Investigator or designee will receive notification of the subject's kit number/randomization assignment once all required data is entered into the eCRF. The Investigator or designee should prepare the assigned treatment accordingly and complete the required documentation and eCRF. (Section 6.1.7).
19. Prior to injection, clean the subject's treatment areas with a suitable antiseptic solution.
20. The Investigator will administer the assigned treatments. See Section 6.1.7.1 for injection technique and treatment procedure requirements. Following treatment administration, subjects will be monitored at the study center for 30 minutes. (Section 6.1.7.2)
21. Obtain the subject's post-treatment vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes after injection (Section 7.2.2).
22. CCI [redacted]
23. Ask the subject about AEs using an open-ended question. Record all events, as appropriate, on the corresponding eCRF form(s).
24. Record post-treatment concomitant therapies/procedures.
25. Schedule the next visit (Day 7 ±1 day).

8.1.3 Day 7/Visit 3 (±1 day)

The Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. CCI [redacted]

4. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessments using the 4-point Photographic Scale (LCL-SLA). (Section 7.1.2 and Appendix 2)
5. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete self-assessment of GL severity at maximum frown using the Static 4-point Categorical Scale. (Section 7.1.4)
6. CCI [redacted]
7. [redacted]
8. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
9. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
10. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.1 and Appendix 1)
11. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.3 and Appendix 3)
12. Investigator to perform a focused PE. (Appendix 6)
13. Schedule the next visit (Day 14 ±3 days).

8.1.4 Day 14/Visit 4 (±3 days)

The Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessment of bilateral LCL severity the 4-point Photographic Scale. (Section 7.1.2 and Appendix 2)
4. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete self-assessment of GL severity using the Static 4-point Categorical Scale. (Section 7.1.4)
5. CCI [redacted]
6. [redacted]

7. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
8. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
9. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.1 and Appendix 1)
10. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.3 and Appendix 3)
11. Investigator to perform a focused PE. (Appendix 6)
12. Schedule the next visit (Month 1 ±5 days).

8.1.5 Month 1/Visit 5 (±5 days)

The Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessment of bilateral LCL severity using the 4-point Photographic Scale. (Section 7.1.2 and Appendix 2)
4. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete self-assessment of GL severity using the Static 4-point Categorical Scale. (Section 7.1.4)
5. CCI [redacted]
6. [redacted]
7. [redacted]
8. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
9. Obtain 12-lead ECG recording after the subject has been resting in a supine position for at least 10 minutes (Section 7.2.3).
10. Collect blood sample for neutralizing antibody testing (Section 7.2.5).
11. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.

12. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.1 and Appendix 1)
13. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.3 and Appendix 3)
14. Investigator to perform a focused PE. (Appendix 6)
15. Schedule the next visit (Month 2 ±5 days).

8.1.6 Months 2-5/Visit 6-9 (±5 days)

The Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessment of bilateral LCL severity using the 4-point Photographic Scale. (Section 7.1.2 and Appendix 2)
4. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete self-assessment of GL severity using the Static 4-point Categorical Scale. (Section 7.1.4)
5. CCI [redacted]
6.
7.
8. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
9. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.1 and Appendix 1)
10. Investigator to complete assessment of the subject's GL severity at CCI [redacted] maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.3 and Appendix 3)
11. Schedule the next monthly visit (± 5 days).

8.1.7 Month 6/Visit 10 or Early Termination visit (±5 days)

At the Final/ET, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Instruct the subject on how to complete the LCL-SLA at CCI [redacted] maximum smile. Subject to complete self-assessment of bilateral LCL severity using the 4-point Photographic Scale. (Section 7.1.2 and Appendix 2)
4. Instruct the subject on how to complete the GL-SLA at maximum frown Subject to complete self-assessment of GL severity using the Static 4-point Categorical Scale. (Section 7.1.4)
5. CCI [redacted]
6.
7.
8. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
9. Obtain 12-lead ECG recording after the subject has been resting in a supine position for at least 10 minutes (Section 7.2.3).
10. Collect blood sample (chemistry and hematology) for analysis at the central laboratory (Section 7.2.4).
11. Collect blood sample for neutralizing antibody testing (Section 7.2.5).
12. If the subject is a female of childbearing potential, collect urine for UPT and complete pregnancy test (see laboratory manual for additional procedures). Document the result.
13. Take subject photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
14. Investigator to complete assessment of the subject's bilateral LCL severity at CCI [redacted] maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.1 and Appendix 1)
15. Investigator to complete assessment of the subject's glabellar line severity at CCI [redacted] maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.3 and Appendix 3)
16. Investigator to perform a focused PE. (Appendix 6)
17. Exit the subject from the study.

8.2 Unscheduled Visits

When necessary, unscheduled visits may be conducted, in particular if an AE occurs and needs to be assessed and/or treated.

8.3 Subject Instructions

CCI [redacted]

Subjects will be advised that any facial make-up will need to be removed before taking study photographs.

Subjects will also be advised of post-treatment care instructions as outlined in Section 6.1.7.2.

9. STATISTICAL METHODS PLANNED

9.1 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical study protocol below. The SAP will be finalized prior to database lock.

A separate SAP for EU will be created. The EU SAP will include a responder definition for the primary endpoint according to the EU requirement.

Any change made to the finalized SAP will be documented in the Clinical Study Report (CSR).

9.1.1 Data Transformations

CCI [redacted]

For antibody testing results, log transformation might be used as necessary.

9.1.2 Populations Analyzed and Evaluability

The statistical analyses will be performed based on the following subject populations.

9.1.2.1 Modified Intent-to-treat (mITT) Efficacy Population

The modified Intention-to-treat (ITT) population includes all subjects who are randomized and dispensed the investigational product, and will be analyzed according to the randomization scheme; subjects with a photographic and categorical scale Month 1 assessment via a remote visit will be excluded from the mITT. The mITT population will be used for primary efficacy analysis.

9.1.2.2 Intent-to-treat (ITT) Efficacy Population

The Intention-to-treat (ITT) population includes all subjects who are randomized and dispensed the investigational product, and will be analyzed according to the randomization scheme. All secondary efficacy CCI [redacted] variables will be analyzed based on the ITT population, as well as a sensitivity analysis of the primary efficacy endpoint.

9.1.2.3 Per-protocol (PP) Efficacy Population

The Per Protocol (PP) population is a subset of the mITT subjects who have no protocol deviations that are considered to have a substantial impact on the primary efficacy outcome. If the PP population contains less than 90% of the subjects in mITT, a sensitivity analysis of the primary efficacy endpoint will be performed based on the PP population.

9.1.2.4 Safety Population

The safety population includes all subjects who were administered the study product, and will be analyzed according to as-treated principle. All safety data will be summarized descriptively based on the safety population.

9.1.2.5 Imputation of Missing Data

The Observed Cases (OC) will be used for all safety analyses as well as the secondary CCI [redacted] efficacy analyses. The primary efficacy analysis will be performed using multiple imputation (MI) and repeated using baseline observation carried forward (BOCF) for missing values. If deemed necessary, any analyses may be repeated using OC, BOCF, or MI as appropriate.

9.1.3 Data Presentation and Graphics

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9).

All efficacy, safety and baseline characteristics variables will be presented using descriptive statistics within each treatment group, and graphs as appropriate. Continuous data will be summarized using n (number of observations), mean, standard deviation, median, minimum and maximum value, while categorical data will be presented by n and percentages. All data will also be listed in subject data listings.

Subject disposition, completion and discontinuation by study visit, protocol deviations, demographics and baseline characteristics, medical history, medical and surgical procedures, prior and concomitant medications, will be summarized by treatment group.

For analysis of duration of response and time to onset of treatment response, Kaplan-Meier plots and estimates of the median event times will be used.

9.1.3.1 Subgroup Analysis

Analysis on the proportion of composite responders at Month 1 as measured by the ILA and the SLA at maximum smile and maximum frown, separately, will be performed in the following subgroups:

- Gender
- Baseline severity score of the ILA of LCL severity at maximum smile
- Baseline severity score of the ILA of GL at maximum frown
- Previous treatment with BoNT-A
- Fitzpatrick skin type

For duration of response, a subgroup analysis using only subjects with at least 2 point improvement on the LCL-ILA and GL-ILA, respectively will be conducted. Thus, duration of response will be analyzed based on the full ITT population as well as a subgroup analysis.

9.1.3.2 Safety Analysis

All treatment related TEAEs by maximum intensity, treatment unrelated TEAEs by maximum intensity, treatment emergent SAEs by causality and maximum intensity, and action taken of treatment related TEAEs will be summarized by SOC and PT including number of subjects with at least one event, percentages, and number of events. All related TEAEs will also be summarized by time to onset and duration. In addition, a short summary of these presentations will be provided.

Data for hematology, blood chemistry, antibodies, and vital signs will be summarized by descriptive statistics with the value at each visit as well as the change from baseline. Results of ECGs will be summarized descriptively. The results of the urine pregnancy tests will be listed

9.1.4 Withdrawals and Deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CSP deviations will be listed individually, including subject number and observed deviation. They will also be summarized by study center and in total (by treatment group and overall). Depending on the seriousness of the deviation, the subject might be excluded from the PP population, which shall be documented prior to database lock.

9.1.5 Inferential Statistical Analyses

The primary efficacy endpoints will be a composite responder rate at Month 1 based on the ILA and SLA of LCL severity at maximum smile, and ILA and SLA of GL severity at maximum frown. A responder is defined as a subject who achieves grade/level 0 or 1 and at least 2 grades improvement from baseline, on both the Investigator and subject scale concurrently. The null hypothesis of no

relationship between treatment and responder rate will be tested against the alternative hypothesis that there is a relationship between treatment and responder rate (for each of the four comparisons). The responder rates of QM1114-DP and placebo will be compared using Cochran-Mantel-Haenszel test (stratified by center) at 5% significance level (2-sided). Depending of the number of centers, pooling of centers might be needed. The group treated in one rhytid area (LCL or GL) alone and the group with concurrent LCL and GL treatment will be analyzed separately. To control the type I error rate among the 4 primary efficacy comparisons, the fixed sequence procedure will be used which requires no adjustment to the level of significance. The comparisons will be done in the following order:

1. GL alone group vs placebo on the GL scale
2. GL + LCL group vs placebo on the GL scale
3. LCL alone group vs placebo on the LCL scale
4. GL + LCL group vs placebo on the LCL scale

The analysis of the primary efficacy endpoint will be based on the mITT population. A sensitivity analysis of the primary efficacy endpoint will be performed using the ITT population.

For registration of the product in the EU, a different definition of the primary efficacy endpoints will be used.

All other endpoints will be analyzed descriptively. For efficacy, percentages of subjects over time will be presented in graphs. Duration of treatment effect and time to onset will be analyzed with Kaplan-Meier methods.

9.2 Sample Size Determination

The sample size is determined by the number of subjects exposed to QM1114-DP in the LCL and GL, and amount of long-term safety data.

Further, due to the public health emergency related to the COVID-19 pandemic during 2020, steps have been taken to ensure patient and practitioner safety in alignment with FDA Guidance dated May 11, 2020 (*Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*). Most notably, in partnership with clinical sites and the IRB, optional remote assessment procedures for efficacy and safety endpoints has been implemented to ensure safety and respect localized and elective restrictions. Therefore, the sample size has been increased during the conduct of the study to ensure a sufficient number of subjects in the mITT population used in the assessment of the primary efficacy endpoint.

9.2.1 Historical Data

The study was initially planned to enroll approximately 350 subjects who will be treated with either:

- 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 100 subjects),
- 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 100 subjects),

- 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 100 subjects), or Placebo in both the LCL and GL (50 subjects).

During the study the sample size was increased due to the public health emergency related to the COVID-19 pandemic to ensure a sufficient number of subjects in the mITT population. The study is planned to enroll approximately 413 subjects who will be treated with either:

- 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects),
- 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects),
- 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or
- Placebo in both the LCL and GL (59 subjects).

No previous data on composite responder rates, with the same definition of composite responder as in the current study, is available for subjects treated with QM1114-DP in the LCL or GL, treated alone or in combination.

For the GL, previous phase 3 studies of BoNT used the same composite responder definition as in the current study, i.e. based on achievement of score 0 or 1 and at least 2 grades reduction from baseline as assessed by both investigator and subject concurrently on the 4-point evaluation scales.

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.2.3 Sample Size Calculation

The study is planned to include approximately 350 subjects in the mITT population: 100 subjects will be treated with QM1114-DP, 200 subjects will be treated with QM1114-DP and placebo, and 50 subjects will be treated with placebo.

9.2.4 Interim Analysis

Not applicable. An interim analysis is not planned for this study.

10. TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel Training

Investigators and other responsible persons should be listed together with their function on the signature and delegation log. Study staff shall provide a curriculum vitae or equivalent, as appropriate.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and documented training in all procedures to be followed.

10.2 Clinical Monitoring

The conduct of the clinical study will be closely monitored by representatives of the Sponsor to verify adherence to the clinical study protocol, ICH-GCP guidelines, and applicable SOPs.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical study records, CRFs, corresponding subject medical records, study product(s) dispensing records, and any other documents considered source documentation. Additionally, the CRO/Sponsor representative is to have access to the study product storage area and clinical study facilities.

The Investigator also agrees to assist the representative if required.

10.3 Data Management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP and CRF template. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

10.4 Quality Assurance/Audit/Inspection

The clinical study is conducted under the sponsorship of the Sponsor in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical study conduct and monitoring from the Sponsor and/or the Contract Research Organization (CRO).

Audits of clinical study centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/IECs before, during, or after the clinical study.

The Investigator will allow and assist the CRO/Sponsor's representatives, IRBs/IECs and any regulatory agency to have direct access to all requested clinical study-related records.

For the audits performed by, or on behalf of, the Sponsor auditors, audit certificate(s) will be provided by Quality Assurance.

10.5 Changes in Clinical Study Conduct/Amendments

10.5.1 Clinical Study Conduct

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical study protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The Investigator should document and explain any deviation from the clinical study protocol.

10.5.2 Amendments

The Sponsor may modify the clinical study protocol at any time for ethical, medical, or scientific reasons. Any amendments will be handled according to applicable local regulations.

The Sponsor does not have to notify non-substantial amendments to the competent authorities or the Ethics Committees. However, non-substantial amendments should be recorded and detailed in subsequent submissions e.g., in the subsequent notification of a substantial amendment.

11. ETHICS AND GENERAL CLINICAL STUDY CONDUCT CONSIDERATIONS

11.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This clinical study protocol and all applicable amendments will be reviewed and approved by the appropriate IECs/IRBs.

11.2 Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

11.3 Subject Information and Consent

All subjects who participate in this clinical study are required to be fully informed about the clinical study in accordance with GCPs guidelines, federal regulations, HIPAA, and guidelines and in accordance with local requirements.

The ICF (inclusive of HIPPA and photo consent), approved by an IRB/IEC, will be fully explained to the subject. The subject must agree to photo consent in order to participate in the clinical study.

Prior to enrollment into the clinical study, the subject and the PI or designee must sign and date the consent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject with a copy of the signed and dated consent form(s).

11.4 Protection of Personal Data

The completion of the study involves the gathering and processing of Personal Data as specified in the Regulation (EU) 2016/679 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, Sponsor will be considered the Data Controller, and Principal Investigator and Institution will both be considered Data Processors.

All processing of Personal Data must be carried out in accordance with national legislation concerning the protection of Personal Data. The Institution and Principal Investigator are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and Principal Investigator are located.

The Principal Investigator understands that clinical studies conducted under an IND are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Access Act of 1996 (HIPAA), as provided at CFR § 512(b)(iii), and the study subject should be made aware of this exception in the informed consent. The Sponsor shall, to the extent feasible, protect study subject identifier information.

The Institution and Principal Investigator are jointly responsible for obtaining the appropriate informed consent of each subject for the processing of Personal Data required in order to complete the study. Such consent shall include the consent to the transfer of Personal Data to government authorities located in countries outside the US.

The Institution and Principal Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the study, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time during or after the study. A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the study but the data collected until the consent was withdrawn may be used in the statistical analyses or to comply with legal or administrative requirements.

All collection, processing and analyses of protected health information, personal data or similar will be conducted in compliance with applicable local, national and international rules, regulations and guidelines.

11.5 Contractual Requirements

A contractual agreement will be signed between the CRO/Sponsor and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical study schedule, third party responsibility, and publication rights.

11.6 Data Collection and Archiving

11.6.1 Data Collection

The Investigator must maintain all required records for all subjects. Data for this clinical study will be recorded in the subject's source documents and in the eCRFs provided by the Sponsor. All data should be recorded in the eCRFs completely and promptly.

11.6.2 Source Documentation

The Investigator must keep accurate separate records (other than the eCRFs) of all subject visits, being sure to include all pertinent clinical study-related information. A statement should be made indicating that the subjects have been included in this clinical study and have provided signed written Informed Consent. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical study should also be included in the source documentation.

11.6.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical study protocol, and all other material relating to the clinical study will be maintained securely in Sponsor/CRO/Investigator/Institution archives for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical study documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

If the Principal Investigator retires, relocates, or withdraws from the responsibility of keeping the clinical study records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

11.7 Insurance

A certificate attesting Third Party coverage of CRO/Sponsor will be provided upon request.

11.8 Publication Policy

The Institution/PI's and the Sponsor's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in a public database (e.g., www.ClinicalTrials.gov) and to a medical journal for publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.[a] Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above-mentioned criteria, one author will be appointed by the Sponsor to take primary responsibility for the overall work as primary author.

[a] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

11.9 Investigator and Administrative Structure

Role	Contact Information
Sponsor Contact:	PPD
Medical Monitor:	
Safety e-mail for SAE, Pregnancy Reporting, and PQC:	E-mail: CCI
CRO:	PPD

12. Summary of Changes in Clinical Study Protocol 43QM1902

12.1 Protocol Version 3.0 to Version 4.0

Remote assessment procedures for efficacy and safety endpoints to ensure safety and respect localized and elective restrictions were implemented due to COVID-19 pandemic. Therefore, the modified Intention-to-treat (mITT) efficacy population is added to the statistical analyses for primary efficacy analysis. Further, the samples size is increased to ensure enough subjects in the mITT population. These actions affect several sections of the Protocol as summarized below.

Section in the clinical study protocol	Rational for changes	Description of changes
Synopsis; Table 1; Figure 1; Section 3, Overall clinical study description; Section 5.1, Number of subjects	Due to COVID-19 pandemic actions. The samples size is increased to ensure enough subjects in the mITT population.	Updated number of subjects. Approximately 454 subjects will be screened in order to get 413 subjects enrolled in a 2:2:2:1 ratio to: • 60 units QM1114-DP (60 units in the LCL and placebo in the GL, 118 subjects), • 50 units QM1114-DP (50 units in the GL and placebo in the LCL, 118 subjects), • 110 units QM1114-DP (60 units in the LCL and 50 units in the GL, 118 subjects), or • Placebo in both the LCL and GL (59 subjects).
Section 9.1.1, Data Transformations	Clarification	CCI [redacted]
Section 9.1.2.1, Modified Intent-to-treat (mITT) Efficacy Population; List of abbreviations and definitions of terms	Due to COVID-19 pandemic actions. The mITT efficacy population will be used for assessment of the primary efficacy endpoint. Subjects with a photographic and categorical scale Month 1 assessment via a remote visit will be excluded from the mITT.	Modified Intent-to-treat (mITT) Efficacy Population added (primary efficacy analysis).
Section 9.1.2.2, Intent to treat (ITT) Efficacy Population	Due to COVID-19 pandemic actions.	The mITT population will be used for primary efficacy analysis. A sensitivity analysis of the primary efficacy endpoint will be based on the ITT population.

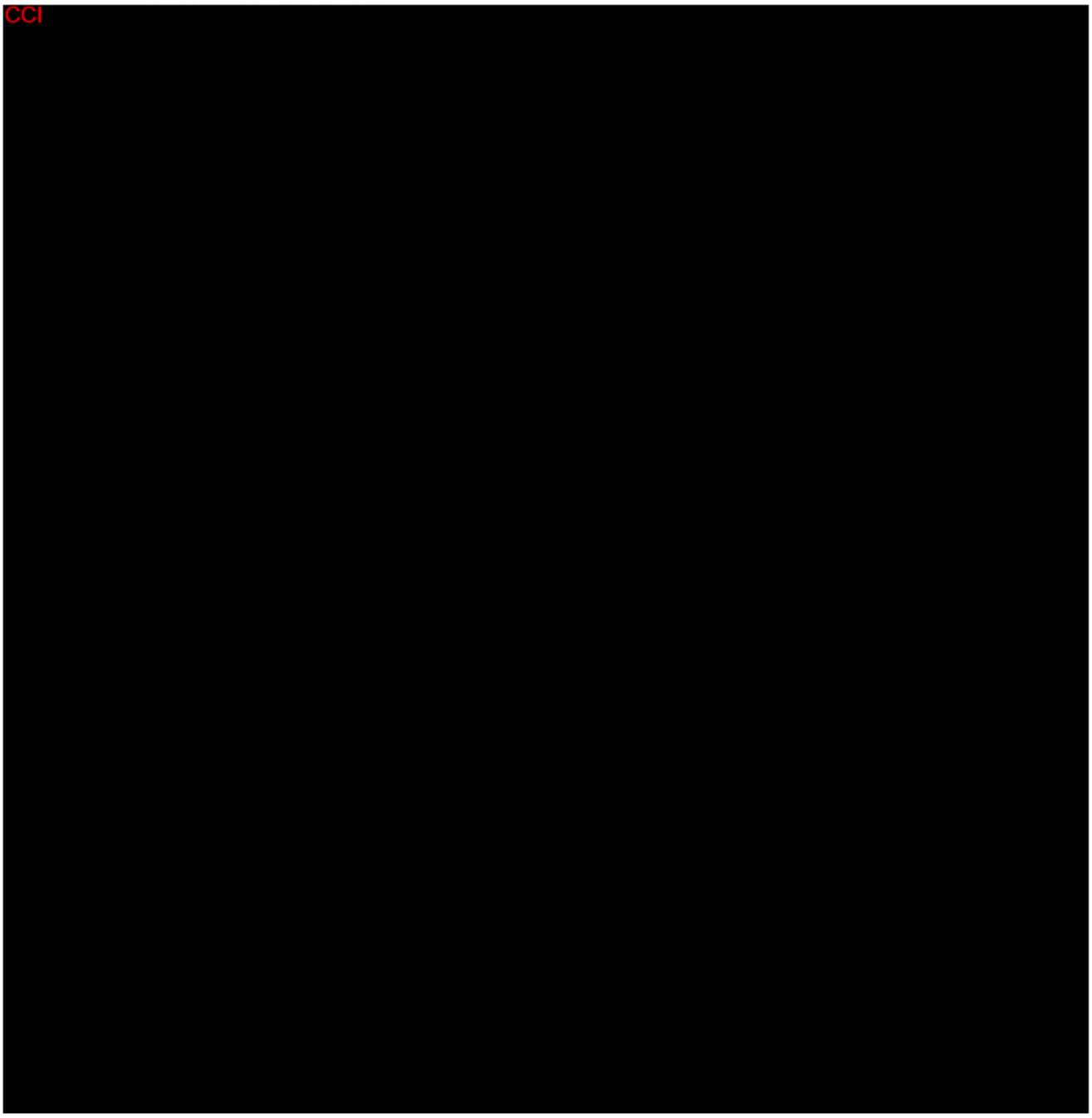
Section in the clinical study protocol	Rational for changes	Description of changes
Section 9.1.2.3, Per-protocol (PP) Efficacy Population	Clarification due to COVID-19 pandemic actions.	Changed from "ITT" to "mITT"
Section 9.1.2.5, Imputation of Missing Data	Due to COVID-19 pandemic actions. An increased number of drop-outs/ missing data at Month 1 visit.	Primary imputation changed to "MI" instead of "BOCF".
Section 9.1.5, Inferential Statistical Analyses	Clarification due to COVID-19 pandemic actions.	Added: "The analysis of the primary efficacy endpoint will be based on the mITT population. A sensitivity analysis of the primary efficacy endpoint will be performed using the ITT population."
Section 9.2, Sample Size Determination	Clarification due to COVID-19 pandemic actions.	Clarification for increased number of subjects during the conduct of the study added. "The sample size is determined by the number of subjects exposed to QM1114-DP in the LCL and GL, and amount of long-term safety data." was moved from Section 9.2.3 to Section 9.2
Synopsis and Section 9.2.1, Historical Data	Clarification due to COVID-19 pandemic actions.	Both the initially planned and the increased sample size included.
Section 9.2.3, Sample Size Calculation	Clarification due to COVID-19 pandemic actions.	Added: "… in the mITT population ……"
Section 12: Section 12.1	Protocol Amendment	Added Section: Summary of Changes Protocol version 3.0 to version 4.0

13. LITERATURE REFERENCE LIST

1. ICH E6: International Conference on Harmonisation Tripartite Guideline: Guideline for Good Clinical Practice. 1996
2. Sundaram, H., M. Signorini, S. Liew, A. R. Trindade de Almeida, Y. Wu, A. Vieira Braz, S. Fagien, G. J. Goodman, G. Monheit, H. Raspaldo and G. Global Aesthetics Consensus (2016). "Global Aesthetics Consensus: Botulinum Toxin Type A--Evidence-Based Review, Emerging Concepts, and Consensus Recommendations for Aesthetic Use, Including Updates on Complications." Plast Reconstr Surg 137(3): 518e-529e.
3. Awan, K. H. (2017). "The therapeutic usage of botulinum toxin (Botox) in non-cosmetic head and neck conditions - An evidence based review." Saudi Pharm J 25(1): 18-24.
4. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980;87: 1044-9.
5. Monheit, G. D. and A. Pickett (2017). "AbobotulinumtoxinA: A 25-Year History." Aesthet Surg J 37(suppl_1): S4-s11.
6. Dressler, D., S. Vogt and F. Saberi (2016). "Der Off-Label Use am Beispiel der Botulinumtoxin-Therapie." Klinische Neurophysiologie 47(02): 87-91.
7. Lupo, M. P. (2016). "Tox Outside the Box: Off-Label Aesthetic Uses of Botulinum Toxin." J Drugs Dermatol 15(9): 1151-1157.
8. Campanati, A., E. Martina, K. Giuliodori, V. Consales, I. Bobyr and A. Offidani (2017). "Botulinum Toxin Off-Label Use in Dermatology: A Review." Skin Appendage Disord 3(1): 39-56.
9. Carruthers, J. and A. Carruthers (2007). "The evolution of botulinum neurotoxin type A for cosmetic applications." J Cosmet Laser Ther 9(3): 186-192.
10. Rzany, B., D. Dill-Muller, D. Grablowitz, M. Heckmann, D. Caird and G. German-Austrian Retrospective Study (2007). "Repeated botulinum toxin A injections for the treatment of lines in the upper face: a retrospective study of 4,103 treatments in 945 patients." Dermatol Surg 33(1 Spec No.): S18-25.
11. Pirazzini, M., O. Rossetto, R. Eleopra and C. Montecucco (2017). "Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology." Pharmacol Rev 69(2): 200-235.
12. Investigators Brochure QM1114-DP (Botulinum Neurotoxin Type A) Upper Facial Wrinkles, edition 5
13. Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetic patients. Clin Plast Surg 2013;40(2):249-260
14. Klassen AF, Cano SJ, Scott AM, Pusic AL. Measuring outcomes that matter to face-lift patients: development and validation of FACE-Q appearance appraisal scales and adverse affects checklist for the lower face and neck. Plast Reconstr Surg 2014;133(1):21-30
15. ICH E2A: International Conference on Harmonisation Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 1994
16. FDA Guidance for Industry. Upper Facial Lines: developing botulinum toxin drug products (draft), 2004.

14. APPENDICES

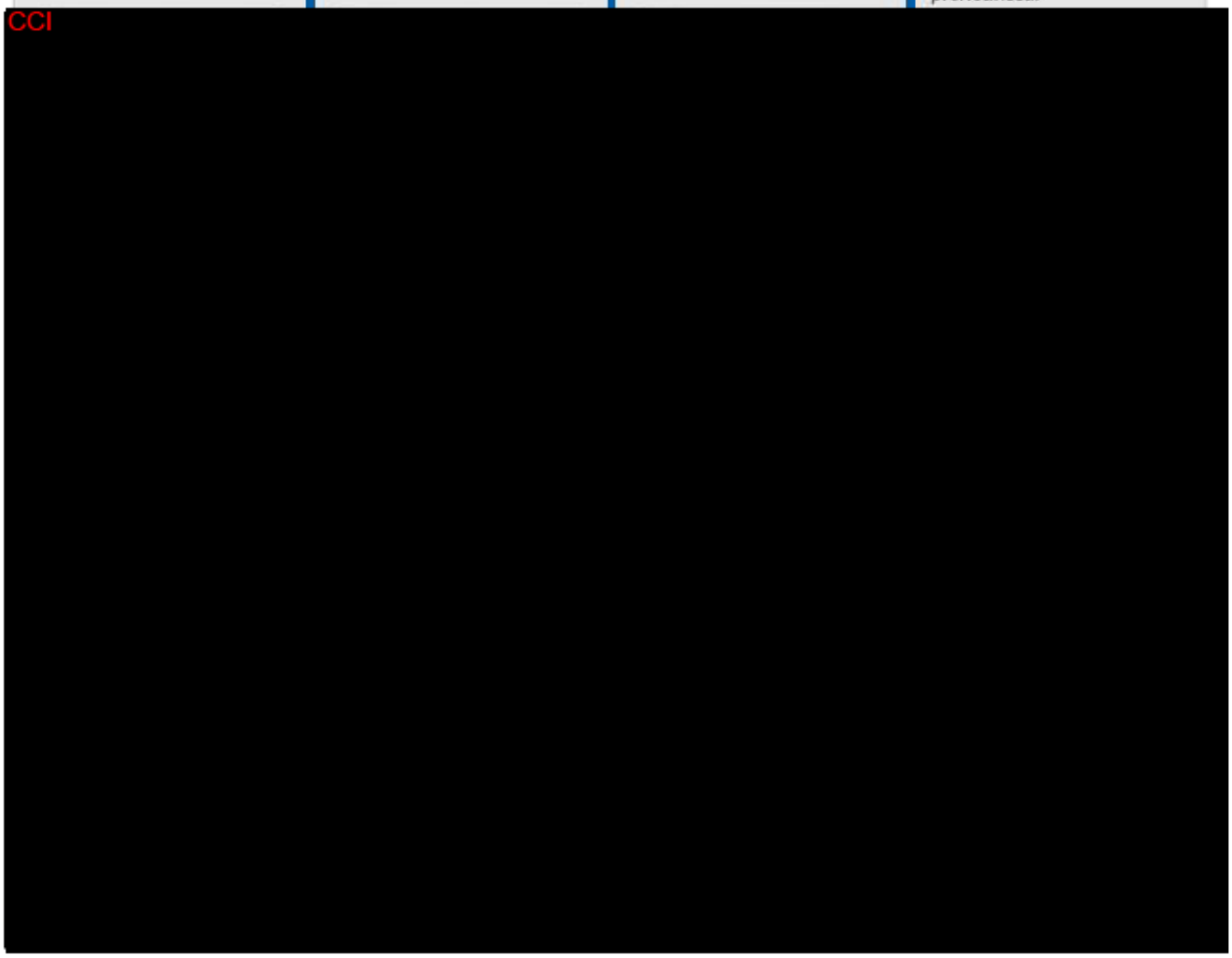
Appendix 1 Validated Investigator 4-point Photographic Scale of Lateral Canthal Line Severity



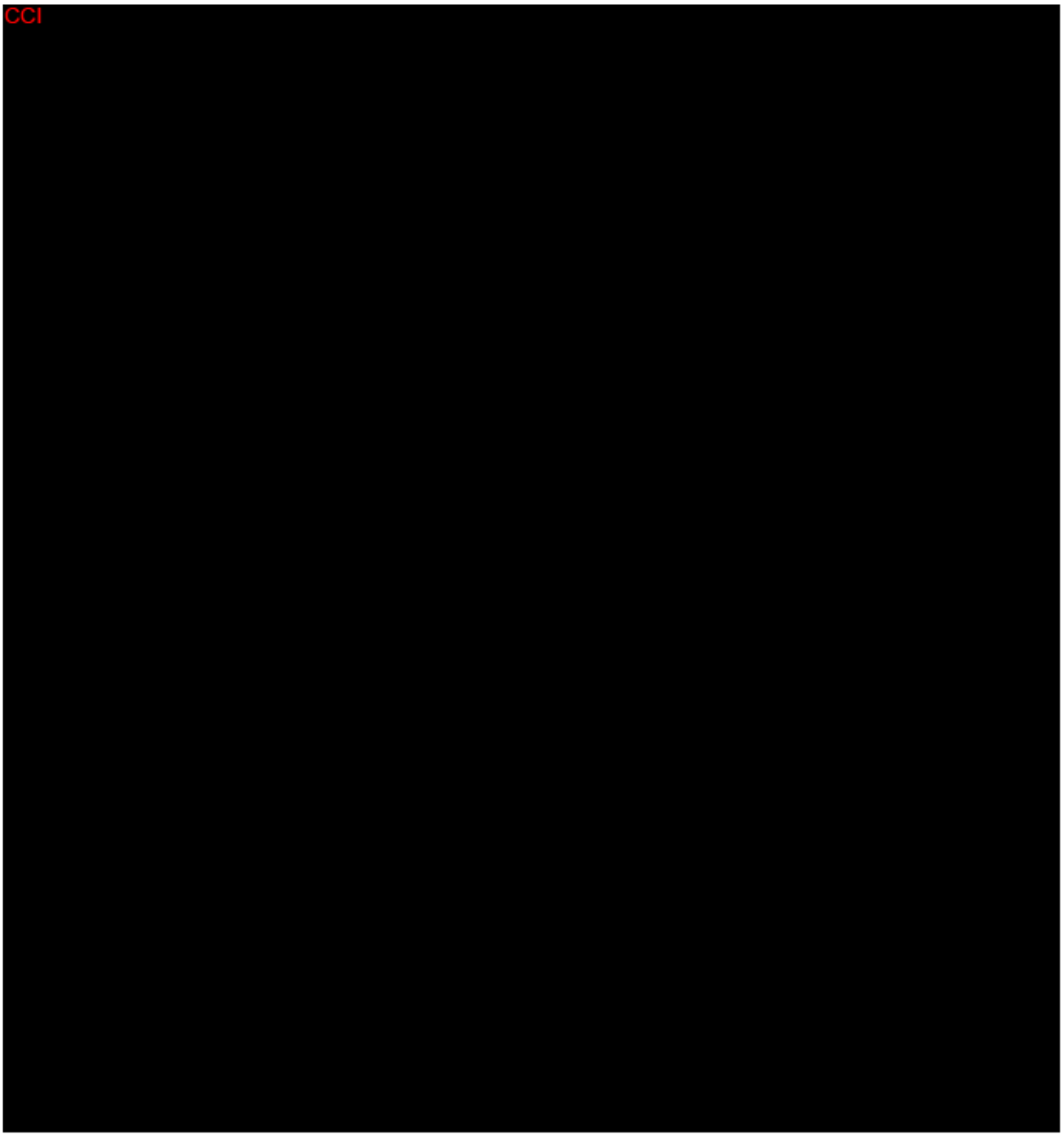
Lateral Canthal Line Investigator Live Assessment (LCL-ILA) Dynamic

0 None	1 Mild	2 Moderate	3 Severe
Smooth skin, no lines that are immediately noticeable.	*Lines that are noticeable but not pronounced.*	*Lines that are immediately noticeable and pronounced.*	*Lines that are immediately noticeable and extremely pronounced.*

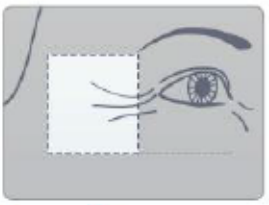
CCI



Appendix 2 Validated Subject 4-point Photographic Scale of Lateral Canthal Line Severity

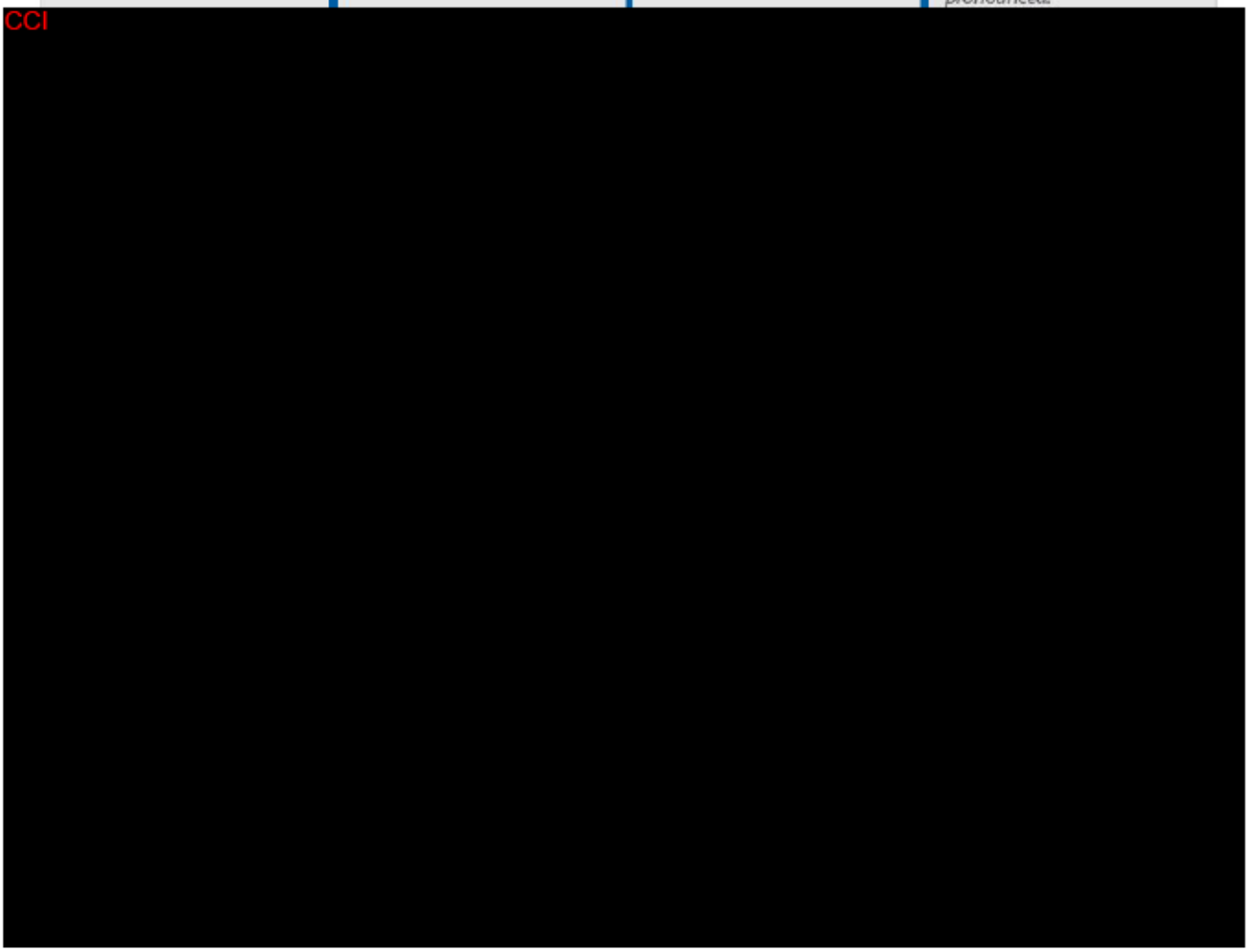


Lateral Canthal Line (Crow's Feet) Subject Live Assessment (LCL-SLA) Dynamic

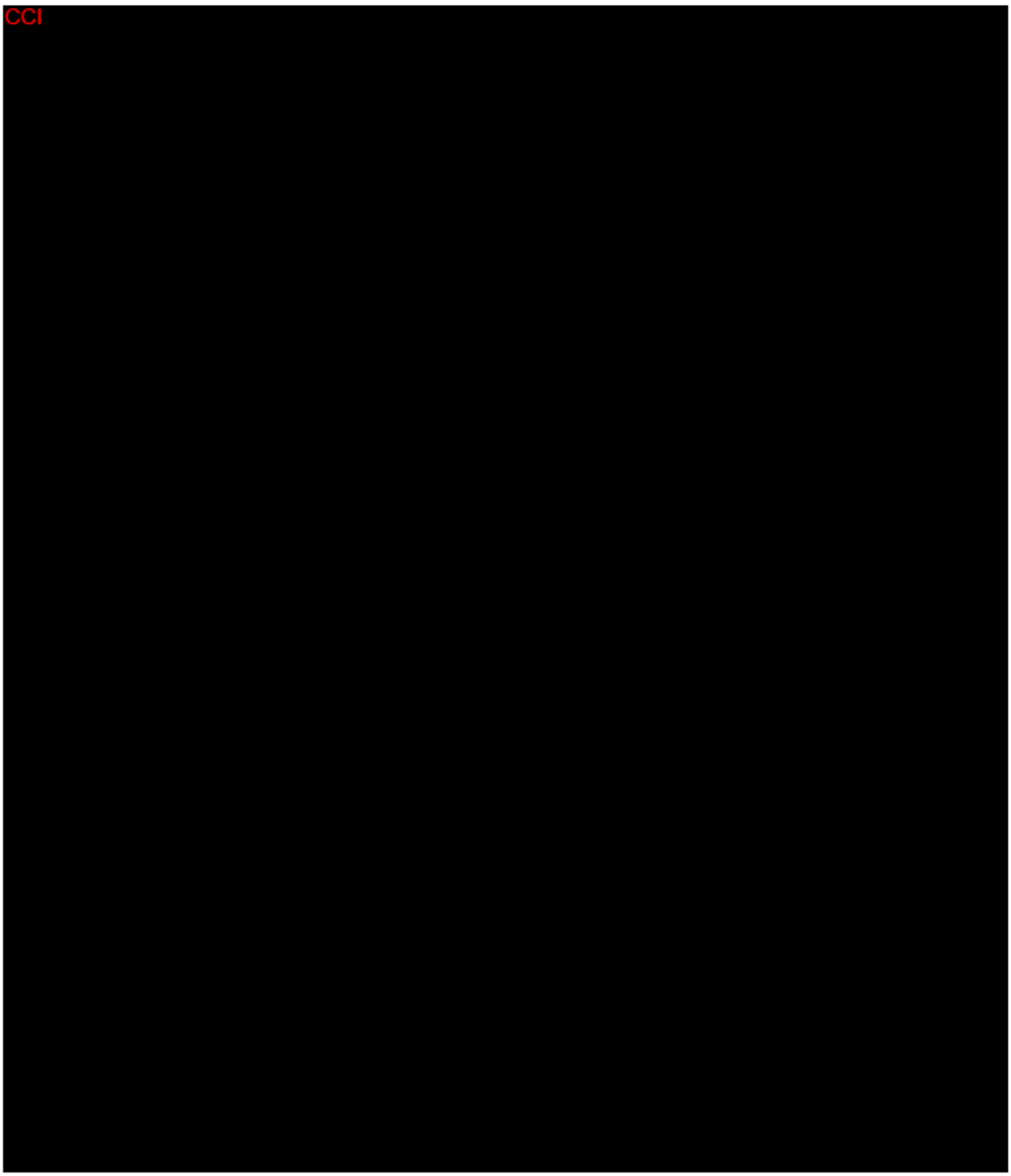


Level 0	Level 1	Level 2	Level 3
Smooth skin, no lines that are immediately noticeable.	*Lines that are noticeable but not pronounced.*	*Lines that are immediately noticeable and pronounced.*	*Lines that are immediately noticeable and extremely pronounced.*

CCI



Appendix 3 Validated Investigator 4-point Photographic Scale of Glabellar Line Severity



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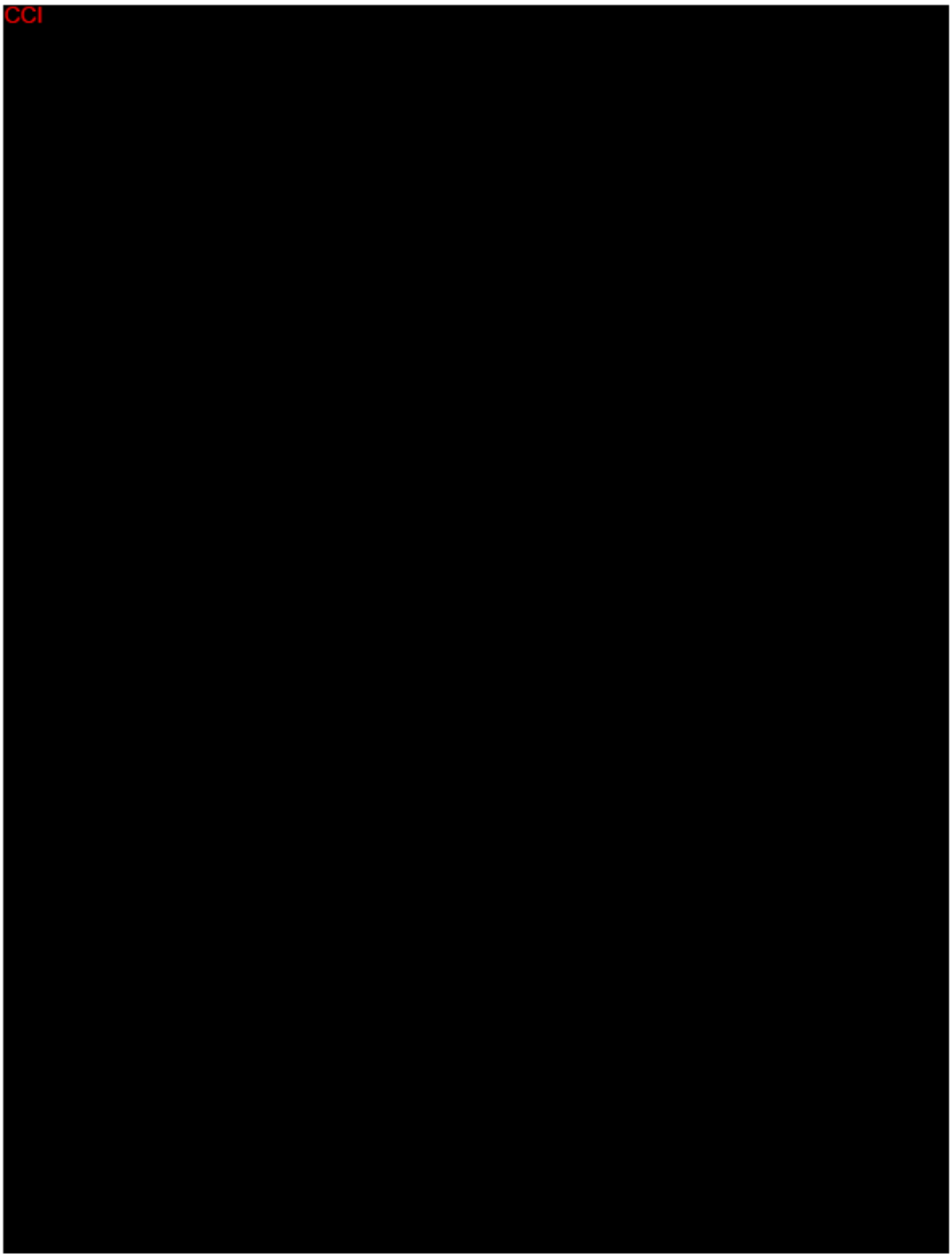

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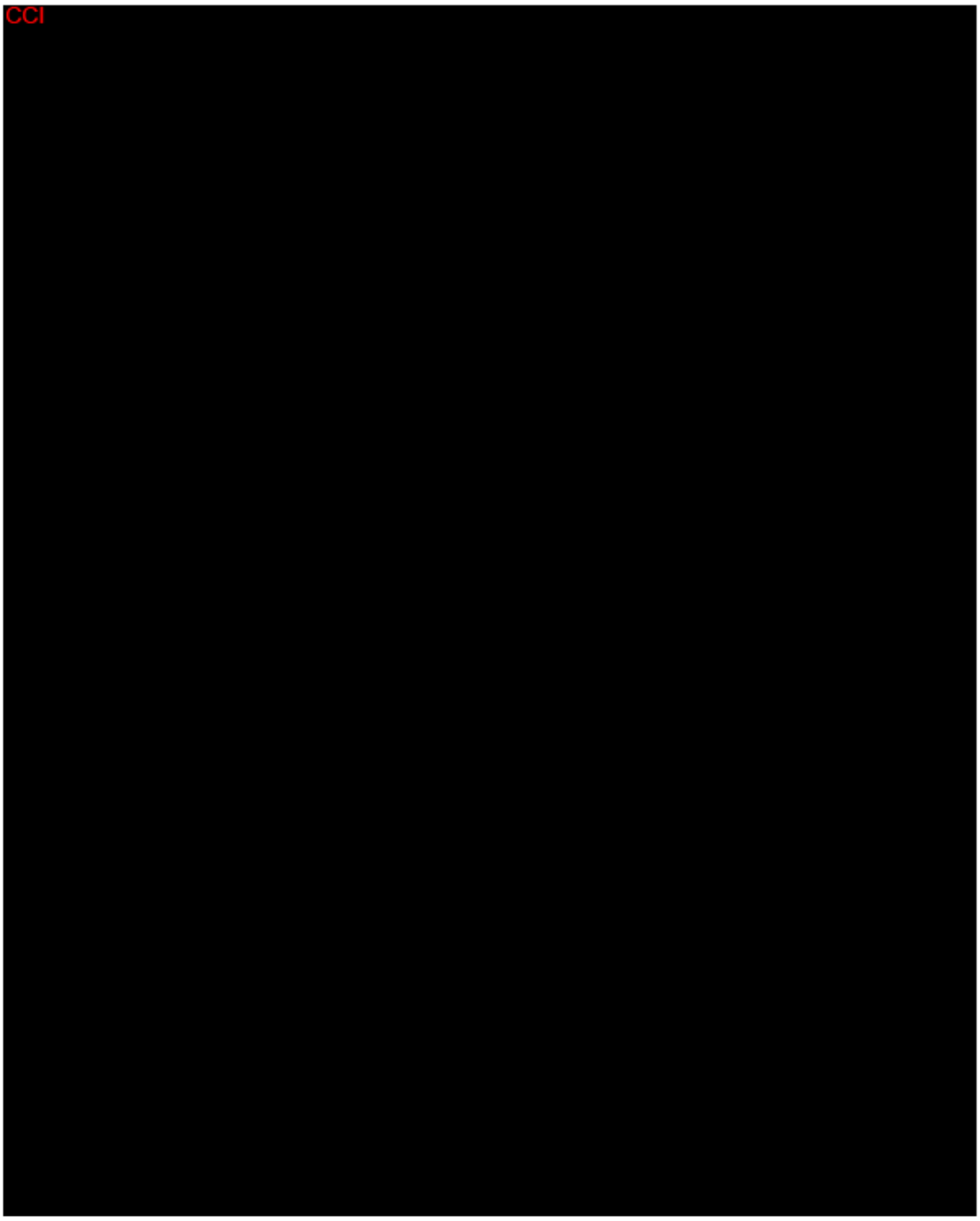
CCI



Appendix 6 Focused Physical Examination Form Example

Not done ☐ **Provide details:** _____

General Health Assessment
Complete at Screening, Baseline (prior to treatment), Day 7, Day 14, Months 1 and 6/ET
Question the subject about their general health (general wellbeing/ bodily functions, *e.g.*, arms, legs, stomach/ bladder/ bowel, also refer to the list of Adverse Events Potentially Suggestive of Distant Spread of Toxin (Appendix 7). Abnormalities noted pre-injection should be recorded as medical history and Investigator should confirm if any abnormalities affect subject eligibility. Abnormalities noted post-injection should be documented as AEs.

Next, proceed to the Focused Physical Examination (Part 1 and 2) as indicated below.

Part 1:
Complete at Screening, Baseline (prior to treatment), Day 7, Day 14, Months 1 and 6/ET
Please perform a targeted examination of the face, head, and neck recording abnormalities.

Part 1 Examination	Normal	Abnormal* (provide details)
Eyelid position		
Eyebrow position		
Vision abnormalities (not refractive errors)		
Throat function (e.g., swallowing/drink water)		
Ability to talk and chew		
Ability to stick out and move tongue		
Ability to lift shoulders		

*** Abnormal findings at the screening and baseline visit, noted pre-injection, should be recorded as medical history and the Investigator should confirm if any abnormalities affect subject eligibility. Abnormalities noted after study treatment should be documented as AEs.**

Investigator Signature _____ **Date** _____

PART 2: Complete at Day 7, Day 14, Months 1 and 6/ET

Not done ☐ **Provide details:** _____

After questioning the subject about their general health and performing Part 1, determine if there are any **clinically significant abnormalities** that may suggest local or remote spread of toxin effect.

- Local Spread of Toxin Effect refers to effects in areas adjacent to the treatment area (*e.g.*, lower frontalis or medial part of temporalis).
- Remote Spread of Toxin Effect refers to effects in other body parts, not adjacent to the treatment area, when effect can **only** be attributed to the toxin and there is **no other medically sound cause.**
- Determine if the event is clinically significant (*i.e.*, would affect subject safety, confound the study data, or requires medical treatment) and document on the source document.

Please refer to the list of remote spread of toxin events (Appendix 7) while doing clinical evaluations based on subject's symptoms and signs. Directed questioning and examination will then be performed as appropriate. If yes, please describe.

Part 2 Examination	**No**	**Yes* (provide details)**
Targeted Physical Examination of Face and Neck to Evaluate Local Spread of Toxin Effect • Local spread of toxin effect event(s) observed?		
General Physical Examination to Evaluate the Remote Spread of Toxin Effect • Remote spread of toxin effect event(s) observed?		

*** Abnormalities should be documented as AE.**

Additional comments for Focused Physical Exam:

_____

_____

_____

_____ _____

Investigator Signature **Date**

Appendix 7 Adverse Events Potentially Suggestive of Remote Spread of Toxin

The following adverse events may potentially be suggestive of remote spread of toxin (based on FDA Guidance for Industry: Upper Facial Lines: Developing Botulinum Toxin Drug Products; August 2014).[16]

accommodation disorder	eyelid function disorder	paresis cranial nerve
areflexia	eyelid ptosis	peripheral nerve palsy
aspiration	facial palsy	peripheral paralysis
blurred vision	facial paresis	pelvic floor muscle weakness
botulism	fourth cranial nerve paresis	pneumonia aspiration
Bradycardia	Hemiparesis	pupillary reflex impaired
bulbar palsy	hypoglossal nerve paresis	quadriparesis
constipation	Hyporeflexia	respiratory arrest
cranial nerve palsies	Hypotonia	respiratory depression
cranial nerve paralysis	Monoparesis	respiratory distress
diaphragmatic paralysis	muscular weakness	respiratory failure
diplopia	neuromuscular toxicity	respiratory paralysis
dry mouth	Paralysis	speech disorder
dysarthria	paralysis flaccid	third cranial nerve paresis
dysphagia	paralysis recurrent laryngeal nerve	trigeminal nerve paresis
dysphonia	paralytic ileus	urinary retention
dyspnea	paraparesis	vocal cord paralysis
extraocular muscle paresis	Paresis	vocal cord paresis

SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

CTN:	43QM1902
CSP title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of QM1114-DP for the Treatment of Moderate to Severe Lateral Canthal Lines and Glabellar Lines Alone or in Combination (READY-3)

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Investigator's Brochure (IB) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study center

GALDERMA	Title 43QM1902 Clinical Study Protocol - QM1114 - LCL and GL	Doc id MA-40371

SIGNATURES PAGE

Date	Signed by
2020-06-08 13:13	PPD
Justification	Approved by Technical Expert

2020-06-08 13:47	PPD
Justification	Approved by Technical Expert

2020-06-08 15:05	PPD
Justification	Compiled by

2020-06-09 07:02	PPD
Justification	Approved by Owner