CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 43QM1903

CONFIDENTIAL

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TITLE PAGE

A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)

Clinical Trial Number (CTN): 43QM1903

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 7.2.5.2.2 and 7.2.5.2.3.

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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SYNOPSIS	
Clinical Study Title: A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)	
Short Title: QM1114-DP Long-term Treatment of GL and LCL	
Clinical Study Population:	Male and female subjects, 18 years of age and older, with moderate to severe glabellar lines (GL) at maximum frown and moderate to severe bilateral lateral canthal lines (LCL) at maximum smile.
Clinical Study Design:	This is a phase 3, multicenter, open-label study to evaluate the safety of QM1114-DP for the long-term treatment of moderate to severe GL and LCL. Eligible subjects will receive up to 4 treatments of QM1114-DP in the GL and/or LCL and will be monitored for safety and efficacy over a period of up to 52 weeks. The first treatment will be administered at Day 0 (Baseline). Re-treatments can be administered at any of the follow-up visits from Week 12 to Week 40, provided that the subject is eligible for re-treatment and there has been at least 12 weeks since the last treatment. Follow-up visits for treated subjects are conducted at Day 7 and Day 14 after each treatment. Follow-up visits, i.e. not treatment dependent, are scheduled at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52. To ensure a sufficient amount of long-term safety data is included in the database per ICH E1 guidelines, approximately 900 subjects will be enrolled; all subjects will be followed for at least 24 weeks and at least 300 subjects will be followed up to 52 weeks. The study may be stopped when at least 300 subjects have completed the Week 52 study visit.
Target Indication:	This study is designed to evaluate the safety of QM1114-DP for the long-term treatment of moderate to severe GL and LCL.
Total Number of Subjects (Planned):	Approximately 900 subjects will be enrolled.
Number of Clinical Study Centers (Planned):	Up to 36 centers
Region(s) / Country(ies) Involved (Planned):	US, 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 16 months.
Duration of Subject Participation:	Clinical study participation is up to 13 months, including the screening period.

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Clinical Study Title: A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)	
Key Inclusion Criteria:	1. Male or female 18 years of age or older. 2. Moderate to severe GL (grade 2 or 3 on the 4-point Photographic Scale ranging from grade 0 [none] to grade 3 [severe]) at maximum frown as assessed by the Investigator (GL-ILA). 3. CCI [redacted] 4. Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the 4-point Photographic Scale ranging from grade 0 [none] to grade 3 [severe]) at maximum smile as assessed by the Investigator live assessment (LCL-ILA). 5. CCI [redacted] 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).
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

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	during the study. 4. Known allergy or hypersensitivity to any component of the investigational product (QM1114-DP) or any botulinum toxin serotype. 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 exam 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 glabella or lateral canthus areas within 6 months before baseline. 9. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc) or semi-permanent (i.e., 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 tattoo(s) (including micro blading 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, micro needling, 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, micro needling, chemical peel, botulinum toxin treatment, or dermal fillers) in the face 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.

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	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 participation in 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):	At each treatment a total dose of 110 U of QM1114-DP will be administered as: • 50 U (10 U per GL injection point) 0.5 mL total (0.1 mL per GL injection point) AND • 60 U (10 U per LCL injection point) 0.6 mL total (0.3 mL per treatment side/0.1 mL per LCL injection point)
Route:	Intramuscular injection
Dose regimen:	Up to four (4) treatments
Location of treated area:	Glabellar and lateral canthus areas

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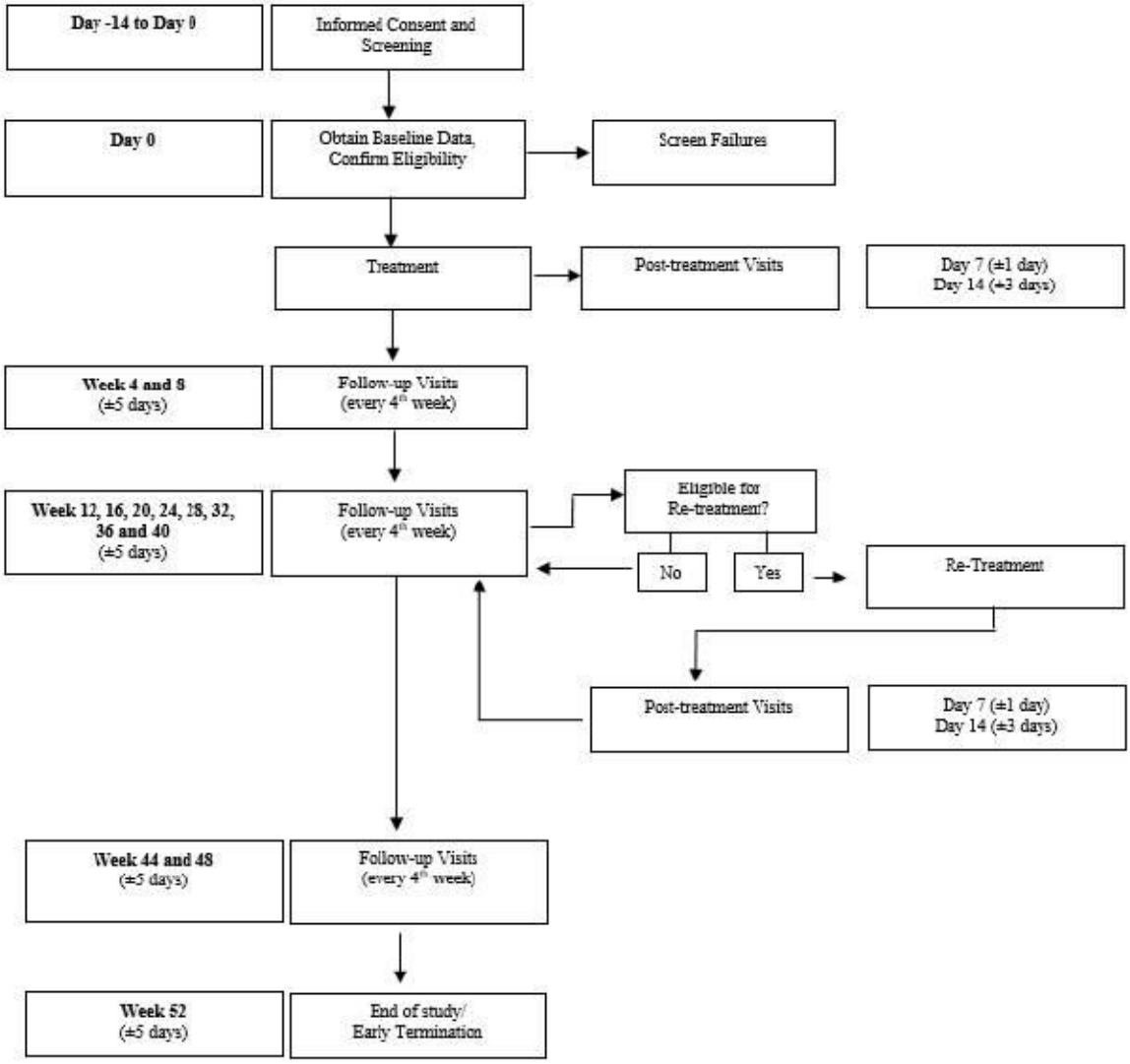
Clinical Study Title: A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)	
Safety Assessments:	• Adverse events (AEs) • Focused physical examination (FPE) • Vital signs • Laboratory safety tests (chemistry and hematology) • Production of neutralizing antibodies against QM1114-DP
Efficacy Assessments:	• Investigator 4-point Photographic Scale of GL Severity at rest and maximum frown (Investigator assessment [GL-ILA]) CCI [redacted] • Investigator 4-point Photographic Scale of LCL Severity at relaxed position and maximum smile (Investigator assessment [LCL-ILA]) CCI [redacted] CCI [redacted] CCI [redacted]
Other Assessments:	• Photography • Pregnancy test
Study Objective:	The objective of this study is to evaluate the safety and efficacy of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL.
Primary Objective and Endpoints:	The primary objective of this study is to evaluate the safety of repeated injections of QM1114-DP for the treatment of moderate to severe glabellar and lateral canthal lines. Endpoints: • Incidence and severity of treatment emergent AEs (TEAEs) • FPE findings

Secondary Objectives and Endpoints:	1. **Objective**: To evaluate the efficacy of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL.
	
	Endpoints:
	• Percentage of subjects who achieve grade/level 0 or 1 at each visit in each treatment cycle using the
	  • GL-ILA 4-point Photographic Scale at maximum frown
	  • LCL-ILA 4-point Photographic Scale at maximum smile
	CCI [redacted]
	• Percentage of subjects who achieve ≥1 grade/level improvement from baseline at each visit in each treatment cycle using the
	  • GL-ILA 4-point Photographic Scale at rest
	  • LCL-ILA 4-point Photographic Scale at relaxed position
	CCI [redacted]

Clinical Study Title: A Multicenter, O Treatment of Moderate to Severe Glabe	
	CCI [redacted]
Blinding:	
Principal Statistical Method:	Continuous data will be summarized by visit using standard statistical measures such as n (number of subjects), mean, median, standard deviation, minimum, and maximum). Both the actual values and the changes from baseline will be shown (where applicable). Categorical data will be summarized in frequency tables presenting absolute (n) and relative frequencies (%) by visit. All adverse events will be summarized and listed by system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA, both for the whole study and per cycle. Graphs will be used as appropriate for visualization of the results. Proportion of responders on the photographic scales will be presented by treatment cycle. CCI [redacted]
Sample Size:	The sample size is not based on a statistical calculation and the selected number is regarded sufficient in order to appropriately capture safety information in an evaluation of QM1114-DP.
Interim Analysis (IA):	Not applicable. An interim analysis is not planned for this study.

CLINICAL STUDY FLOW CHART

Figure 1 Study Flow Chart



SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Follow-up visit (every 4th week) windows are calculated from Baseline/Day 0. Post-treatment visits (Day 7 and Day 14) windows are calculated from date of current treatment cycle.	Visit 1[1]	Visit 2[1]	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5-12	Visit 5a-12a	Visit 5b-12b	Visit 13	Visit 14	Visit 15 EOS/ET[9]
	Screening	Baseline/ Day 0	Post-treatment		Week 4	Week 8	Every 4th week[10]	Post-treatment Performed only if re-treatment at Visit 5-12		Week 44	Week 48	Week 52
		(within 2 weeks after screening)	Day 7 (±1 day)	Day 14 (±3 days)	(±5 days)	(±5 days)	(+5 days)	Day 7 (±1 day)	Day 14 (±3 days)	(±5 days)	(±5 days)	(±5 days)
Informed Consent	X											
Demographic Data[2] including Fitzpatrick skin type, medical history & concurrent diseases, previous facial treatments/procedures (toxin naïve/non-toxin naïve)	X											
Inclusion /Exclusion Criteria	X	X[3]										
Concomitant Therapies/ Procedures	X	X[4]	X	X	X	X	X[4]	X	X	X	X	X
Adverse Events	X	X[4]	X	X	X	X	X[4]	X	X	X	X	X
Urine Pregnancy Test[5]	X	X[3]					X[3]					X
Vital Signs[6]		X[4]	X	X	X	X	X[4]	X	X	X	X	X
Blood sample clinical chemistry and hematology		X[3]										X
Blood sample for serum antibody testing		X[3]					X[11]			X[11]		X
Glabellar Line Severity (GL-ILA)	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X
Lateral Canthal Lines Severity (LCL-ILA)	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X
Focused Physical Examination (face, head, neck)	X	X[3]	X	X				X	X			X
Photography		X[3]	X	X	X	X	X[3]	X	X	X	X	X
Treatment		X[7]										
Eligibility for re-treatment							X					
Re-treatment							X[8]					
CCI CCI 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. *Includes date of birth, gender, race, ethnicity, height, and weight.*
3. *To be performed before treatment (as applicable post-baseline if re-treatment performed).*
4. *To be performed before treatment and post-treatment (as applicable post-baseline if retreatment performed).*
5. *To be performed only if female of childbearing potential and eligible for treatment.*
6. *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).
7. *Following treatment administration, subjects will be monitored at the study center for 30 minutes.*
8. *Only if subject meets re-treatment criteria.*
9. *If the subject withdraws before the final visit the ET visit should be completed, if possible.*
10. *Week 12, 16, 20, 24, 28, 32, 36 and 40.*
11. *Blood sample for serum antibody testing if subjects are eligible for re-treatment: before each re-treatment and 4 weeks after each re-treatment.*

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
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
EOS	End of Study
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
CCI [redacted]	
FOCBP	Females of child bearing potential
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.
IPR	Independent Photographic Review
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine Device
kDa	Kilodalton
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 Scales™
MD	Medical Doctor

Abbreviation/Term	*Definition*
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
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
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.
CCI [redacted]	
Study Files	The Investigator file and the Sponsor file
Study Product	The investigational product under study
Study Site	The location(s) where the study-related activities are actually conducted
TEAE	Treatment Emergent Adverse Event
UPT	Urine Pregnancy Test
US	United States
v/v	Volume/volume

Abbreviation/Term	*Definition*
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 long-term 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]

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 [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

1.2.3 Clinical Documentation

CCI [redacted]

CCI [redacted]

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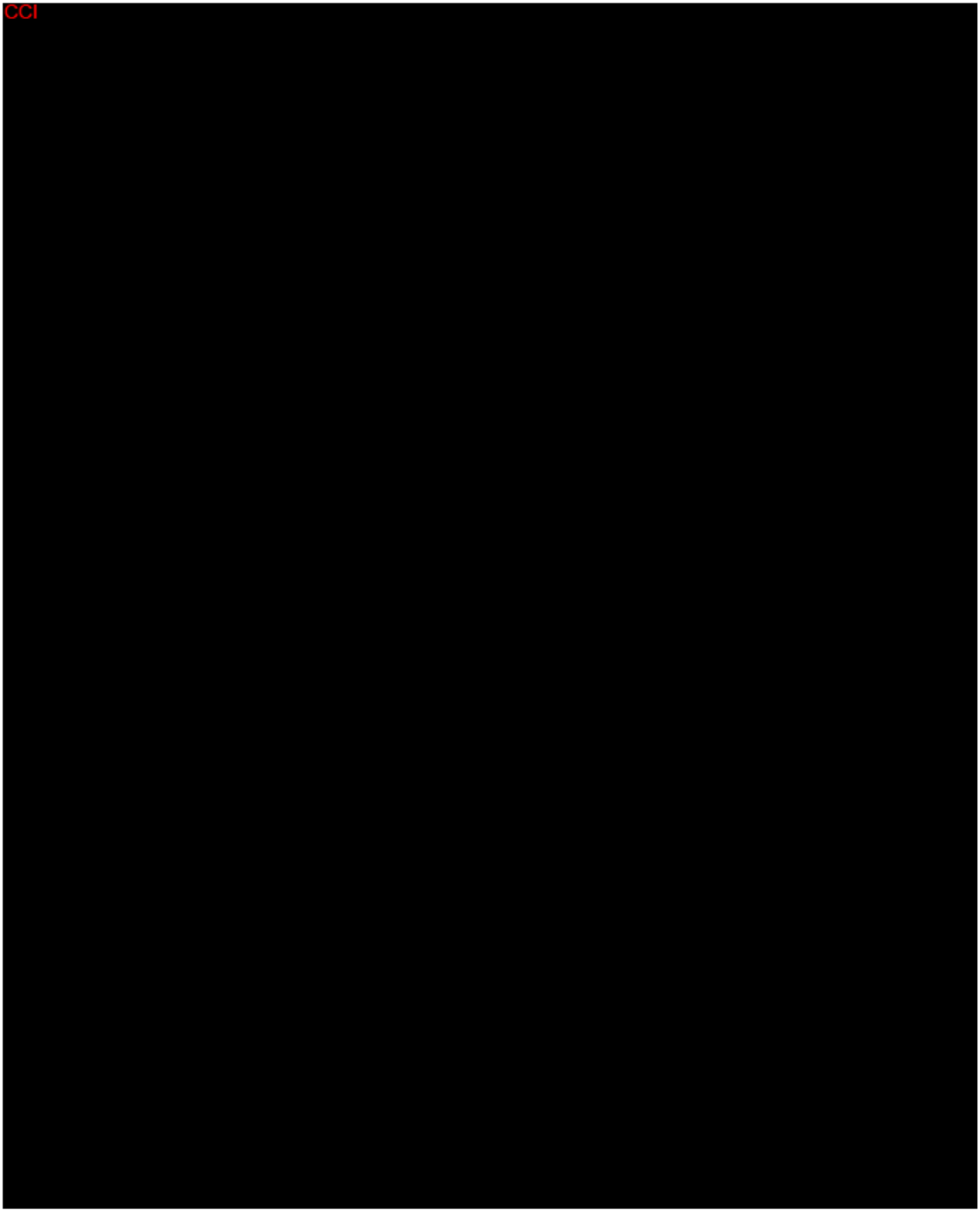
CCI [redacted]

CCI [redacted]

GALDERMA	Title **43QM1903 Clinical Study Protocol - QM1114 - LTS for LCL/GL**	Doc id



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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.

CCI

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CCI [redacted]

1.2.4 Dose Rationale

Non-clinical studies have shown a similarity between QM1114-DP potency units and Speywood units (Dysport®). Both safety and efficacy for the 30-60 U dose range of QM1114-DP were established in the phase 2 study (study CTN 43QM1313). In the treatment of GL with Speywood unit products (Dysport®/Azzalure®), the recommended dose is 50 U. Based on the evaluation of results for the different dose levels studied to date in the clinical program of QM1114-DP, the Sponsor has concluded that a 50 unit dose offers an appropriate balance between efficacy, duration of effect and safety.

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 is 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 GL and LCL, and additional treatments throughout the study when eligible.

No additional risks specific of the 110 U dose of QM1114-DP (50 U in the GL, 60 U in the LCL) 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 long-term treatment of moderate to severe GL and LCL, 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 this study is to evaluate the safety and efficacy of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL.

2.1.1 Primary Objectives and Endpoints

The primary objective of this study is to evaluate the safety of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL.

Primary endpoints include:

- Incidence and severity of treatment emergent AEs (TEAEs)
- Focused physical examination (FPE) findings

2.1.2 Secondary Objectives and Endpoints

The secondary objectives and endpoints of the study are:

1. Objective: To evaluate the efficacy of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL.

   Endpoints:

   - Percentage of subjects who achieve grade/level 0 or 1 at each visit in each treatment cycle using the
     - GL-ILA 4-point Photographic Scale at maximum frown
     - LCL-ILA 4-point Photographic Scale at maximum smile

     CCI [redacted]
   - Percentage of subjects who achieve ≥1 grade/level improvement from baseline at each visit in each treatment cycle using the
     - GL-ILA 4-point Photographic Scale at rest

- LCL-ILA 4-point Photographic Scale at relaxed position

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

2.2 Clinical Hypothesis

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

3. OVERALL CLINICAL STUDY DESCRIPTION

This is a phase 3, multicenter, open-label study to evaluate the safety of QM1114-DP for the long-term treatment of moderate to severe GL and LCL.

Eligible subjects will receive up to 4 treatments of QM1114-DP in the GL and/or LCL and will be monitored for safety and efficacy over a period of up to 52 weeks.

The first treatment will be administered at Day 0 (Baseline). Re-treatments can be administered at any of the follow-up visits from Week 12 to Week 40, provided that the subject is eligible for re-treatment and there has been at least 12 weeks since the last treatment. Follow-up visits for treated subjects are conducted at Day 7 and Day 14 after each treatment. Follow-up visits, i.e. not treatment dependent, are scheduled at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

To ensure a sufficient amount of long-term safety data is included in the database per ICH E1 guidelines, approximately 900 subjects will be enrolled; all subjects will be followed for at least 24 weeks and at least 300 subjects will be followed up to 52 weeks. The study may be stopped when at least 300 subjects have completed the Week 52 study visit.

All subjects that meet the eligibility criteria and are enrolled in the study will be treated on Day 0. Additional treatment can be administered at any of the follow-up visits from Week 12 to Week 40, provided that the following criteria are met:

- It has been at least 12 weeks since the previous treatment.
- Moderate (grade 2) or severe (grade 3) GL and/or LCL at maximum contraction (i.e., frown and smile, respectively) as assessed by the Investigator CCI [redacted] (ILA CCI [redacted]). In order to treat LCL, both sides should meet severity criteria and be treated at the same visit.
- There are no ongoing adverse events assessed as related to the treatment, which could exclude the subject from re-treatment.
- Subject agrees to receive re-treatment.
- If the subject is a female of child bearing potential, must be willing to take a pregnancy test and the result must be negative in order to receive re-treatment.
- There is no other medical or surgical condition that would put the subject at undue risk in case he/she receives an additional treatment cycle, according to Investigator's judgment.

After each treatment, subjects will return for study visits at Day 7 and Day 14. Follow up visits, i.e. not treatment dependent, are scheduled at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

Efficacy assessments will include (Section 7.1):

- 4-point Photographic Scale of GL Severity at rest and maximum frown (Investigator assessment [GL-ILA])

CCI [redacted]

- 4-point Photographic Scale of LCL Severity at relaxed position and maximum smile (Investigator assessment [LCL-ILA])

CCI [redacted]

CCI [redacted]

CCI [redacted]

Safety assessments will include (Section 7.2):

- Adverse Events (AEs)
- Focused physical examination (FPE)
- Vital signs
- 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 1. 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 16 months.

To ensure a sufficient amount of long-term safety data is included in the database per ICH E1 guidelines, approximately 900 subjects will be enrolled; all subjects will be followed for at least 24 weeks and at least 300 subjects will be followed up to 52 weeks. The study may be stopped when at least 300 subjects have completed the Week 52 study visit.

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 990 subjects will be screened in order to get 900 subjects enrolled.

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 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).
3. CCI [redacted]
4. 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).
5. CCI [redacted]
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. 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) or any botulinum toxin serotype.

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 exam 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 glabella or lateral canthus areas within 6 months before baseline.

9. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc) or semi-permanent (i.e., 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 tattoo(s) (including micro blading 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, micro needling, 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, micro needling, chemical peel, botulinum toxin treatment, or dermal fillers) in the face 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 participation in 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 product.

- 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 and 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 Week 52/ 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 enrolled 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 7.2.5.2.3. 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 each treatment a total dose of 110 U of QM1114-DP will be administered as:

- 50 U (10 U per GL injection point)
  0.5 mL total (0.1 mL per GL injection point)

AND

60 U (10 U per LCL injection point)
0.6 mL total (0.3 mL per treatment side/0.1 mL per LCL injection point)

CCI [redacted]

6.1.2 Study Product Description

Table 2 Description and Usage of the Study Product

	Investigational product
Name of drug substance	QM1114-DS
Internal Code	QM1114-DP
Pharmaceutical Form	Solution for injection
Concentration	100 units/mL, buffered solution
CCI [redacted]	
Dosage	At each treatment a total dose of 110 U of QM1114-DP will be administered as: • 50 units (10 U per GL injection point) 0.5 mL total (0.1 mL per GL injection point) AND • 60 units (10 U per LCL injection point) 0.6 mL total (0.3 mL per treatment site/ 0.1 mL per LCL injection point)
Route	Intramuscular injection
Dose regimen	Up to four (4) treatments
Location of treated area	Glabellar and lateral canthus areas

6.1.3 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.

6.1.4 Method of Treatment Assignment

Not applicable. This is an open-label study.

6.1.5 Kit Number/Randomization Number

Not applicable. This is an open-label study.

6.1.6 Instructions for Use and Administration

QM1114-DP will be administered at baseline, and at follow up visits when the subject meets the re-treatment eligible criteria (see Section 6.1.6.3). Subjects may receive up to four (4) treatments during the study.

All treating Investigators will be trained in the administration technique prior to the study start. See also QM1114-DP Investigators Brochure.[12]

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

6.1.6.1 Treatment Procedure

6.1.6.1.1 Glabellar Lines

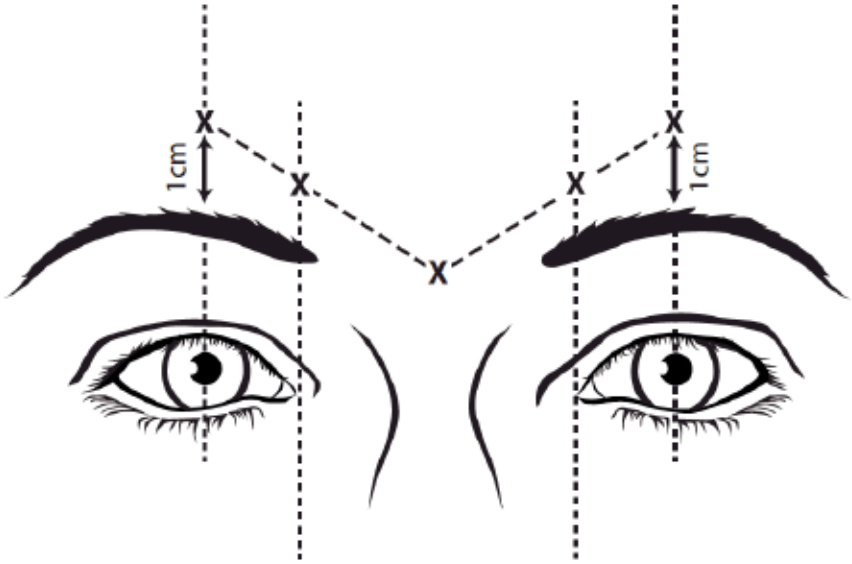
Prior to injection, the treatment area should be cleaned with a suitable antiseptic solution. An appropriately sized syringe and needle (e.g. 30-33 gauge needle) should be used to administer treatment.

Subjects will receive treatment with QM1114-DP in the GL at baseline, and at follow up visits when eligible (see Section 6.1.6.3). Each treatment includes 5 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 2).

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.

Figure 2 Injection Sites for Treating Glabellar Lines



6.1.6.1.2 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.

Subjects will receive treatment with QM1114-DP in the LCL at baseline, and at follow up visits when eligible (see Section 6.1.6.3). At each treatment visit, 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 3 and Figure 4 below. The injection site option for each subject is based on Investigator discretion, and should be consistent for the right and left treatment sides.

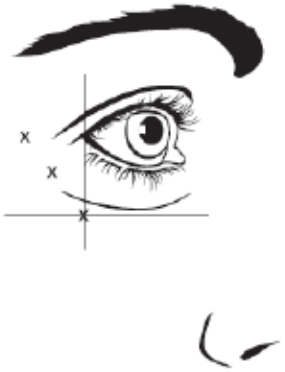
Injections should be performed at a 20-30° angle to the skin, with bevel of needle tip pointed up and away from the eye and very superficial. All injection points, three per side, should be at the external part of the orbicularis oculi muscle and sufficiently far from the orbital rim (at least 1 - 2 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 3. In case lines in the lateral canthal region are mainly below the lateral cantus, inject per Figure 4.

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.

Figure 3 Injection Sites for Treating LCL Option 1

Figure 4 Injection Sites for Treating LCL Option 2



6.1.6.2 Post-treatment Care

Following treatment administration, 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.

6.1.6.3 Treatment Regimen

Subjects will receive up to four treatments with QM1114-DP in their glabellar and lateral canthal lines during the study period, each treatment cycle is at least 12 weeks apart. Follow-up assessments for treated subjects are conducted at Day 7 and Day 14 post-treatment. All subjects are followed up every 4th week for a period of up to 52 weeks.

The following conditions are required to be met for re-treatment post-baseline:

- It has been at least 12 weeks since the previous treatment in the intended area
- For GL re-treatment:
  - Moderate (grade 2) or severe (grade 3) rhytides at maximum frown as assessed by the Investigator (ILA).

CCI [redacted]

- For LCL re-treatment:
  - Moderate (grade 2) or severe (grade 3) rhytides at maximum smile as assessed by the Investigator (ILA).

CCI [redacted]

  - In order to treat LCL, both sides should meet severity criteria and be treated at the same visit.
- There are no ongoing adverse events assessed as related to the treatment, which could preclude the subject from re-treatment.
- Subject agrees to receive re-treatment.
- If subject is a female of child-bearing potential, agrees to take a pregnancy test and test result must be negative in order to receive re-treatment.
- There is no other medical or surgical condition that would put the subject at undue risk in case he/she receives an additional treatment cycle, according to investigator's judgment.

6.2 Study Product Packaging and Labeling

QM1114-DP is manufactured under aseptic conditions. CCI [redacted]

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

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

6.3.2 Storage of Study Product

Study product must be stored in a safe and secure area with restricted access, under the storage conditions specified by the Sponsor (see Table 2).

6.3.3 Dispensing and Return

All study product 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.

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

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

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

Not applicable. This is an open-label study.

6.4.1 Verification of Blinding

Not applicable. This is an open-label study.

6.4.2 Unblinding During the Clinical Study

Not applicable. This is an open-label study.

7. CLINICAL STUDY ASSESSMENT

7.1 Efficacy Assessments

7.1.1 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 1) includes two grading systems: one for Investigator live assessments at maximum frown, and one for Investigator live assessments at rest. The scale represents the severity of glabellar lines from none (grade 0), mild (grade 1), moderate (grade 2) to severe glabellar lines (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 rest and maximum frown respectively, at screening, baseline (prior to treatment), and at all post-baseline visits (prior to treatment, as applicable).

CCI [redacted]

CCI

CCI

CCI

7.1.3 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 2), developed by Galderma, includes two grading systems: one for the Investigator live assessments at maximum smile, and one for the Investigator live assessments at relaxed position. 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 relaxed position and maximum smile.

CCI

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CCI

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CCI

CCI

CCI

7.2 Safety Assessments

Safety assessments will be conducted for all subjects at the time points indicated in Schedule of Assessments (Table 1). Safety parameters include an evaluation of AEs, FPE, vital signs, 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 1), 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 5.

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 6). 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 1), 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 Laboratory Safety Tests

Blood samples will be collected at baseline (prior to treatment) and at Week 52/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.

7.2.4 Neutralizing Antibody Testing

Subjects will have blood samples taken at baseline prior to treatment, before any re-treatment, 4 weeks after re-treatment, and at Week 52/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.

7.2.5 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.

7.2.5.1 Definitions

7.2.5.1.1 Adverse Events (AE)

According to ICH E2A,[13] 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 7.2.5.2.3.
- 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.

7.2.5.1.2 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.

7.2.5.1.3 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).

7.2.5.1.4 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).

7.2.5.1.5 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.

7.2.5.1.6 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.

7.2.5.1.7 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 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.

7.2.5.2 Reporting Procedures

7.2.5.2.1 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 7.2.5.2.2) and pregnancies (see Section 7.2.5.2.3), the Sponsor is to be informed immediately by e-mail. The event must be reported to the Safety email within 24 hours of receipt of the information (contact details in Section 7.2.5.2.2).

7.2.5.2.2 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 7.2.5.1.3).

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.

7.2.5.2.3 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:

10. 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, no dosing of the investigational product).

11. 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).

12. 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.

13. 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.

14. 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 7.2.5.2.2).

7.3 Other Assessments

7.3.1 Photography

Standardized digital photographs will be taken of the subject's glabellar region, lateral canthus 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 (FOCBP), a urine pregnancy test will be performed at screening, baseline (prior to treatment), prior to each re-treatment when eligible, and at Week 52/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 1.

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, 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 1).
4. CCI [redacted]
5. CCI [redacted]
6. Investigator to complete assessment of the subject's GL severity at rest and 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 7.1.1 and Appendix 1)
7. Investigator to complete assessment of the subject's LCL severity at relaxed position and 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. (Section 7.1.3 and Appendix 2)

8. Investigator to perform a focused PE (Appendix 5). 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. 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 (Treatment, 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. CCI [redacted]
5. CCI [redacted]
6. 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).
7. 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.

8. Collect blood sample (chemistry and hematology) for analysis at the central laboratory (Section 7.2.3).
9. Collect blood sample for neutralizing antibody testing (Section 7.2.4).
10. Take subject photographs (refer to photo manual for completion instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.
11. Investigator to complete assessment of the subject's GL severity at rest and 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 7.1.1 and Appendix 1)
12. Investigator to complete assessment of the subject's LCL severity at relaxed position and 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. (Section 7.1.3 and Appendix 2)
13. Investigator to perform a focused PE (Appendix 5). Clinically significant abnormal findings are exclusionary; document as screen fail and do not enrolled the subject in the study.
14. Review the inclusion/exclusion criteria, and confirm if subject meets study eligibility requirements.
    - If yes, enroll the subject in the clinical study. Proceed to next steps.
    - If no, document the subject as a screen failure.
    - For all subjects, enter appropriate data into the eCRF; the SIN should have been assigned via the eCRF system at the screening visit.
15. For subjects who meet all eligibility criteria, the Investigator or designee should prepare the treatment accordingly and complete the required documentation and eCRF (Section 6.1.6).
16. Prior to injection, clean the subject's treatment areas with a suitable antiseptic solution.
17. The Investigator will administer the treatments. See Section 6.1.6.1 for treatment procedure requirements. Following treatment administration, subjects will be monitored at the study center for 30 minutes. (Section 6.1.6.2)
18. Obtain the subject's post-treatment vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated at least 10 minutes after study injections are completed.
19. Ask the subject about AEs using an open-ended question. Record all events, as appropriate on the corresponding eCRF form(s).
20. Record post-treatment concomitant therapies/procedures.
21. Schedule the next visit (Day 7 ±1 day).

8.1.2.1 Day 7 post treatment / Visit 2a (±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. CCI [redacted]
5. CCI [redacted]
6. 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.
7. Investigator to complete assessment of the subject's GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
8. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
9. Investigator to perform a focused PE. (Appendix 5)
10. Schedule the next visit (Day 14 ±3 days).

8.1.2.2 Day 14 post treatment / Visit 2b (±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. CCI [redacted]
4. CCI [redacted]
5. 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).

6. 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.
7. Investigator to complete assessment of the subject's GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
8. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
9. Investigator to perform a focused PE. (Appendix 5)
10. Schedule the next visit (Week 4 ±5 days).

8.1.3 Week 4 and 8 / Visits 3-4 (±5 days)

The Investigator or designee will:

11. 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.
12. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
13. CCI [redacted]
14. CCI [redacted]
15. CCI [redacted]
16. CCI [redacted]
17. 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).
18. 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.
19. Investigator to complete assessment of the subject's GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
20. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
21. Schedule the next visit (+5 days). NOTE: Treatments must be at least 12 weeks apart.

8.1.4 Week 12, 16, 20, 24, 28, 32, 36 and 40 / Visits 5-12 (±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. CCI [redacted]
4. CCI [redacted]
5. CCI [redacted]
6. CCI [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. ONLY for re-treated subjects: collect blood sample for neutralizing antibody testing (Section 7.2.4) 4 weeks after each re-treatment.
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 GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
11. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
12. Investigator to assess if subject meets re-treatment criteria. (Section 6.1.6.3)
    - If yes, proceed to next steps.
    - If no, do not proceed to next steps. Schedule the next visit (±5 days).
13. For subjects who meet re-treatment criteria:
    - 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 re-treatment.
    - Collect blood sample for neutralizing antibody testing prior to re-treatment (Section 7.2.4).
    - The Investigator or designee should prepare the treatment accordingly and complete the required documentation and eCRF (Section 6.1.6).

- Prior to injection, clean the subject's treatment areas with a suitable antiseptic solution.
- The Investigator will administer the treatment(s). See Section 6.1.6.1 for treatment procedure requirements. Following treatment administration, subjects will be monitored at the study center for 30 minutes. (Section 6.1.6.2)
- 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 rest (Section 7.2.2).
- Ask the subject about AEs using an open-ended question. Record all events, as appropriate, on the corresponding eCRF form(s).
- Record post-treatment concomitant therapies/procedures.
- Schedule the next visit (Day 7 ±1 day). NOTE: Treatments must be at least 12 weeks apart.

8.1.4.1 Day 7 post re-treatment/Visit a (±1 day)

Visit to be performed only if the subject was treated at the previous 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. CCI [redacted]
5. 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).
6. 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.
7. Investigator to complete assessment of the subject's GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
8. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
9. Investigator to perform a focused PE. (Appendix 5)
10. Schedule the next visit (Day 14 ±3 days).

8.1.4.2 Day 14 post re-treatment/Visit b (±3 days)

Visit to be performed only if the subject was treated at the previous follow-up visit (Section 8.1.4).

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. CCI [redacted]
5. 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).
6. 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.
7. Investigator to complete assessment of the subject's GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
8. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
9. Investigator to perform a focused PE. (Appendix 5)
10. Schedule the next follow-up visit (±5 days).

8.1.5 Week 44 and 48 / Visits 13-14 (±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. CCI [redacted]
4. CCI [redacted]

5. CCI [redacted]
6. CCI [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. ONLY Week 44 visit for subjects re-treated at Week 40: collect blood sample for neutralizing antibody testing (Section 7.2.4).
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 GL severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
11. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
12. Schedule the next follow-up visit (±5 days).

8.1.6 Week 52 / Visit 15 – End of Study, or Early Termination visit (±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. CCI [redacted]
4. CCI [redacted]
5. CCI [redacted]
6. CCI [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. Collect blood sample (chemistry and hematology) for analysis at the central laboratory (Section 7.2.3).
9. Collect blood sample for neutralizing antibody testing (Section 7.2.4).

10. 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.
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 glabellar line severity at rest and maximum frown using the 4-point Photographic Scale (GL-ILA). (Section 7.1.1 and Appendix 1)
13. Investigator to complete assessment of the subject's bilateral LCL severity at relaxed position and maximum smile using the 4-point Photographic Scale (LCL-ILA). (Section 7.1.3 and Appendix 2)
14. Investigator to perform a focused PE. (Appendix 5)
15. Complete End of Study assessments (blood samples and UPT for FOCBP) and 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

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 6.1.6.2.

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.

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

9.1.1 Data Transformations

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 Safety Population

The safety population includes all subjects who were administered the study product at least once. All safety data will be summarized descriptively based on the safety population.

9.1.2.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were administered the study product at least once and who have at least one post-baseline efficacy measurement. All efficacy variables will be analyzed based on the FAS.

9.1.3 Handling of Drop-Outs and Missing Data

No imputation of missing data will be performed.

9.1.4 Data Presentation and Graphics

All statistical analyses will be descriptive, and performed using the SAS® system (version 9).

In general, 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 frequency and percentage. Graphs may be used as appropriate.

Subject disposition, demographics and baseline characteristics, medical history, concomitant medication and procedures, and number of treatment cycles will be summarized.

All analyses of AEs will be done both for the whole study and per cycle. Treatment-emergent Adverse Events (TEAEs) will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on MedDRA. Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study product(s), and AEs leading to discontinuation. For related AEs, action taken, intensity, duration, and onset will be presented. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

Consistency of the AE incidences will be analyzed in subgroups by gender, prior use of botulinum toxin, race, Fitzpatrick skin type, treatment area, and center.

In addition, AEs with an onset prior to the baseline visit will be listed separately.

Results from physical examination, vital signs, clinical chemistry and hematology tests, and presence or absence of NAB will be summarized by visit and cycle. For continuous data both the value at each visit as well as the change from baseline will be used.

9.1.5 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.

9.1.6 Inferential Statistical Analyses

All statistical analysis will be descriptive.

9.2 Sample Size Determination

The study is planned to include approximately 900 subjects, at least 300 subjects will be treated and followed for 52 weeks and another 600 subjects will complete at least 24 weeks.

The sample size is not based on a statistical calculation and the selected number is regarded sufficient in order to appropriately capture safety information in an evaluation of QM1114-DP.

9.2.1 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 Adm

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

12. Summary of Changes in Clinical Study Protocol 43QM1903

12.1 Protocol Version 4.0 to Version 5.0

Section in the clinical study protocol	Rational for changes	Description of changes
Schedule of assessments	Collection of neutralizing antibody blood sample before re-treatment and at 4 weeks after re-treatment	Blood sample for neutralizing antibody testing added at week 12, 16, 20, 24, 28, 32, 36, 40, and 44. Footnote 11 added ("*Blood sample for serum antibody testing if subjects are eligible for re-treatment: before each re-treatment and 4 weeks after each re-treatment*").
Section 7.2.4 (neutralizing antibody testing)	Collection of neutralizing antibody blood sample before re-treatment and at 4 weeks after re-treatment	"…before any re-treatment, 4 weeks after re-treatment…" added.
Section 8.1.4 (description of study visits)	Collection of neutralizing antibody blood sample before re-treatment and at 4 weeks after re-treatment	"Collect blood sample for neutralizing antibody testing prior to re-treatment" and "ONLY for re-treated subjects: collect blood sample for neutralizing antibody testing 4 weeks after each re-treatment" added for week 12, 16, 20, 24, 28, 32, 36 and 40.
Section 8.1.5 (description of study visits)	Collection of neutralizing antibody blood sample before re-treatment and at 4 weeks after re-treatment	"ONLY Week 44 visit for subjects re-treated at Week 40: collect blood sample for neutralizing antibody testing" added for week 44.

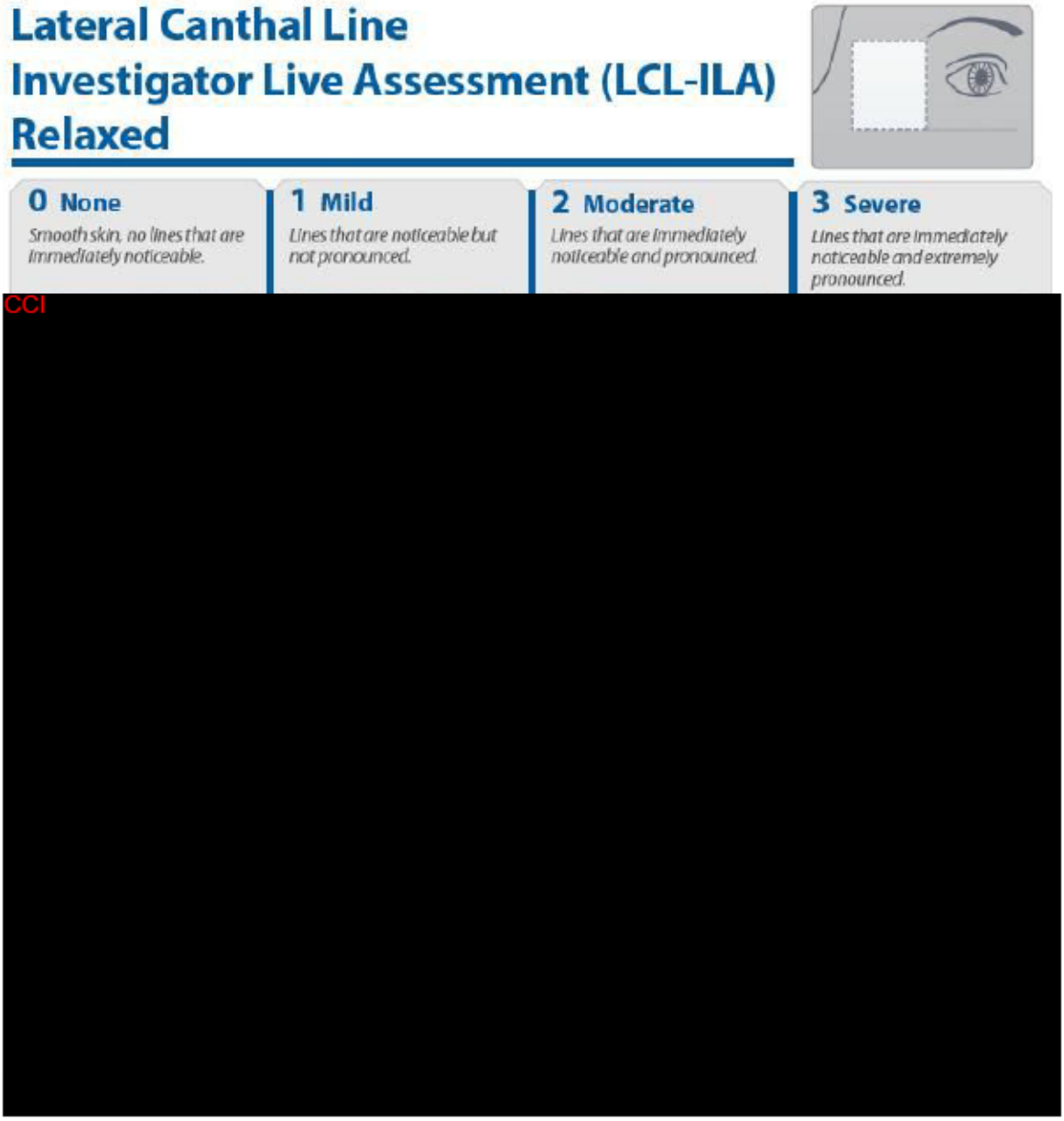
13. LITERATURE REFERENCE LIST

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. ICH E2A: International Conference on Harmonisation Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 1994
14. FDA Guidance for Industry. Upper Facial Lines: developing botulinum toxin drug products (draft), 2004.

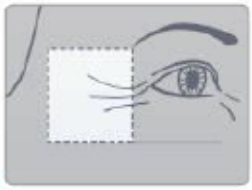
14. APPENDICES

Appendix 1 Validated Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA)

Appendix 2 Validated Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA)



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

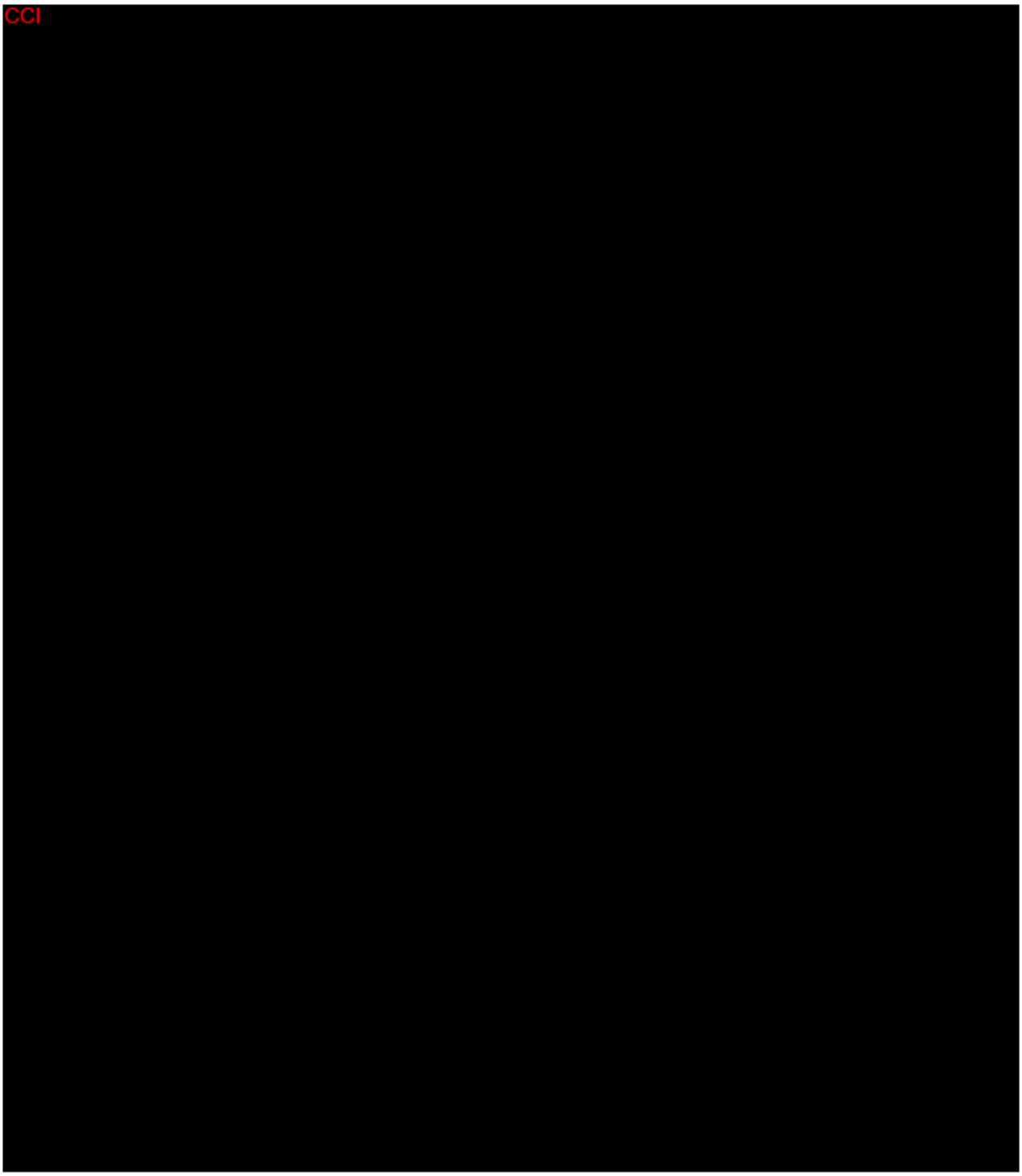


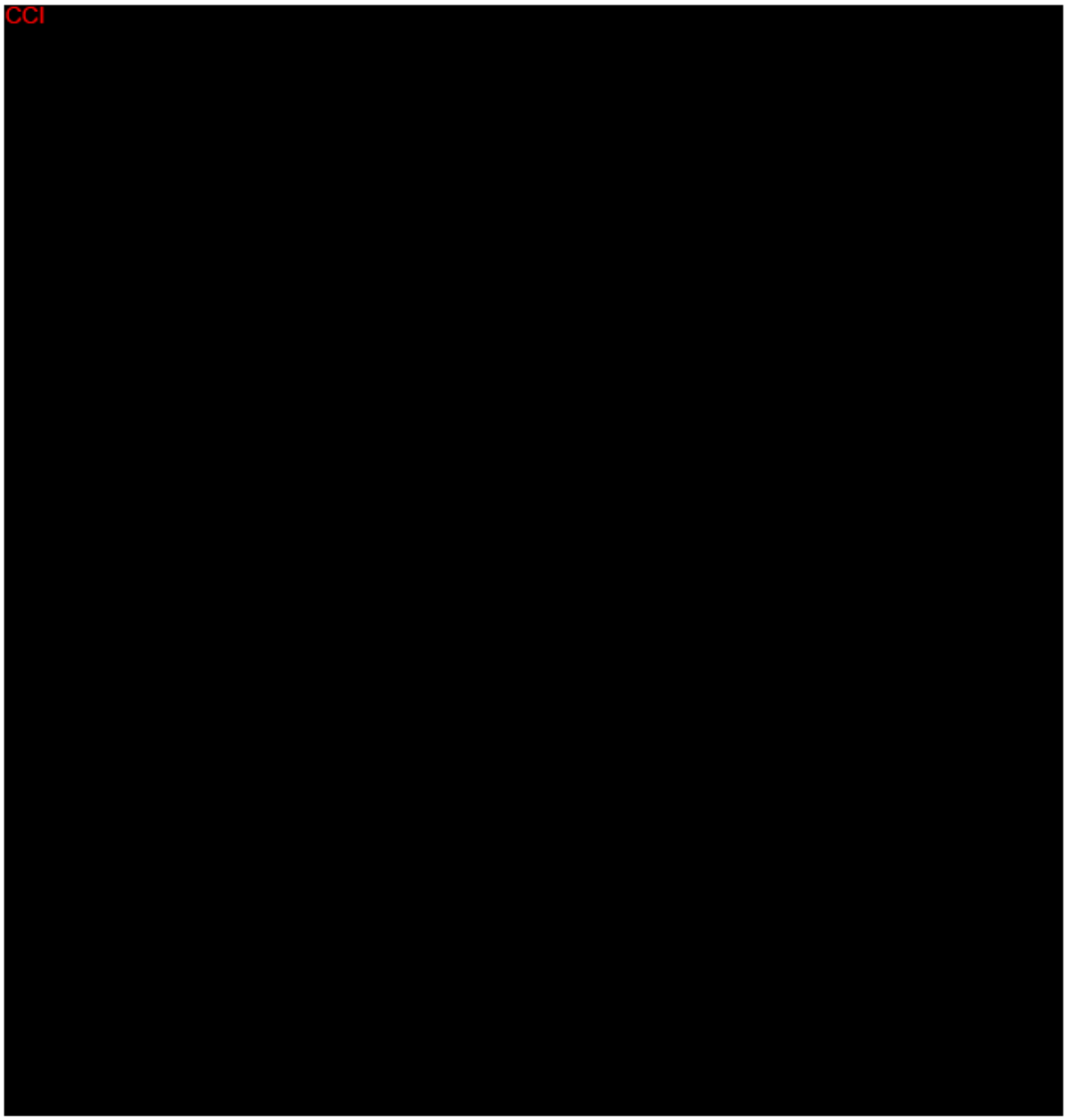
0 None	1 Mild	2 Moderate	3 Severe
Smooth skin, no lines that are immediately noticeable.	*Lines that are noticeable but not pronounced.*	*Lines that are immediately noticeable and pronounced.*	*Lines that are immediately noticeable and extremely pronounced.*

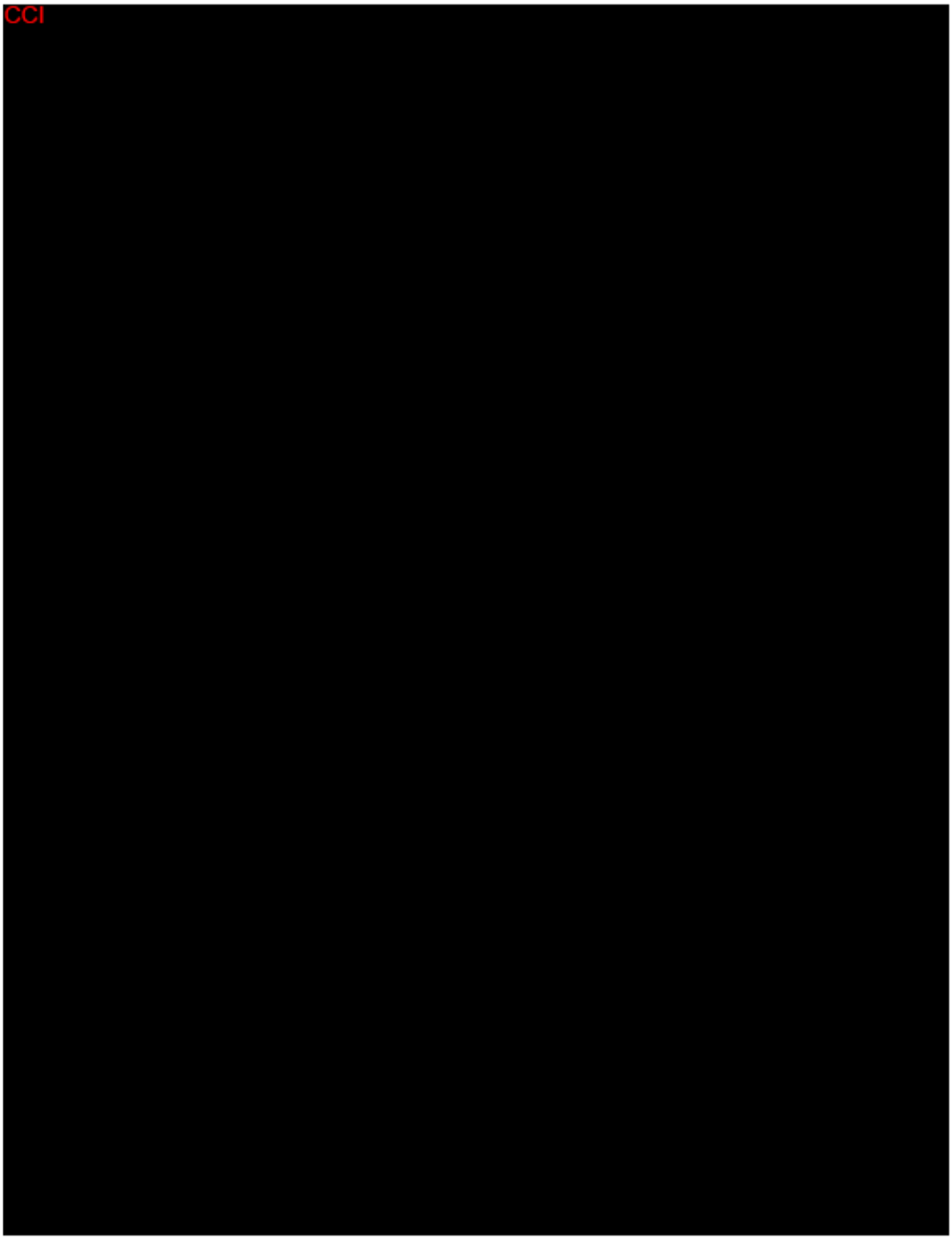
CCI

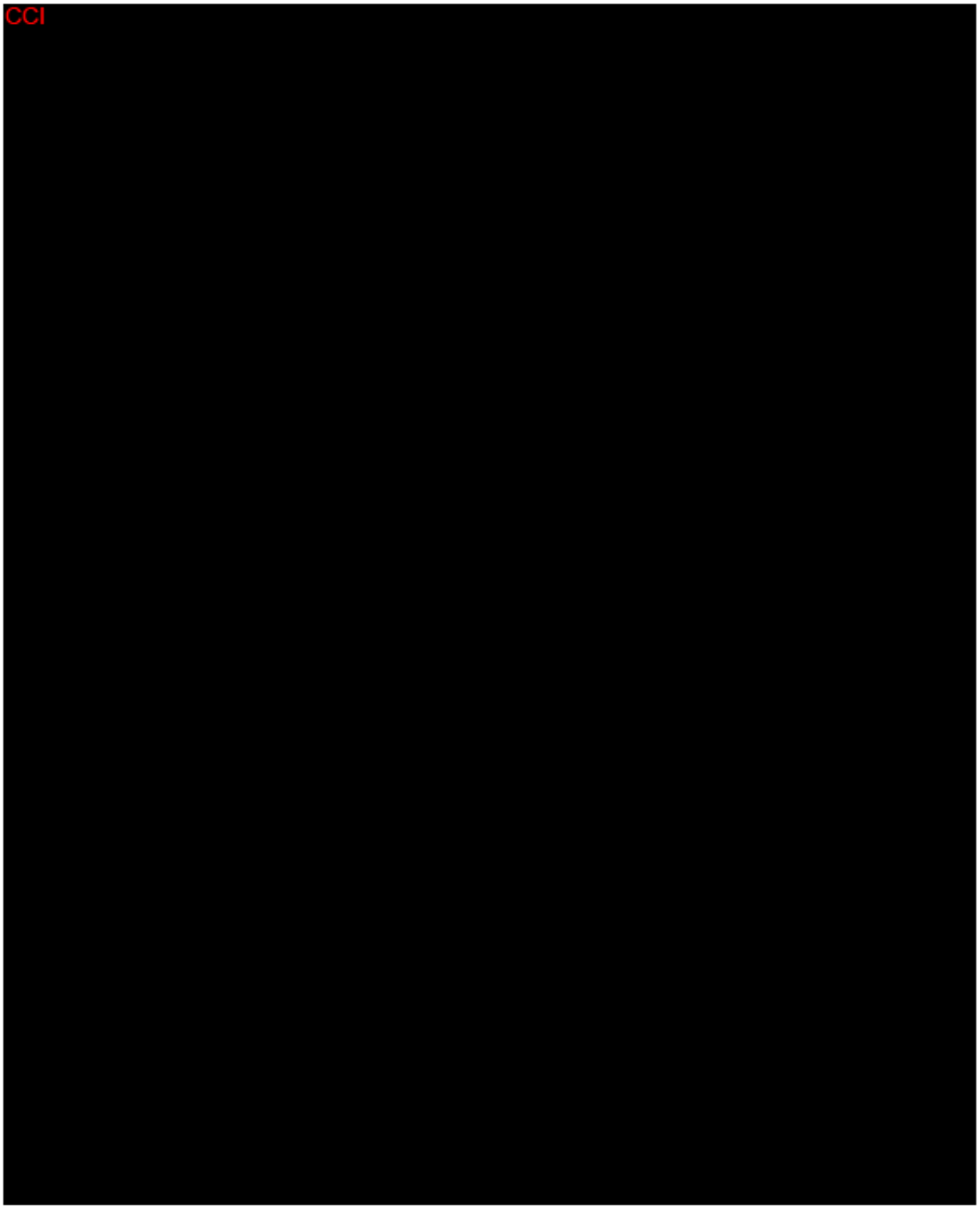
[redacted]

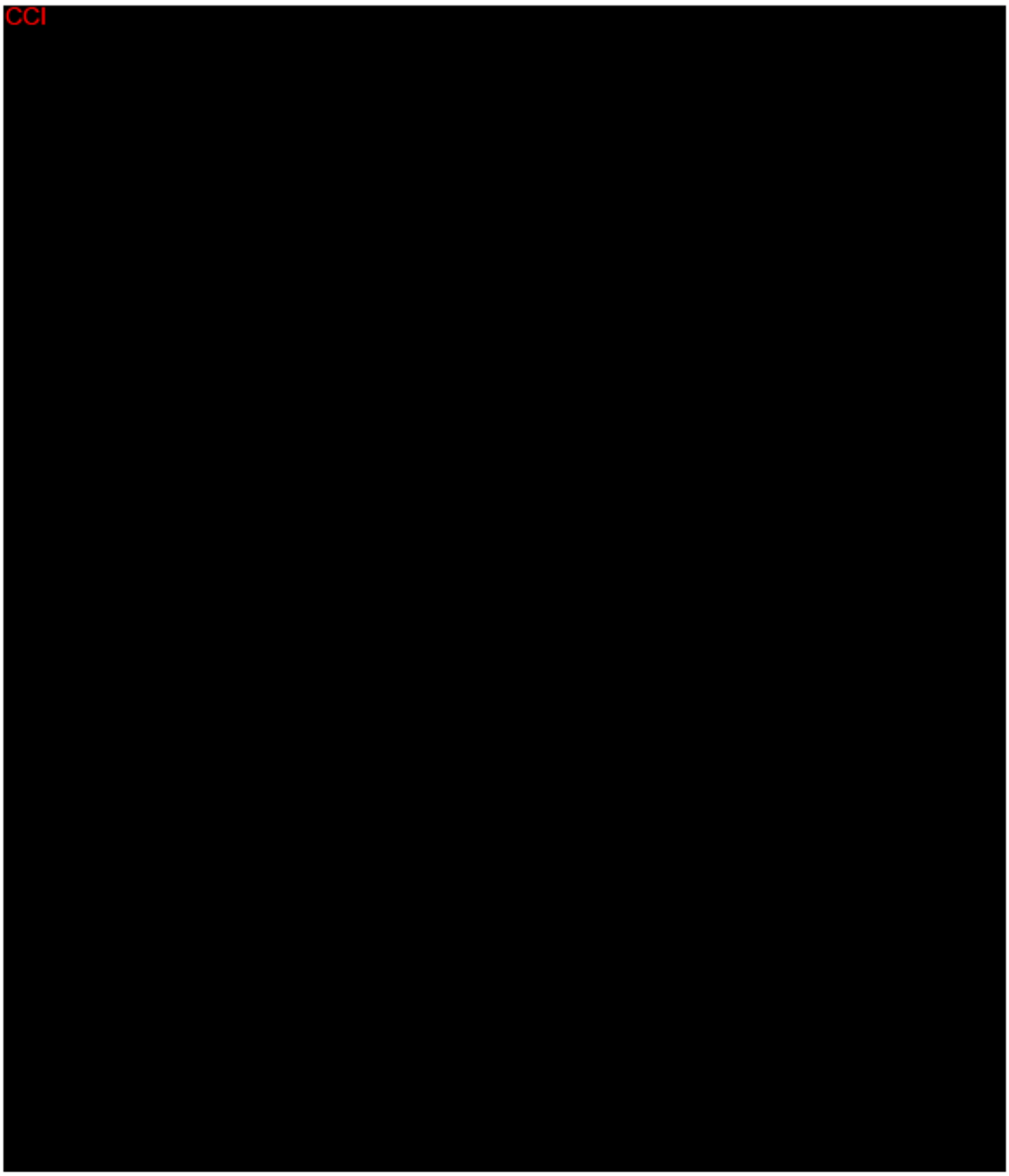
CCI






CCI





Appendix 5 Focused Physical Examination Form Example

Not done ☐ **Provide details:** _____

General Health Assessment: Complete at Screening, Baseline (prior to treatment), Days 7 and 14 after each treatment, and Week 52/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 6). 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 assessed for clinical significance and recorded as AEs when appropriate.

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

Part 1: Complete at Screening, Baseline (prior to treatment), Days 7 and 14 after each treatment and Week 52/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 Days 7 and 14 after each treatment and Week 52/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, medial part of temporalis, zygomaticus minor, zygomaticus major, superior and inferior tarsal muscle).
- 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 6) 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 6 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).[14]

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: 43QM1903

CSP title: A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY – 4)

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 43QM1903 Clinical Study Protocol - QM1114 - LTS for LCL/GL	Doc id MA-40372

SIGNATURES PAGE

Date	Signed by
2020-08-26 18:25	PPD
Justification	Approved by Technical Expert

2020-08-26 18:47	PPD
Justification	Compiled by

2020-08-26 18:56	PPD
Justification	Approved by Owner

2020-08-26 19:44	PPD
Justification	Approved by Technical Expert