

CCI

CCI

GALDERMA

EST. 1981

Title

43QM2107 Clinical Study Protocol – QM1114 – GL and LCL

CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER: 43QM2107

CCI

TITLE PAGE

A Phase 3b, Open-label, Single-center Study to Assess Aesthetic Improvement Following Treatment with QM1114-DP in Subjects with Moderate to Severe Lateral Canthal Lines and Glabellar Lines

Clinical Trial Number (CTN): 43QM2107

Investigational New Drug (IND) Number: 110196

SPONSOR:

Q-Med AB, part of the Galderma Group
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00

Galderma Research and Development, LLC
2001 Ross Avenue, Suite 1600
Dallas, TX 75201
United States
Telephone: +1 817 961 5000

CCI

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 7.2.3.2.2 and 7.2.3.2.3.

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), International Council for Harmonisation Good Clinical Practice (ICH 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/>).

TABLE OF CONTENTS

TITLE PAGE.....	2
TABLE OF CONTENTS	3
SYNOPSIS	9
CLINICAL STUDY SCHEMATIC AND FLOW CHART.....	16
SCHEDULE OF ASSESSMENTS	18
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	20
1. BACKGROUND AND RATIONALE	24
1.1 Medical Background and Short Rationale for the Clinical Study.....	24
1.2 Study Product Profile	25
1.2.1 Drug Profile	25
1.2.2 Pre-Clinical Documentation.....	25
1.2.3 Clinical Documentation	26
1.2.4 Dose Rationale.....	29
1.3 Risk/Benefit Assessment.....	29
2. CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS.....	30
2.1 Clinical Study Objectives	30
2.1.1 Primary Efficacy Objectives and Endpoints	30
2.2 Clinical Hypothesis	33
3. OVERALL CLINICAL STUDY DESCRIPTION.....	33
4. CLINICAL STUDY DURATION AND TERMINATION	33
5. SELECTION AND DISPOSITION OF CLINICAL STUDY POPULATION.....	34
5.1 Number of Subjects.....	34
5.2 Clinical Study Population Characteristics.....	34
5.2.1 Inclusion Criteria	34
5.2.2 Exclusion Criteria	35
5.3 Medical History.....	36
5.4 Previous and Concomitant Therapies	37

5.4.1	Definition	37
5.4.2	Categories	37
5.4.3	Recording.....	37
5.4.4	Authorized Concomitant Therapies	37
5.4.5	Prohibited Concomitant Therapies	37
5.5	Procedures/Reasons for Subject Discontinuation	39
6.	CLINICAL SUPPLIES	40
6.1	Clinical Supply Identification and Use.....	40
6.1.1	QM1114-DP	40
6.1.2	Study Products(s) Description	41
6.1.3	Subject Identification Number	41
6.1.4	Method of Treatment Assignment.....	41
6.1.5	Kit Number/Randomization Number	42
6.1.6	Instructions for Use and Administration	42
6.1.6.1	Treatment Procedure	42
6.1.6.2	Post-treatment Care	44
6.1.6.3	Treatment Regimen	44
6.2	Study Products(s) Packaging and Labeling.....	44
6.3	Supplies Management.....	45
6.3.1	Accountability	45
6.3.2	Storage of Study Product	45
6.3.3	Dispensing and Return	45
6.3.4	Treatment Compliance Management and Record.....	45
6.3.5	Dose Modification	45
6.3.6	Product Quality Complaints	45
6.4	Blinding.....	46
6.4.1	Verification of Blinding	46
6.4.2	Unblinding During the Clinical Study	46
7.	CLINICAL STUDY ASSESSMENTS	46

CCI

7.1	Efficacy Assessments.....	46
7.1.1	Global Aesthetic Improvement Scale	46



7.2.3	Adverse Events.....	50
7.2.3.1	Definitions.....	50
7.2.3.1.1	<i>Adverse Events.....</i>	<i>50</i>
7.2.3.1.2	<i>Treatment Emergent Adverse Event</i>	<i>51</i>
7.2.3.1.3	<i>Serious Adverse Events.....</i>	<i>51</i>
7.2.3.1.4	<i>Unexpected Adverse Drug Reaction.....</i>	<i>52</i>
7.2.3.1.5	<i>Adverse Event Reporting Period</i>	<i>52</i>
7.2.3.1.6	<i>Severity</i>	<i>52</i>
7.2.3.1.7	<i>Relationship to the Study Product and/or Clinical Study Procedure</i>	<i>52</i>
7.2.3.2	Reporting Procedures.....	53
7.2.3.2.1	<i>Procedures for Reporting Adverse Events.....</i>	<i>53</i>
7.2.3.2.2	<i>Procedure for Reporting a Serious Adverse Event.....</i>	<i>54</i>
7.2.3.2.3	<i>Procedures for Reporting Pregnancies</i>	<i>55</i>
7.3	Other Assessments	56
7.3.1	Pregnancy Test.....	56

7.3.2	Professional Photography	56
7.4	Appropriateness of Measurements.....	56
8.	CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES	56
8.1	Description of Clinical Study Visits.....	56
8.1.1	Screening/Visit 1 (-14 days to Day 0).....	56
8.1.2	Baseline/Visit 2 (Day 0).....	57
8.1.3	Days 1, 2, 3, 4/Visits 3, 4, 5, 6	59
8.1.4	Month 1/Visit 7 (± 5 days)	60
8.1.5	Months 2, 3/Visits 8, 9 (± 5 days)	61
8.1.6	Month 4 or Early Termination/Visit 10 (± 5 days).....	62
8.2	Unscheduled Visits	63
8.3	Subject Instructions	63
9.	STATISTICAL METHODS PLANNED	64
9.1	General.....	64
9.2	Data Transformations.....	64
9.3	Analysis populations	65
9.4	Imputation of Missing Data	65
9.5	Efficacy analysis	65
9.5.1	Primary analysis	65
9.6	Sample Size Determination	66
9.7	Interim Analysis	66
10.	TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE	66
10.1	Personnel Training.....	66
10.2	Clinical Monitoring.....	67
10.3	Data Management.....	67
10.4	Quality Assurance/Audit/Inspection	67
10.5	Changes in Clinical Study Conduct/Amendments	68
10.5.1	Clinical Study Conduct.....	68
10.5.2	Amendments.....	68

CCI

11.	ETHICS AND GENERAL CLINICAL STUDY CONDUCT CONSIDERATIONS	68
11.1	Institutional Review Board	68
11.2	Ethical Conduct of the Clinical Study.....	68
11.3	Subject Information and Consent	68
11.4	Protection of Personal Data	69
11.5	Contractual Requirements.....	69
11.6	Data Collection and Archiving.....	70
11.6.1	Data Collection.....	70
11.6.2	Source Documentation.....	70
11.6.3	Archives	70
11.7	Insurance	70
11.8	Publication Policy.....	70
11.9	Investigator and Administrative Structure	72
12.	LITERATURE REFERENCE LIST.....	73

CCI

List of Tables

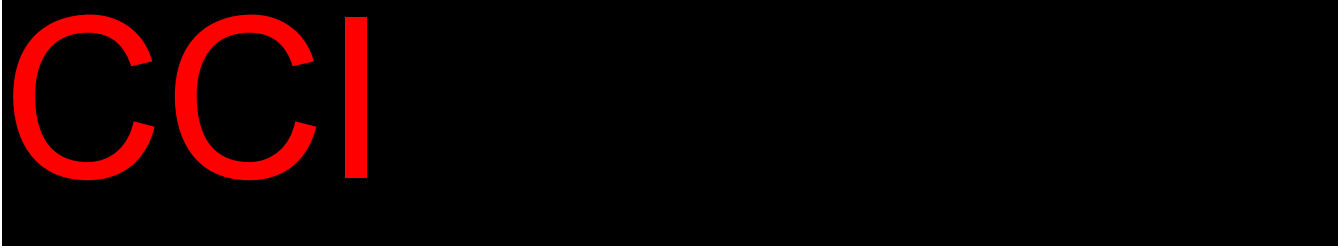
Table 1 Clinical Study Schematic..... 16

Table 2 Schedule of Assessments 18

Table 3 Description and Usage of the Study Products(s) 41

List of Figures

Figure 1 Study Flow Chart..... 17



SYNOPSIS

SYNOPSIS	
Clinical Study Title: A Phase 3b, Open-label, Single-center Study to Assess Aesthetic Improvement Following Treatment with QM1114-DP in Subjects with Moderate to Severe Lateral Canthal Lines and Glabellar Lines	
Short Title: EXPRESSION Study (EXP anding REL abotulinumtoxin Assessment of S ubject S atisfact ION and Aesthetic Improvement)	
Clinical Study Population:	Male and female subjects, 18 years of age and older with moderate to severe lateral canthal lines (LCL) at maximum smile, and moderate to severe glabellar lines (GL) at maximum frown.
Clinical Study Design:	<p>This is an open-label, single-center study to evaluate aesthetic improvement following treatment with QM1114-DP.</p> <p>Following signature of informed consent and the screening process, eligible subjects will be treated at the baseline visit (Day 0) with 60 units (U) of QM1114-DP in the lateral canthus areas, and 50 U of QM1114-DP in the glabellar region.</p> <p>Following treatment at baseline, subjects will be monitored for safety and efficacy according to the Schedule of Assessments for 4 months.</p>
Target Indication:	Lateral canthal and glabellar lines
Total Number of Subjects (Planned):	Approximately 24 subjects.
Number of Clinical Study Centers (Planned):	One study center.
Region(s) / Country(ies) Involved (Planned):	United States (US).
Clinical Study Duration:	<p>The planned duration of recruitment (i.e. from First Subject First Visit [FSFV] to Last Subject First Visit [LSFV]) is approximately 2 months.</p> <p>The planned clinical study duration (i.e. from FSFV to Last Subject Last Visit [LSLV]) is approximately 6.5 months.</p>
Duration of Subject Participation:	Clinical study participation for each subject is up to 4.5 months.
Key Inclusion Criteria:	<ol style="list-style-type: none"> 1. Male or female 18 years of age or older. 2. Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum smile as assessed by the investigator live assessment (ICI-II A) 3. [Redacted] 4. Moderate to severe GL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum frown as assessed by

CCI

CCI

SYNOPSIS

CCI

Key Exclusion Criteria:

1. Botulinum toxin treatment in facial areas within CCI in the LCL and GL regions prior to study treatment.

CCI

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).

CCI

SYNOPSIS

CCI

SYNOPSIS	
Study Product:	QM1114-DP, is a BoNT-A, supplied as a sterile, buffered solution for injection containing the drug substance (QM1114-DS)
Strength/Concentration:	100 U/mL
Dosage (total daily dose):	<u>Lateral Canthal Lines</u> <ul style="list-style-type: none"> 60 U total (0.6 mL total/0.3 mL per treatment side) 10 U per LCL injection point (0.1 mL per LCL injection point) <u>Glabellar Lines</u> <ul style="list-style-type: none"> 50 U total (0.5 mL) 10 U per GL injection point (0.1 mL per GL injection point)
Route:	Intramuscular injection
Dose regimen:	Single treatment at baseline visit
Location of treated area:	Lateral canthus and glabellar areas
Efficacy Assessments:	<ul style="list-style-type: none"> 7-point GAIS of GL (Subject assessment)
Study Objective:	The objective of the study is to evaluate aesthetic improvement following treatment with QM1114-DP in subjects with moderate to severe lateral canthal and glabellar lines.
Primary Efficacy Objectives and Endpoints:	<ol style="list-style-type: none"> To evaluate aesthetic improvement of the LCL following a single dose of QM1114-DP as assessed by the subject using the GAIS at maximum smile at Month 1. <i>Endpoint:</i> Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least “Improved” on the GAIS at maximum smile. To evaluate aesthetic improvement of the GL following a single dose of QM1114-DP as assessed by the subject using the GAIS at maximum frown at Month 1. <i>Endpoint:</i> Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least “Improved” on the GAIS at maximum frown.

SYNOPSIS



SYNOPSIS

CCI

Other Assessments:	<ul style="list-style-type: none">Urine Pregnancy Test (UPT)Professional Photography
Blinding:	Not applicable.
Principal Statistical Method:	In general efficacy, safety and baseline characteristics variables will be presented using descriptive statistics. Continuous endpoints will be summarized using descriptive statistics, e.g. mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.



SYNOPSIS	
Sample Size:	The sample size of approximately 24 subjects is not based on a statistical calculation. The selected number of subjects will be used for descriptive evaluation of efficacy and safety in this study.
Interim Analysis:	Not applicable.

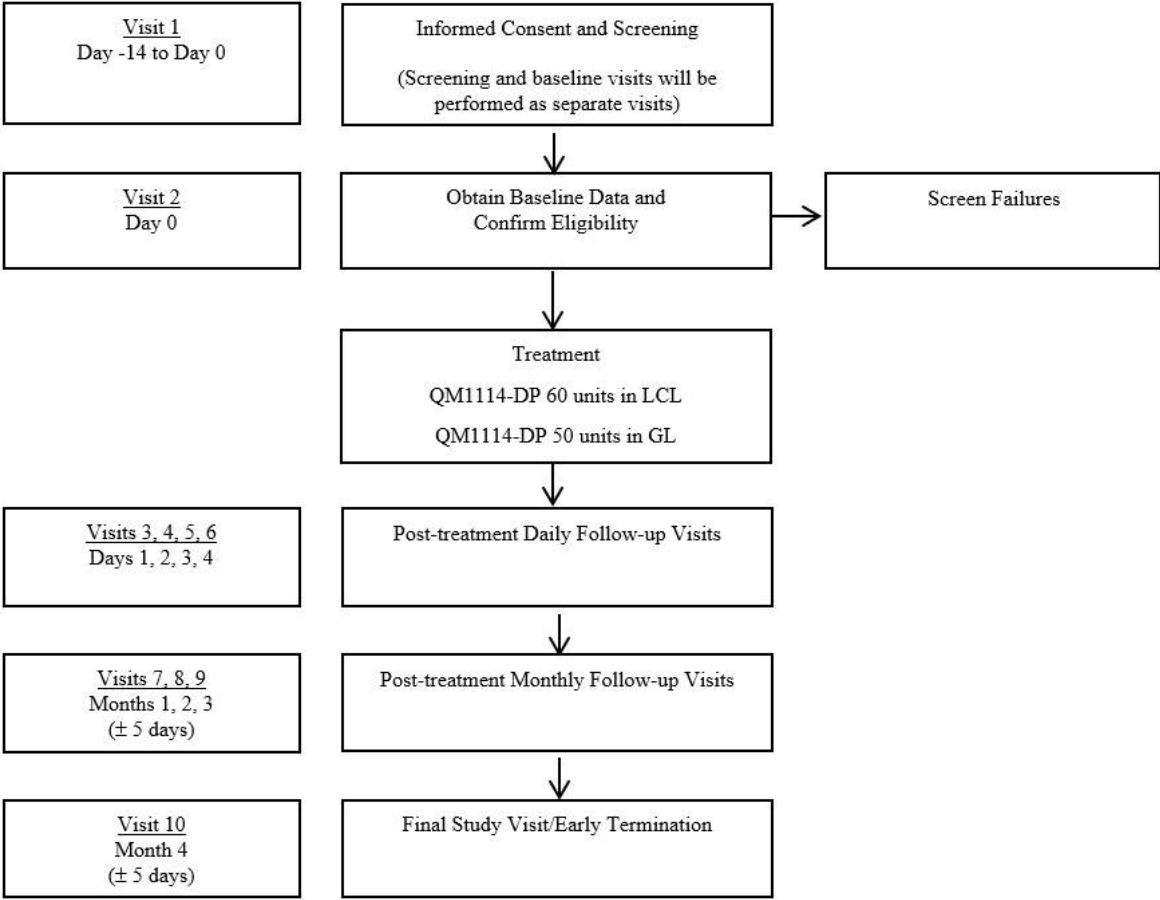


CLINICAL STUDY SCHEMATIC AND FLOW CHART

Table 1 Clinical Study Schematic

Screening ↓ Baseline/Treatment (Day 0) ↓	
Treatment	QM1114-DP 60 units in LCL QM1114-DP 50 units in GL
Treatment Frequency	Single treatment at baseline visit
↓ Follow-up Visits Days 1, 2, 3, 4 Months 1, 2, 3, 4	

Figure 1 Study Flow Chart



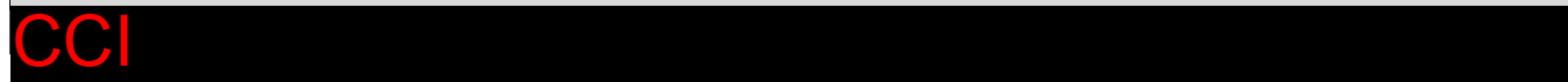
SCHEDULE OF ASSESSMENTS

Table 2 Schedule of Assessments

Visit 1 month = 4 weeks/28 days' and ' All visit windows are calculated from Baseline/Day 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8-9	Visit 10
	Screening 1	Day 0 Baseline ¹	Day 1 ¹¹	Day 2 ¹¹	Day 3 ¹¹	Day 4 ¹¹	Month 1	Months 2-3	Month 4/ EOS/ET ²
Window	(≤ 2 weeks of Visit 2)						(± 5 days)	(± 5 days)	(± 5 days)
Informed Consent	X								
Demographic Data ³	X								
Medical History	X								
Previous Medication/Procedures ⁴	X								
Urine Pregnancy Test ⁵	X	X ⁶							X
CCI									
Inclusion/Exclusion Criteria	X	X ⁶							
Professional Photography ¹¹	X						X		X
Standard Photography		X ⁶	X	X	X	X	X	X	X
Facial Expression Videography		X ⁶	X	X	X	X	X	X	X
Treatment		X							
CCI									
Adverse Events	X	X ⁹	X	X	X	X	X	X	X
Concomitant Medication/Procedures		X ⁹	X	X	X	X	X	X	X
SUBJECT ASSESSMENTS									
CCI									
GAIS			X	X	X	X	X	X	X
CCI									
CCI									

Visit 1 month = 4 weeks/28 days' and ' All visit windows are calculated from Baseline/Day 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8-9	Visit 10
	Screening 1	Day 0 Baseline ¹	Day 1 ¹¹	Day 2 ¹¹	Day 3 ¹¹	Day 4 ¹¹	Month 1	Months 2-3	Month 4/ EOS/ET ²
Window	(≤ 2 weeks of Visit 2)						(± 5 days)	(± 5 days)	(± 5 days)

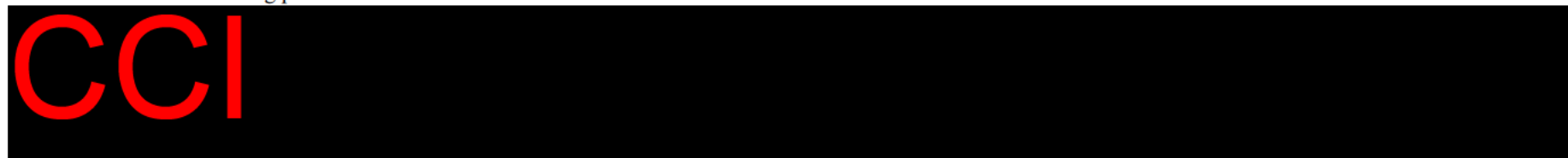
INVESTIGATOR ASSESMENTS



Abbreviations:

EOS = End of Study; ET = Early Termination; Beauty QoL = Beauty Quality of Life; GAIS = Global Aesthetic Improvement Scale; GL = Glabellar Lines; LCL = Lateral Canthal Lines; ILA = Investigator Live Assessment; SLA = Subject Live Assessments

1. Screening and baseline visits may be performed on the same day. If performed on the same day, study activities should only be completed once (i.e., UPT, subject and investigator GL/LCL severity assessments, focused physical exam, vital signs, and inclusion/exclusion criteria.
2. If the subject withdraws before the final visit the assessments at Month 4/EOS/ET should be completed, if possible.
3. Includes date of birth, gender, race, ethnicity, height, weight, Fitzpatrick skin type, and toxin naïve or non-toxin naïve.
4. For subjects that have had toxin treatment(s) prior to the screening/baseline visit (i.e., non-toxin naïve), capture brand, area(s) treated, and date(s) on the previous medications/procedures form.
5. Females of childbearing potential.



11. Professional Photography will only be performed on a subset of subjects. Visits on Day 1 – 4 (Visit 3 – 6) are optional for subjects selected for professional photography.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<i>Abbreviation/Term</i>	<i>Definition</i>
°C	Degrees Celsius
AE	Adverse event
BCOP	Bovine corneal opacity and permeability
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin type A
CFR	Code of Federal Regulations
CM	Centimeter
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)
EOS	End of study
ET	Early termination
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FL	Forehead lines
FPE	Focused physical examination
FSFV	First subject first visit (first subject screened, i.e. who signs the informed consent form)
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice

CCI

GLP

Good Laboratory Practices

HIPAA

Health Insurance Portability and Accountability Act of 1996

CONFIDENTIAL

Page 20 of 84

<i>Abbreviation/Term</i>	<i>Definition</i>
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
i.e.	That is (Latin: id est)
ILA	Investigator live assessment
IM	Intramuscular
IND	Investigational New Drug
Investigator	The principal investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator File	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the investigator.
Investigational Product	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
IRB	Institutional review board
ITT	Intention-to-treat
IUD	Intrauterine device
kDa	Kilodalton
LCL	Lateral canthal lines

CCI

LSFV	Last subject first visit (last subject screened, i.e. who signs the informed consent form)
LSLV	Last subject last visit (last subject who completed its last clinical study visit)
MAS	Merz Aesthetics Scale™
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram

<i>Abbreviation/Term</i>	<i>Definition</i>
mL	Milliliter
MTD	Maximum tolerated dose
N or n	Number
N/A	Not applicable
OC	Observed cases
OTC	Over-the-counter
PI	Principal investigator; qualified person responsible for conducting the study at a study site
PQC	Product quality complaint
PT	Preferred term
QA	Quality assurance
QoL	Quality of Life
RA	Regulatory authority
SAE	Serious adverse event
SAP	Statistical analysis plan
SIN	Subject identification number
SNAP-25	Synaptosomal-associated protein of 25kDa
SOC	System organ class
SOP	Standard operating procedure
Sponsor File	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the sponsor.
SLA	Subject live assessment
Study Files	The investigator file and the sponsor file
Study Products	The investigational product and the reference product under study
Study Site	The location(s) where the study-related activities are actually conducted
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment emergent adverse event
U	Unit
UPT	Urine pregnancy test
US	United States
v/v	Volume/volume

<i>Abbreviation/Term</i>	<i>Definition</i>
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 kilodalton (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 United States (US) for the aesthetic indications of glabellar lines (GL), lateral canthal lines (LCL) and forehead lines (FL), together with therapeutic indications such as strabismus, blepharospasm, hemifacial spasm, cervical dystonia, focal spasticity, prophylactic treatment of chronic migraine, overactive bladder and hyperhidrosis.

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

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

1.2 Study Product Profile

1.2.1 Drug Profile

QM1114 is a protein dimer of 150 kDa consisting of a 100 kDa heavy chain and 50 kDa light chain. The two chains are connected by a disulphide bond of two cysteine residues. The light chain is an enzyme that cuts the synaptosomal-associated protein of 25kDa (SNAP-25). The heavy chain mediates binding and internalization of the toxin protein. Unlike other commercially available BoNTs, QM1114-DS is manufactured and formulated without any animal or human proteins, thereby reducing the potential risk of viral contamination in the product.

QM1114 is supplied as a sterile solution for injection. QM1114 is diluted in a sodium phosphate buffer formulation at pH 6.6-6.9 and osmolality 270-310 mosm/kg.

The vial is a 2-mL, Type I plus borosilicate glass vial closed with a 13-mm, grey, Flurotec-coated, bromobutyl stopper and sealed with an aluminum overseal.

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) in the GL and 60 U in the LCL, for combined total dose of 110 U, which will be evaluated in this study.

Proof-of-concept pharmacology studies have been performed with QM1114-DP in a mouse hind limb paralysis assay to demonstrate that intramuscular (IM) administration of the product induces partial muscle paralysis at the local injection site in a manner similar to the currently marketed BoNT-A products.

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.

General toxicology studies were conducted for QM1114-DP, including pilot single IM dose administration toxicity studies in Wistar rats and Beagle dogs. These were non-GLP studies performed for the purpose of determining the maximum tolerated dose (MTD) for QM1114-DP to allow the appropriate dose levels for a pivotal Good Laboratory Practices (GLP) toxicology study to be established. The results of these pilot toxicology studies clearly demonstrated that the Wistar rat was more sensitive to the toxic effects of QM1114-DP than the dog, and therefore the pivotal GLP toxicology study was only conducted in Wistar rats.

A repeat-dose GLP toxicology study was also performed in Wistar rats. Hind limb paralysis and reversibility of effects were evaluated in the study. A reversible lower body weight gain was observed in all treated groups and demonstrated a dose relationship. The incidence of limping increased with the subsequent administrations. Histological changes in the injected muscles were only minimal or slight. No degenerative or necrotic muscle inflammatory

changes were noted in any dose groups during the recovery periods, indicating a good local tolerance.

An ex-vivo bovine corneal opacity and permeability (BCOP) GLP assay was also performed to assess the corneal irritation and/or corrosivity of QM1114-DP. QM1114-DP did not induce ocular irritation and no classification is therefore required for eye irritation or serious eye damage.

1.2.3 Clinical Documentation

(CTN) 43QM1302

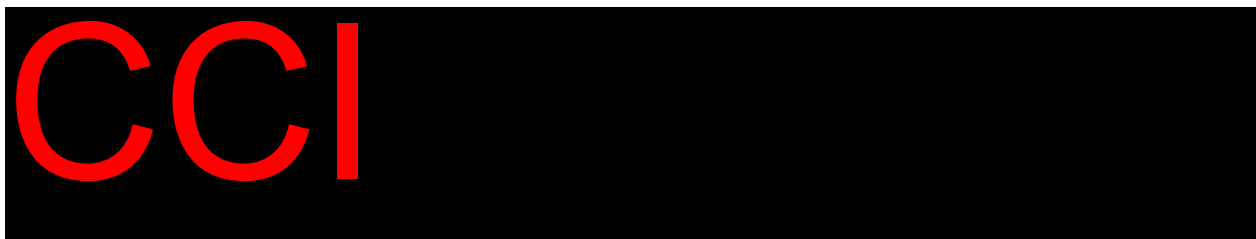
This was a randomized, double-blind, placebo-controlled, single treatment, dose-escalation study to evaluate the safety and efficacy of QM1114-DP in healthy male and female adult subjects aged 18 to 65 years with moderate to severe upper facial wrinkles. The study was divided into three parts: Part I studied the GL indication only, Part II studied the LCL indication only, and Part III studied both the GL and LCL indications in combination. Following treatment, subjects were monitored for safety and efficacy for 28 days. The clinical results demonstrated that QM1114-DP was safe and well tolerated.

Part I (GL only)

In Part I, a total of 30 subjects were enrolled: 22 subjects received a single dose of QM1114-DP in the GL area at four ascending dose levels (i.e., 10, 25, 50 or 75 U), and 8 subjects received placebo.

All treatment emergent adverse events (TEAEs) reported were mild to moderate. TEAEs were reported by 50.0%, 66.7%, 83.3% and 100% of subjects treated with 10, 25, 50 and 75 U, respectively. TEAEs were reported by 75.0% of subjects treated with placebo. The most commonly observed, treatment-related TEAEs were: headache, pruritus, asthenopia, eyelid ptosis and sensation of pressure. Eyelid ptosis and asthenopia were only observed in the 75 U treatment group. There were no serious adverse events (SAEs) and no withdrawals due to adverse events (AEs) or any other reasons. A detailed description of the TEAEs is included in the current Investigator's Brochure (IB).¹²

The effect of QM1114-DP in reduction of GL severity was evaluated using a 5-point Merz Aesthetic Scale (MAS) (both dynamic – maximum frown - and at rest). The decrease in GL severity began within a few days post-treatment, and the maximum effect (at least a 2-grade improvement) was reached within two weeks post-treatment for the 10, 25 and 50 U treatment groups, and within one week for the 75 U treatment group. The results showed that QM1114-DP is efficacious in reducing GL severity both at rest and at maximum frown for up to 28 days, in comparison to placebo treatment.



CCI

CCI

CTN 43QM1313

Following successful completion of clinical study CTN 43QM1302, a randomized, double-blind, placebo controlled, dose finding study of QM1114-DP using three different single doses of QM1114-DP (30, 45, 60 U) in male or female subjects aged over 18 years with moderate to very severe GL was performed.

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

The primary efficacy endpoint at Day 14 confirmed the efficacy of all QM1114 DP doses (30, 45, and 60 U) versus placebo. The MAS Dynamic responder rate (at least 2-grade improvement at maximum frown, compared to baseline) at Day 14 was high in all of the treatment groups (73% to 91%) versus placebo (6% to 8%).

Efficacy over time at maximum frown (at least 2-grade improvement compared to baseline): when the study subjects assessed the efficacy themselves, all doses were efficacious in reducing GL severity at maximum frown in comparison to placebo up to 6 months. When efficacy was assessed by the investigator, the 30 and 45 U doses were efficacious up to 5 months and the 60 U dose was efficacious up to 6 months.

Efficacy over time at rest (at least 1-grade improvement compared to baseline): when the study subjects assessed the efficacy themselves, all doses were efficacious in reducing GL severity in comparison to placebo, for up to and including 6 months. When efficacy was assessed by the investigator, the 30 and 45 U doses were efficacious up to 4 months and the 60 U dose was efficacious up to 5 months.

The treatment-related TEAEs reported in study CTN 43QM1313 were of similar type as reported for other toxins used for GL treatment. The most common treatment-related TEAEs (reported by at least 1% of subjects) in all QM1114 DP treatment groups pooled were injection site pain (15.6%), headache (10.4%), eyelid ptosis (3.9%), injection site swelling (1.3%),

CONFIDENTIAL

Page 28 of 84

injection site pruritus (1.0%) and visual impairment (1.0%). The incidence of treatment-related eyelid ptosis in this study ranged from 3% to 5%. There were no related SAEs. No deaths or AEs leading to withdrawal occurred during the study. Four unrelated SAEs occurred in the study. There were three pregnancies reported during the study. A detailed description of the TEAEs is found in the current IB.

1.2.4 Dose Rationale



1.3 Risk/Benefit Assessment

Based on the clinical experience from the phase 1 study (43QM1302) the most commonly reported treatment related AEs in all QM1114-DP treatment groups pooled were: pruritus, headache, eyelid ptosis, asthenopia and sensation of pressure.¹²

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. The most common (at least 1% of subjects in all QM1114- DP treatment groups pooled) treatment-related TEAEs were: injection site pain, headache, eyelid ptosis, injection site swelling, injection site pruritus and visual impairment. The majority of the treatment-related TEAEs were mild or moderate and transient. Ptosis occurred in 3-5% of the subjects treated with QM1114-DP.

The risk of AEs occurring may be reduced by using physicians who are experienced in the botulinum toxin injection technique. All treating Investigators will be trained in the administration technique of QM1114-DP prior to the study start. The benefit to subjects receiving QM1114-DP in this study will be a temporary reduction in the appearance of their LCL and/or GL.

CCI

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. AEs will be recorded at each study visit, and subjects will also be queried for any potential signs and symptoms of local and remote spread of the toxin effect.

Due to the COVID-19 pandemic, the feasibility and immediate necessity of starting a new clinical trial should be critically assessed and additional risks to trial participants should be addressed. Thus, a risk benefit assessment of the impact of COVID-19 potentially affecting trial participants and COVID-19 related measures affecting clinical trial conduct will be performed before the study starts to decide if the study can start or if it needs to be postponed. If the conclusion of the assessment is that the risk benefit is currently negative the study will not start until the outbreak is under control with a substantially reduced risk for subjects being infected by COVID-19, as guided by relevant research and local and international health authorities' guidelines and regulations. Measures to minimize the risk of exposure to COVID-19 for study subjects include, but is not limited to, replacing site visits with telephone call visits, replacing live assessments with remote digital assessments, postponing site visits and cancellation of site visits not needed for evaluation of the primary endpoint.

2. CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS

2.1 Clinical Study Objectives

The objective of the study is to evaluate aesthetic improvement following treatment with QM1114-DP in subjects with moderate to severe LCL and GL.

2.1.1 Primary Efficacy Objectives and Endpoints

The primary efficacy objectives and endpoints are:

1. To evaluate aesthetic improvement of the LCL following a single dose of QM1114-DP as assessed by the subject using the Global Aesthetic Improvement Scale (GAIS) at maximum smile at Month 1.

Endpoint: Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least “Improved” on the GAIS at maximum smile.

2. To evaluate aesthetic improvement of the GL following a single dose of QM1114-DP as assessed by the subject using the GAIS at maximum frown at Month 1.

Endpoint: Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least “Improved” on the GAIS at maximum frown.

CCI

CCI

CCI

2.2 Clinical Hypothesis

The clinical hypothesis of the study is that QM1114-DP will demonstrate aesthetic improvement in subjects treated with QM1114-DP for moderate to severe lateral canthal lines and glabellar lines, and has an acceptable safety profile.

3. OVERALL CLINICAL STUDY DESCRIPTION

This is an open-label, single-center study to evaluate aesthetic improvement following treatment with QM1114-DP.

Following the informed consent and screening process, eligible subjects will receive a single treatment at baseline (Day 0) of 60 U of QM1114-DP in the lateral canthus areas, and 50 U of QM1114-DP in the glabellar region.

Following treatment at baseline, subjects will be monitored for safety and efficacy according to the Schedule of Assessments for 4 months.

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 2 months.

The planned clinical study duration from FSFV to last subject last visit (LSLV) is approximately 6.5 months.

Clinical study participation for each subject is approximately 4.5 months.

The sponsor may decide to prematurely terminate or suspend the participation of a particular clinical study center (for example, lack of subject enrollment or non-compliance with clinical study protocol, regulation, or Good Clinical Practice [GCP]) or prematurely suspend the clinical study (for example, for safety, study products(s) 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% is anticipated; therefore, approximately 27 subjects will be screened in order to get approximately 24 subjects enrolled.

5.2 Clinical Study Population Characteristics

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

5.2.1 Inclusion Criteria

1. Male or female 18 years of age or older.
2. Moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the 4-point Photographic Scale ranging from 0 [none] to 3 [severe]) at maximum smile as assessed by the investigator live assessment. (LCL-ILA).

CCI

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

CCI

CCI

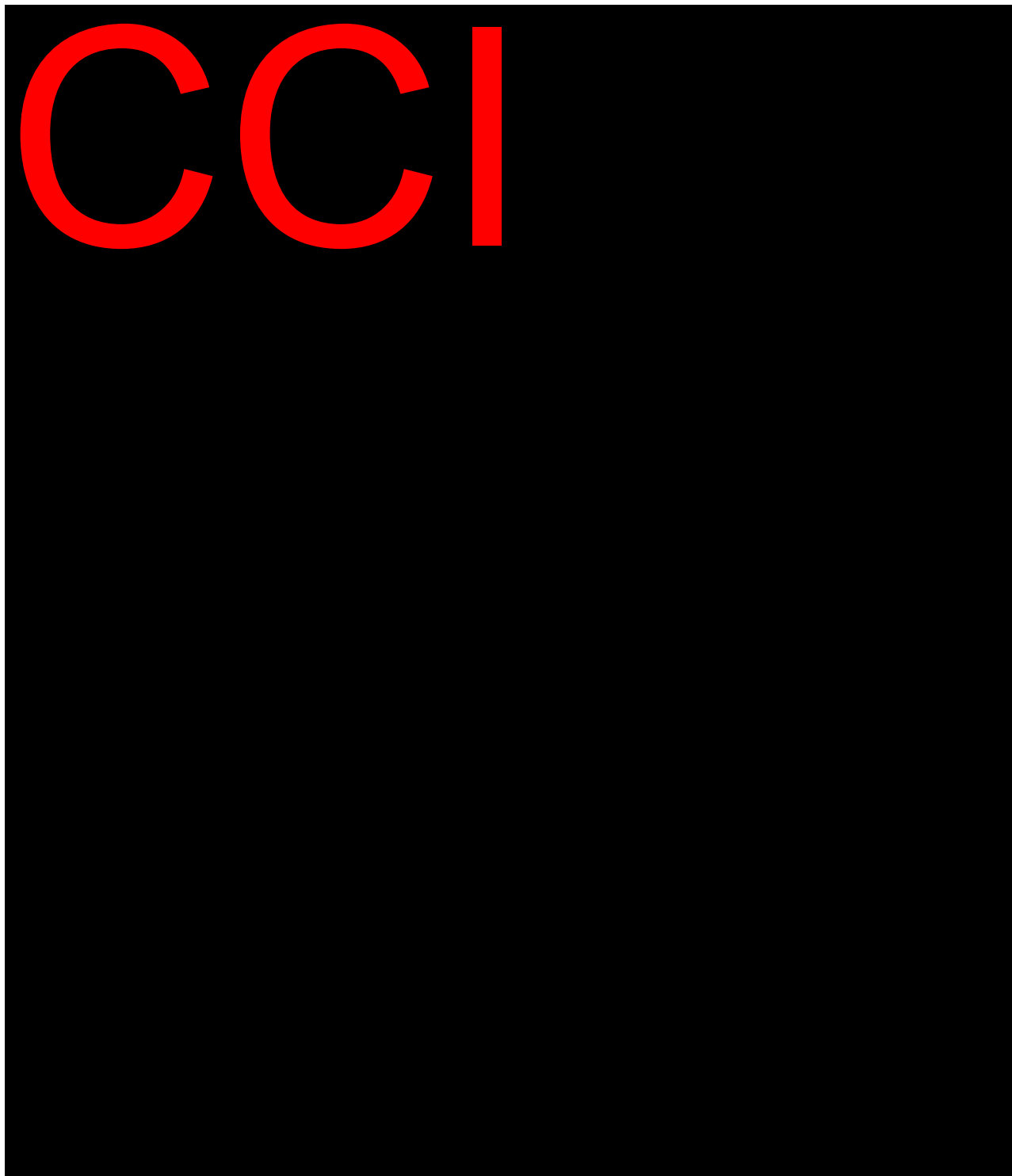
5.2.2 Exclusion Criteria

1. Botulinum toxin treatment in facial areas CCI in the LCL and GL regions prior to study treatment.

CCI

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).

CCI



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 4 weeks preceding the screening visit or within timeframes specified in the inclusion/exclusion criteria.

Concomitant therapies are defined as follows:

any existing therapies ongoing at the time of the screening visit,

any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical study, or

any new therapies received by the subject since the screening visit.

5.4.2 Categories

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

Drugs including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.

Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers (area of treatment should be indicated), X-rays, surgeries, tooth extractions.

5.4.3 Recording

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

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

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

5.4.4 Authorized Concomitant Therapies

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

5.4.5 Prohibited Concomitant Therapies

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

Botulinum toxin of any serotype.

Any other investigational new drug or device.

CONFIDENTIAL

Page 37 of 84

Any absorbable (temporary) or non-absorbable (permanent) material in the treatment area.

Facial aesthetic procedures (e.g., ablative skin resurfacing, laser treatment, micro needling, photodynamic therapy, tattooing or chemical peel) or any other procedures in the treatment area.

Facial surgery or eye surgery (including LASIK procedure).

Medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics.

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

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

5.5 Procedures/Reasons for Subject Discontinuation

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

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

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Month 4/early termination (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.

Additional subjects could be enrolled 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 7.2.3.2.3. 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 IB.¹²

6.1 Clinical Supply Identification and Use

6.1.1 QM1114-DP

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

At the baseline visit 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)

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

6.1.2 Study Products(s) Description

Table 3 Description and Usage of the Study Products(s)

	Investigational product
Name of drug substance	QM1114-DS
Internal Code	QM1114-DP
Pharmaceutical Form	Solution for injection
Concentration	100 units/mL, buffered solution
Buffer composition	Sodium chloride 140 mM Sodium phosphate 10 mM Potassium chloride 3 mM L-Tryptophan 1 mg/mL Polysorbate 0.1% (v/v) WFI (Water for injection)
Packaging	Glass vial. Fill volume 1.5 mL
Storage conditions	2-8°C (36 °F – to 46 °F)
Dosage	At treatment a total dose of 110 U of QM1114-DP will be administered as: <ul style="list-style-type: none"> • 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	IM injection
Dose regimen	Single treatment at baseline visit
Location of treated area	Glabellar region and lateral canthus areas

6.1.3 Subject Identification Number

Each study participant who has signed the ICF will be entered into the eCRF system and a subject identification number (SIN) 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 the baseline visit following confirmation of eligibility criteria. All treating investigators will be trained in the administration technique prior to the study start.

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

See also QM1114-DP IB.¹²

6.1.6.1 Treatment Procedure

CCI



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

Each subject will receive a single treatment with QM1114-DP in the glabellar region and lateral canthus areas at the baseline visit.

6.2 Study Products(s) Packaging and Labeling

QM1114-DP is manufactured under aseptic conditions. The container is a glass vial, closed with a Flurotec stopper and sealed with an aluminum overseal. The study products should be transported and stored at 2-8°C (36 °F – to 46 °F).

CONFIDENTIAL

Page 44 of 84

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 US) 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 3](#)).

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/contract research organization (CRO) and properly documented.

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

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

6.3.4 Treatment Compliance Management and Record

The treatment is an injection administered by the investigator or authorized treating 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 (PQC) 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 ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Global Aesthetic Improvement Scale

Subjects will rate the global aesthetic improvement of their LCL at maximum smile and GL at maximum frown, separately, relative to their pre-treatment appearance, using the following categorical scale at all post-treatment time points as indicated in the Schedule of Assessments.

Rating
Very Much Improved
Much Improved
Improved
No Change
Worse
Much Worse
Very Much Worse

For the LCL assessment, subjects will be asked:

“How would you rate the change in appearance of your lateral canthal lines (crow’s feet) at maximum smile compared with immediately before the injection?”

For the GL assessment, subjects will be asked:

“How would you rate the change in appearance of your glabellar lines (lines between your eyebrows) at maximum frown compared with immediately before the injection?”

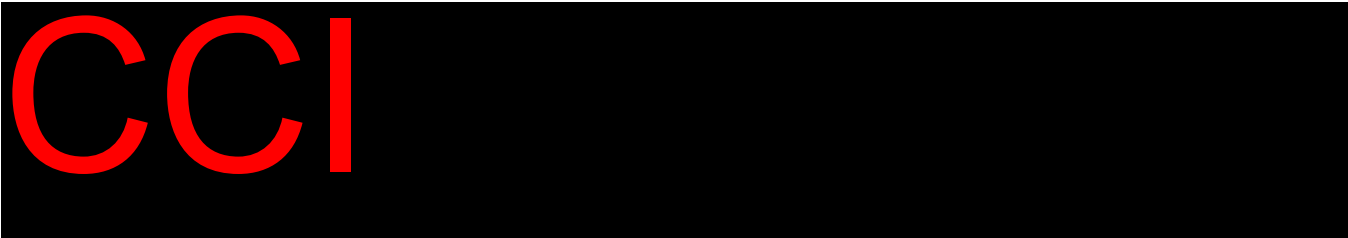
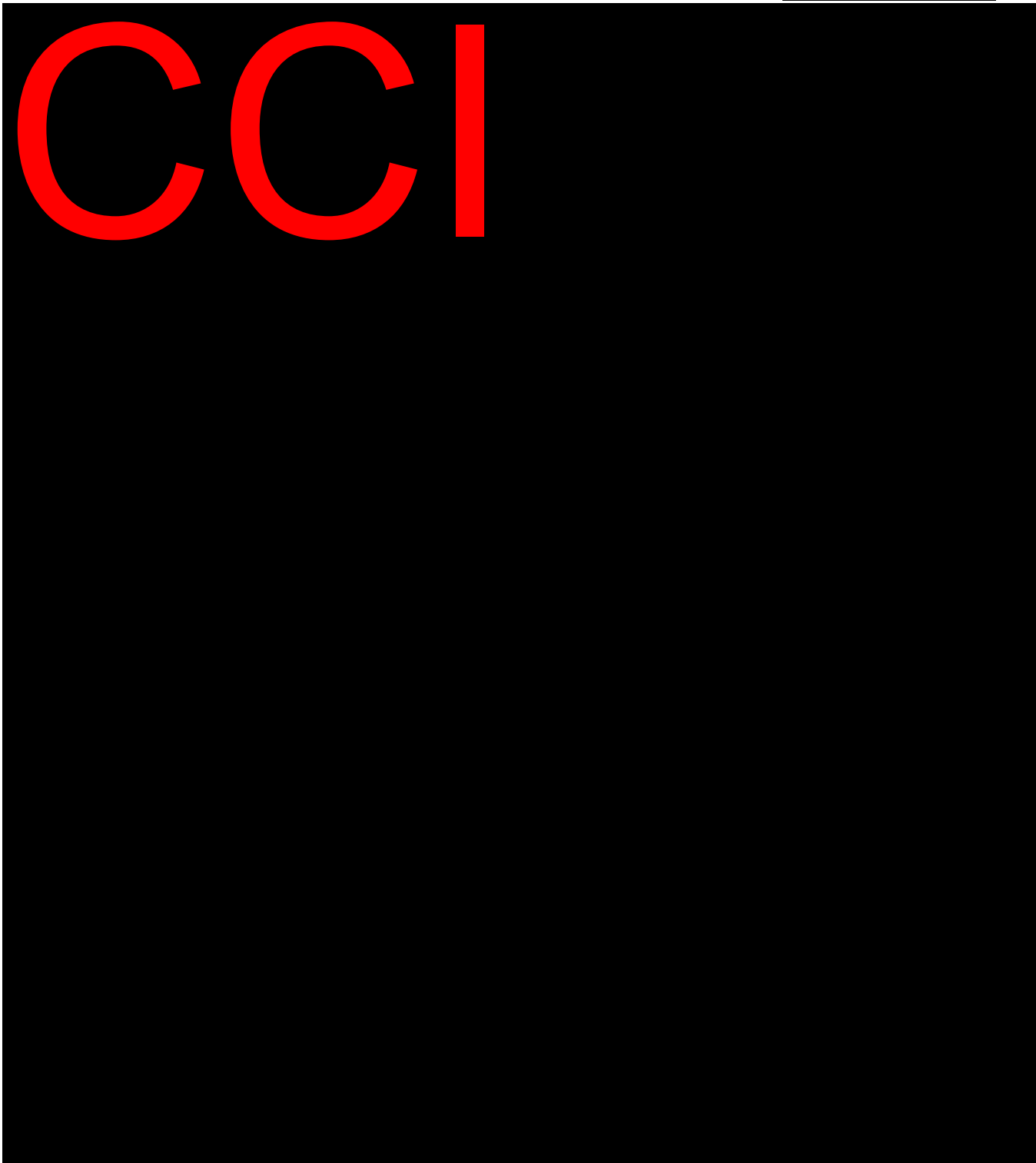
Subjects will be instructed to select the one rating that best describes the degree to which the appearance of their lateral canthal lines at maximum smile and glabellar lines at maximum frown has changed relative to baseline. The subject may review the baseline photographs to aid in the assessment.

CCI

CCI



Title
43QM2107 Clinical Study Protocol – QM1114 – GL and LCL



CCI



7.2.3 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.

7.2.3.1 Definitions

7.2.3.1.1 Adverse Events

According to International Council for Harmonisation (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 7.2.3.2.3.

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.

7.2.3.1.2 *Treatment Emergent Adverse Event*

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

7.2.3.1.3 *Serious Adverse Events*

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).

7.2.3.1.4 *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., IB for an unapproved investigational product).

7.2.3.1.5 *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.

7.2.3.1.6 *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.

7.2.3.1.7 *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.

7.2.3.2 Reporting Procedures

7.2.3.2.1 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, action taken, 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 7.2.3.2.2) and pregnancies (see Section 7.2.3.2.3), the sponsor is to be informed immediately by e-mail. The event must be reported to the Safety e-mail within 24 hours of receipt of the information (contact details in Section 11.9).

7.2.3.2.2 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 7.2.3.1.3).
3. Complete the AE form provided in the eCRF as fully as possible.

Print and complete the SAE form. 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 electronic data capture (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: DrugSafetyPV@advancedclinical.com

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 all pertinent medical records and information regarding the SAE in the subject's study file.
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 (RA) and other regulatory agencies about the safety of a product under clinical investigation.

CONFIDENTIAL

Page 54 of 84

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 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.

7.2.3.2.3 *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 screen failures; they are recorded as such in the eCRF and no pregnancy form is to be completed.

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

1. The subject does not need to be withdrawn from the clinical study, i.e. she may continue to attend the planned study visits, but no invasive procedure should be conducted (e.g. no sample taken for lab test).
2. Complete the Pregnancy Report Part A as fully as possible. Send the form within 24 hours of receipt of the information to the Safety e-mail listed above in Section 7.2.3.2.2.
3. Monitor and record the progress of the pregnancy until its outcome. If necessary and approved by the subject or their legal health care representative, contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow up information.
4. At the outcome of the pregnancy, complete the Pregnancy Report Part B. For all the additional evaluations, send the follow-up information to the Safety e-mail within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.
5. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.3.2.2).

7.3 Other Assessments

7.3.1 Pregnancy Test

For females of childbearing potential, a urine pregnancy test (UPT) will be performed prior to treatment at screening, baseline (prior to treatment) and Month 4/ET. A negative pregnancy test is required for study inclusion. The result will be documented.

7.3.2 Professional Photography

A professional photographer will take photographs at screening, Month 1/Visit 7, and at Month 4/Visit 10 on a subset of subjects. No study restrictions are applicable for the professional photography.

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.

8. CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of Clinical Study Visits

Please refer to the Schedule of Assessments [Table 2](#).

A written, signed ICF (inclusive of Health Insurance Portability and Accountability Act of 1996 (HIPAA), and photo and video 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 and video consent); provide a fully completed dated and signed copy to the subject.
3. Collect information regarding demographics (i.e., date of birth, gender, race, ethnicity, height, and weight), Fitzpatrick skin type, relevant medical history and concurrent diseases, previous facial treatments/procedures (including toxin naïve/non-toxin naïve), previous medications and procedures, and concomitant medications and procedures (see [Table 2](#)).

4. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).
5. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
6. Investigator to complete assessment of the subject's lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
7. Investigator to complete assessment of the subject's glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
8. Investigator to perform a FPE (Appendix 5). Record abnormal findings as medical history. Clinically significant abnormal findings are exclusionary; document as screen fail and do not enroll the subject in the study.
9. If the subject is a female of childbearing potential, collect urine for UPT and complete pregnancy test. Document the result. A negative result is required for study inclusion.
10. 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).
11. Record any AEs on the eCRF. AEs will be collected starting from the time of informed consent signature.
12. Review the inclusion/exclusion criteria (Section 5.2.1 and 5.2.2), and confirm if subject meets study eligibility requirements.
 - If yes, schedule the baseline visit and proceed to next steps.
 - If no, document the subject as a screen failure.
13. Take professional subject photographs, if applicable per the subject (refer to photo manual for complete instructions).
14. For all subjects, enter the subject information into the eCRF; a SIN will be assigned via the eCRF system.

8.1.2 Baseline/Visit 2 (Day 0)

If the screening and baseline visits are performed as on same day, only perform study assessments once (i.e., AE, concomitant therapies/procedures, UPT, GL/LCL-SLA, GL/LCL-ILA, FPE, vital signs, 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:

CONFIDENTIAL

Page 57 of 84

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).
4. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
5. Investigator to complete assessment of the subject’s lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
6. Investigator to complete assessment of the subject’s glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
7. Investigator to perform a FPE (Appendix 5). Record abnormal findings as medical history. Clinically significant abnormal findings are exclusionary; document as screen fail and do not enroll the subject in the study.
8. 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.
9. Obtain the subject’s vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
10. Record any AEs on the eCRF. AEs will be collected starting from the time of informed consent signature.
11. Review the inclusion/exclusion criteria (Section 5.2.1 and 5.2.2), and confirm if subject meets study eligibility requirements.
 - If yes, schedule the baseline visit and proceed to the next visit procedure.
 - If no, document the subject as a screen failure.
12. For all subjects, enter appropriate data into the eCRF; the SIN should have been assigned via the eCRF system at the screening visit.
13. Take subject standard photographs (refer to photo manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking photographs.

14. Take subject video of facial expression (refer to videography manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking video.
15. Perform skin elasticity measurements. Assessments should be carried out in air-conditioned room under standardized climate conditions i.e., constant temperature and humidity. Measurement can start following subject's acclimatization for at least 30 minutes (Section 7.1.10).
16. Prior to injection, clean the subject's treatment area with a suitable antiseptic solution.
17. The investigator will administer the treatment. See Sections 6.1.6.1.1 and 6.1.6.1.2 for injection technique and 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 after 10 minutes rest (Section 7.2.2).
19. Dispense the subject diary, and instruct the subject on proper completion.
20. Ask the subject about AEs using an open-ended question. Record all events, as appropriate, on the corresponding eCRF form(s).
21. Record post-treatment concomitant therapies/procedures.
22. Schedule the next visit.

8.1.3 Days 1, 2, 3, 4/Visits 3, 4, 5, 6

The investigator or designee will (**NOTE:** Days 1, 2, 3, 4/Visits 3, 4, 5, 6 are optional if the subject has been selected for professional photography):

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. Take subject standard 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.
4. Take subject video of facial expression (refer to videography manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking video.
5. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).

6. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
7. Review GAIS of LCL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
8. Review GAIS of GL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
9. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
10. Investigator to complete assessment of the subject's lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
11. Investigator to complete assessment of the subject's glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
12. Investigator to perform a FPE (Appendix 5).
13. Schedule the next visit.

8.1.4 Month 1/Visit 7 (± 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. Collect the subject's diary and review for completion.
4. Take professional subject photographs, as applicable per subject (refer to photo manual for complete instructions).
5. Take subject standard 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.
6. Take subject video of facial expression (refer to videography manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking video.
7. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).

8. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
9. Review instructions for Beauty QoL questionnaire with the subject. Subject to complete the Beauty QoL questionnaire (Appendix 1). Collect the questionnaire and review for completeness.
10. Review GAIS of LCL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
11. Review GAIS of GL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
12. 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).
13. Investigator to complete assessment of the subject's lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
14. Investigator to complete assessment of the subject's glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
15. Investigator to perform a FPE (Appendix 5).
16. Perform skin elasticity measurements. Assessments should be carried out in air-conditioned room under standardized climate conditions i.e., constant temperature and humidity. Measurement can start following subject's acclimatization for at least 30 minutes (Section 7.1.10).
17. Schedule the next visit.

8.1.5 Months 2, 3/Visits 8, 9 (± 5 days)

The investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate.
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes.
3. Take subject standard 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.
4. Take subject video of facial expression (refer to videography manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking video.

5. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).
6. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
7. Review GAIS of LCL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
8. Review GAIS of GL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
9. Obtain the subject's vital signs (blood pressure, heart rate, and respiratory rate). Vital signs are to be taken seated after 10 minutes rest (Section 7.2.2).
10. Investigator to complete assessment of the subject's lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
11. Investigator to complete assessment of the subject's glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
12. Investigator to perform a FPE (Appendix 5).
13. Perform skin elasticity measurements. . Assessments should be carried out in air-conditioned room under standardized climate conditions i.e., constant temperature and humidity. Measurement can start following subject's acclimatization for at least 30 minutes (Section 7.1.10).
14. Schedule the next visit.

8.1.6 Month 4 or Early Termination/Visit 10 (± 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. 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.
4. Take professional subject photographs, as applicable per subject (refer to photo manual for complete instructions).

5. Take subject standard 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.
6. Take subject video of facial expression (refer to videography manual for complete instructions). If the subject is wearing make-up, instruct the subject to remove it prior to taking video.
7. Instruct the subject on how to complete the LCL-SLA at maximum smile. Subject to complete LCL-SLA at maximum smile using the Subject 4-point Photographic Scale of Lateral Canthal Line Severity (Section 7.1.3 and Appendix 2).
8. Instruct the subject on how to complete the GL-SLA at maximum frown. Subject to complete GL-SLA at maximum frown using the Subject Static 4-Point Categorical Scale of Glabellar Line Severity (Section 7.1.4).
9. Review GAIS of LCL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
10. Review GAIS of GL completion instructions with the subject. Subject to complete the GAIS (Section 7.1.1).
11. 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).
12. Investigator to complete assessment of the subject's lateral canthal line severity at maximum smile using the Investigator 4-point Photographic Scale of Lateral Canthal Line Severity (LCL-ILA) (Section 7.1.5 and Appendix 3).
13. Investigator to complete assessment of the subject's glabellar line severity at maximum frown using the Investigator 4-point Photographic Scale of Glabellar Line Severity (GL-ILA) (Section 7.1.6 and Appendix 4).
14. Investigator to perform a FPE (Appendix 5).
15. Perform skin elasticity measurements. Assessments should be carried out in air-conditioned room under standardized climate conditions i.e., constant temperature and humidity. Measurement can start following subject's acclimatization for at least 30 minutes (Section 7.1.10).
16. 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 instructed to complete a diary card daily, Day 0 through Day 7, following treatment with study product, and return the diary to the study center at their Month 1 visit.

CONFIDENTIAL

Page 63 of 84

Subjects will be advised that any facial make-up will need to be removed before taking study photographs (except for the professional photography).

Subjects will also be advised of post-treatment care instructions as outlined in Section 6.1.6.2.

9. STATISTICAL METHODS PLANNED

9.1 General

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.4 or higher).

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

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

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).

9.2 Data Transformations

Responder rate (%) regarding GAIS will be calculated as (number of subjects (or thighs) being at least improved/number of subjects reporting at the specified visit)*100.

Responder rate (%) regarding Beauty QoL will be calculated as (number of subjects (or thighs) being at least improved/number of subjects reporting at the specified visit)*100.

Time to onset of an AE will be derived as the start date minus the date of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given

Beauty QoL questionnaire composed of 42 question structured in five dimensions: Social Life, Self-confidence, Mood, Vitality, and Attractiveness

9.3 Analysis populations

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

The following populations will be defined:

- Safety Set Includes all subjects who were injected in at least one of the GL or LCL
- Full Analysis Set (FAS) Includes all subjects who were injected in both GL and LCL

FAS is the primary population for all effectiveness analyses.

Safety analysis is performed based on the Safety Set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set

9.4 Imputation of Missing Data

No imputation of missing data will be performed. Analysis will be based on Observed Cases (OC).

9.5 Efficacy analysis

9.5.1 Primary analysis

Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least “Improved” on the GAIS at maximum smile.

The GAIS assessment by the Treating Investigator at Month 1 will be presented in a frequency table. In addition, the proportion of improved subjects (assessed as at least improved on both thighs) will be presented together with a 95% confidence interval (based on the binomial distribution).



9.5.2.1 *Safety Analysis*

All treatment related TEAEs by maximum intensity, treatment unrelated TEAEs by maximum intensity, treatment emergent SAEs by causality and maximum intensity, and action taken of treatment related TEAEs will be summarized by SOC and preferred term (PT) including number of subjects with at least one event, percentages, and number of events. All related TEAEs will also be summarized by time to onset and duration. In addition, a short summary of the analysis of TEAEs will be provided. AEs occurring before treatment will only be provided in subject data listings.

Data for vital signs will be summarized by descriptive statistics with the value at each visit as well as the change from baseline. The number and percentage of subjects with normal/abnormal results in physical examination will be presented by visit. A shift table will be created to present any change from baseline in normal/abnormal results in physical examination across the study visits. The results of the urine pregnancy tests will be listed.

All AEs will be monitored by the Sponsor to determine if they meet the criteria of remote spread of effect of the toxin or hypersensitivity. A list of preferred terms for these types of events will be referenced to in the Data Management Plan (DMP), and will be further analyzed to determine if there is a plausible possibility that they represent remote spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternative etiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of QM1114-DP administration, and temporal relationship to QM1114-DP administration will be considered by the Sponsor.

9.6 **Sample Size Determination**

The sample size of approximately 24 subjects is not based on a statistical calculation. The selected number of subjects will be used for descriptive evaluation of efficacy and safety in this study.

9.7 **Interim Analysis**

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 principal investigator (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 standard operating procedures (SOPs).

The investigator will allow the CRO/sponsor's representatives, to have direct access to all clinical study records, eCRFs, corresponding subject medical records, study product 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 DMP.

The database, the data entry screens and program will be designed in accordance with the CSP and eCRF 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) 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 CRO.

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

The investigator will allow and assist the CRO/sponsor's representatives, IRBs 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 (QA).

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 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. 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 Institutional Review Board

This clinical study protocol and all applicable amendments will be reviewed and approved by the appropriate 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 and video consent), approved by an IRB 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 PI 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 PI are responsible for complying with all requirements pursuant to national legislation in the country in which the institution and PI are located.

The PI understands that clinical studies conducted under an Investigational New Drug (IND) application are exempt from the study subject identifier confidentiality provisions of HIPAA, as provided at Code of Federal Regulations (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 PI 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 PI 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 PI 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 clinical trial agreement (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 study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content;

and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.^a Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by the sponsor to take primary responsibility for the overall work as primary author.

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

11.9 Investigator and Administrative Structure

Role	Contact Information
Sponsor Contact:	Courtney Maguire Head Clinical Project Management Galderma Research and Development, LLC 2001 Ross Avenue, Suite 1600 Dallas, TX 75201 United States Telephone: +1 817 961 5000E-mail: Courtney.Maguire@galderma.com

CCI

12. 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. Investigator's Brochure QM1114-DP (Botulinum Neurotoxin Type A) Upper Facial Wrinkles, edition 6, 2021-07-02.
13. ICH E2A: International Conference on Harmonisation Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 1994
14. Food and Drug Administration (FDA) Guidance for Industry. Upper Facial Lines: developing botulinum toxin drug products (draft), 2014.
15. Beresniak A, de Linares Y, Krueger GG, Talarico S, Tsutani K, Duru G, Berger G. Validation of a new international quality-of-life instrument specific to cosmetics and physical appearance: BeautyQoL questionnaire. *Arch Dermatol*. 2012 Nov;148(11):1275-82.



CCI

CCI

GALDERMA

EST. 1981

Title

43QM2107 Clinical Study Protocol – QM1114 – GL and LCL

CCI

BEAUTYQOL

USA English version 3.0

1

 DATA MINING
INTERNATIONAL

CCI

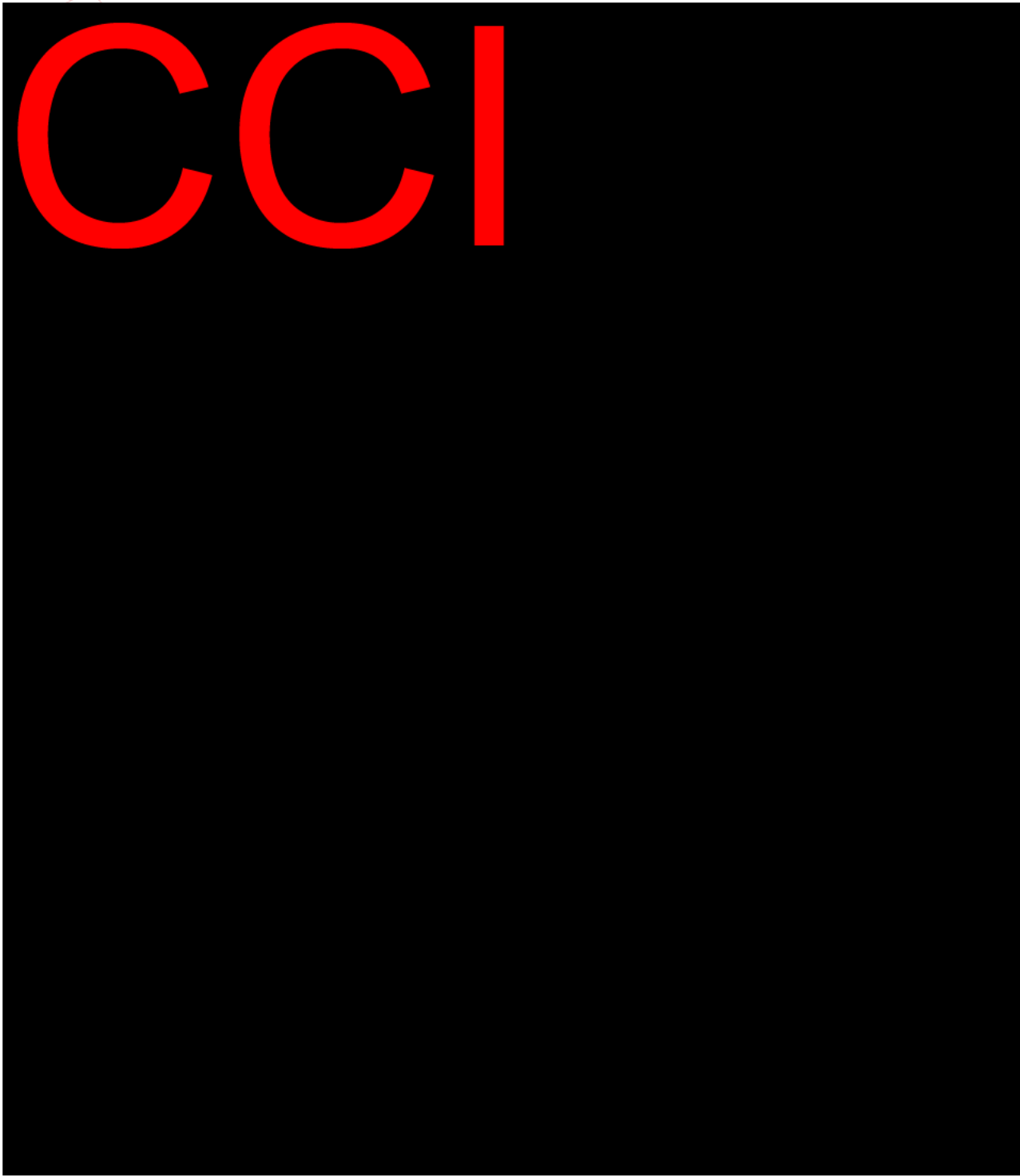
BEAUTYQOL

USA English version 3.0

2

CONFIDENTIAL

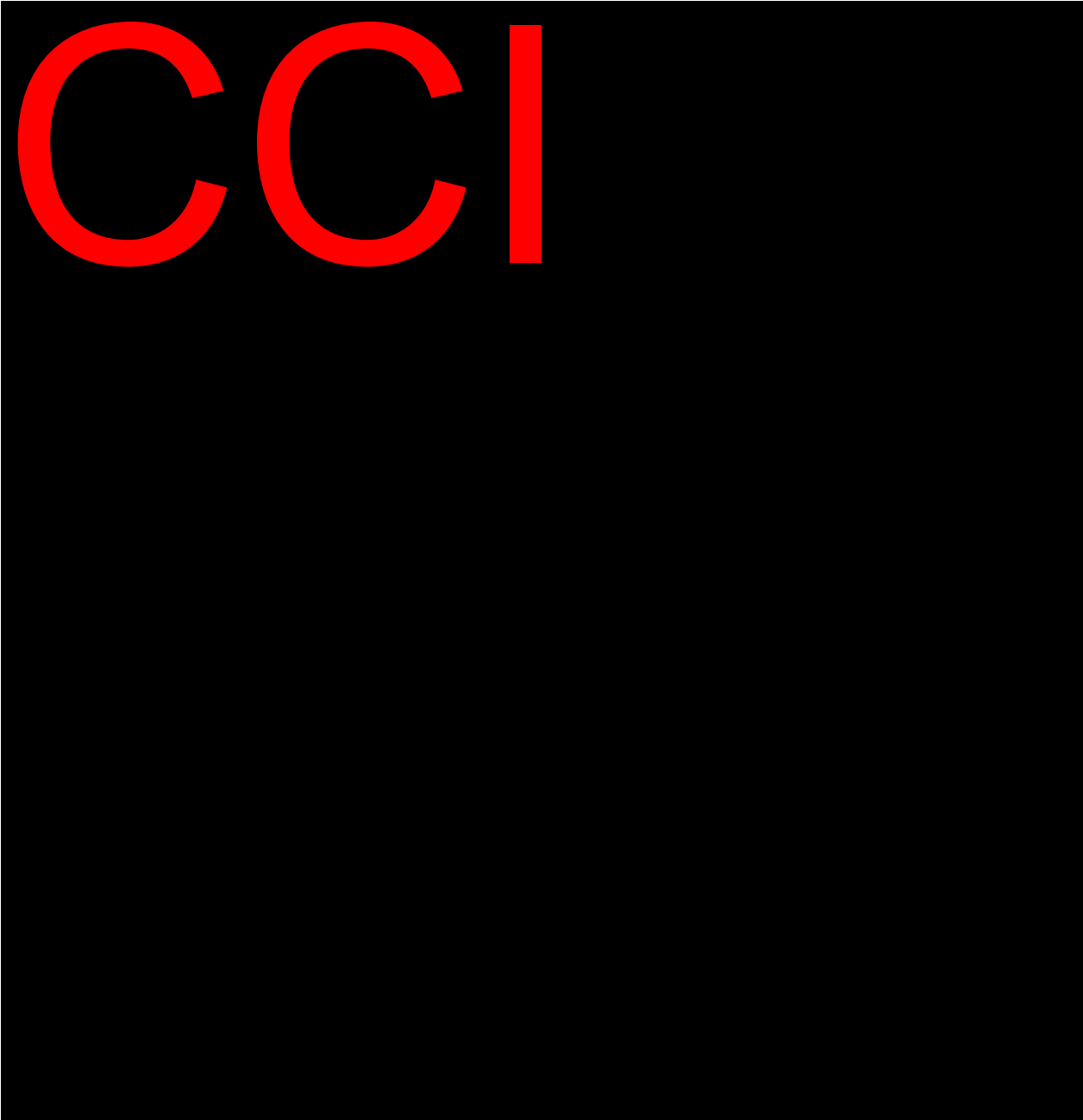
Page 75 of 84

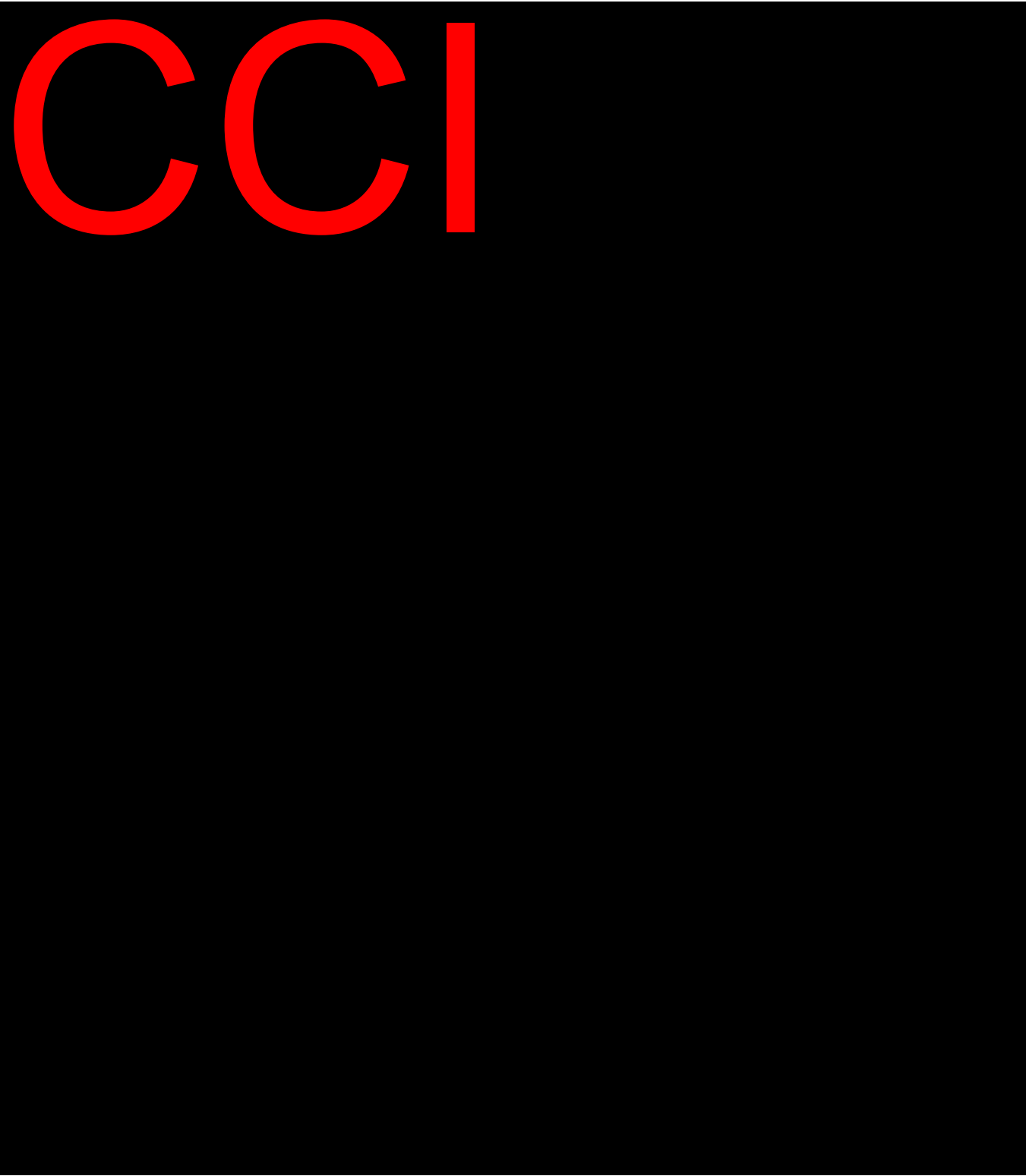


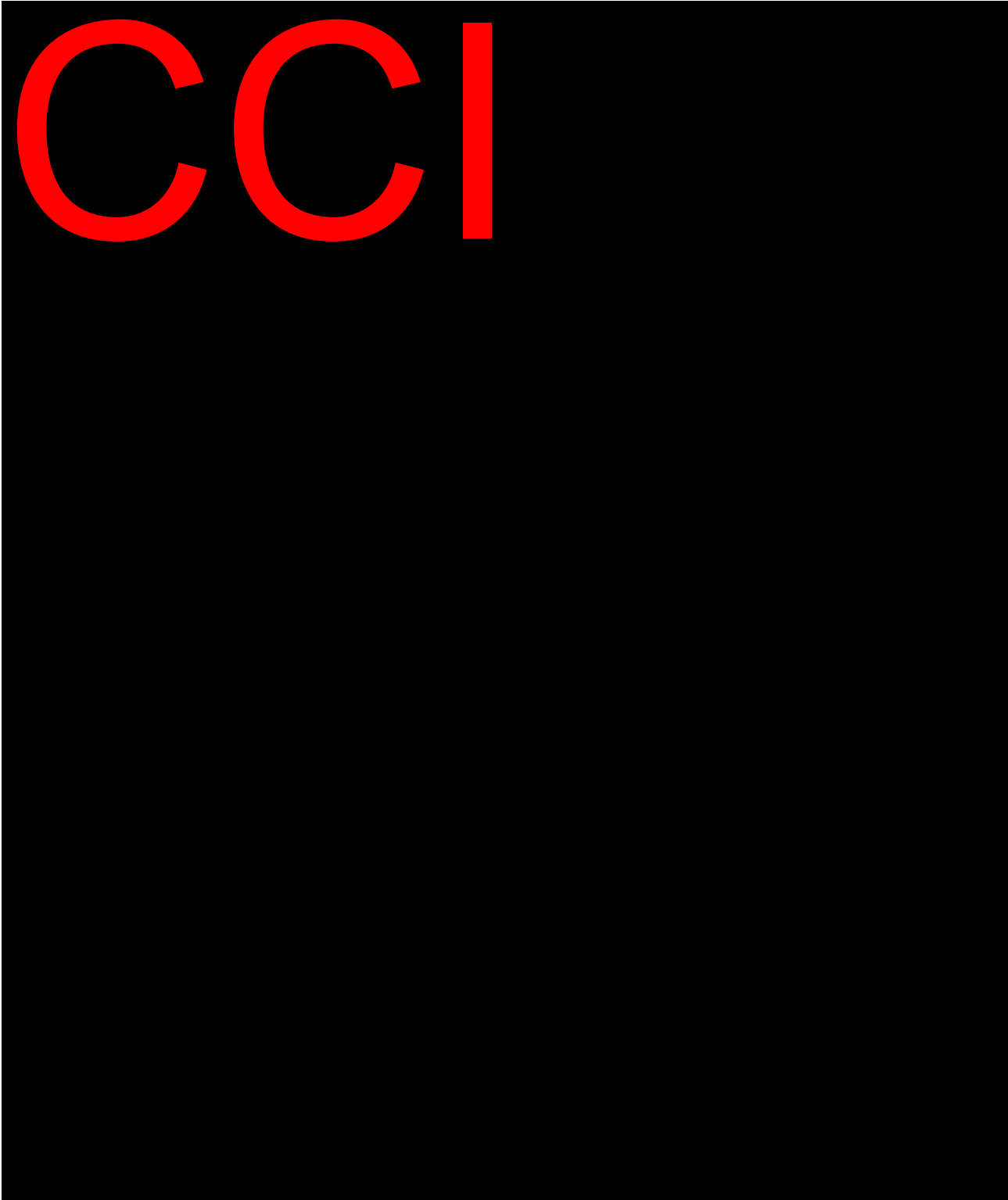
CCI



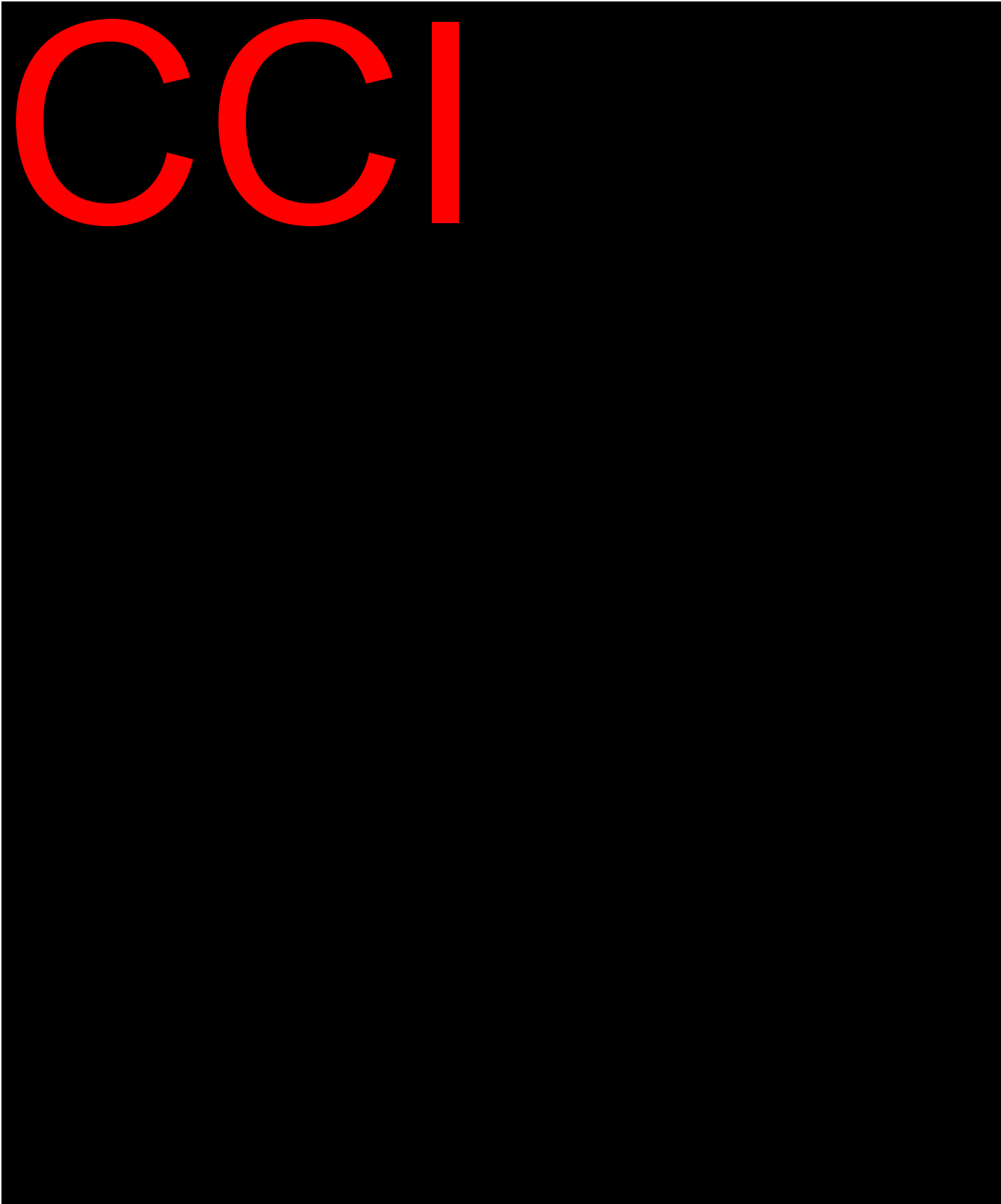
Thank you











CCI

SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

Clinical Trial Number (CTN): 43QM2107

CSP title: A Phase 3b, Open-label, Single-center Study to Assess Aesthetic Improvement Following Treatment with QM1114-DP in Subjects with Moderate to Severe Lateral Canthal Lines and Glabellar Lines

I, the undersigned, have read and understand the Clinical Study Protocol (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

SIGNATURES PAGE

PPD