Statistical Analysis Plan

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IND Number: 110196

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

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APPROVAL SIGNATURE PAGE

Protocol 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

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PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

PPD

1. Study Information

This statistical analysis plan (SAP) describes the efficacy and safety summaries and analyses that will be performed for the Clinical Trial Number (CTN) 43QM2107, *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* CCI

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1.1. Background

1.1.1. Study Design

This is a Phase 3b, open-label, single-center study to evaluate the aesthetic improvement of QM1114-DP in the treatment of moderate to severe lateral canthal lines (LCL) and glabellar lines (GL).

Eligible subjects will be treated at baseline with CCI of QM1114-DP in the lateral canthus areas, and CCI 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.

1.1.2. Number of Subjects

Approximately 27 subjects will be screened in order to get approximately 24 subjects enrolled at one study site. The sample size of 24 subjects is not based on a statistical calculation. Subjects will be male and female adults, 18 years of age or older, with moderate to severe bilaterally symmetrical LCL (grade 2 or 3 on the LCL-ILA and the LCL-SLA) and moderate to severe GL (grade 2 or 3 on the GL-ILA and the GL-SLA). The selected number of subjects will be used for descriptive evaluation of efficacy and safety in this study.

Following the screening process, eligible subjects will be treated with QM1114-DP at their baseline visit.

1.2. 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.

1.2.1. Primary Efficacy Objectives

The co-primary efficacy objectives of the study as assessed using the endpoints in Section 1.4.1 are:

(i) To evaluate aesthetic improvement in the LCL following a single dose of QM1114-DP as assessed by the subject using the Global Aesthetic Improvement Scale (GAIS) (as described in Section 1.3.1) at maximum smile at Month 1.

(ii) 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.

1.2.2. Secondary Efficacy Objectives

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1.3. Efficacy Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study injection on Day 0. Likewise, in general change from baseline (Δ) will be calculated as the value at a given time point, *X*, minus the baseline value:

$$\Delta = X\ Value - Baseline\ (Day\ 0)\ Value$$

1.3.1. Global Aesthetic Improvement Scale

The GAIS consists of seven ratings used to rate the global aesthetic improvement of LCL at maximum smile and GL at maximum frown, separately, relative to their pre-treatment appearance.

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. Ratings will also be recoded with numeric values 1-7 (as seen in Table 1). The subject may review the baseline photograph to aid in the assessment.

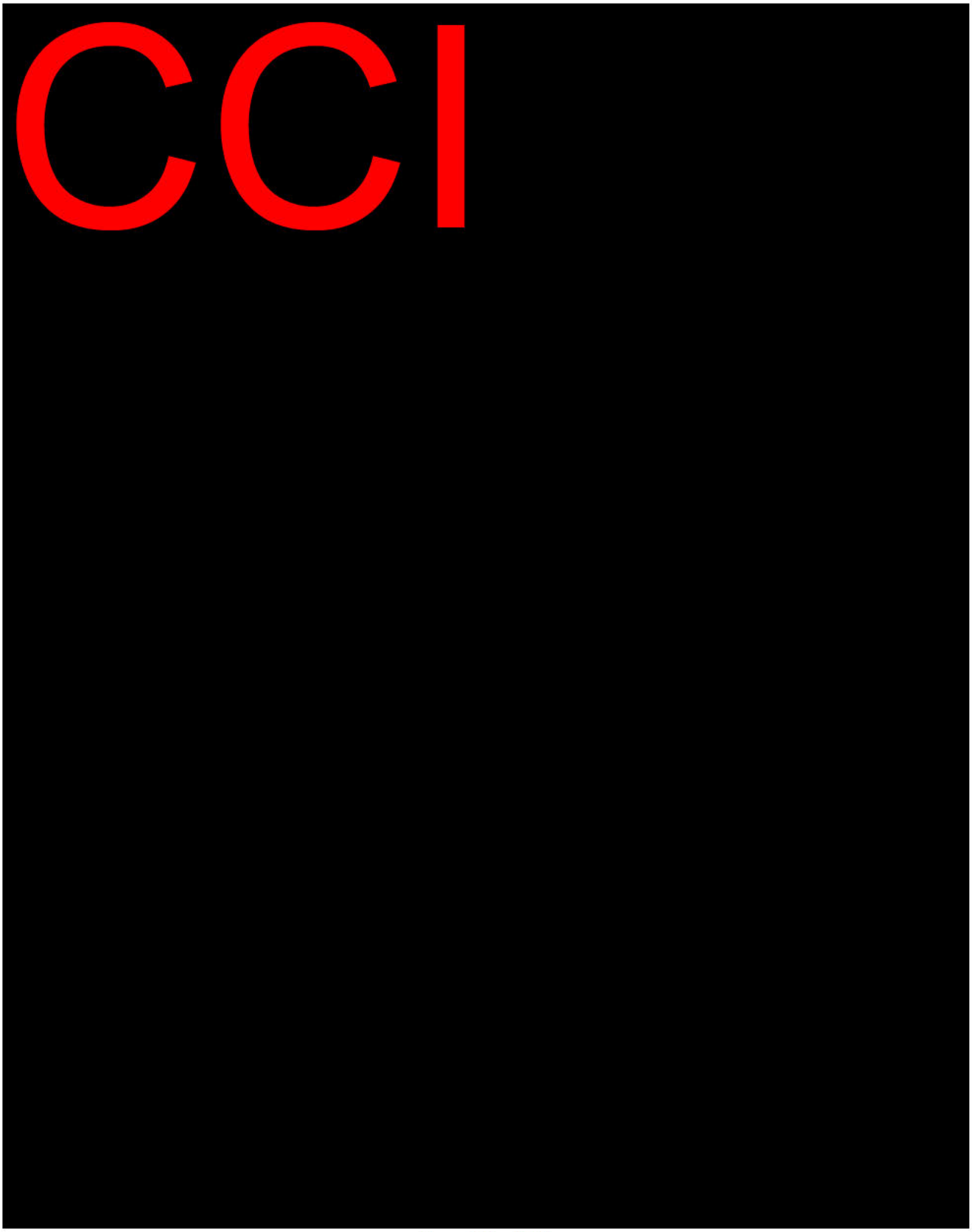
Subjects will rate the global aesthetic improvement of their LCL at maximum smile and their GL at maximum frown, separately, relative to baseline, at all post-treatment visits.

Table 1. Global Aesthetic Improvement Scale

Recorded Value	Rating
1	Very Much Improved
2	Much Improved
3	Improved
4	No Change
5	Worse
6	Much Worse
7	Very Much Worse

Multiple responder indicators will be created to identify subjects that experienced an improvement in aesthetic appearance of their LCL at maximum smile and their GL at maximum frown as follows:

- If at any given visit the subject selects 'Improved', 'Much Improved', or 'Very Much Improved' on the LCL at maximum smile GAIS, the subject will be considered a LCL Responder at that visit. The subject will be considered a Month 1 LCL Responder only if they are a responder at the Month 1 visit.
- If at any given visit the subject selects 'Improved', 'Much Improved', or 'Very Much Improved' on the GL at maximum frown GAIS, the subject will be considered a GL Responder at that visit. The subject will be considered a Month 1 GL Responder only if they are a responder at the Month 1 visit.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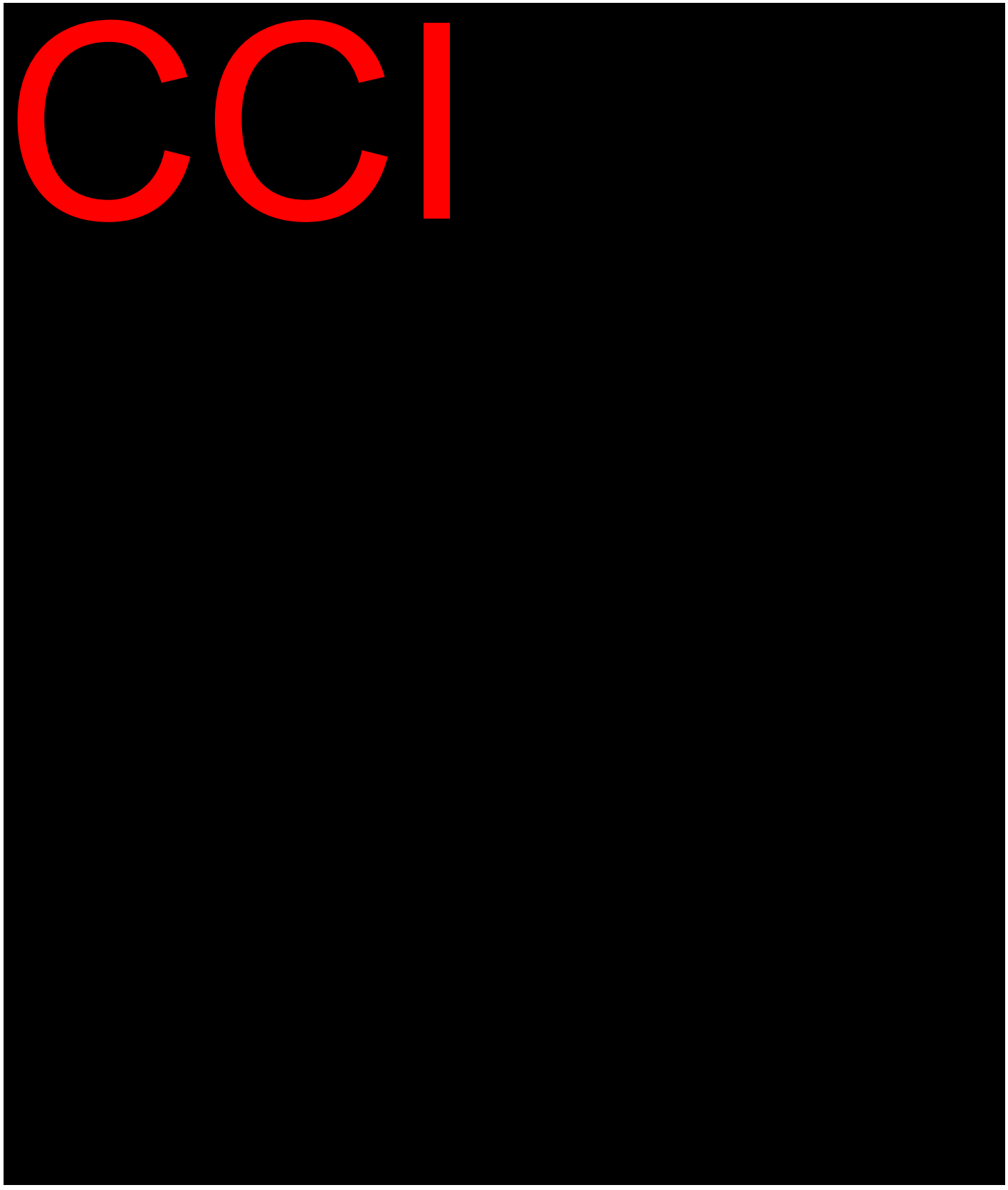
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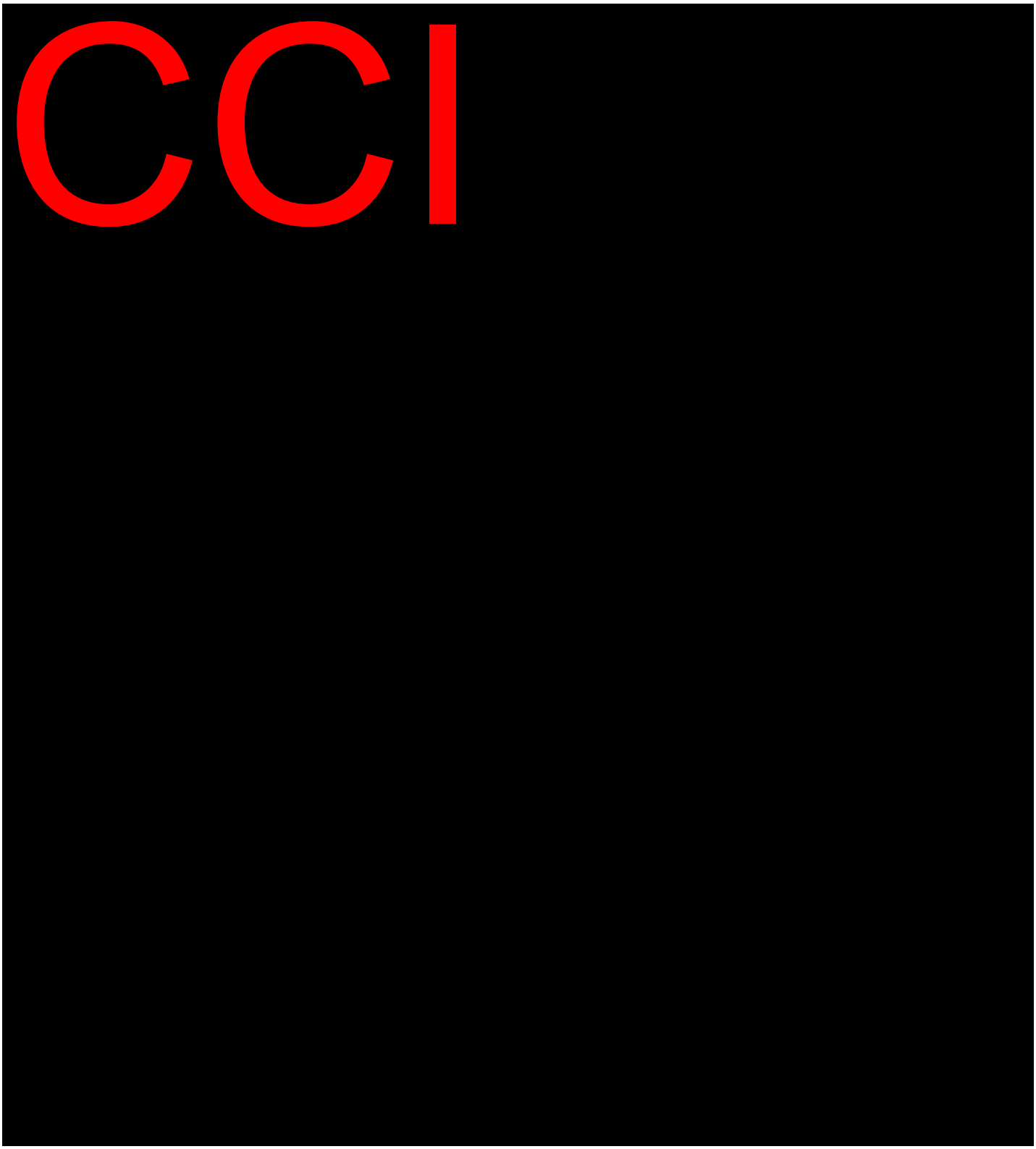
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1.4. Efficacy Endpoints

For all endpoints using responder rate, the responder rate is defined as $\frac{m}{n} \times 100$ where *m* is the number of responder subjects and *n* is the total number of subjects in the FAS population.

For all endpoints using proportion, the proportion will be calculated as $\frac{m}{n} \times 100$ where *m* is the number of subjects reporting the specified values on each question of the specified efficacy assessment, and *n* is the total number of subjects in the FAS population.

Percent of subjects in each response category will be calculated as $\frac{m}{n} \times 100$ where *m* is the number of subjects in each response category and *n* is the number of subjects that responded to that question.

The definition of *n* will change based on the population used in the output.

1.4.1. Primary Efficacy Endpoints

The primary efficacy endpoints include:

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

(ii) Responder rate based on the 7-point GAIS. A responder is defined as a subject who responds at least ”Improved” on the GL GAIS at maximum frown.

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1.5.1. Adverse Events

Adverse events (AEs) reporting on each subject will start once a subject is enrolled (i.e. treated) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting will continue during each follow-up visit until the last scheduled visit in the study. All AEs reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.1) and classified by MedDRA preferred term (PT) and system organ class (SOC). AEs will be defined as treatment-emergent adverse events (TEAEs) if the AE had an onset time greater than or equal to the time of study treatment. The study period for the purpose of AE collection is defined as the period from the signing of a study specific informed consent to study exit.

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?*

- *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.

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 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. Sponsor determination will be cross-referenced with Investigator-reported potential remote spread of the toxin or hypersensitivity AEs. As a part of preparations for database lock, the study team will review and adjudicate all AEs to create a finalized list of remote spread of toxin or toxin hypersensitivity events for the analysis.

Refer to Galderma Work Instruction 00.INS.01569 effective 16MAR2022 and to the Data Management Plan V1.0 for more details on this process.

AE endpoints include incidence, severity and seriousness of TEAEs.

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2. Statistical Methods

2.1. General Methods

All tables, listings, and figures will be programmed using SAS Version 9.4 or higher. Data collected in this study will be documented using summary tables and subject data listings created by the SAS® system. Confidence intervals (CI) and p-values will be 2-sided and performed at a significance level of 5%, unless otherwise specified. Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. Any changes from the SAP will be detailed in the clinical study report.

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 (SD), median, minimum and maximum value, unless otherwise specified. Categorical data will be presented in frequency tables with number (n) and percentage of observations for each level. All data will be listed in subject data listings.

Study days will be calculated relative to the injection of study drug. Day 0 will be the day of study drug administration. Baseline will be the last assessment prior to the injection of study drug unless otherwise indicated. The Screening visit (Day -14 to Day 0) will be considered the visit prior to injection of study drug. Because Screening and Baseline visit (Day 0) may be performed on the same day, the Screening visit can also be Day 0.

Adverse events, cosmetic/aesthetic procedures and implant history events, medical history events, previous neuromodulator treatments, and concomitant treatments/procedures will be coded using MedDRA, Version 25.1. Prior/concomitant medications and procedural anesthetics will be coded using the World Health Organization (WHO) Drug Dictionary Global B3, September 2022 or higher.

In general, efficacy, safety, and CCI [redacted] will be performed and summarized by overall subjects in the applicable population, unless otherwise stated.

2.1.1. Visit Windows

Study visits are expected to occur according to the Schedule of Assessments in Appendix A. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, relative study day (in relation to date of study drug administration) of all dates will be presented. There will not be any windowing for unscheduled visits in the analysis, and unscheduled visits will not be included in any analysis. Unscheduled visits, if any, will be presented in listings only.

Measures to minimize the risk of exposure to COVID-19 for study subjects include, but are 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.

2.1.2. Handling of Missing/Partial Dates

The handling of missing/partial dates for adverse events and concomitant medications is outlined below.

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

While every effort will be made to obtain full, complete information on every reported medication, the following imputation rules will be followed for any respective missing medication data:

For the purpose of determining whether a medication is considered prior or concomitant, the following date imputation rules will be used. Dates will be presented as collected in the listings.

- Start Date
  - If the start date is completely missing, it will be assumed that the medication started on the study treatment date.
  - If the start date is missing the day, the first of the month will be used (i.e., UNK-JAN-2023 becomes 01-JAN-2023), provided the imputed date is on or after the subject's study treatment date; otherwise, the day of study treatment will be used.
  - If the start date is missing the month, the month of January will be used (i.e., 01-UNK-2023 becomes 01-JAN-2023), provided the imputed date is on or after the subject's treatment date; otherwise the subsequent month after study treatment will be used.
  - If the start date is missing the year, the year of study treatment will be used (i.e., 01-JAN-UNK becomes 01-JAN-2023), provided the imputed date is on or after the subject's study treatment date; otherwise the subsequent year after treatment will be used.
- End Date
  - If the end date is completely missing, it will be assumed that the medication is still ongoing and will not be imputed.
  - If the end date is missing the day, the last day of the month will be used (i.e., UNK-JAN-2023 becomes 31-JAN-2023).
  - If the end date is missing the month, the subsequent month after the start date of the medication will be used.
  - If the end date is missing the year, the year of study treatment will be used (i.e., 01-JAN-UNK becomes 01-JAN-2023), provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.

While every effort will be made to obtain full, complete information on every reported AE, the handling of any respective missing AE data will follow the rules above, but for adverse events.

These rules will be used to calculate treatment emergence, onset time, and duration. Dates will be presented as collected in the listings.

2.2. Analysis Populations

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

- Safety Set – The Safety Set (SS) includes all subjects who were injected in at least one of the GL or LCL. Safety analysis will be performed using the Safety Set.
- Full Analysis Set – The Full Analysis Set (FAS) includes all subjects who were injected in both GL and LCL. The FAS is the primary population for all effectiveness analyses.

2.3. Study Subjects

2.3.1. Subject Dispositon

The number of subjects in each study population (i.e. Safety Set and Full Analysis Set) will be summarized. Study population variables will also be presented in a data listing. Subject screening, treatment, study completion, as well as early discontinuation will be summarized and presented in data listings for all subjects.

Reasons for early discontinuation will be summarized and listed. All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed, along with relevant comments recorded on the eCRF.

2.3.2. Protocol Deviations

A protocol deviation occurs when a subject deviates from the protocol procedures. Protocol deviations will be summarized.

All protocol deviations will be presented in a data listing individually, including subject number and observed deviation.

2.3.2.1. Out of Window Visit Duration

When a subject performs a planned study visit outside of the protocol-specified visit windows as specified in the Schedule of Assessments, the subject has an out of window study visit, which is considered a type of protocol deviation for this study. Knowing a subject's Screening visit (Visit 1) and Baseline visit (Visit 2) and using the protocol-specified visit windowing, one can calculate a subject's target study visit window date range for each planned study visit. Then, by comparing a subject's actual study visit date to the target study visit window date range, one can calculate the days over/under the actual study visit in relation to the target study visit date, or study visit out of window duration.

The duration, in days, a study visit is out of window will be summarized by visit. Duration will be split into the following below categories. Duration categories will include both days before and days after the target planned visit date.

- +/- 1-2 days
- +/- 3-7 days
- +/- 8-20 days
- +/- 21 or more days

The number and percentage of subjects within each out of window duration category will be presented descriptively. For the overall analysis, percentages will be calculated using the number of subjects with an out of window visit at the respective visit as the denominator.

2.3.3. Demographic Characteristics

Demographic assessments for this study include:

- Age (years)
- Height (inches)
- Weight (lbs.)
- Sex (Male, Female)
- Gender Identity (Female, Male, Transgender woman/trans woman/male-to-female (MTF), Transgender man/trans man/female-to-male (FTM), Genderqueer/gender nonconforming neither exclusively male nor female, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Fitzpatrick Skin Type (FST) Score (I, II, III, IV, V, VI)
- Toxin Naive Status (Toxin Naive, Non-Toxin Naive)

Subject demographic data will be summarized by overall subjects in the SS population. Age, height, and weight will be analyzed as continuous variables. Gender, race, ethnicity, FST, and toxin naive status will be analyzed as categorical variables.

2.3.4. Medical History and Prior Cosmetic/Aesthetic Procedures or Implants

All summaries will be done using overall subjects in the SS population. History of relevant or clinically significant surgical events and medical conditions, including any prior cosmetic/aesthetic procedures or implants, will be collected. Medical History will be coded according to MedDRA; the version used will be noted as a footnote in the tables and listings.

The number and percentage (where the denominator is the number of subjects in the SS population) of subjects reporting medical history will be summarized by system organ class (SOC) and preferred term (PT). System organ class and PTs will be presented in descending frequency first, and then alphabetically if there are ties. Each subject will contribute at most one

count per summarization category. In other words, if a subject has more than one medical history event with the same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one medical history event for a SOC, the subject will be counted only once in that SOC.

Cosmetic/aesthetic procedures will also be presented and will follow the same methods specified above.

Medical history and prior cosmetic/aesthetic procedures or implants will be provided in subject data listings.

2.3.5. Concomitant Procedures

All summaries will be done using overall subjects in the SS population. Concomitant procedures/treatments are defined as any new procedures/treatments received by the subject prior to the date of injection. Concomitant procedures/treatments include those that had changes to existing therapies during the course of the study and those that are ongoing since the date of injection.

Concomitant procedures/treatments will be coded according to MedDRA; the version will be noted as a footnote in the tables and listings. Concomitant procedures/treatments that started due to a related AE will be summarized separately from those who did not start due to an AE.

The number and percent (where the denominator is the number of subjects in the SS population) of subjects with previous neuromodulator treatment will be summarized by neuromodulator treatment and separately by treatment location.

Concomitant procedures/treatments will be presented by a subject in a data listing. Previous neuromodulator treatments will be presented in a separate data listing.

2.3.6. Prior and Concomitant Medications

All summaries will be done using overall subjects in the SS population. Concomitant medications for this study are defined as any ongoing medications with a start date on or after the Screening visit, any changes to existing medications (such as dose or formulation) during the course of the study, or any new medications received by the subject since the Screening visit. Prior medications are medications with stop dates within 4 weeks preceding the Screening visit.

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. The versions for the coding will be noted as a footnote in the tables and listings. Medications that started due to a related AE will be summarized separately from those that did not start due to a related AE.

The number and percentage of subjects who receive prior and concomitant medications will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 4th Level (ATC-4) and the preferred name (where the denominator is the number of subjects in the SS population). If the 4th level term is not available, the next available level (e.g. ATC-3) will be used.

In addition, the number and percentage of subjects reporting a concomitant medication/therapy will be summarized by reason administered (medical history condition, adverse event, concomitant procedure, contraception, or other).

The ATC-4 and preferred name will be presented in descending frequency first, and then alphabetically if there are ties. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one medication with the same preferred name, the subject will only be counted once for that preferred name. Similarly, if a subject has more than one medication for an ATC-4 level, the subject will be counted only once in that ATC-4 level and preferred name.

Prior and concomitant medications will be presented by subject in a data listing. For handling of missing/partial dates, please see Section 2.1.2.

2.4. Efficacy Analysis

2.4.1. Datasets Analyzed

All primary efficacy, secondary efficacy, and exploratory endpoints will be analyzed based on the FAS population using OC, unless otherwise specified below. All primary efficacy, secondary efficacy, and exploratory endpoints will be included in separate data listings.

2.4.2. Primary Analysis

The co-primary efficacy endpoints are LCL responder rate based on the GAIS at maximum smile and the GL responder rate based on the GAIS at maximum frown at Month 1 (described in Section 1.4.1). To evaluate the aesthetic improvement of the LCL and the GL following a single dose of QM1114-DP, the proportion of subjects responding with at least 'Improved' on the LCL GAIS assessment and the GL GAIS assessment separately will be presented with a 95% confidence interval based on the binomial distribution. The GAIS assessments for LCL and GL will also be presented in frequency tables.

The Clopper-Pearson method will be performed to calculate the 95% CIs for both the LCL GAIS and the GL GAIS responder rates. The proportion of subjects responding at least 'Improved' will be presented in figures by visit for both LCL and GL.

2.4.3. Primary Efficacy Estimand

The primary estimand is the proportion of subjects that have at least "Improved" from baseline; the number of subjects that select "Improved", "Much Improved", or "Very Much Improved" on the LCL GAIS assessment and the GL GAIS assessment at Month 1, separately, divided by the number of subjects that completed the GAIS at Month 1, for subjects in the FAS population:

<table>
<tr><th>Primary Endpoint</th><th colspan="2">Estimand</th></tr>
<tr><td rowspan="4">Responder rate in aesthetic improvement of at least 'Improved' at Month 1 as assessed by the subject using the GAIS (for GL and LCL separately)</td><td colspan="2">Population: all subjects who were injected in both LCL and GL (FAS population)</td></tr>
<tr><td colspan="2">Endpoint: the number of subjects that select "Improved", "Much Improved", or "Very Much Improved" on the GAIS at Month 1 (separately for LCL and GL), divided by the number of subjects in the FAS population that completed the GAIS at Month 1</td></tr>
<tr><td>Intercurrent Events:
1. Missing Month 1 observation
2. Administered treatment not according to protocol
3. Use of prohibited treatment/procedure in or near the treatment area between 6 months prior to study treatment and Month 1 after study treatment
4. History or presence of eyelid or eyebrow ptosis at Baseline</td><td>Handling of intercurrent events:
1. Use worst observed case.
2. Use observed response.
3. Remove subjects who used a prohibited treatment/procedure in or near the treatment area between 6 months prior to study treatment and Month 1 after study treatment and repeat analysis.
4. Remove subjects with history or presence of eyelid or eyebrow ptosis at Baseline and repeat analysis.</td></tr>
<tr><td colspan="2">Summary measure: 95% CI presenting the proportion of subjects that have at least "Improved" from baseline.</td></tr>
</table>

Note that intercurrent events is defined as events occurring after treatment initiation that affect either the interpretation or the existence of measurements associated with the clinical question of interest.

2.4.3.1. Sensitivity Analysis

To account for the potential of missing GAIS data at the primary endpoint Month 1 visit, sensitivity analysis will be performed. The co-primary endpoint tables specified in Section 2.4.2 will be repeated based on the FAS population where missing data will be imputed using the worst observed case.

2.4.3.2. Subgroup Analysis

Additionally, to evaluate the consistency of the results of the primary analysis across different subgroups of interest, the co-primary endpoint tables specified in Section 2.4.2 may be repeated based on the FAS population using OC for each of the following subgroups specified below:

- Sex (Male, Female)
- FST (I-III, IV-VI)
- Previous neuromodulator treatments (Y/N)
- Race (White, Black, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

The subgroup analyses will only be performed for subgroups that have at least 20% of subjects in two or more of the subgroup categories.

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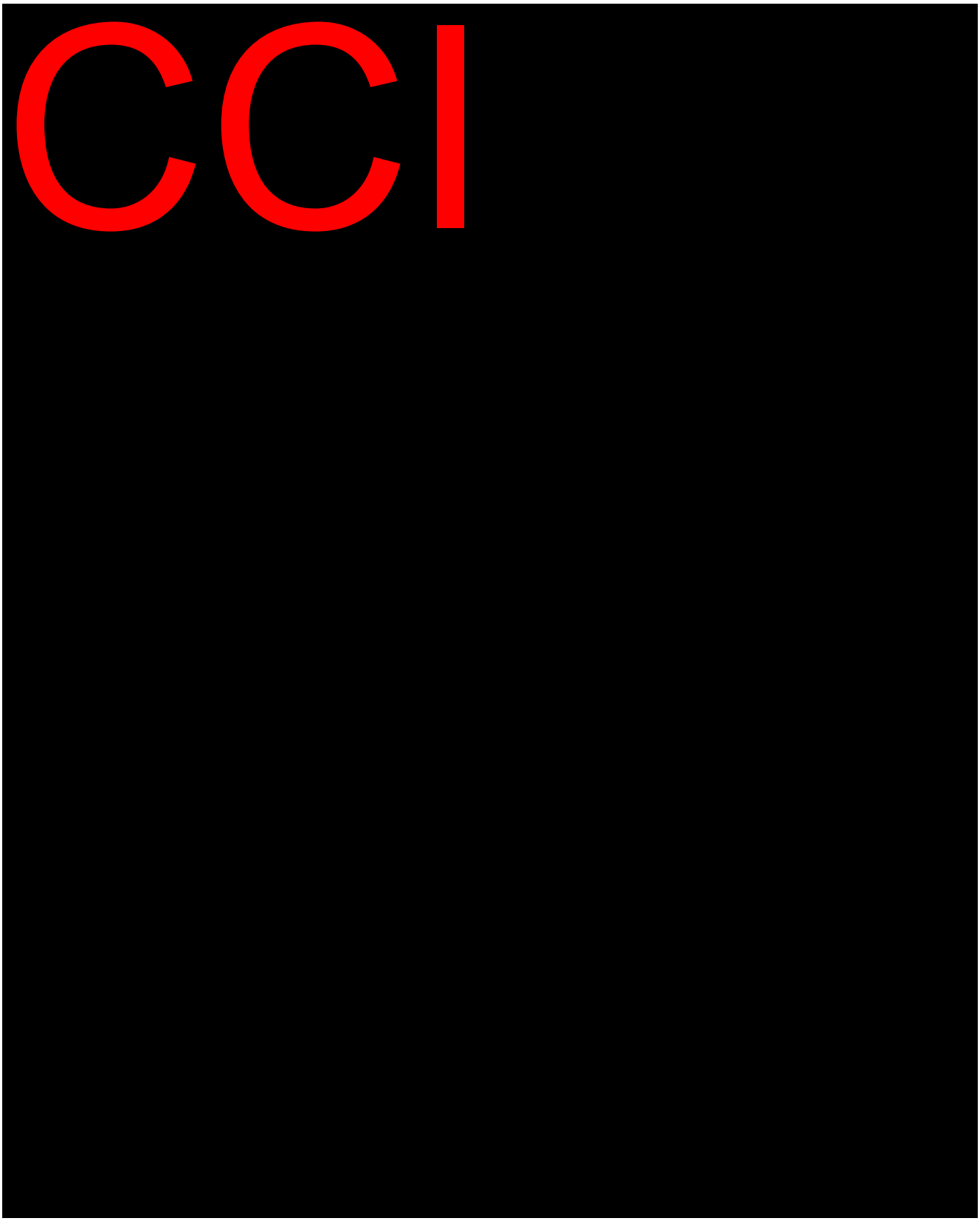
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2.4.4.2. Analyses of GAIS Responder Rates

The GAIS assessment as determined by the subject separately for LCL at all applicable post-treatment time points will be a responder rate based on the subject GAIS at maximum smile (described in Section 1.3.1). The responder rate will be presented by visit. The 95% CIs around the estimates will also be provided by visit. The actual GAIS ratings of the subject will be presented in a frequency table by visit.

Analysis will be repeated for the GAIS assessment of GL at maximum frown. Graphs will be provided showing the LCL and GL responder rates over time.

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2.5.1. Extent of Exposure

There will be a limited exposure to QM1114-DP since it is administered only at baseline. The injection volume in mL in subjects receiving a single dose of QM1114-DP will be presented using descriptive statistics. In addition, injections characteristics will be summarized.

2.5.2. Adverse Events

AEs will be summarized by SOC and PT. AEs occurring before treatment will be presented in listings only. The MedDRA version used for the coding will be noted as a footnote in the tables and listings. In general, percentages for the number of subjects will be calculated using the number of subjects in the SS population for the denominator.

A summary of all AEs will be provided, which will include:

- Number (%) of subjects who did not have an AE
- Number (%) of subjects with at least one TEAE and number of events
- Number (%) of subjects with at least one TEAE related to study product of injection procedure and number of events
- Number (%) of subjects with at least one TEAE not related to study product or injection procedure and number of events
- Number (%) of subject with at least one TEAE leading to discontinuation and number of events
- Number (%) of subjects with at least one serious TEAE and number of events
- Number (%) of subjects with at least one serious related TEAE and number of events
- Number (%) of subjects with at least one AE that meets the criteria of remote spread of toxin and hypersensitivity and number of events

Summaries of TEAEs (including the total number of events, number and percentage of subjects) will be displayed according to the following:

- All TEAEs by SOC and PT
- Treatment-emergent SAEs by SOC, PT, maximum intensity (mild, moderate, severe), and causality
- Related TEAEs by SOC, PT, and maximum intensity (mild, moderate, severe)
- Unrelated TEAEs by SOC, PT, and maximum intensity (mild, moderate, severe)
- Related TEAEs by SOC, PT, and action taken (none, medical treatment, non-pharmacological treatment, subject withdrawn)
- TEAEs that meet the criteria of remote spread of effect by SOC, PT

The number and percentage of subjects who experienced at least one of the events listed above will be summarized for each SOC and each PT. System organ class and PTs will be presented in descending frequency first in descending frequency, and then alphabetically if there are ties. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one TEAE with the same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than TEAE for a SOC, the subject will be counted only once in that SOC and PT. For the ”action taken” summary specifically, subjects will only be counted in ’None’ category if no other action was taken and counted in all applicable action categories if more than one action was taken.

All related TEAEs will also be summarized by time to onset and duration. These summaries will be presented at the event level (i.e., will include multiple AEs within the same SOC and PT). Number of days to onset and duration of event will be summarized by SOC and PT, using mean, SD, minimum, maximum, and median statistics. Time to onset will be calculated as the first day with the AE *minus* the Day 0. Duration will be calculated as the last day with the AE *minus* the first day with the AE *plus* one.

For handling of missing/partial dates, see Section 2.1.2. A completely 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. If the intensity assessment is missing, the intensity of “Severe” will be assumed. Missing relationships will be considered related. If the seriousness of an AE is missing, the AE will be assumed to be an SAE.

2.5.3. Assessment of Remote Toxin Spread and Hypersensitivity

Any potential or suspected remote toxin spread or toxin hypersensitivity events will be evaluated separately. The identification of these events is described in Section 1.5.1. Suspected remote toxin spread events and suspected toxin hypersensitivity events will be summarized in separate tables, following the same methods specified in Section 2.5.2.

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[redacted]

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2.6. Interim Analsis

Not applicable.

2.7. Determination of 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.

2.8. Changes in Analysis Planned in the Protocol

At this point, there are no changes in analysis from what was planned in the protocol.

3. Reference List

1. Medical Dictionary for Regulatory Activities Terminology (MedDRA), Verxion 25.1, MedDRA MSSO, September 2022.

2. WHO Drug Dictionary, September2022 – Global Version B3, Uppsala Monitoring Centre (UMC) Box-1051, SE-751 40 Uppsala, Sweden.

3. Center for Drug Evaluation and Research. ”E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands.” *U.S. Food and Drug Administration*, FDA, May 2021.

4. Cassell, David L. “Don't Be Loopy: Re-Sampling and Simulation the SAS® Way.” Design Pathways, Corvallis, OR. *SAS Global Forum 2007*, 2007.

5. Rick Wicklin on The DO Loop. “The Bootstrap Method in SAS: A T Test Example.” The DO Loop, 20 June 2018, blogs.sas.com/content/iml/2018/06/20/bootstrap-method-example-sas.html.

6. Bhatnagar , Sahir, and James A Hanley. “EPIB607.” *Chapter 12 Confidence Intervals with Bootstrapping*, sahirbhatnagar.com/EPIB607/foundations-bootstrapping.html. Accessed 31 May 2023.

7. Appendix A: Schedule of Assessments

Visit 1 month = 4 weeks/28 days' and ' All visit windows are calculated from Baseline/Day 0	**Visit 1** Screening 1	**Visit 2** Day 0 Baseline[1]	**Visit 3** Day 1[f]	**Visit 4** Day 2[f]	**Visit 5** Day 3[f]	**Visit 6** Day 4[f]	**Visit 7** Month 1	**Visit 8-9** Months 2-3	**Visit 10** 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								
CCI									
Inclusion/Exclusion Criteria	X	X[6]							
CCI									
CCI									
Adverse Events	X	X[6]	X	X	X	X	X	X	X
Concomitant Medication/Procedures		X[6]	X	X	X	X	X	X	X
SUBJECT ASSESSMENTS									
CCI									
GAIS			X	X	X	X	X	X	X
CCI									
INVESTIGATOR ASSESMENTS									
CCI									

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

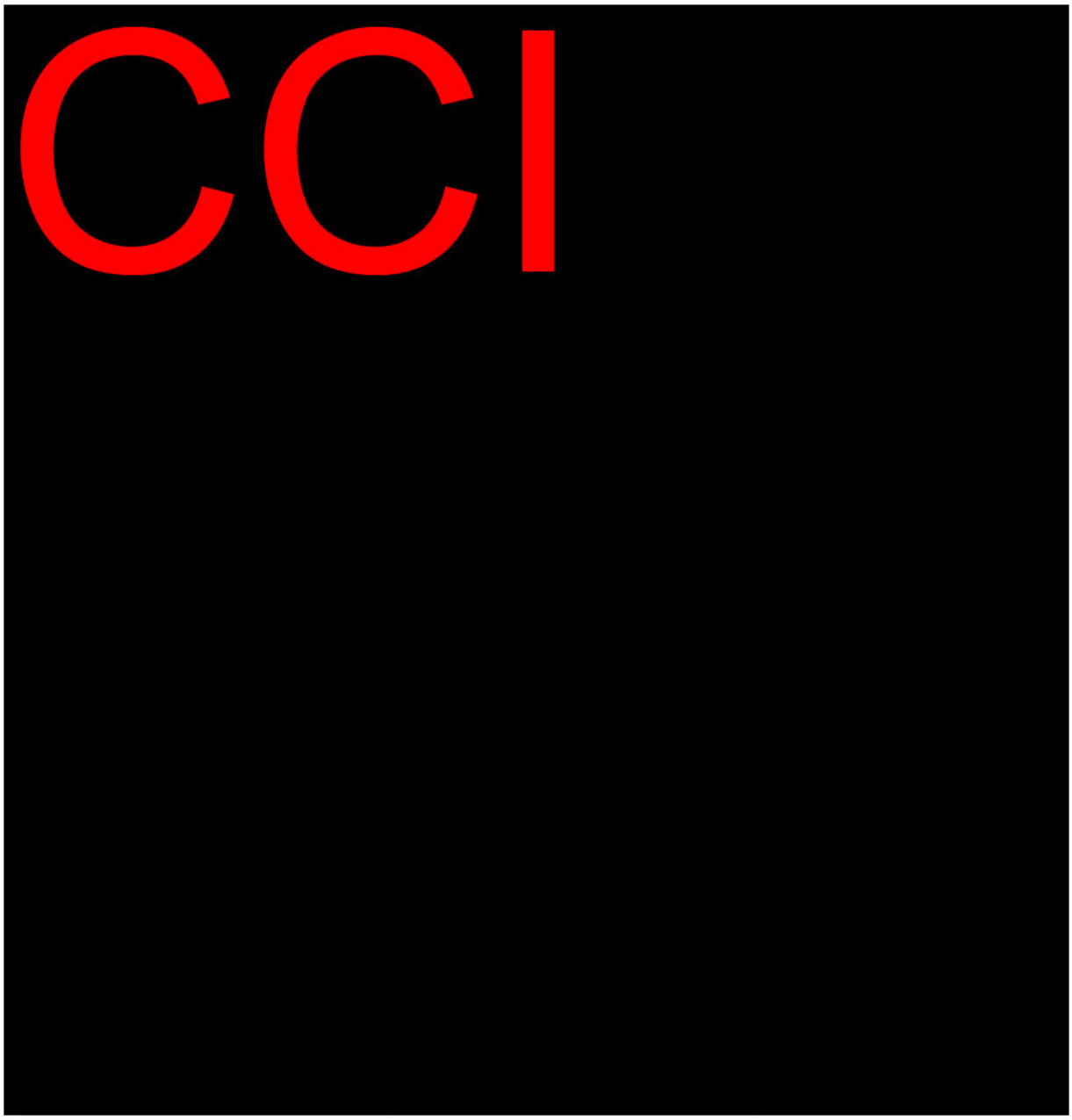
1. Screening and baseline visits may be performed on the same day. If performed on the same day, study activities should only be completed once (i.e., UPT, subject and investigator GL/LCL severity assessments, focused physical exam, vital signs, and inclusion/exclusion criteria.
2. If the subject withdraws 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.
6. Performed pre-treatment.
7. Post-baseline, events suggestive of remote spread of toxin are also considered while doing clinical evaluations based on the subject's symptoms and signs. Directed questioning and examination will then be performed as appropriate.

CCI

9. Performed pre- and post-treatment.
10. Subject will make his/her assessment independently of the investigator's assessment.

CCI


CCI



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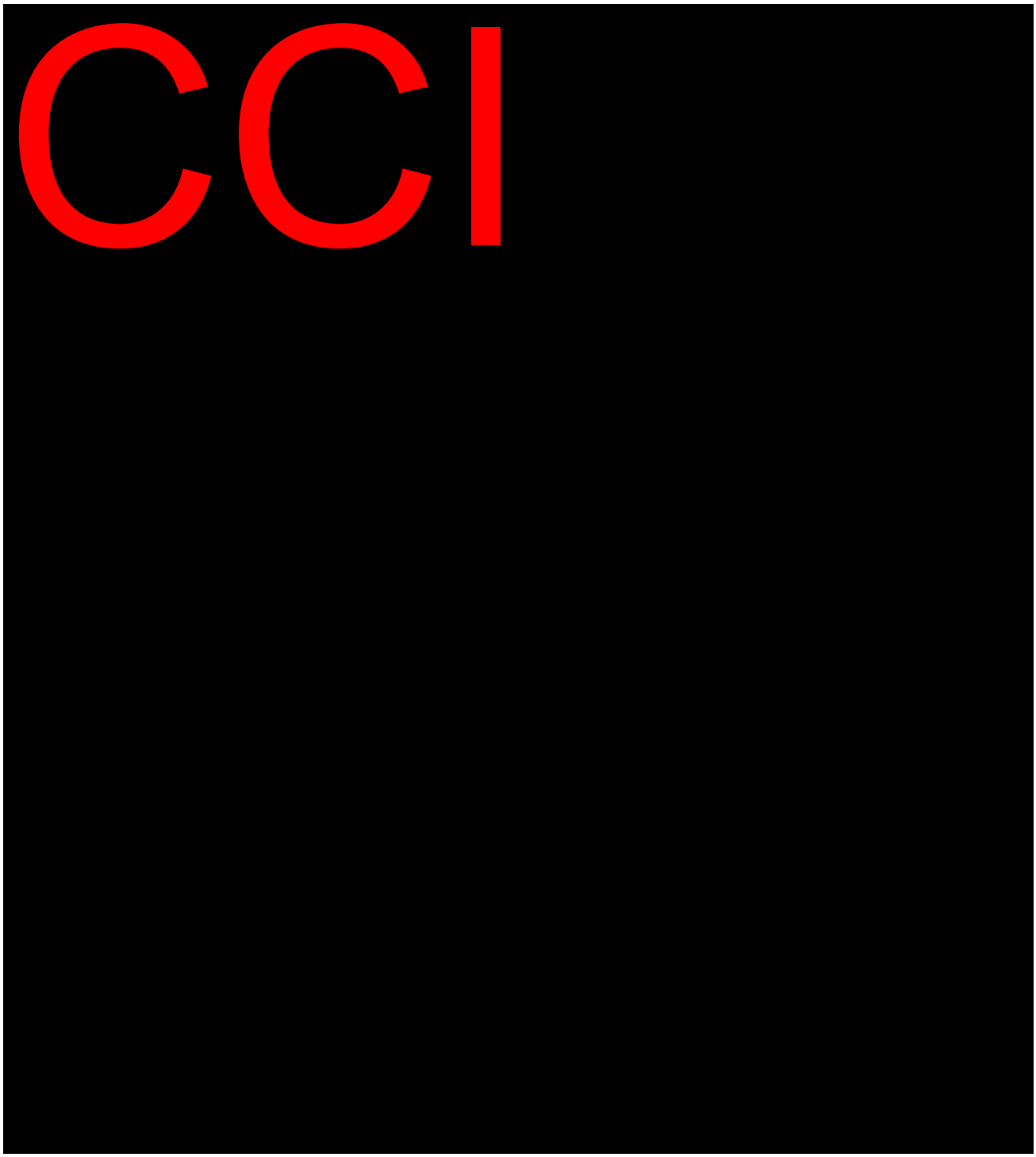
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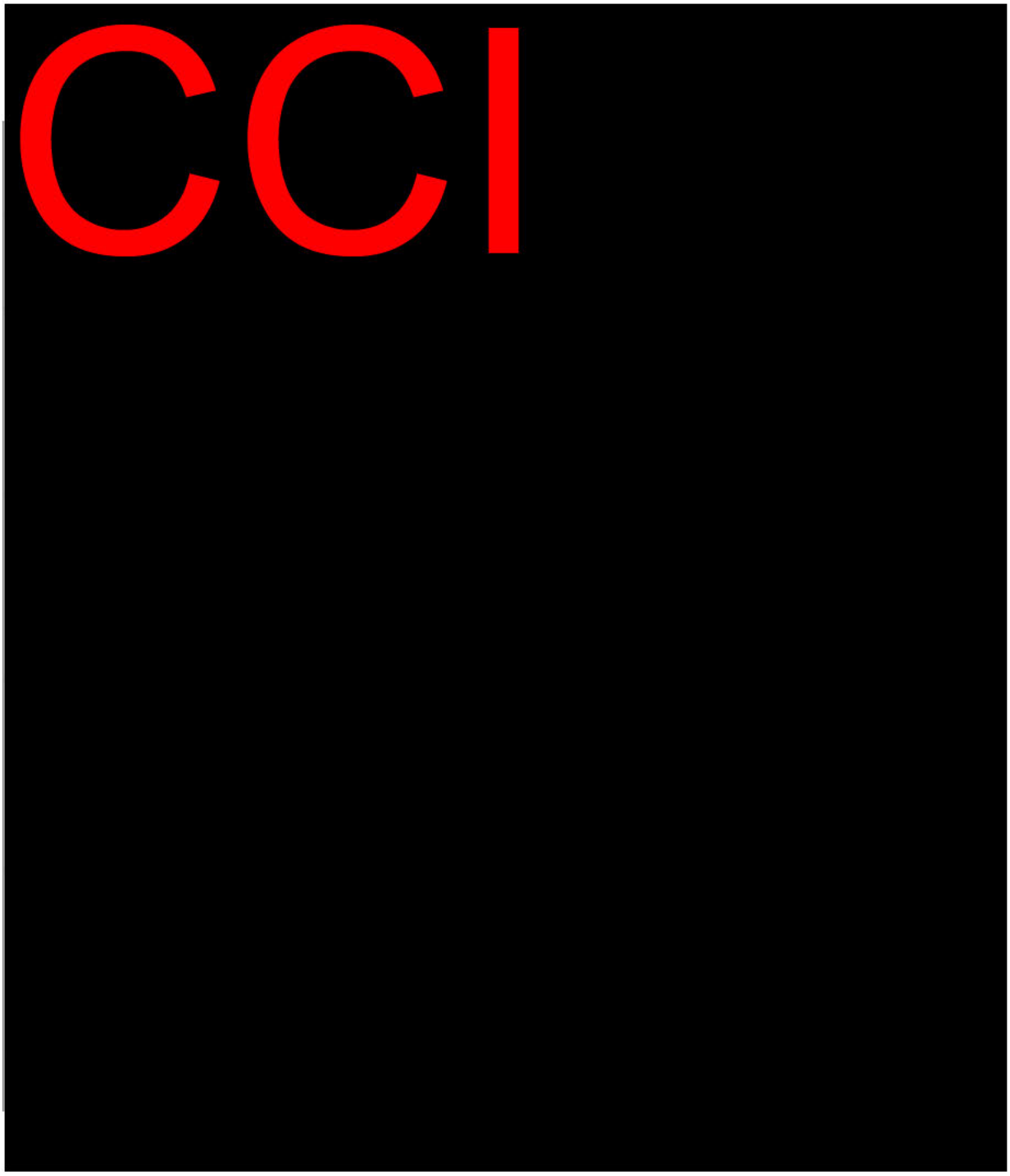
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