Statistical Analysis Plan

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A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study to Assess Aesthetic Improvement and Onset of QM1114-DP Treatment Effect in Subjects with Moderate to Severe Glabellar Lines

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APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study to Assess Aesthetic Improvement and Onset of QM1114-DP Treatment Effect in Subjects with Moderate to Severe Glabellar Lines

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CCI [redacted] **Author:**

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.

Sponsor Signatory:

PPD
Galderma PPD

Signature:_____

Date:_____

1 Study Information

This statistical analysis plan (SAP) describes the efficacy and safety summaries and analyses that will be performed for Clinical Trial Number (CTN) 43QM2108, *A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study to Assess Aesthetic Improvement and Onset of QM1114-DP Treatment Effect in Subjects with Moderate to Severe Glabellar Lines* and is based on the study protocol Version 3 dated 21MAR2022.

1.1 Background

1.1.1 Study design

This is a phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QM1114-DP in the treatment of moderate to severe glabellar lines (GL).

Eligible subjects will be randomized to receive a single treatment at baseline of 50 units (U) of QM1114-DP or placebo in the glabellar region. Following treatment at baseline, subjects will be monitored for safety and efficacy according to the Schedule of Assessments for 12 months.

1.1.2 Number of subjects and randomization

The study will screen approximately 134 male and female adults, 18 years of age or older, with moderate to severe glabellar lines at maximum frown and previous treatments with BoNT-A products within the 3 years prior to screening visit. A total of approximately 120 subjects will be randomized and enrolled at least 5 study sites. Following the screening process, eligible subjects will be randomized at the baseline visit (Day 0) in a 3:1 ratio to QM1114-DP or placebo, stratified by site.

1.2 Study Objectives

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

1.2.1 Primary efficacy objective

The primary efficacy objective of the study is to demonstrate superiority in aesthetic improvement following a single dose of 50 units of QM1114-DP compared to placebo for the treatment of moderate to severe GL using the Global Aesthetic Improvement Scale (GAIS) (described in Section 1.3.1) at maximum frown at Month 1.

1.2.2 Secondary efficacy objectives

The secondary efficacy objectives of the study as assessed using the endpoints in Section 1.4.2 are:

- To evaluate onset of treatment effect following a single dose of 50 units of QM1114-DP and placebo as assessed by the subject using the diary card on Days 0 through 7 post-treatment (as described in Section 1.3.2).

- To evaluate aesthetic improvement following a single dose of 50 units of QM1114-DP and placebo as assessed by the subject using the GAIS at maximum frown at all applicable time points (Section 1.3.1).

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1.2.4 Safety objective

The safety objective of the study is to evaluate the safety of a single dose of 50 units of QM1114-DP and placebo in the treatment of moderate to severe GL.

1.3 Efficacy assessment

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 (GAIS)

The GAIS consists of seven ratings used to assess the aesthetic improvement of the GL at maximum frown relative to pre-treatment appearance. 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, using the below categorical scale (Table 1), that best describes the degree to which the appearance of their GLs at maximum frown has changed relative to baseline. Ratings will also be recoded with numeric values 0-6 (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 GL at maximum frown, relative to their pre-treatment appearance, at all post-treatment visits.

Table 1. Global Aesthetic Improvement Scale

Recoded Value	Rating
0	Very Much Improved
1	Much Improved
2	Improved
3	No Change
4	Worse
5	Much Worse
6	Very Much Worse

A responder indicator will be created to identify subjects that experienced an improvement in aesthetic appearance of their GL at maximum frown. If at any given visit the subject selects 'Improved', 'Much Improved', or 'Very Much Improved' on the GAIS, the subject will be considered a Responder at that visit. The subject will be considered a Month 1 Responder only if they are a responder at the month 1 visit.

1.3.2 Subject Diary Card

Subjects will be asked to record their assessment of study treatment response in a diary card on Day 0 (baseline post-treatment) through Day 7. They will be asked to respond "Yes" or "No" to the following question:

- *"Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows) when you frown?"*

Subjects will complete the diary card daily, starting on the day of treatment (Day 0), and will return the diary to study site at their Month 1 visit.

For each subject, time, in days, to onset of treatment response will be computed. A flag will be created to determine the diary date of when the subject first answers 'Yes' to "Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows) when you frown?" Time, in days, to onset of treatment response will be calculated as follows:

Number of days to onset = Date of Diary Flag – Date of Day 0

Subjects who never notice an improvement will be censored at Day 7. Subjects dropping out before noticing improvement will also be censored at Day 7 or date of withdrawal, whichever comes first. Subjects who never return their diary will be censored on Day 7.

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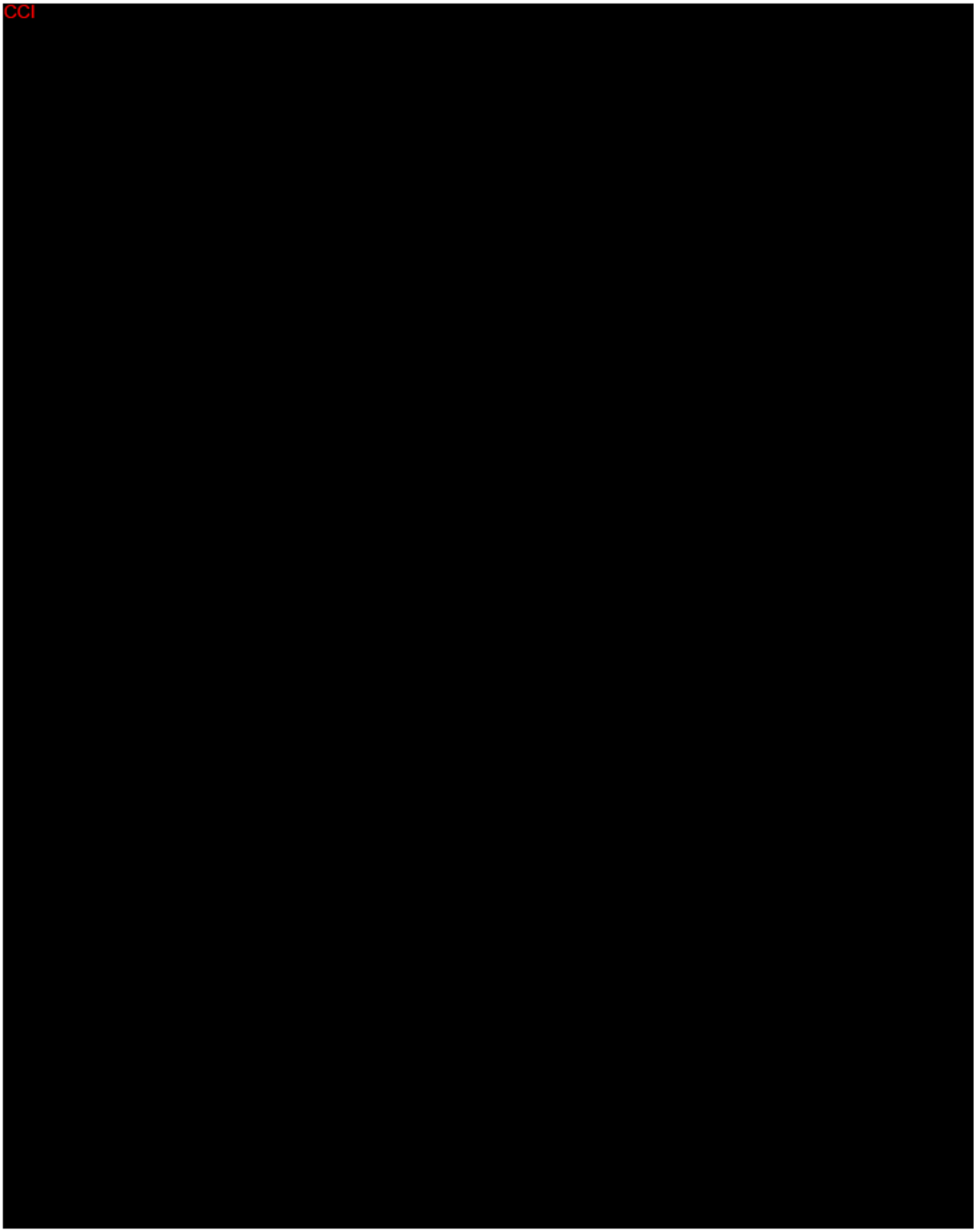
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1.4 Efficacy endpoints

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 ITT 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 at each visit, and n is the total number of subjects in the ITT 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

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

1.4.1 Primary efficacy endpoint

The primary efficacy endpoint is the responder rate based on the 7-point GAIS at Month 1. A responder is defined in Section 1.3.1.

1.4.2 Secondary efficacy endpoints

Secondary endpoints include:

(i) Time (days) to onset of treatment effect following a single dose of QM1114-DP and placebo based on the subject's diary card. Derivation of the endpoint is described in Section 1.3.2.

(ii) Responder rate based on the 7-point GAIS at each post-treatment visit at maximum frown. Responder is defined as a subject who respond "Improved", "Much improved", or "Very much improved".

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1.5 Safety assessments and endpoints

For details regarding the safety assessments, please refer to Section 7.2 of the Protocol.

1.5.1 Adverse events

Adverse events (AEs) are to be monitored throughout the course of the study. All AEs reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0 – March 2022 or higher) 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) will be used for the causality assessments. The Treating Investigator should be asked to indicate a response to each of the following questions in the electronic Case Report Form (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 either of these questions is answered with a 'Yes', the AE will be 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, which will be included as an AE endpoint. A list of preferred terms for these types of events will be analyzed to determine if there is a plausible possibility that they represent remote spread of toxin or hypersensitivity. The Sponsor will consider variables including alternative etiology (medical history, concomitant medications, or diagnosis which could account for the symptoms), location of QM1114-DP administration, and temporal relationship to

QM1114-DP administration in order to perform the analysis. Sponsor determination will be cross-referenced with Investigator-reported potential remote spread of the toxin or hypersensitivity AEs. Before unblinding the subject data, and as a part of preparations for the 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 QMS-13549 effective 16MAR2022 and to the Data Management Plan V1.0 for more details on this process.

AE endpoints include incidence and severity of TEAEs.

1.5.2 Focused physical examination

Physical examination will be done at screening/baseline (before treatment), Day 1, Day 2, Day 3, Day 4, Month 1, Month 3, Month 6, Months 7-11, Month 12/EOS/ET. Normal, abnormal and clinically significant findings will be assessed.

1.5.3 Vital signs

Vital signs will be assessed from screening/baseline (before treatment), Day 1, Day 2, Day 3, Day 4, Month 1, Month 3, Month 6, Months 7-11, Month 12/EOS/ET. Vital signs endpoints include:

- Values collected at each visit
- Changes from baseline

1.5.4 Anti-drug Antibodies (ADA)

Blood samples will be taken for measurement of serum neutralizing antibody testing against QM1114-DP at baseline (before treatment), Month 1, and Month 6.

Analysis of the blood samples include in vitro screening and confirmatory (if positive screening result) ELISA assays to test for the presence of binding antibodies, and in vivo mouse protection assay (MPA) to test for the presence of neutralizing antibodies. The MPA will only be conducted if the subject has a positive confirmatory result. ADA categories outlined in Section 2.5.3 will be determined based on the confirmatory assay results.

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 within each treatment group, and graphs as appropriate. Continuous variables will be summarized using descriptive statistics (n [number of observations], mean, standard deviation [SD], median, minimum, and maximum), unless otherwise specified. Categorical variables will be presented in frequency tables with number and percentage of observations for each level.

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 1 (Day -14 to Day 0) will be considered the visit prior to injection of study drug. Because the Screening visit 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 25.0 or higher. Prior/concomitant medications and procedural anesthetics will be coded using the World Health Organization (WHO) Drug Dictionary Global, March 2022 B3 or higher.

In general, efficacy, safety, and exploratory analyses will be performed and summarized by treatment group (QM1114-DP, placebo), unless otherwise stated.

2.1.1 Visit windows

Study visits are expected to occur according to the protocol 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, the 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 analyses. 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 primary endpoint.

2.1.2 Handling of Missing/Partial Dates

The handling of missing/partial dates for Adverse Events and Concomitant Medications/Procedures is outlined below. See Section 2.4.2 for handling of missing data for the efficacy analyses.

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 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-2022 becomes 01-JAN-2022), 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 'June' will be used (i.e., 01-UNK-2022 becomes 01-JUN-2022), provided the imputed date is on or after the subject's study 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-2022), 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-2022 becomes 31-JAN-2022).
  - If the end date is missing the month, the subsequent month after the start date 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-2022), 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 three subject populations:

- Intention-to-treat Population - The Intent-to-treat (ITT) population includes all subjects who are randomized and dispensed the investigational product and will be analyzed according to the randomization scheme.

- Per-protocol Population - The Per-protocol (PP) population includes the ITT subjects who complete the Month 1 visit and have no protocol deviations that are considered to have a substantial impact on the primary efficacy outcome.
- Safety Population - The safety population includes all subjects who were administered the study product and will be analyzed according to as-treated principle.

2.3 Study subjects

2.3.1 Subject disposition

Subject disposition will be presented by treatment group and overall. The number of subjects in each study population (i.e., ITT, PP and Safety) will be summarized. Study population variables will also be presented in a data listing. Study completion, as well as early discontinuation, randomization, and study visits will be 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 the relevant comments recorded on the eCRF.

2.3.2 Protocol deviations

A protocol deviation occurs when a subject deviates from the protocol procedures. Depending on the seriousness of the deviation, the subject might be excluded from the Per-Protocol (PP) population, which will be documented prior to database lock. Protocol deviations will be summarized by study site and in total (by treatment group and overall). Since PP population will be used for the sensitivity analysis of the primary endpoint at Month 1 only, the focus will be on deviations occurring before and on Month 1 visit day, as they might compromise the primary endpoint.

For this study, the protocol deviations that will exclude subjects from PP population will be established pre-database lock, with the reasoning for exclusion documented. Protocol deviations that will exclude subjects from the PP population include, but are not limited to, deviations that impact the primary efficacy endpoint. Subjects excluded from the PP population will be presented in a data listing.

Before unblinding the subject data, and as a part of preparations for the database lock, the study team will review all protocol deviations. 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 (Appendix A), the subject has an out of window study visit, which is considered a type of protocol deviation for this study. Knowing a subjects 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 treatment group, overall, and by visit. Out of window visit durations will be presented by site as well. 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; for the by site analysis, percentages will be calculated using the number of subjects at the respective site as the denominator.

2.3.3 Demographic characteristics

Demographic assessments for this study include:

- Age (years)
- Height (in)
- Weight (lbs.)
- Gender (Male, Female)
- 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)

Subject demographic data will be summarized for the ITT population by treatment group and overall. Age, height, and weight will be analyzed as continuous variables. Gender, race, ethnicity, and FST will be analyzed as categorical variables.

Demographics and baseline characteristics will be presented by subject in a data listing.

2.3.4 Medical History and Prior Cosmetic/Aesthetic Procedures or Implants

All summaries will be done by treatment group and overall based on the ITT 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 ITT 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 based on the QM1114-DP group, 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 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 and/or implant history 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 the subject data listing.

2.3.5 Previous and Concomitant Procedures

All summaries will be done by treatment group and overall based on the ITT 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. Previous procedures/treatments are procedures/treatments with stop dates within 4 weeks prior to screening visit.

Previous and concomitant procedures/treatments will be coded according to MedDRA. Therapies and procedures that started due to a related AE will be summarized separately from those who did not start due to an AE. Previous and concomitant procedures/treatments will also be presented and will follow the same methods specified in Section 2.3.4 for medical history.

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

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

2.3.6 Prior and Concomitant Medications

All summaries will be done by treatment group and overall based on the ITT population. Concomitant medications for this study are defined as any ongoing medications with a start date prior to the date of injection, 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 date of injection. Prior medications are medications with stop dates prior to study treatment and used within 4 weeks preceding screening visit. Medications will be coded using the World Health Organization (WHO) Drug Dictionary. The versions used for the coding will be noted as a footnote in the tables and listings.

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 percentage is defined as the number of subjects who receive prior and concomitant medications divided by the number of subjects in the ITT population times 100. If the 4th level term is not available, the next available level (e.g., ATC-3) will be used. Medications that started due to a related AE will be summarized separately from those who did not start due to an AE.

In addition, the number and percentage of subjects reporting a concomitant medication/therapy will be summarized by reason administered (medical history, adverse event, concomitant procedure, contraception, or other), where percentage is defined as the number of subjects with a specific reason administered divided by the number of subjects who received concomitant medications times 100.

ATC-4 and preferred name will be presented in descending frequency first based on the QM1114-DP group, 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 same preferred name, the subject will be counted only 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 2.1.3.

2.4 Efficacy analysis

2.4.1 Datasets analyzed

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

2.4.2 Handling of missing data

In general, the number of subjects with missing values will be summarized and reported as appropriate in all outputs. The primary analysis will be performed using the result of 'No Change' for any missing Month 1 GAIS assessment as the primary imputation method.

In addition, to further evaluate the impact of missing data on the primary endpoint, additional sensitivity analyses will be performed:

1. The primary analysis will be repeated using multiple imputation (MI) based on the ITT population
2. The primary analysis will be repeated using Observed Cases (OC) based on the ITT population (i.e., no imputation will be done)

The secondary efficacy analyses, exploratory analyses and safety analyses will be performed using OC. If deemed necessary, any analyses may be repeated using OC, 'No Change' imputation, baseline observation carried forward (BOCF), or MI as appropriate. Calculations for the FACE-Q and FLTSQ will follow the methods specified in the manuals for the handling of the data.

Missing data for Month 1 GAIS responses will be imputed using the following steps:

1. The imputation using MI will assume the Missing Completely at Random (MCAR) missing data assumption. Regardless of the actual pattern of missing data, the Markov Chain Monte Carlo (MCMC) method of the MI procedure from the SAS® system will first be used to create a monotonic pattern of missing data. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. The maximum value for imputed variables will be

set to 6, in order to force PROC MI to redraw another value for imputation when an intended imputed value is greater than 6. Imputed values will be rounded to the nearest integer. The seed number to be used will be the number 110196.

2. Then, a second SAS PROC MI procedure will be used for imputing missing values of data with monotone missing pattern. Imputations will be made using the MCMC-imputed dataset from step one (1). A linear regression will be employed to model the missing GAIS scores with the following covariates included in each imputation model: treatment group and all non-missing GAIS scores from earlier scheduled time points, including baseline. The seed number to be used will be the number 110196 and five (5) sets of imputations will be created. The Month 1 GAIS responder variable will be calculated from the imputed GAIS values as detailed in Section 1.3.1.
3. The imputed datasets will be analyzed as specified in Section 2.4.3.
4. The results from the CMH analysis of the multiple imputed datasets will be combined using the Wilson-Hilferty transformation by Ratitch et al. [1] to produce a pooled CMH statistic and p-value. The differences in proportions and standard errors will be combined using the SAS PROC MIANALYZE. The resulting pooled difference and standard error will be used to produce the 95% CI based on the large-sample approximation method for binary data without using continuity correction.

2.4.3 Primary analysis

The primary efficacy endpoint will be a responder rate based on the subject GAIS at maximum frown at Month 1 (described in Section 1.4.1). To evaluate the effectiveness and superiority in aesthetic improvement of QM1114-DP versus placebo in the treatment of moderate to severe GL, the responder rates of QM1114-DP and placebo will be compared using a Cochran-Mantel-Haenszel (CMH) test stratified by site at the 5% significance level (2-sided). The primary efficacy endpoint will be based on the ITT population where missing Month 1 GAIS data will be imputed with 'No Change'.

The null hypothesis of no relationship between treatment and responder rate (i.e., the responder rates are the same in both groups) will be tested against the alternative hypothesis that there is a relationship between treatment and responder rate (i.e., the responder rates are different in the two groups). For a significant result, the two-sided p-value of the comparison of the GAIS responder rate between the QM1114-DP and placebo subjects at Month 1 using the CMH test needs to be smaller than 0.05. For consistency across strata (site), the Breslow-Day test will be used to assess the homogeneity of odds ratios across all sites. If the Breslow-Day test is significant, then the responder rates between the QM1114-DP and Placebo treatment groups will be presented by site.

The estimates of the GAIS responder rates in each treatment group will be presented as well as the difference in responder rates (QM1114-DP responder rate – placebo responder rate). Corresponding 95% CI for the treatment group GAIS responder rates and the difference in responder rates along with the p-value for the difference will also be presented. The normal approximation (Wald) method will be used to calculate both the 95% CI for the individual treatment group GAIS responder rates and the 95% CI for the difference in responder rates. The above responder rates will be presented in figures by visit and treatment group.

2.4.4 Primary Efficacy Estimand

The primary estimand is the treatment difference between QM1114-DP and placebo in 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 GAIS at Month 1, divided by the number of subjects that completed the GAIS at Month 1, in all randomized subjects (ITT population).:

Primary Endpoint	**Estimand**	
Responder rate in aesthetic improvement at Month 1 as assessed by the subject using the GAIS	**Population**: all randomized subjects (ITT population)	
	Endpoint: the number of subjects that select "Improved", "Much Improved", or "Very Much Improved" on the GAIS at Month 1, divided by the number of subjects that completed the GAIS at Month 1	
	Intercurrent Events: 1. Missing Month 1 observation 2. Administered treatment not according to randomization 3. Use of prohibited treatment/procedure in or near the treatment area between 9 months prior to study treatment and Month 1 after study treatment 4. History or presence of eyelid or eyebrow ptosis at Baseline	**Handling of intercurrent events**: 1. Impute using the result of 'No Change' 2. Use observed response 3. Use observed response 4. Use observed response
	Summary measure: treatment difference of QM1114-DP and placebo in proportion of subjects that have at least "Improved" from baseline.	

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.

2.4.4.1 Sensitivity analysis

To account for the impact of protocol deviations on the primary endpoint, sensitivity analyses will be performed. The primary analysis specified in Section 2.4.3 will be repeated using the PP population using OC.

2.4.4.2 Subgroup analysis

Additionally, to evaluate the consistency of the results of the primary analysis across different subgroups of interest, the primary analysis specified above (Section 2.4.3) will be repeated based on the ITT population and using the 'No Change' imputation method, stratifying for each of the following subgroups specified below:

- Gender (Male, Female)

- Baseline Severity score of the ILA at maximum frown (Grade 2 (Moderate), Grade 3 (Severe))
- Prior botulinum toxin use (Botox, Xeomin, Dysport, Jeaveau, Other)
- Fitzpatrick skin type (I-III, IV-VI)

The Breslow-Day test will not be used to assess the homogeneity of odds ratios across subgroup categories. For each subgroup, the responder rates, difference in responder rates between the treatment groups, and the corresponding 95% CI will be presented.

2.4.5 Secondary analysis

The secondary analysis will be based on the ITT population, using OC unless otherwise specified.

2.4.5.1 Secondary Efficacy Estimands

The estimands of the secondary endpoints can be written out in a similar manner as the estimand of the primary endpoint. Secondary endpoints share the following attributes of estimands:

Population: all randomized subjects (ITT population)	
Intercurrent Events: 1. Missing observations for assessments 2. Administered treatment not according to randomization 3. Use of prohibited treatment in or near treatment area between 9 months prior to study treatment and prior to study end 4. History or presence of eyelid or eyebrow ptosis at Baseline	1. Use observed cases, leave response missing. 2. Use observed response. 3. Use observed response. 4. Use observed response.

High-level descriptions of summary measures for the secondary efficacy endpoints are outlined below:

- Time to onset of treatment effect:
  - Endpoint: Onset of effect is defined as the first day a subject answers "yes" to the diary question.
  - Summary measure: descriptive statistics of time-to-event of subject responding "yes" to the diary question for QM1114-DP and placebo.
- GAIS responder rate:
  - Endpoint: Responder rate based on the 7-point GAIS where a responder is defined as a subject who responds at least "Improved" on the GAIS at maximum frown.
  - Summary measure: descriptive statistics of proportion of subjects that have at least "Improved" for QM1114-DP and placebo by visit.

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2.4.5.3 GAIS

The GAIS aesthetic improvement (overall appearance) as determined by the subject at all applicable post-treatment time points will be a responder rate based on the subject GAIS at maximum frown at Month 1 (described in Section 1.3.1). The responder rate will be presented separately by treatment group by visit. The 95% CIs around the estimates will also be provided. The normal approximation (Wald) method will be used to calculate the 95% CIs. The actual GAIS ratings of the subject will also be presented similarly by treatment group and visit. A graph will be provided showing the responder rates over time.

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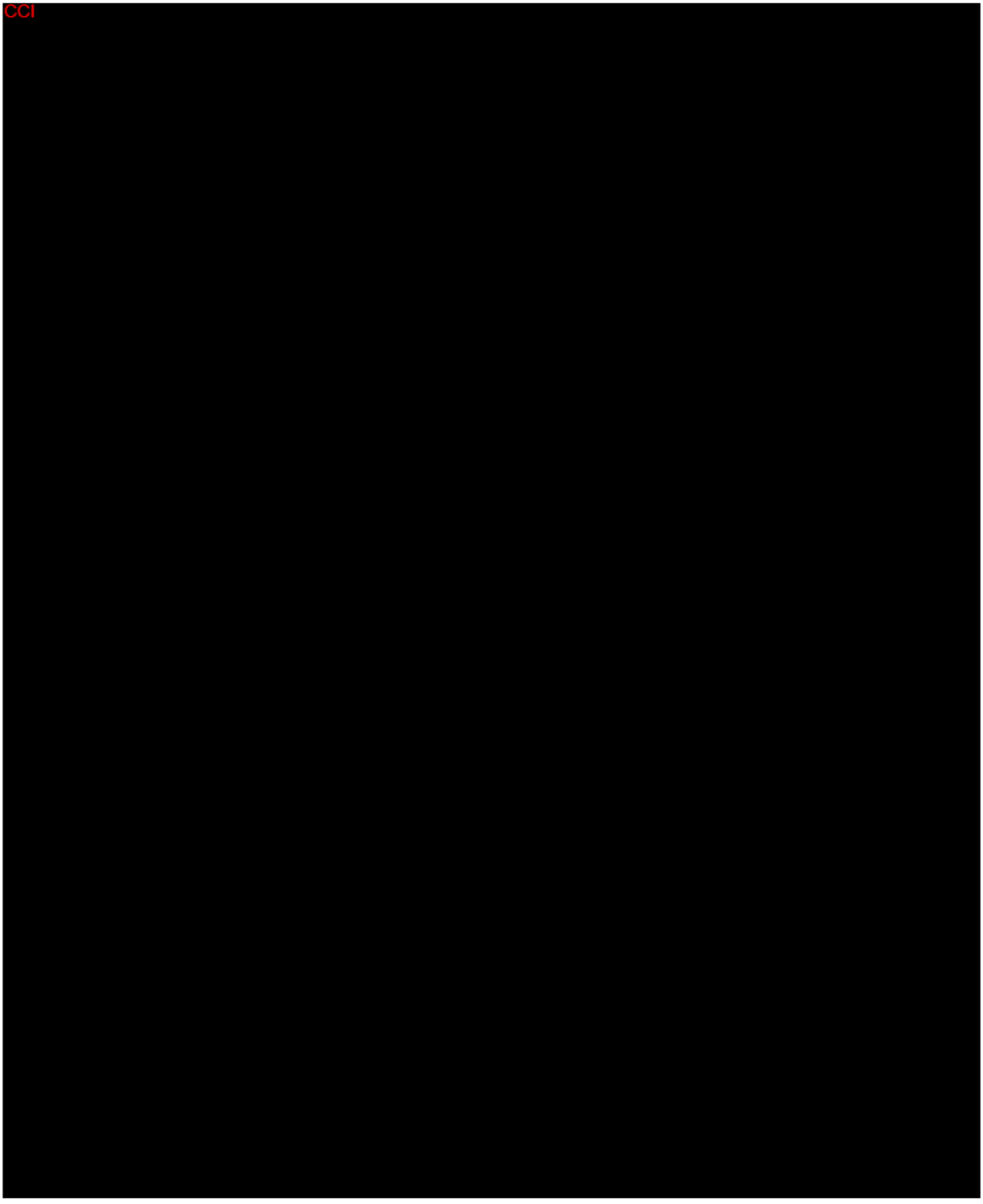

2.5 Safety analysis

All safety data will be summarized descriptively based on the Safety population. All of the safety analyses will be done using OC. If deemed necessary, any analyses may be repeated using OC, BOCF, or MI as appropriate. Safety data will be included in separate data listings.

2.5.1 Extent of exposure

There will only be limited exposure to QM1114-DP since it is administered only at baseline. The number of subjects receiving a single dose of QM1114-DP and placebo, respectively, will be presented. In addition, injection characteristics will be summarized descriptively in a separate table.

2.5.2 Adverse events

All AE data will be summarized by treatment group. Missing dates will be imputed as described below. 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 safety 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 and events with at least one TEAE related to study product or injection procedure and number of events
- number (%) of subjects and events with at least one TEAE not related to study product or injection procedure and number of events
- number (%) of subjects and events with at least one TEAE leading to discontinuation and number of events
- number (%) of subjects and events with at least one serious TEAE and number of events
- number (%) of subjects and events with at least one serious related TEAE and number of events
- number (%) of subjects and events with at least one AE that meets the criteria of remote spread of effect of toxin or hypersensitivity and number of events

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

- All TEAEs by SOC and PT
- Treatment emergent SAE by SOC, PT, maximum intensity (mild, moderate, severe), and causality
- Related TEAEs by SOC and PT, and maximum intensity (mild, moderate, severe)
- Unrelated TEAEs by SOC and PT, and maximum intensity (mild, moderate, severe)
- TEAEs leading to discontinuation by SOC and PT, and maximum intensity (mild, moderate, severe)
- 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 of toxin or hypersensitivity by SOC, PT, and maximum intensity (See Section 2.5.2.2)

The number and percentage of subjects who experienced at least one of the events listed above will be summarized overall and for each SOC and each PT. System organ class and PTs will be presented in descending frequency first (by QM1114-DP group), 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 same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one TEAE for a SOC, the subject will be counted only once in that SOC and PT. For the "action taken" summary specifically, subjects will be only counted in 'None' category if no other action was taken and counted in all 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.

Section 2.1.3 lists the imputation rules for partial/completely missing dates. 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.

2.5.2.1 Subgroup analysis

To evaluate the consistency of the AE data, subgroup analyses will be performed. All TEAEs related to study product or injection procedure by SOC, PT, and maximum intensity will be repeated by the following subgroups. The same methods specified above (Section 2.5.2) will be followed. Percentages will be calculated using the number of subjects in the safety population for each respective sub-category will be used for the denominator.

- Gender (Male, Female)
- Race (White, Black, Asian, Other)
- Fitzpatrick skin type (I-III, IV-VI)
- Site

2.5.2.2 Assessment of remote toxin spread and hypersensitivity

Any potential or suspected remote toxin spread or toxin hypersensitivity event 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.

2.5.3 Anti-drug Antibodies (ADA)

Sampling for antibody testing will be conducted at baseline Day 0, Month 1, and Month 6. The following ADA categories will be determined based on the confirmatory assay results:

- ADA positive at any point in time, baseline or post-baseline.

- ADA positive post-baseline and positive at baseline.
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA).
- ADA not detected post-baseline and positive at baseline.
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) from baseline following drug administration.
- Treatment-emergent ADA positive, defined as either treatment-induced ADA or treatment-boosted ADA.
- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or an ADA positive result at the last available assessment. The category may include subject meeting these criteria who are ADA positive at baseline.
- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The category may include subjects meeting these criteria who are ADA positive at baseline.
- nAb positive at any point in time, baseline or post-baseline.

The number and percentage of subjects who develop detectable ADA within each ADA response category listed above will be summarized by treatment group, including ADA prevalence and ADA incidence (proportion of ADA-positive and treatment-emergent ADA-positive subjects, respectively, in the ADA Evaluable population). The titer values of ADA-positive subjects will be summarized descriptively (using n, min, Q1, median, Q3, max) by treatment group and visit. The kinetics of ADA development will be assessed by summarizing the number and percentage of ADA-positive subjects at each visit by treatment group.

The impact of ADA on safety data (inclusive but not limited to) any AEs, any SAEs, and any adverse events of special interest (AESIs) will be evaluated by summary statistics based on ADA status.

ADA safety tables will be summarized by treatment group and will include: (1) the number of subjects who had at least 1 AE in any category will be summarized by ADA category (ADA positive, ADA negative, treatment-emergent ADA positive, and nAb positive); (2) a summary of subjects with injection site reactions or hypersensitivity events by ADA status will be presented; (3) a data listing of adverse events among subjects who developed anti-drug antibodies.

A line plot of ADA positivity in each treatment group will be presented by visit. A box plot of titer values in each treatment group will be presented by visit.

If there are more than 20 subjects in the QM1114-DP treatment group who are treatment-emergent ADA positive, a summary of the duration and onset of ADA may be generated as well as the impact of ADA on the primary efficacy endpoint.

2.5.4 Physical examinations and vital signs

The number and percentage of subjects with normal/abnormal results in physical examination will be presented by visit and treatment. A shift table will be created to present any change from baseline in normal/abnormal results in physical examination across the study visits for each treatment group.

Vital signs and the changes from baseline will be summarized by treatment and visit using descriptive statistics.

2.5.5 Urine pregnancy test

A data listing will be provided to summarize the results of the urine pregnancy tests.

2.6 Interim Analysis

Not applicable.

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3 Reference List

1. Bohdana Ratitch, et al. "Combining Analysis Results from Multiply Imputed Categorical Data", 2013, PharmaSUG Proceedings, Paper SP-03

2. Medical Dictionary for Regulatory Activities Terminology (MedDRA), Version 25.0, MedDRA MSSO, March 2022.

3. WHO Drug Dictionary, March 2022 – Version B3, Uppsala Monitoring Centre (UMC) Box-1051, SE-751 40 Uppsala, Sweden.

4. 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 Appendix A: Schedule of Assessments

Visit 1 month = 4 weeks All visit windows are calculated from Baseline/Day 0	Visit 1 Screening[1]	Visit 2 Day 0 Baseline[1]	Visit 3 Day 1	Visit 4 Day 2	Visit 5 Day 3	Visit 6 Day 4	Visit 7 Month 1	Visit 8 Month 3	Visit 9 Month 6	Visits 10-14 Months 7-11	Visit 15 Month 12/ EOS/ET[2]
Window	(≤ 2 weeks of Visit 2)						(± 5 days)	(± 5 days)	(± 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[7]									X
Focused Physical Examination[6]	X	X[7]	X	X	X	X	X	X	X	X	X
Vital Signs[8]	X	X[10]	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X[7]									
Photography		X[7]	X	X	X	X	X	X	X	X	X
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Blood sample for serum antibody testing		X[7]					X		X		
Randomization		X[7]									
Treatment		X									
Dispense Subject Diary Card		X									
Collect Subject Diary Card							X				
Adverse Events	X	X[10]	X	X	X	X	X	X	X	X	X
Concomitant Medication/Procedures	X	X[10]	X	X	X	X	X	X	X	X	X
SUBJECT ASSESSMENTS											
CCI											
GAIS			X	X	X	X	X	X	X	X	X
INVESTIGATOR ASSESMENTS											
CCI											

Abbreviations:
EOS = End of Study; ET = Early Termination; CCI GAIS = Global Aesthetic Improvement Scale; CCI

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 severity assessments, focused physical exam, vital signs, and inclusion/exclusion criteria review).
2. If the subject withdraws before the final visit the assessments at Month 12/EOS/ET should be completed, if possible.
3. Includes date of birth, gender, race, ethnicity, height, weight, Fitzpatrick skin type.
4. For previous toxin treatments, capture; brand, area(s) treated, and date(s) on the previous medications/procedures form.
5. Females of childbearing potential.
6. 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.
7. Performed pre-treatment.
8. Vital signs include blood pressure, heart rate and respiratory rate. Vital signs are taken seated, after approximately 10 min rest.
9. Only at select sites.
10. Performed pre- and post-treatment.
11. Subject will make his/her assessment independently of the investigator's assessment.
12. Performed at month 9 only
13. Part 1 to be completed post-treatment at baseline (Visit 2) and Part 2 to be completed at Month 1 (Visit 7).

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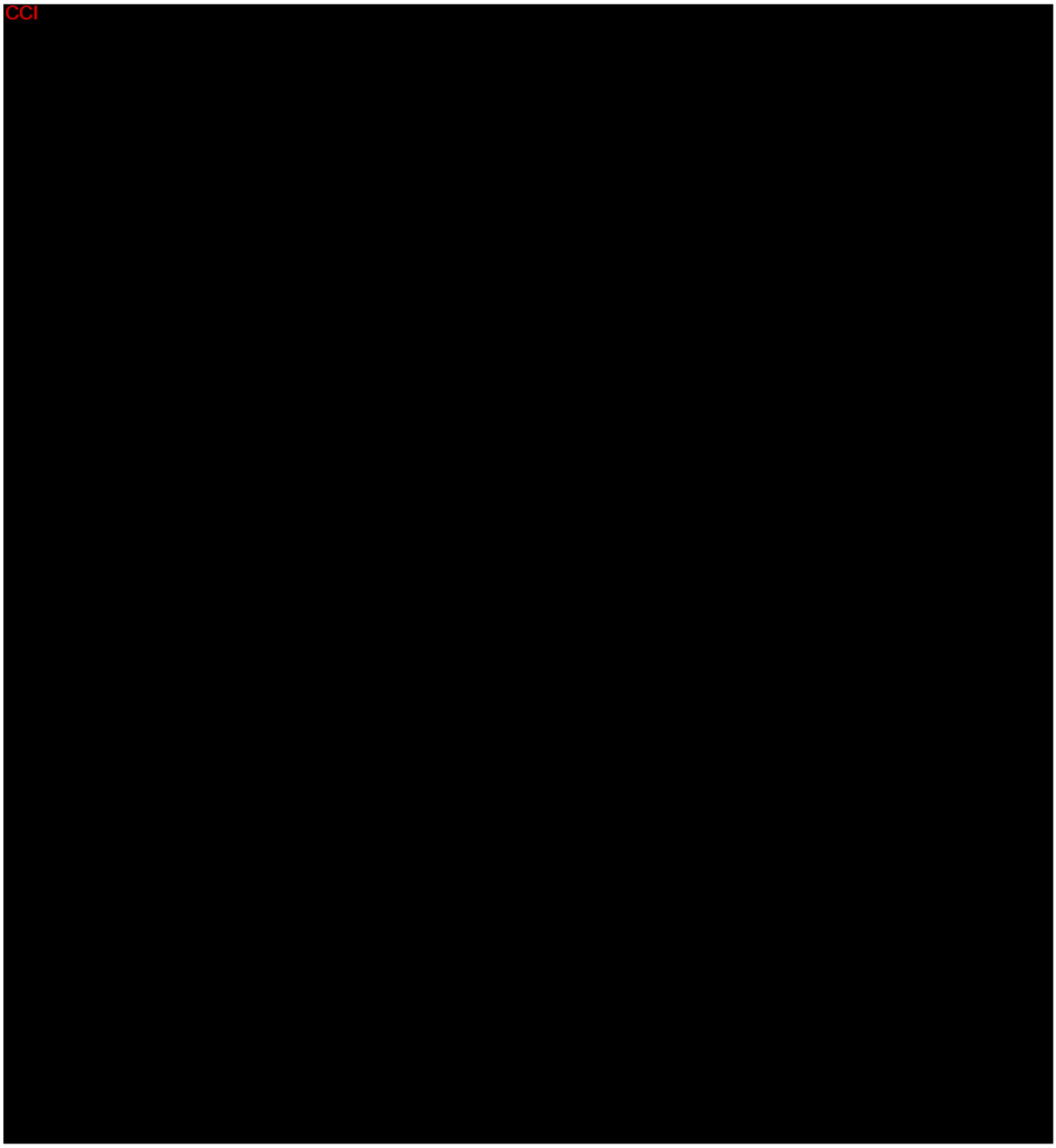

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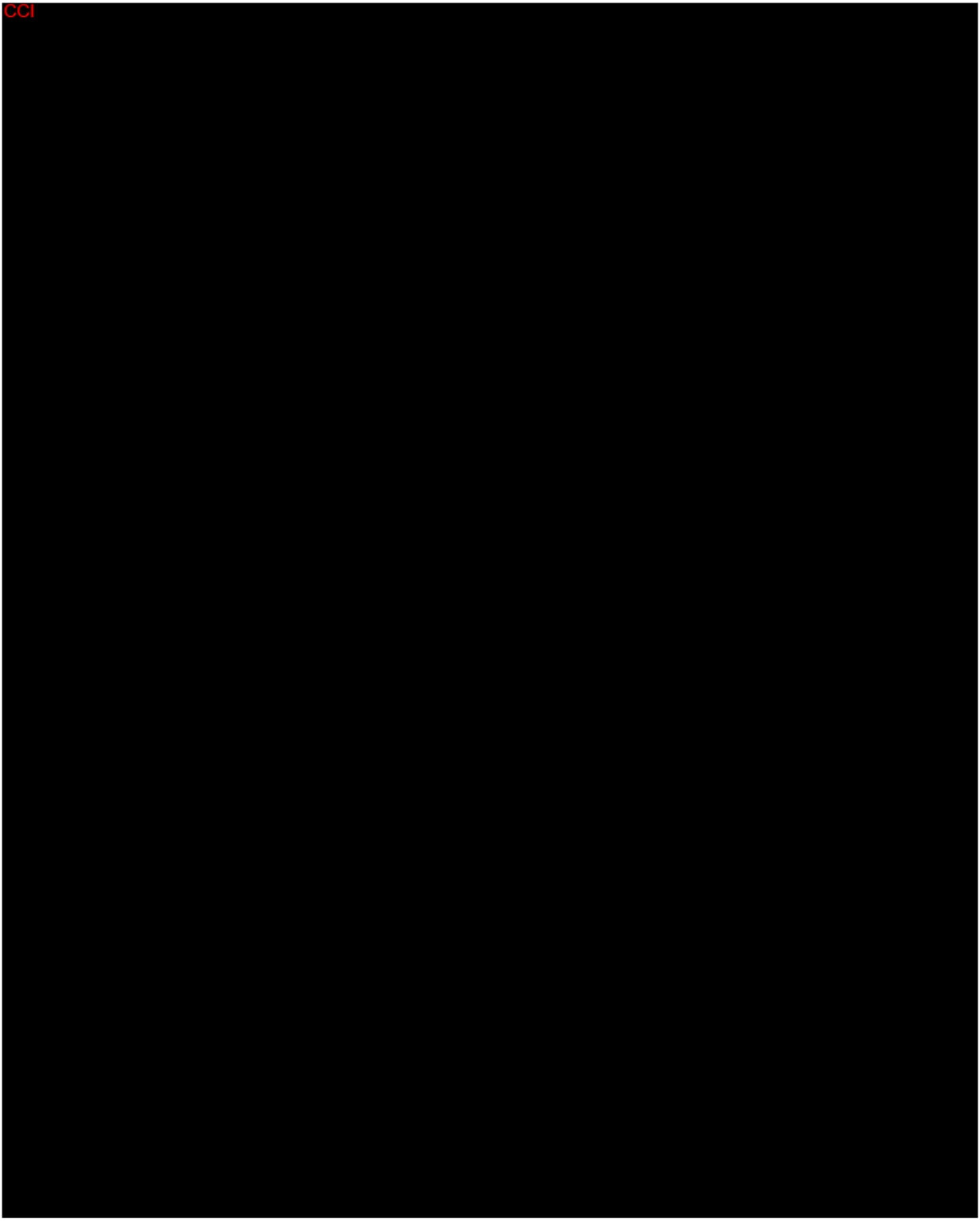

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