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Statistical Analysis Plan

Clinical Trial Number: 43QM1903

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1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the efficacy and safety summaries and analyses that will be performed for Clinical Trial Number (CTN) 43QM1903, *A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)* and is based on the study protocol Version 5.0 dated 26AUG2020.

1.1.1 Study design

This is a phase 3, multicenter, open-label study to evaluate the safety of QM1114-DP for the long-term treatment of moderate to severe GL and LCL. Eligible subjects will receive up to 4 treatments of QM1114-DP in the glabellar lines (GL) and/or lateral canthal lines (LCL) region and will be monitored for safety and efficacy over a period of up to 52 weeks.

Following treatment at baseline, re-treatments can be administered at any of the follow-up visits from Week 12 to Week 40, provided that the subject is eligible for retreatment and there has been at least 12 weeks since the last treatment. All subjects will be followed for at least 24 weeks and at least 300 subjects will be followed up to 52 weeks. The study may be stopped when at least 300 subjects have completed the Week 52 study visit.

1.1.2 Number of subjects and randomization

As a screen failure rate of approximately 10 percent is anticipated, approximately 990 subjects will be screened in order to get 900 subjects enrolled. It is expected that each center will recruit a similar number of subjects.

As the study is open-label, there is no randomization or blinding.

1.2 Study objectives

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

1.2.1 Primary objective

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

1.2.2 Secondary objectives

The secondary objectives of the study are:

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

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1.3 Efficacy assessments

For all assessments, overall study 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:

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

For each treatment cycle *X* (defined in Section 2.1.2), cycle X baseline will be defined as the observation that is closest to but prior to the additional treatment location study injection. Likewise, in general, change from cycle baseline (Δ_c) will be calculated as the value at a given time point, *Y*, minus the cycle X baseline value:

$$\Delta_c = Y\ Value - Cycle\ X\ Baseline\ Value$$

1.3.1 Validated 4-point Photographic Scale of Glabellar Line Severity: Investigator Live Assessment (GL-ILA)

The GL-ILA is a 4-point validated scale for assessment of glabellar lines (Appendix A). The validated 4-point Photographic Scale of Glabellar Line Severity includes two grading systems: one for investigator live assessments at maximum frown, and one for investigator live assessments at rest. The scale represents the severity of GL from none (grade 0), mild (grade 1), moderate (grade 2) to severe GL (grade 3) as shown in

Multiple responder indicators will need to be created as follows:

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Table 1. The static 4-point categorical scale.

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

The Investigators will use the GL-ILA for direct, live comparison with the subject's face at rest and at maximum frown. The Investigator will perform the GL-ILA at:

- Screening/Baseline (prior to treatment) visit(s)
- all post-baseline visits.

Multiple responder indicators will need to be created as follows:

- Subjects that achieve a score of 0 or 1 at maximum frown score. If at each respective post-baseline visit, the GL-ILA at maximum frown score is 'None' or 'Mild', the subject will be considered a responder for that visit.

- Subjects that achieved at least 1 grade improvement from baseline at rest. If at each respective post-baseline visit, the GL-ILA at rest change from baseline score is at least -1, the subject will be considered a responder for that visit.

1.3.3 Validated 4-point Photographic Scale of Lateral Canthal Line Severity: Investigator Live Assessment (LCL-ILA)

The LCL-ILA is a 4-point validated scale for assessment of lateral canthal lines (Appendix B). The validated 4-point Photographic Scale of Lateral Canthal Line Severity includes two grading systems: one for investigator live assessments at maximum smile, and one for investigator live assessments at relaxed position. The scale represents the severity of LCL from none (grade 0), mild (grade 1), moderate (grade 2) to severe GL (grade 3). Each grade is also depicted by an individual photograph and descriptive text.

The Investigators will use the LCL-ILA for direct, live comparison with the subject's face at rest and at maximum smile. The Investigator will perform the LCL-ILA at:

- Screening/Baseline (prior to treatment) visit(s)
- all post-baseline visits.

Multiple responder indicators will need to be created as follows:

- Subjects that achieve a score of 0 or 1 at maximum smile, for both left and right LCL concurrently. If at each respective post-baseline visit, the LCL-ILA at maximum smile score is 'None' or 'Mild' for both the left and right-side assessments concurrently, the subject will be considered a responder for that visit.
- Subjects that achieved at least 1 grade improvement from baseline at relaxed position, for both left and right LCL concurrently. If at each respective post-baseline visit, the LCL-ILA

at relaxed position change from baseline score is at least -1 for both left and right-side assessments concurrently, the subject will be considered a responder for that visit.

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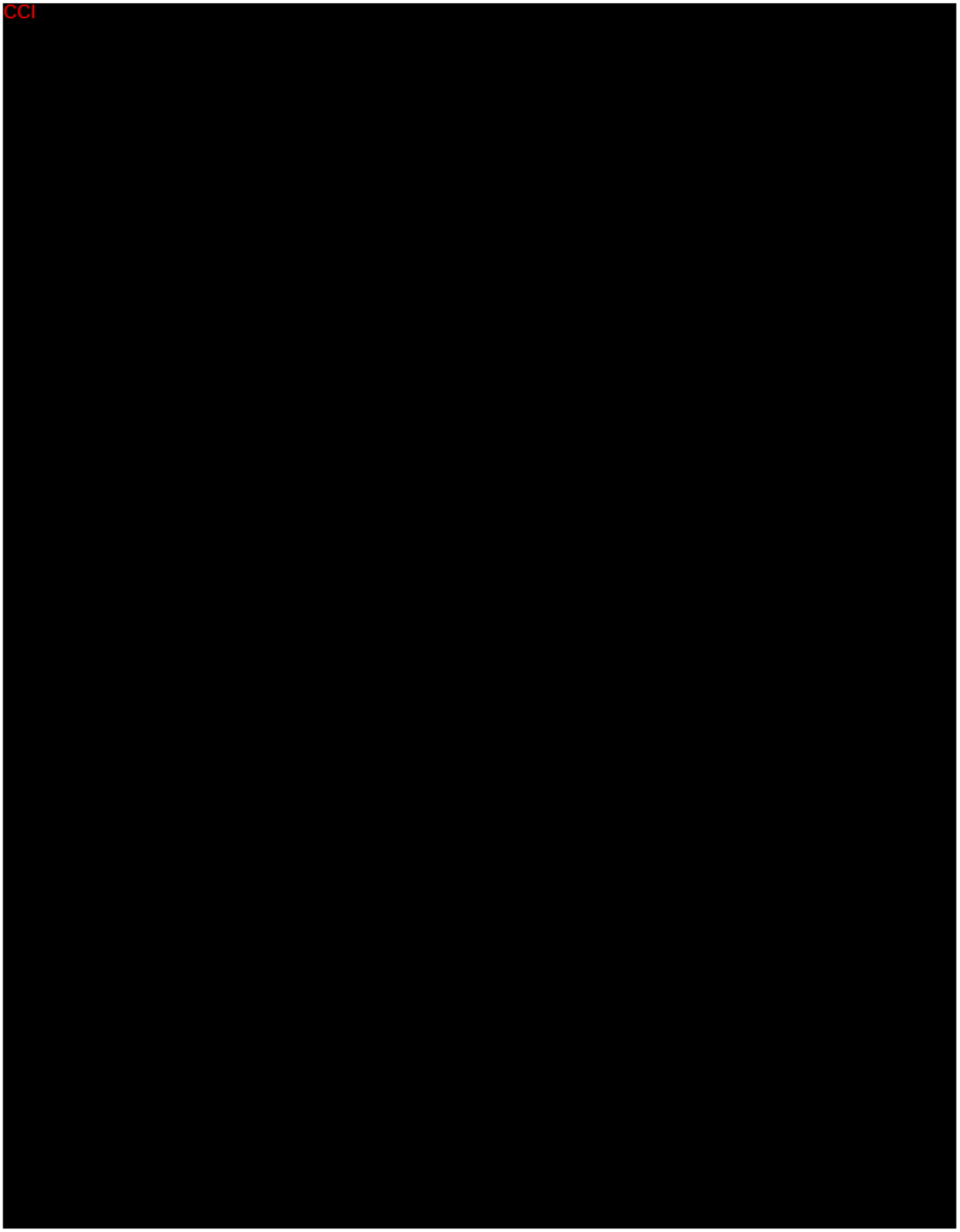

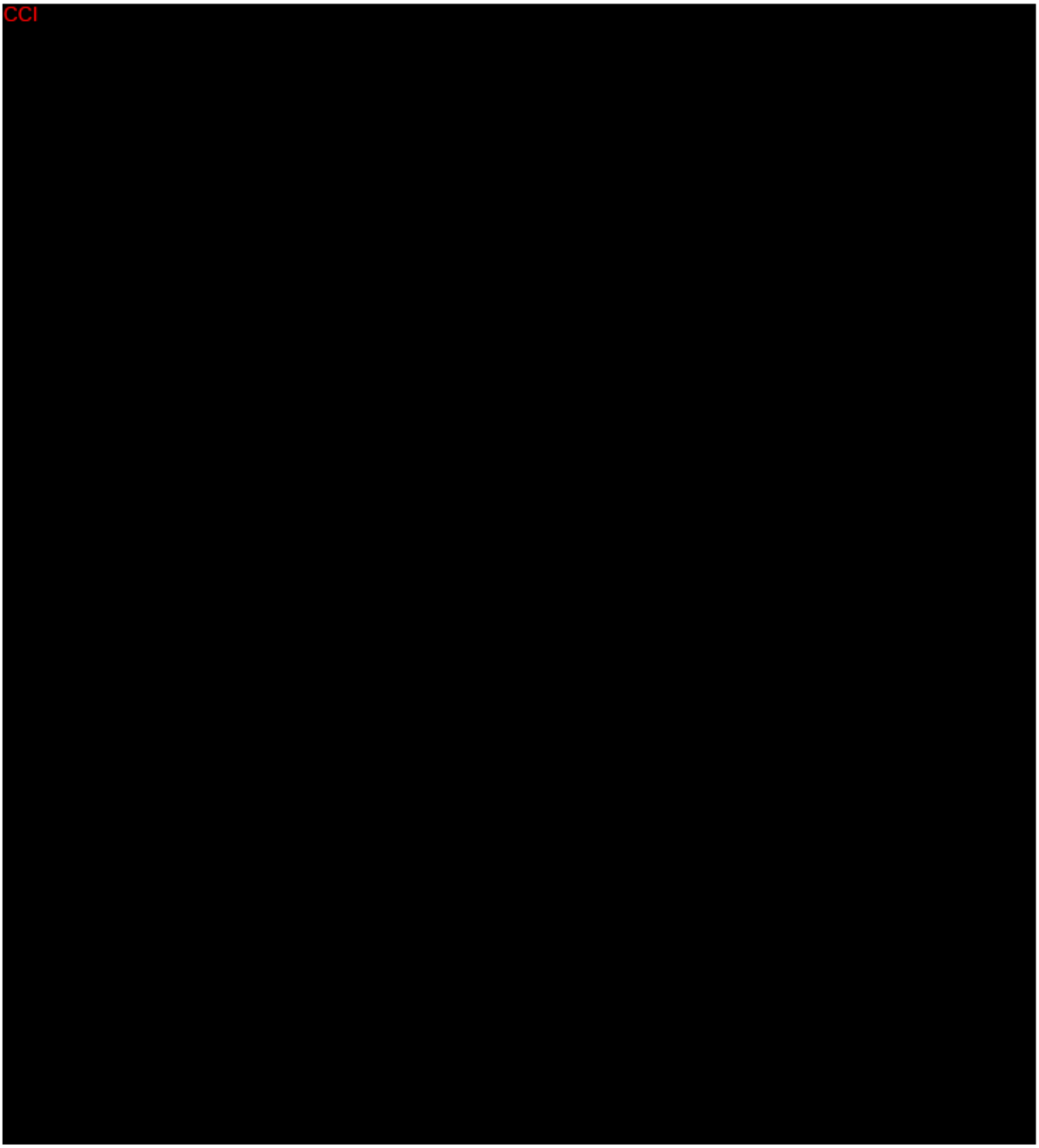

1.4 Efficacy endpoints

Efficacy endpoints for the study include:

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

ii. Percentage of subjects who achieve grade/level 0 or 1 at each visit in each treatment cycle, for both left and right sides, using the LCL-ILA 4-point Photographic Scale at maximum smile

iii. CCI

iv.

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

vi. Percentage of subjects who achieve ≥1 grade/level improvement from baseline at each visit in each treatment cycle, for both left and right sides, using the LCL-ILA 4-point Photographic Scale at relaxed position

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1.5 Safety assessments

Safety assessments will be conducted for all subjects at the time points indicated in Schedule of Assessments (Appendix E). Safety parameters include an evaluation of AEs, focused physical

examination (FPE), vital signs, laboratory safety tests (chemistry and hematology), and neutralizing antibody production.

1.5.1 Focused physical examination

Physical examination will be done at screening/baseline (before treatment), Day 7, Day 14, Weeks 12 – 40 (only if subject received a re-treatment injection) and Week 52. Normal and abnormal findings regarding potential remote/local spread of toxin or hypersensitivity will be assessed.

1.5.2 Vital signs

Vital signs (systolic/diastolic blood pressure, heart rate, and respiratory rate) will be assessed from baseline (before and after treatment), and at every post-baseline visit. Vital signs endpoints include:

- Values collected at each visit
- Changes from baseline

1.5.3 Laboratory safety tests

Hematology and blood chemistry laboratory tests will be performed at baseline (before treatment) and Week 52. Laboratory safety test endpoints include:

- Values collected at each visit
- Changes from baseline

1.5.4 Neutralizing antibody testing

Blood samples will be taken for measurement of serum neutralizing antibody testing against QM1114-DP at baseline (before treatment), before any re-treatment, 4 weeks after re-treatment, and at Week 52. 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.

1.5.5 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 in force at the time of database freeze) 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 first 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 forms (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 with a 'Yes', the AE will be considered related.

1.6 Safety endpoints

There are two primary safety endpoints for this study:

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

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 using the SAS® system. Confidence intervals (CI) will be 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.

All efficacy, safety and baseline characteristics variables will be presented using descriptive statistics and graphs as appropriate. Continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables will be presented in frequency tables with number and percent of observations for each level. Missing counts for all variables will be presented for informational purposes only and will not be included in percentage calculations.

Study days will be calculated relative to the first injection of study drug. Day 0 will be the first day of study drug administration in the study. Baseline will be the last assessment prior to the first injection of study drug unless otherwise indicated. The Screening Visit 1 (Day -14 to Day 0) will be considered the visit prior to first 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, and concomitant treatments/procedures will be coded using MedDRA, Version 23.0 or higher. Prior/concomitant medications and procedural anesthetics will be coded using the World Health Organization (WHO) Drug Dictionary Global, 1 Sep 2019 B3 or higher.

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

2.1.1 Visit windows

Study visits are expected to occur according to the protocol schedule in Appendix E. To accurately determine which treatment cycle (defined below in Section 2.1.2) study assessments were conducted under, study visits will undergo re-labeling in the tables, listings, and figures. Instead of the evaluation visit as recorded on the eCRF, visits will be re-labeled in relation to treatment cycle and days after treatment. For example, 'Visit 3 (Week 4)' will be relabeled as 'Cycle 1, Week 4 after Treatment'; 'Visit 5 (Week 12)' could be 'Cycle 1, Week 12 after Treatment' or 'Cycle 2 Baseline', dependent on if a subject was treated at that visit. In data listings, the relative study day (in relation to date of first 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.

2.1.2 Treatment Cycles

Throughout the study, subjects may receive up to four treatments of QM1114-DP in their GL and/or LCL, for a total of up to eight injections (four in LCL region and four in GL region). To better evaluate the safety and efficacy of repeat injections of QM1114-DP in the different treatment areas, safety and efficacy analyses will use one of three separate cycle types: any GL treatment cycle, any LCL treatment cycle, and overall treatment cycle (not location based). Treatment cycles will be determined using the subject's GL and LCL injection dates. Safety analyses will be summarized

using the non-location based overall treatment cycle. Efficacy analyses will be summarized by the location-based cycles of any GL treatment and any LCL treatment, regardless of whether the treatment was given alone or in combination with the other location. A cycle will be a minimum of 12 weeks in duration but may be longer depending on the time of the next treatment and the subject's overall course of treatment throughout the study. All efficacy and safety analyses will be done using the treatment cycle framework.

Safety Analyses

The overall treatment cycle will be used for the safety analyses. Since all subjects are injected in both their GL and LCL regions at baseline, each subject will be included, at minimum, in treatment cycle 1; depending on a subject's course of treatment a subject can have a maximum of seven total treatment cycles. Overall treatment cycle 2, and any other subsequent treatment cycles, will only occur if a subject receives additional injections starting at Visit 5 through Visit 12.

- Overall Cycle 1: the time between the baseline visit up until a subject receives a post-baseline injection, regardless of treatment location (alone or in combination at the same visit).
- Overall Cycle 2 - 7: The time between the post-baseline visit injection, regardless of treatment location, up until the next subsequent visit a subject receives another injection, or end of study if a subject does not receive additional injections.

For example, a subject is injected at: Day 0 (GL and LCL), Visit 5 (LCL only), Visit 6 (GL only), Visit 8 (LCL only), Visit 9 (GL only) and Visit 12 (LCL only).

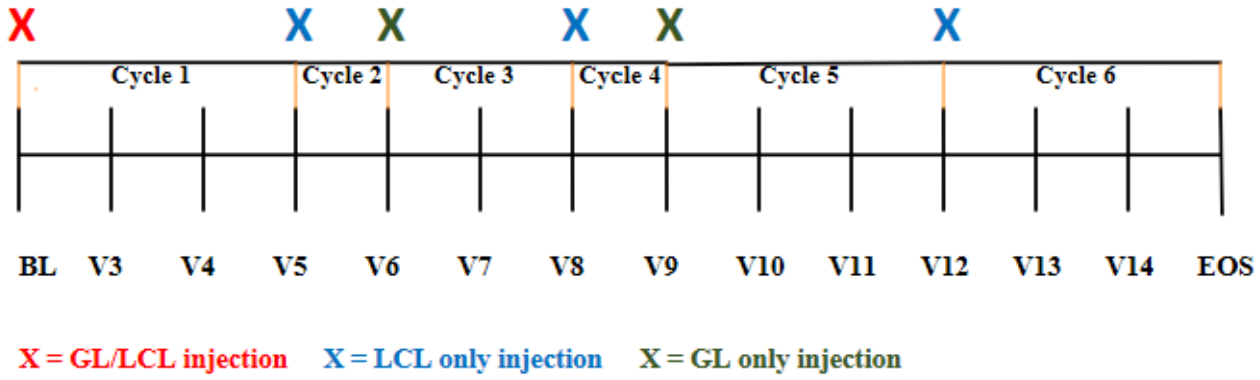

Figure 1. Example Safety Treatment Cycles

Note this subject received treatment injections at six different visits, regardless of treatment location, so the subject would have a total of, or overall, six treatment cycles.

Efficacy Analyses

Separate treatment cycles for GL treatments and LCL treatments will be used for the efficacy analyses as the GL and LCL regions are assessed separately on all efficacy scales/questionnaires. Since all subjects are injected in both their GL and LCL regions at baseline, each subject will be included, at minimum, in any GL treatment cycle 1 and any LCL treatment cycle 1; depending on the course of treatment, a subject can have a maximum of eight cycles (up to four in any GL treatment cycles, up to four in any LCL treatment cycles).

- Any GL treatment cycle: If a GL injection was administered at a study visit, it will be considered a GL injection and counted as part of the GL treatment cycle, even if an LCL injection occurred on the same visit.
- Any LCL treatment cycle: If an LCL injection was administered at a study visit, it will be considered an LCL injection and counted as part of the LCL treatment cycle, even if a GL injection occurred on the same visit.

Using the example subject above, the efficacy treatment cycles would look like the below:

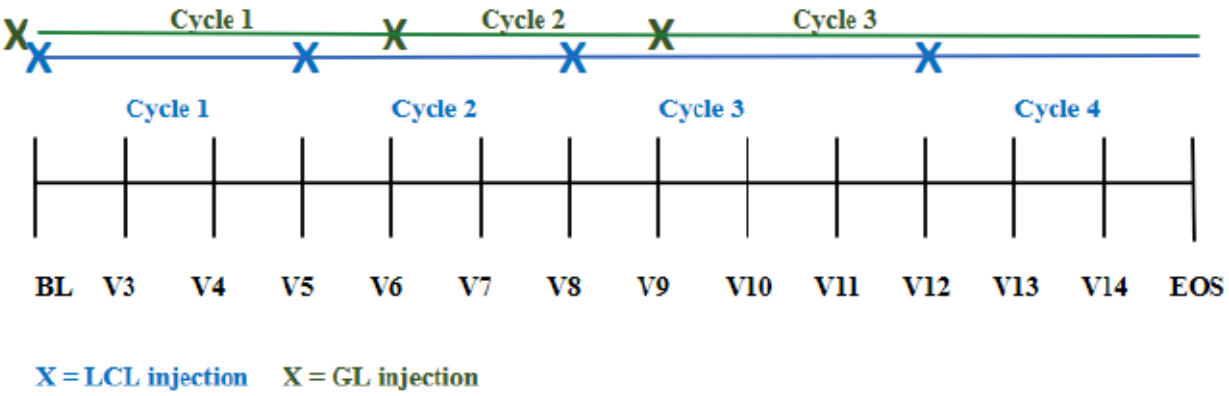

Figure 2. Example of Efficacy Treatment Cycles

Note this subject still received treatment injections at six different visits.

A treatment cycle includes the day of treatment injection and all assessments conducted until the start of the next same-treatment cycle, or end of study if a second same-treatment cycle never occurs (i.e. Any GL treatment cycle 1 includes Day 0 until the day any GL treatment cycle 2 occurs, or end of study if a subject never receives a second GL injection). Since all efficacy assessments conducted on the day of re-treatment are conducted prior to the re-treatment injection (Appendix E), these efficacy assessments will be counted as the last visit from the previous cycle.

2.2 Analysis Populations

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

- Safety population - The safety population includes all subjects who were administered the study product at least once.
- Full Analysis Set (FAS) – The FAS population includes all subjects who were administered the study product at least once and who have at least one post-baseline efficacy measurement.

2.3 Study subjects

2.3.1 Subject disposition

The disposition of subjects will be presented in total, including numbers of subjects that were:

- Screened, including screen failures
- Enrolled

- Study Completers
- Early withdrawals/discontinuations
- Safety population
- FAS population

Specifically, the number and percentage of subjects in each of the specified categories above will be presented. The discontinuation reason as specified on the eCRFs will also be summarized by number and percent.

As stated in Section 1.1.1, the study may be stopped early. If the study is stopped early, all currently enrolled subjects, regardless of which study visit they were at, will be considered study completers. Since subjects may have completed the study at various visits, the number of study completers will be further broken down into the following categories based on number of weeks on study: completed 52 weeks, completed 48 weeks, and completed 44 weeks. Number of weeks on study will be derived as:

$$Weeks\ on\ Study = \frac{Date\ of\ Last\ Visit - Date\ of\ Enrollment}{7}$$

These categories will be mutually exclusive (i.e. subjects who completed 52 weeks are not also counted in the 48-week and 44-week categories).

All withdrawn/discontinued subjects and inclusion/exclusion data will be presented by subject in data listings.

2.3.2 Protocol deviations

A protocol deviation occurs when a subject deviates from the protocol procedures. Since the main objective of this study is to evaluate long-term safety, subjects with any kind of protocol deviation will not be excluded from any analysis; a per-protocol analysis population will not be created.

Handling of Protocol Deviations During COVID-19

Due to the public health emergency related to the COVID-19 pandemic during 2020, steps have been taken to ensure patient and practitioner safety in alignment with FDA Guidance dated May 11, 2020 (Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency). Most notably, in partnership with clinical sites and the Institutional Review Board (IRB), optional remote assessment procedures for efficacy and safety endpoints have been implemented to ensure safety and respect localized and elective restrictions.

Protocol deviations will be presented descriptively. The total number of deviations, the type of protocol deviation, and if the deviation was reportable to the IRB will be summarized. These summaries will be stratified by relatedness to COVID-19 (related, not related). The above summary of protocol deviations will be further repeated by site as well.

A listing of all protocol deviations reported throughout the study, including their relatedness to COVID-19, will be provided.

2.3.3 Demographic characteristics

Demographic assessments for this study include:

- Age (years)
- Height (in)
- Weight (lbs.)
- BMI (kg/m^2)

- 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)
- FST score (I, II, III, IV, V, VI)
- Prior use of botulinum toxin (Naïve, Non-Naïve)

The demographic and baseline characteristic analyses will be presented overall and will be based on the safety population using the appropriate descriptive statistics for continuous and categorical variables. Age, height, weight and BMI will be analyzed as continuous variables. Gender, race, ethnicity, FST score and prior botulinum toxin status will be analyzed as categorical variables.

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

2.3.4 Medical surgical history

All summaries will be done based on the safety population. History of relevant or clinically significant surgical events and medical conditions, including any prior dermatological/cosmetic 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 percent 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 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 information and prior cosmetic/aesthetic procedures or implants will be presented by subject in a data listing.

2.3.5 Concomitant medication/procedures

All summaries will be done based on the Safety Population. Concomitant medications/therapies/procedures for this study are defined as any ongoing medications/therapies/procedures at the time of the first study injection, any changes to existing medications/therapies (such as dose or formulation) during the course of the study, or any new medications/therapies received by the subject since the date of first study injection. Concomitant medications/therapies will be coded using the World Health Organization (WHO) Drug Dictionary; concomitant procedures will be coded according to MedDRA. The versions used for the coding will be noted as a footnote in the tables and listings.

The number and percentage of subjects reporting prior and concomitant medications/therapies will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and the preferred name. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. In addition, the number and percentage of subjects reporting a concomitant medication/therapy will be summarized by reason. Concomitant medications/procedures that started due to an AE will be summarized separately.

ATC-3 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 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-3 level, the subject will be counted only once in that ATC-3 level and preferred name.

Concomitant procedures will also be presented, and will follow the same methods specified for medical history (Section 2.3.4).

Prior and concomitant medications/procedures will be presented by subject in a data listing.

2.4 Safety analysis

2.4.1 Datasets analyzed

All safety data will be summarized descriptively based on the safety population.

2.4.2 Handling of missing data

In general, number of missing values will be summarized and reported as appropriate. While every effort will be made to obtain full, complete information on every reported AE, the following imputation rules will be followed for any respective missing AE data:

For the purpose of calculating onset time, duration, and treatment cycle (defined in Section 2.1.2) the following date imputation rules will used. Dates will be presented as is in the listings.

- Start Date
  - If start date is completely missing, it will be assumed that the AE started at baseline.
  - If the start date is missing the day, the first of the month will be used (i.e. UNK-JAN-2019 becomes 01-JAN-2019), provided the imputed date is on or after the subject's date of first injection of study drug (Day 0); otherwise, the day of first injection of study drug will be used.
  - If the start date is missing the month, the month of 'June' will be used (i.e. 01-UNK-2019 becomes 01-JUN-2019), provided the imputed date is on or after the subject's date of first injection of study drug; otherwise, the subsequent month after first injection of study drug will be used.
  - If the start date is missing the year, the year of first injection of study drug will be used (i.e. 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is on or after the subject's date of first injection of study drug; otherwise, the subsequent year after first injection of study drug will be used.
- End Date
  - If end date is completely missing, it will be assumed that the AE is still ongoing and will not be imputed.
  - If the end date is missing the day, the last of the month will be used (i.e. UNK-JAN-2019 becomes 31-JAN-2019)
  - 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 first injection of study drug will be used (i.e. 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used. For the purpose of determining a medication as prior or concomitant (defined in Section 2.3.5), the following date imputation rules will used. Dates will be presented as is 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-2019 becomes 01-JAN-2019), 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-2019 becomes 01-JUN-2019), 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-2019), 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-2019 becomes 31-JAN-2019).
  - 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-2019), provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.

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No imputation of any other missing data will be performed.

2.4.3 Primary analysis

All safety variables will be summarized descriptively based on the safety population.

2.4.3.1 Incidence and severity of TEAEs

All TEAE data will be summarized both for the whole study period and by overall treatment cycle separately (defined in Section 2.1.2). Missing dates will be imputed as described in Section 2.4.2. 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.

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 or injection procedure
- number (%) of subjects with at least one TEAE not related to study product or injection procedure

- number (%) of subjects with at least one TEAE leading to discontinuation
- number (%) of subjects with at least one serious TEAE.

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 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)
- Related TEAEs by action taken (none, medical treatment, non-pharmacological treatment, subject withdrawn)
- Duration of related TEAEs by SOC and PT
- Time to onset of related TEAEs by SOC and PT
- Time since first injection of related TEAEs by SOC and PT

For the subject level analyses, 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, 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 event level analyses, the counts of each respective event will be presented. In general, percentages will be calculated using the number of subjects in the safety population will be used for the denominator. For the subgroup analyses (described in Section 2.4.3.1.1) percentages will be calculated using the number of subjects in the safety population for each respective sub-category will be used for the denominator.

For the "action taken" summary specifically, subjects will be only counted in 'None' category if no other action was taken. The onset/duration 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 date of the most recent injection. Duration will be calculated as the last day with the AE *minus* the first day with the AE *plus* one. Section 2.4.2 lists the imputation rules for partial/completely missing dates. 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.

Time since first injection will be calculated as the first day with the AE *minus* the date of the baseline (Day 0) injection, and will be summarized using the following categories: 0-3 months, >3-6 months, >6-9 months, and >9-12 months. Within each time period, subjects will be counted only once for each SOC and PT; however, subjects could be counted across multiple time periods for the same SOC and PT if a subject experiences a new TEAE of the same SOC and PT at different time

periods (i.e. a subject with a headache during 0-3 months and another headache during >6-9 months would be counted in both time periods).

2.4.3.1.1 Subgroup Analysis

To evaluate the consistency of the results of the primary analysis, for the related TEAEs only, the number of events, and number and percentage of subjects will be presented by SOC and PT and maximum intensity for the following subgroups specified below:

- Gender (Male, Female)
- Prior botulinum toxin use (Naïve, Non-Naive)
- Fitzpatrick skin type (I-III, IV-VI)
- Treatment area (LCL, GL)
- Site
- Age grouping 1 (< 65 years, ≥ 65 years)
- Age grouping 2 (median split)
- Race (White, All Other Races)
- Ethnicity (Hispanic, Not Hispanic)
- Baseline Severity (Moderate, Severe)
    - For the Overall summaries: the more severe grade/level on the Baseline GL-ILA at Maximum Frown or LCL-ILA at Maximum Smile will be used

2.4.3.1.2 Assessment of local/remote toxin spread and hypersensitivity

Any potential or suspected toxin spread, or toxin hypersensitivity events will be evaluated separately. The same methods specified in Section 2.4.3.1 will be followed. Suspected toxin spread events and suspected hypersensitivity events will be summarized in separate tables. The investigator will conduct the investigation and evaluate if an AE is also a suspected toxin spread or hypersensitivity event; however, Appendix 6 in the CSP lists AEs potentially suggestive of spread of toxin.

2.4.3.2 Physical examination findings

The number and percentage of subjects with normal/abnormal results in physical examination will be presented by visit and each treatment cycle (defined in Section 2.1.2) separately. A shift table will be created to present any change from baseline in normal/abnormal results in physical examination across the study visits and by each treatment cycle separately. Abnormal findings will be listed by subject and will include the visit, treatment cycle, and description of the abnormality.

2.4.4 Extent of exposure

The number of subjects receiving QM1114-DP in the GL and LCL, number of each treatment cycle (Any GL, Any LCL, Overall), and how many treatments were given in combination at the same visit will be summarized. In addition, the number of GL and LCL treatments administered at each visit, and how many were in combination, will also be presented.

Injection Characteristics

Injection characteristics include, for each injection administered, injection administration and procedural anesthetics used. The following parameters will be summarized descriptively:

- Needle size used (30G, 31G, 32G, 33G, Other)

- Injection done per protocol (Yes, No)
- LCL injection option (Option 1, Option 2; where applicable)

The following parameters will be summarized for each treatment cycle:

- Procedural anesthetics (No, Yes)
- Type of Anesthetics (Topical, Local Injection)

To ensure adequate amount of safety follow-up is achieved for the study (specified in Section 1.1.1) subjects' time on study will be calculated and presented. Time on study, in weeks, will be calculated as follows:

$$Time\ on\ study\ (weeks) = \frac{(End\ of\ Study\ Date - Signed\ Informed\ Consent\ Date) + 1}{7}$$

Where *End of Study Date* is the completed Visit 15 (Week 52) date for subjects that complete the study, and the study withdrawal date for subjects that terminate early from the study, for any reason.

Time on study throughout the entire study period will be summarized descriptively using summary statistics. The number and percentage of subjects that were on study for 52 weeks and at least 24 weeks will also be presented.

2.4.5 Adverse events

See Section 2.4.3.1

2.4.6 Vital signs

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

2.4.7 Laboratory assessments

The laboratory data (hematology and clinical chemistry) and the changes from baseline to Week 52 will be summarized by descriptive statistics. Throughout the study it is possible that certain laboratory parameter results are below the limit of quantification (BLQ). Laboratory results that are BLQ will be imputed, for table summaries only, by multiplying the lower limit by 50%:

$$Imputed\ Lab\ Value = 0.5 * X$$

Where X is the lower limit of a given laboratory parameter. However, the value will be presented as is (i.e. "< x.x") in the data listings.

All clinically significant out-of-range laboratory values for blood samples collected at baseline will be recorded in the subject's medical history and all clinically significant out of range laboratory values for blood samples collected after baseline are to be reported as an AE if this abnormality was not present at the baseline visit or is assessed as having worsened since the baseline visit.

All laboratory data will be presented in data listings.

2.4.8 Neutralizing antibody testing

Sampling for antibody testing will be conducted at baseline Day 0 and Week 52. Due to the timing and availability of the antibody testing results, data will be presented in a separate report.

2.4.9 Urine pregnancy test

A data listing will be provided to summarize the results of the urine pregnancy tests. All pregnancy SAEs will be flagged within the data listing.

2.5 Efficacy Analysis

All efficacy variables will be summarized descriptively based on the FAS population.

2.5.1.1 Analyses of GL-ILA, CCI , LCL-ILA, CCI responder rates

To evaluate the efficacy of repeated injections of QM1114-DP for the treatment of moderate to severe GL and LCL, the various GL-ILA, CCI , LCL-ILA, CCI responders will be presented in frequency tables. The respective responder rates (specified in Section 1.4.2) will be calculated and presented by each treatment cycle and visit. Corresponding 95% CI for the various responder rates will also be presented. The Clopper-Pearson (Exact) method will be used to calculate the CIs. The actual scores/levels will also be presented similarly by each treatment cycle and visit.

Results will include tables and graphs showing the responder rates over time.

CCI

2.6 Interim Analysis

There are no interim analyses planned for this study.

2.7 Determination of Sample Size

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

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

2.8 Changes in the Analysis Planned in the Protocol

The table below outlines all rationale and changes in the analyses specified in the SAP that differ from the analyses specified in the protocol.

Table 4. Changes in Analysis Planned in the Protocol

CSP Section	SAP section	Description/Rationale of Change

3 Reference List

4 Appendix A GL-ILA Scales

At Rest

Maximum Frown

5 Appendix B LCL-ILA Scales

Relaxed

Dynamic

CCI

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GALDERMA	Title 43QM1903 Statistical analysis plan - LTS	Doc id MA-42529

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[redacted]

8 Appendix E Schedule of Events

Follow-up visit (every 4th week) windows are calculated from Baseline/Day 0. Post-treatment visits (Day 7 and Day 14) windows are calculated from date of current treatment cycle.	Visit 1[1]	Visit 2[1]	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5-12	Visit 5a-12a	Visit 5b-12b	Visit 13	Visit 14	Visit 15 EOS/ET[9]
	Screening	Baseline/ Day 0	Post-treatment		Week 4	Week 8	Every 4th week[10]	Post-treatment Performed only if re-treatment at Visit 5-12		Week 44	Week 48	Week 52
		(within 2 weeks after screening)	Day 7 (±1 day)	Day 14 (±3 days)	(±5 days)	(±5 days)	(+5 days)	Day 7 (±1 day)	Day 14 (±3 days)	(±5 days)	(±5 days)	(±5 days)
Informed Consent	X											
Demographic Data[2] including Fitzpatrick skin type, medical history & concurrent diseases, previous facial treatments/procedures (toxin naïve/non-toxin naïve)	X											
Inclusion /Exclusion Criteria	X	X[3]										
Concomitant Therapies/ Procedures	X	X[4]	X	X	X	X	X[4]	X	X	X	X	X
Adverse Events	X	X[4]	X	X	X	X	X[4]	X	X	X	X	X
Urine Pregnancy Test[5]	X	X[3]					X[3]					X
Vital Signs[6]		X[4]	X	X	X	X	X[4]	X	X	X	X	X
Blood sample clinical chemistry and hematology		X[3]										X
Blood sample for serum antibody testing		X[3]										X
Glabellar Line Severity (GL-ILA)	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X
Lateral Canthal Lines Severity (LCL-ILA)	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X
Focused Physical Examination (face, head, neck)	X	X[3]	X	X				X	X			X
Photography		X[3]	X	X	X	X	X[3]	X	X	X	X	X
Treatment		X[7]										
Eligibility for re-treatment							X[3]					
Re-treatment							X[7]					
CCI [redacted]												

1. *Screening and baseline visits may be on the same day. If completed on the same day, only perform study assessments once (i.e., PE, UPT, SLA, ILA, AE, concomitant therapies/procedures, inclusion/exclusion review)*
2. *Includes date of birth, gender, race, ethnicity, height, and weight.*
3. *To be performed before treatment (as applicable post-baseline if re-treatment performed).*
4. *To be performed before treatment and post-treatment (as applicable post-baseline if retreatment performed).*
5. *To be performed only if female of childbearing potential and eligible for treatment.*
6. *Vital signs are taken seated after 10 minutes rest.*
   Vital signs are taken prior to any blood draw (excluding post-treatment measurements on Day 0).
7. *Following treatment administration, subjects will be monitored at the study center for 30 minutes.*
8. *Only if subject meets re-treatment criteria.*
9. *If the subject withdraws before the final visit the ET visit should be completed, if possible.*
10. *Week 12, 16, 20, 24, 28, 32, 36 and 40*

GALDERMA	Title 43QM1903 Statistical analysis plan - LTS	Doc id MA-42529

PPD

Statistical Analysis Plan Approval Form

Client:	Galderma	
Identifier (e.g., Protocol Name and Number, ISS, ISE, SCS, or CSE):	43QM1903	
Version (Protocol Only):	☐ Original, Date:	☒ Amendment, Number 5.0; Date: 26AUG2020
Title:	A Multicenter, Open-Label Study to Evaluate the Safety of QM1114-DP for the Long-term Treatment of Moderate to Severe Glabellar Lines and Lateral Canthal Lines (READY - 4)	
Statistical Analysis Plan Version:	☒ Original, Date: 15JAN2021	☐ Amendment, Number ; Date:

AC Statistical Analysis Plan Author:

PPD, Senior Biostatistician
Printed Name & Title

Handwritten Signature **OR** *Electronic Signature*

Signature: _____

Date: _____
(dd/mmm/yyyy)

PPD
DocuSign

AC Statistical Analysis Plan Reviewer:

PPD, Sr. Biostatistician
Printed Name & Title

Handwritten Signature **OR** *Electronic Signature*

Signature: _____

Date: _____
(dd/mmm/yyyy)

PPD
DocuSign

First Client Statistical Analysis Plan Approval:

PPD, Senior Biostatistician
Printed Name & Title

Signature: PPD *Handwritten Signature* _____ Date: PPD
(dd/mmm/yyyy)

Second Client Statistical Analysis Plan Approval ☐ Not Applicable

PPD, Biostatistical Consultant
Printed Name & Title

Signature: PPD PPD *Handwritten Signature* _____ Date: PPD
(dd/mmm/yyyy)

GALDERMA	Title 43QM1903 Statistical analysis plan - LTS	Doc id MA-42529

SIGNATURES PAGE

Date	Signed by
2021-01-22 07:39	PPD
Justification	Approved by Owner

2021-01-22 08:47	PPD
Justification	Approved by Technical Expert

2021-02-05 13:15	PPD
Justification	Approved by