Statistical Analysis Plan

NCT ID: NCT05110287

Clinical Trial Number: 43BBJ1911

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Abbreviations and Definitions of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline Observation Carried Forward
CCI	[redacted]
CIs	Confidence intervals
CSR	Clinical Study Report
eCRF	Electronic case report form
EOS	End of Study
ET	Early termination
FDA	Food and Drug Administration
FST	Fitzpatrick skin type
CCI	[redacted]
GJS	Galderma Jawline Scale
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per protocol
PT	Preferred term
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System organ class
TC	Telephone call
TU	Touch-up (repeated injection to be performed after treatment, if necessary to achieve optimal correction)
Tx	Treatment
WHODD	World Health Organization Drug Dictionary

1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol 43BBJ1911 (v3.0), dated 11 OCT 2021. No subjects were enrolled prior to Protocol v3.0.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 Study Design

This is a prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter study in the United States to evaluate the effectiveness and safety of GP0109 for jawline definition. Approximately 224 subjects will be included in the study, randomized (3:1) to a GP0109 treatment group or to a no treatment control group. The adult population will have Grade 2 to 4 (moderate to very severe) on the Galderma Jawline Scale (GJS) with the intent to undergo bilateral jawline treatment.

The study will be conducted in two stages. Stage 1 includes the first approximately 50 eligible subjects randomized. The Sponsor will submit the 3-month data after baseline from subjects in Stage 1 to the Food and Drug Administration (FDA) for review and await the agency's agreement prior to continued enrollment into Stage 2.

The planned clinical study duration (from First Subject First Visit to Last Subject Last Visit) will be approximately 33 months across the two stages. This includes approximately 4 months of recruitment time and approximately 4 months for data collection and the FDA review of Stage 1 prior to enrollment of subjects in Stage 2.

See SAP Section 5 for a complete schedule of events; a summary follows.

Eligible subjects randomized to GP0109 treatment will be injected by the Treating Investigator at baseline (Day 1). A follow-up telephone call should be made 72 hours after treatment and a follow-up visit should be completed 14 days after treatment. Optional touch-up treatment may be administered 1 month after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. Optimal aesthetic improvement is defined as at least 1 grade improvement, from baseline, on the GJS, and best correction that can be achieved as agreed by the Treating Investigator and the subject. If optional touch-up is performed, a 72-hour follow-up telephone call, a 14-day follow up visit, and a 1-month follow-up visit should be scheduled.

At the Month 12 visit, subjects in the no treatment control group will be offered optional GP0109 treatment. Subjects in the no treatment control group who do not receive treatment at Month 12 will end the study at Month 12. The subjects who received GP0109 treatment at baseline will also be offered an optional additional treatment at the Month 12 visit if aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). If optional treatment is performed, a 72-hour follow-up telephone call, a 14-day follow up visit, and a 1-month follow-up visit should be scheduled.

Effectiveness and safety data will be collected for up to 24 months from baseline. Follow-up visits in addition to those mentioned above will occur at 3, 6, 9, 12, 15, 18, 21, and 24 months after baseline. A subject will be involved in the study for up to 25 months, including a 30-day screening period. For subjects in the no treatment control group who do not receive GP0109 treatment at Month 12, the clinical study participation will be approximately 13 months including the screening period. Subjects who receive GP0109 treatment at baseline and decline optional additional treatment at Month 12 will continue to be followed through 24 months after baseline.

Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments. Safety assessments will be performed by non-blinded personnel. The Blinded Evaluator will not be blinded to study treatment following the Month 12 visit. The Sponsor representative(s) will not be blinded during the course of the study.

1.1.2 Number of Subjects and Randomization

Approximately 224 subjects will be randomized (3:1) to either a GP0109 treatment group or to a no treatment control group. At least 45 subjects will be Fitzpatrick skin type (FST) IV through VI. This includes at least 23 subjects with FST V-VI, where at least 12 subjects will be FST V and at least 11 subjects will be FST VI.

Approximately 15 sites are planned for the study, with approximately 5 sites using needle for injection, approximately 5 using cannula for injection, and approximately 5 with a combination of needle and cannula for injection. The aim is to achieve an even distribution of subjects between the assigned sites.

In the GP0109 treatment group, approximately 56 subjects will receive injection with needle, 56 with cannula, and 56 with both needle and cannula combined. Approximately 56 subjects will be randomized to a no treatment control group at baseline.

Details of the enrollment to be conducted in two stages follow:

- Stage 1: will include the first approximately 50 eligible subjects randomized. At least 10 of these subjects will be FST IV-VI, where at least 3 subjects will be FST V and at least 2 subjects will be FST VI. The aim is to achieve an even distribution of subjects to a minimum 1 site using needle for injection, 1 site with cannula for injection, and 1 site with combination of needle and cannula for injection.
- Stage 2: will include approximately 174 eligible subjects.

The subject randomization list for each stage will be stratified by injection tool (needle, cannula, and combination) and FST group (FST I-III, FST IV, and FST V-VI). The FST I-III group only will be further stratified by study site. Study sites are assigned in advance to 1 of the 3 injection tool categories.

1.2 Study Objectives and Endpoints

1.2.1 Primary Effectiveness Objective and Endpoint

The primary objective of the study is to demonstrate superiority of GP0109 versus no treatment control in jawline definition, using a responder rate endpoint based on the Blinded Evaluator's live assessment of the GJS at 3 months after baseline. A responder is defined as a subject with at least 1 grade improvement from baseline, on both jawlines concurrently.

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1.3 Effectiveness Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1 for treated subjects. For non-treated subjects, baseline will be defined as the observation that is closest to but prior to randomization. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 Galderma Jawline Scale (GJS)

The GJS is a validated 5-grade scale for assessment of jawline area (see Table 1 below). Each grade in the GJS is exemplified by photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject´s left and right jawline separately. CCI

[redacted]

Table 1. Galderma Jawline Scale

Grade	Assessment	Description
0	None to Minimal	None to minimal volume deficiency posterior to the jowl along the jawline
1	Mild	Mild volume deficiency posterior to the jowl along the jawline
2	Moderate	Moderate volume deficiency posterior to the jowl along the jawline
3	Severe	Severe volume deficiency posterior to the jowl along the jawline
4	Very Severe	Extreme volume deficiency posterior to the jowl along the jawline with redundant skin

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Effective date: 2022-04-15 11:43
Effective
Version: 1.0

1.4 Safety Assessments

The methods for collecting safety data are described in Section 8 of the protocol. Data to be collected include the following:

- Adverse events.
- Subject diaries to be completed daily for 28 days following each treatment session with direct questioning for the following pre-identified symptoms: pain (including burning), tenderness, redness, bruising, swelling, itching, lumps/bumps, and other.
- Urine pregnancy test for women of childbearing potential performed at screening and all treatment visits (prior to treatment).
- Assessments for jaw mobility, intra-oral exam, pronunciation, jawline sensation, facial nerve function, and palpation at screening, baseline, and each physical follow-up visit.
- Visual function assessments (Snellen visual acuity, extraocular muscular function, and confrontation visual field) performed both prior to and 30 minutes post injection of the study product at screening, baseline, and each physical follow-up visit.
- Clinically significant changes in hair growth (e.g., loss or growth) in the treated area at each physical follow-up visit after baseline. Such changes will be determined by the Treating Investigator and reported as an AE.
- Device deficiencies assessed at all treatment visits.

2 Statistical Methods

2.1 General Methods

Any change made to the finalized SAP before database lock will result in an SAP amendment. Otherwise, changes will be documented in the Clinical Study Report (CSR). However, if additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR.

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Programming Conventions

CCI will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The electronic case report form (eCRF) data for all subjects will be provided in Study Data Tabulation Model (SDTM) datasets. Analysis Data Model (ADaM) datasets will be developed from the SDTM datasets for use in table and figure production.

2.1.2 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

Study data from the eCRFs as well as derived variables will be provided in subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study site number concatenated with subject number, treatment group, assessment dates, and/or time point.

The following conventions will be applied to all data presentations and analyses:

- Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.
- Quantitative variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data.
- Categorical variables will be summarized by the number and percentage of subjects (and number of events where appropriate) within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as ‘0’ rather than ‘0 (0)’.
- All summary tables will include the analysis population sample size (i.e., number of subjects) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.1.3 Data Transformations

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2.2 Analysis Populations

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

2.2.1 Intent-to-Treat (ITT) Population

The ITT population includes all subjects who were randomized, and will be analyzed according to the randomization scheme. All effectiveness variables will be analyzed based on the ITT population.

2.2.2 Per-Protocol (PP) Population

The PP population includes all ITT subjects who complete the 3 months after baseline visit, and are without any deviations considered to have substantial impact on the primary effectiveness outcome. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary effectiveness endpoint will be performed based on the PP population. If the primary effectiveness analysis needs to be stratified (i.e., conducted separately) for the needle-treated group, the cannula-treated group, and the combination group (see SAP Section 2.4.3), then this sensitivity analysis will be performed separately for each injection tool stratum if the PP population contains less than 90% of ITT subjects within the stratum.

2.2.3 Safety Population

The Safety population includes all subjects who were treated with GP0109 or randomized to the no treatment control group, and will be analyzed according to the as-treated principle. All safety data will be summarized descriptively based on the Safety population.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics by treatment group and overall based on the ITT population using observed cases. There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

The number of subjects screened will be shown in total and by study site.

The number of subjects in each study population (i.e., ITT, PP, and Safety) will be summarized by study site and in total (by treatment group and overall).

The disposition of subjects will be presented by treatment group, and in total, including numbers of subjects who were completed and withdrawn (including primary reason for withdrawal). These numbers will also be presented by study site.

The number of subjects expected, completed, withdrawn, and missed will be summarized by scheduled visit, using the following definitions:

- Expected = all subjects at screening minus subjects who have withdrawn up to that visit.
- Completed = subjects who showed up at that visit.
- Withdrawn = all subjects who have withdrawn up to that visit (cumulative).
- Missed = expected subjects minus completed subjects.

The end of study status will be listed for all subjects (both completed and withdrawn) individually, including at least subject number, end of study date, and last visit performed. In addition, reason for withdrawal will be provided for withdrawn subjects.

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by treatment group, overall, by site, and by type. Subjects with out-of-window visit protocol deviations will be presented by visit and number of days out of window for each treatment group and overall.

Depending on the seriousness of a protocol deviation, a subject might be excluded from the PP population, which shall be documented prior to database lock. Since the PP population will be used for the primary analysis at 3 months after baseline only, the focus will be on major deviations occurring before and at the Month 3 visit which are considered to have a substantial impact on the primary effectiveness outcome, see Table 3 below for list. Reasons for exclusion from the PP population also will be summarized.

Table 3. Major Protocol Deviations Causing Exclusion from Per-Protocol Population

Major Deviation
Month 3 visit out of window by greater than 21 days or earlier than 7 days
Subject did not receive treatment as randomized
Galderma Jawline Scale live assessment by Blinded Evaluator not done on at least one side of face at Month 3 (primary endpoint)
Galderma Jawline Scale live assessment by Blinded Evaluator not done on at least one side of face at screening or baseline
Galderma Jawline Scale live assessment by Blinded Evaluator at baseline is not grade 2 to 4 (moderate to very severe) on at least one side of face
More than one grade difference in Galderma Jawline Scale between left and right side of face at baseline as assessed live by Blinded Evaluator
Prohibited concomitant treatments/procedures prior to Month 3 visit considered to have substantial impact on primary effectiveness outcome
Prohibited medical history, unstable medical history condition, or medical history condition that worsens prior to Month 3 visit considered to have substantial impact on primary effectiveness outcome

2.3.3 Demographic Characteristics

Age and body mass index will be summarized as continuous variables.

Gender, race, ethnicity, FST, childbearing potential, and baseline GJS (Blinded Evaluator and Treating Investigator) will be summarized as categorical variables.

2.3.4 Medical History, Medications, and Procedures

Prior and concomitant medications and vaccines will be coded using the World Health Organization Drug Dictionary (WHODD). Medical history, prior cosmetic treatments/procedures, procedural anesthetics, and concomitant procedures/treatments will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications/procedures are the medications/procedures with stop dates prior to first study treatment session for the GP0109 treatment group and prior to randomization for the no treatment control group. Medications/procedures after the first study treatment session or randomization will be considered concomitant.

Subjects reporting medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be summarized by System Organ Class (SOC) and Preferred Term (PT). Procedural anesthetics will only be listed.

Subjects reporting concomitant medications and vaccines will be summarized separately, by WHODD Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, the highest class available will be used) and WHODD preferred name. Prior medications will only be listed.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

The ITT population is primary for all effectiveness analyses. The primary effectiveness analysis will be repeated using the PP analysis population if there is at least a 10% difference in the number of subjects between the PP and ITT populations. If the primary effectiveness analysis needs to be stratified (i.e., conducted separately) for the needle-treated group, the cannula-treated group, and the combination group (see SAP Section 2.4.3), then this analysis will be repeated separately for each injection tool stratum if the PP population contains less than 90% of ITT subjects within the stratum.

2.4.2 Handling of Missing Data

Number of missing values will be summarized and reported as appropriate.

For the ITT analysis of the Blinded Evaluator GJS responder rates and CCI [redacted] at 3 months after baseline (primary and first secondary endpoint), missing values will be assumed to be missing due to lack of effect. Therefore, the primary method of imputation will use the baseline observation carried forward (BOCF) method. Impact of missing data on the primary and first secondary endpoint will be evaluated by performing sensitivity analysis based on the observed cases in the ITT set.

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All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

2.4.3 Primary Effectiveness Analysis

Responder rate based on the GJS, as assessed live by the Blinded Evaluator at 3 months after baseline, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 grade improvement from baseline on both sides of the face concurrently.

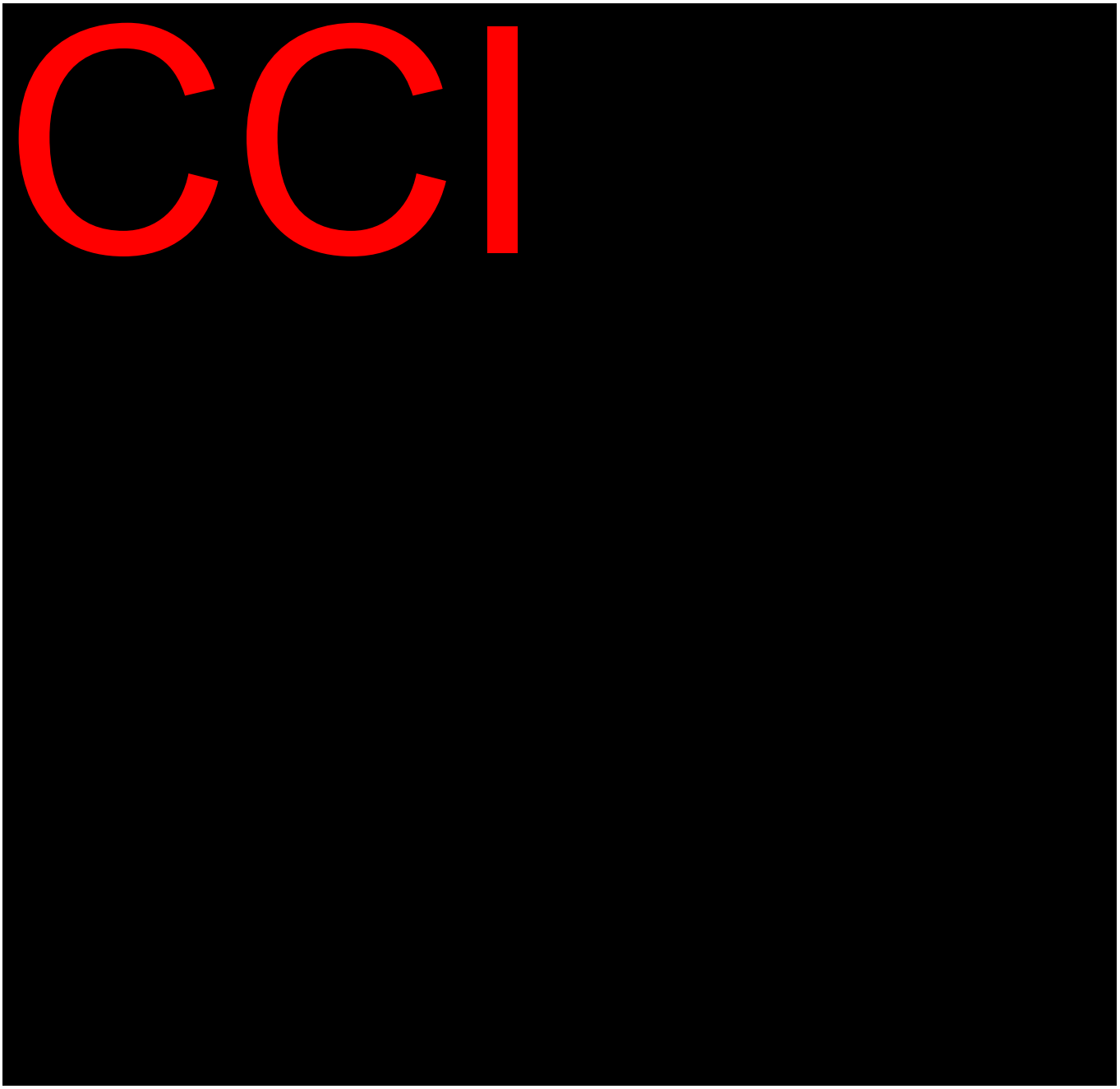
The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e., the responder rate is the same in treated and untreated subjects). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e., the responder rate is different in treated subjects compared to untreated subjects).

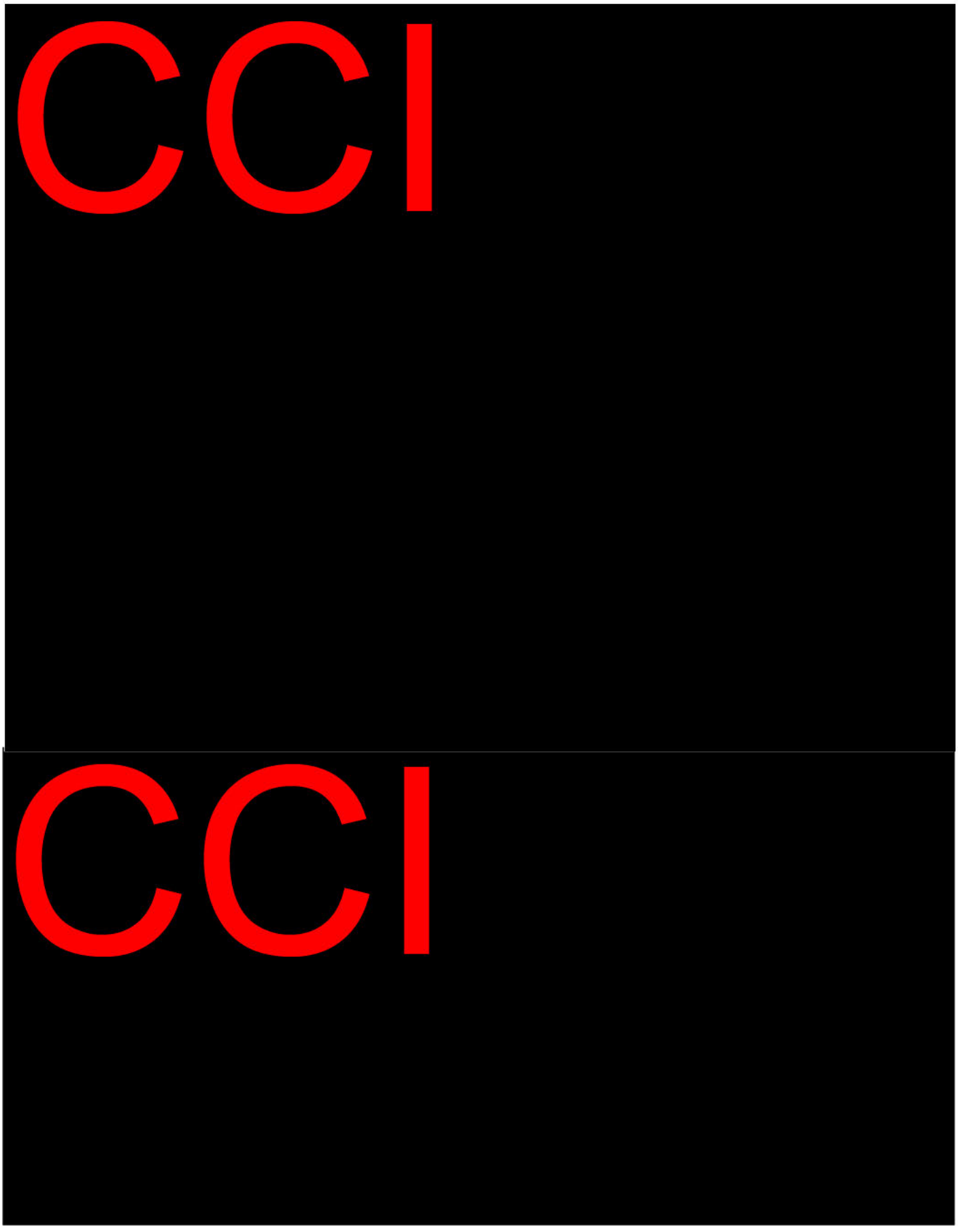
The estimates of the responder rate in each treatment group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates (via Clopper-Pearson) and the difference in responder rates (via normal approximation) along with the p-value (via Fisher's exact test) for the difference will also be presented.

First, the Breslow-Day test for homogeneity of odds ratios will be used to assess consistency of GJS odds ratios across all injection tool strata (the needle-treated group, the cannula-treated group,

and the combination group). A significance level of 0.05 will be used to determine if the responder rates are non-homogenous. If the Breslow-Day p-value is less than or equal to 0.05, the primary analysis will be stratified (i.e., conducted separately) for the needle-treated group, the cannula-treated group, and the combination group, using a significance level of 1.7% to account for multiplicity. If the Breslow-Day p-value is greater than 0.05, the analysis will be carried out on pooled groups, using a significance level of 5%. Regardless of whether the primary analysis will be based on pooled injection tool groups, or done separately, the no treatment control group subjects will be pooled across all study sites. In either case, the primary analysis will be repeated in each injection tool stratum as part of the pre-planned subgroup analyses (see SAP Section 2.4.5).

In order to assess the poolability of study sites, a Breslow-Day test for homogeneity of odds ratios across sites will be performed. Regardless of results, the primary analysis will be repeated for each study site as part of the pre-planned subgroup analyses (see SAP Section 2.4.5).





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2.4.5 Subgroup Analyses

In order to investigate the homogeneity of the results of the analyses of the primary endpoint, as well as the first secondary endpoint, across different subgroups, the following factors will be used for definition of subgroups: injection tool (needle, cannula, and combination), study site, FST (I-III and IV-VI), race, ethnicity, gender, age group (≤ median age and > median age), and total injection volume group (≤ median total injection volume and > median total injection volume). Pooling of subgroup categories may be needed based on observed data. The no treatment control group subjects will be pooled across all study sites for the injection tool and injection volume subgroup analyses.

For the primary endpoint, Fisher's exact tests will be used for comparison of responder rates, as well as confidence intervals of the differences in responder rates within each subgroup. These will be displayed in graphs.

If the primary effectiveness analysis is stratified by injection tool, the subgroup tables will also be stratified, although interpretation should be cautious given sample sizes may be small.

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2.5 Safety Analysis

Safety endpoints will be summarized using descriptive statistics by treatment group based on the Safety population using observed cases. There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Treatment Administration, Post-injection Procedures, and Procedural Anesthetics

Treatment administration endpoints will be summarized for each treatment session (initial, optional touch-up, and optional re-treatment) by treatment area, including injection method, depth of injection, needle size, cannula size, and introducer needle for cannula.

The number of subjects with any post-injection procedures and procedural anesthetics will be summarized by type.

Injection volume will be summarized for each treatment session (initial, optional touch-up, initial + touch-up, optional re-treatment) and overall by treatment area.

2.5.2 Adverse Events (AEs)

All AEs will be summarized relative to treatment session timing using the following categories:

- No Treatment at Baseline: For subjects who receive no treatment at baseline, include AEs before any optional GP0109 treatment at Month 12.
- Initial Treatment with GP0109: Pool AEs for the following (whether optional touch-up treatment received or not):
    - For subjects treated with GP0109 at baseline:
        - include AEs before optional GP0109 re-treatment at Month 12,
        - include AEs through end of study if no re-treatment at Month 12.
    - For subjects who receive no treatment at baseline, include AEs after initial GP0109 treatment at Month 12.
- Re-treatment with GP0109: For subjects treated with GP0109 at baseline, include AEs after optional GP0109 re-treatment at Month 12.

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT), and treatment session timing as described above. The number of subjects with at least one event, associated percentage, and number of events will be provided.

For subject counts, a subject will only be counted once per SOC and once per PT in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.

The number of subjects with AEs related to study product or study product injection procedure and unrelated AEs, as well as the number of events, will be presented by SOC, PT, and maximum intensity. Action taken for related AEs will also be summarized by SOC and PT using number of events. AEs related to study product or injection procedure with late onset (> 21 days after most recent treatment session) will be listed.

Serious AEs and AEs of special interest (AESIs) will be listed. See Section 8.2.1 of the protocol for a list of visual disturbances considered to be AESIs.

For AEs related to study product or study product injection procedure, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, standard deviation, median, minimum, and maximum. Days to onset of an AE will be derived as the start date minus the date of most recent treatment session. Duration of an AE will be derived as the stop date minus the start date + 1. Missing stop date will not be imputed, and therefore no duration will be calculated in these cases.

In addition, a summary of all AEs will be provided, which will include (but is not limited to):

- number of subjects with at least one AE and number of events (in total as well as serious AEs),
- number of subjects with at least one related AE and number of events (in total as well as serious AEs),
- number of subjects with at least one AESI and number of events,
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs),
- number of subjects who did not have an AE.

To evaluate consistency of AEs across different subgroups, related AEs by SOC, PT, and maximum intensity will also be summarized by subgroups, specifically injection tool (needle, cannula, and combination), study site, FST (I-III and IV-VI), race, ethnicity, gender, age group (≤ median age and > median age), and total injection volume group (≤ median total injection volume and > median total injection volume). Pooling of subgroup categories may be needed based on observed data.

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2.5.4 Other Safety Analyses

Assessments of jawline mobility, intra-oral exam, pronunciation, jawline sensation, facial nerve function, palpation, visual function (Snellen visual acuity test, extraocular muscular function test, and confrontation visual field test), and device deficiencies will be summarized descriptively as appropriate.

For subjects who received no treatment at baseline, other safety assessments will be summarized in the tables under one column for "No Treatment at Baseline". Based on visit timing, results at or prior to Month 12 will reflect assessments after no treatment at baseline. Results after Month 12 will reflect assessments after the optional GP0109 treatment at Month 12 (since subjects declining such treatment will end the study). For subjects treated with GP0109 at baseline (whether optional touch-up treatment received or not), other safety assessments will be summarized in the tables under one column for "GP0109", where results >Month 12 will use subjects re-treated or not at

Month 12 (since subjects will continue in the study if optional re-treatment at Month 12 is declined).

2.6 Interim Analysis

A safety review will occur after all subjects randomized in Stage 1 complete the follow-up visit at 3 months after baseline. The sponsor will submit select baseline and all safety data to the FDA for review and will await the agency's agreement prior to continued enrollment into Stage 2. The tables and listings to be included in this submission will include the following:

- Table for subject disposition and reasons for study discontinuation,
- Table for demographics and baseline characteristics,
- All safety tables for adverse events, subject diary symptoms, treatment administration characteristics, injection volume, jawline mobility, intra-oral exam, pronunciation, jawline sensation, facial nerve function, palpation, and visual function assessments.
- Listings for product complaints and related adverse events with late onset.

In addition, an interim analysis based on 12 months data from baseline is planned for this study to be used for early regulatory submission. This includes data for all subjects (both Stage 1 and Stage 2) up to this timepoint. The study will continue without modification afterwards, i.e., subjects will have no further treatment and will continue follow-up through 24 months after baseline. All data collected up to the interim analysis will be verified and cleaned; however, data may be updated later, if applicable, until final closure of the study database.

2.7 Determination of Sample Size

2.7.1 Sample Size

A total sample size of approximately 224 subjects will be included in this study.

Approximately 168 subjects will be randomized to treatment with GP0109 (~56 will be injected using needle, ~56 will be injected using cannula, and ~56 will be injected using both combined) and approximately 56 will be randomized to a no treatment control group. Sample size justifications are given below.

2.7.2 Previous Data

Since the primary endpoint will be based on a new scale, no existing data is available. CCI [redacted]

2.7.3 Assumptions

Based on results in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a responder rate of at least 70% in the GP0109 treatment group at 3 months after baseline. For the no treatment control group, responder rates up to almost 30% have been observed in the data on file. Based on this, it is assumed that the response rate will be maximum 32% in the no treatment control group at 3 months after baseline.

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2.7.4 Calculations

A two-sided test at the 5% significance level will have more than 99% power to demonstrate a difference between a responder rate of 70% in the GP0109 group and a responder rate of 32% in the no treatment control group when the sample sizes are 150 and 50, respectively.

Performing the same test, but in needle, cannula, and combination subjects separately (at the 1.7% level of significance for each test to account for multiplicity), the power will be approximately 90% (assuming the same responder rate of 70% in all GP0109 groups (needle, cannula, and combination). All no treatment control group subjects will be included in each of the by strata tests.

Accounting for approximately 10% dropouts at 3 months after baseline, approximately 224 subjects need to be randomized in a 3:1 ratio (GP0109 to no treatment control group).

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2.7.5 Safety Considerations

With 168 treated subjects, there will be a probability of approximately 80% for the study to detect at least one subject having an adverse event with an assumed population incidence of 1%.

2.8 Changes in the Analysis Planned in the Protocol

Other than the addition of analyses described in SAP Section 2.4.4 CCI here have been no substantial changes from the statistical methods described in the protocol.

3 Reference List

There are no other references beyond those that are included in the protocol.

5 Schedule of Events

Procedure	Visit 1a	Visit 1b	Visit 2a[4]	Visit 2b[4]	Visit 3	Visit 3a[4]	Visit 3b[4]	Visit 3c[4]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 7a[4]	Visit 7b[4]	Visit 7c[4]	Visit 8	Visit 9	Visit 10	Visit 11
	Visits may be combined if subject meets eligibility criteria		72 hrs after Tx (±24 hrs)	14 days after baseline (+7 days)	1 month[10] after baseline (+7 days)	72 hrs after optional TU (±24 hrs)	14 days after optional TU (+7 days)	1 month[10] after optional TU (+7 days)	3 months[10] after baseline (±7 days)	6 months[10] after baseline (±7 days)	9 months[10] after baseline (±7 days)	12 months[10] after baseline (±7 days)	72 hrs after optional Tx (±24 hrs)	14 days after optional Tx (+7 days)	1 month[10] after optional Tx (+7 days)	15 months[10] after baseline (±7 days)	18 months[10] after baseline (±7 days)	21 months[10] after baseline (±7 days)	24 months[10] after baseline (+7 days)
	Screening Day -30 to 1	Baseline/ Tx Day 1	TC	Follow-up	Follow-up/ Optional TU	TC	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up/ Optional Tx/EOS[11]	TC	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up/ EOS
Informed Consent	X																		
Med. Hx/prior therapies	X	X[1,2]																	
Demographics	X																		
Height/Weight[6]		X[1,6]																	X[6]
Inclusion/Exclusion Criteria	X	X[1,2]			X[1,5,]							X[1,5]							
Urine pregnancy test[3]	X	X[1,2]			X[1,5,]							X[1,5]							X
Randomization		X																	
Treatment with study product		X[9]			X[5,9]							X[5]							
Evaluate device deficiencies		X[9]			X[5,9]							X[5]							
Dispense Subject Diary		X[9]			X[5,9]							X[5]							
Collect/Review Subject			X[7]	X	X[9]	X[7]	X	X					X[7]	X	X				
Photography		X[1]		X	X[1]		X	X	X	X	X	X[1]		X	X	X	X	X	X
Concomitant therapies	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments[8]: Jaw mobility and function test Jawline sensation Palpability Visual function assessments Facial nerve function test	X	X[1]		X	X[1]		X	X	X	X	X	X[1]		X	X	X	X	X	X
Evaluate change in facial hair				X	X[1]		X	X	X	X	X	X[1]		X	X	X	X	X	X
Assessment of AEs		X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treating Investigator																			
CCI																			
Galderma Jawline Scale	X	X[1,2]			X[1]							X[1]							
Blinded Evaluator																			
Galderma Jawline Scale	X	X[1,2]							X	X	X	X[1]				X	X	X	X
Subject Assessments																			
CCI																			

[1]Prior to any planned treatment
[2]Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed
[3]For females of childbearing potential
[4]Visit is scheduled only if initial treatment, optional touch-up or optional treatment has been performed
[5]Omitted if optional touch-up or optional treatment is not performed
[6]Subject self-reported. Height only needs to be collected at baseline
[7]Review diary with subject over the phone
[8]As required at screening to confirm study eligibility. The safety assessments should be done prior to treatment. At the treatment visits the visual function assessment tests will be performed prior to and approximately 30 minutes post injection of the study product.
[9]For subjects randomized to study treatment
[10] One month is defined as 4 weeks in the study
[11]For subjects in the no treatment/control group if not receiving optional treatment
CCI

ET = Early Termination
EOS = End of Study
CCI
TC= Telephone call
TU = Touch-up
Tx = Treatment

PPD