Sponsor	[redacted]
Protocol Title:	A RANDOMIZED, BLINDED EVALUATOR, NO-TREATMENT CONTROL, MULTICENTER, PROSPECTIVE CLINICAL STUDY OF RHA[redacted] FOR THE TREATMENT OF MODERATE TO SEVERE TISSUE VOLUME DEFICIENCIES IN THE INFRAORBITAL REGIONS
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List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BLE	Blinded Live Evaluator
CI	Confidence Interval
CIP	Clinical Investigation Plan
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
CTR	Common Treatment Response
eCRF	electronical Case Report Form
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic Acid
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption

Abbreviation	Definition
[redacted]	[redacted]
ITT	Intent-to-Treat population
LTFU	lost-to-follow-up
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PP	Per Protocol population
PSAQ	Periorbital Subject Assessment Questionnaire
PT	Preferred Term
[redacted]	[redacted]
SAFT	Safety population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TI	Treating Investigator
TIOHS	Teoxane Infraorbital Hollows Scale
[redacted]	[redacted]
UPT	Urine Pregnancy Test

Abbreviation	Definition
US	United States
[redacted]	[redacted]
WHO-DD	world health organization drug dictionary

1. Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for [redacted] protocol/clinical investigation plan (CIP) [redacted] (A Randomized, Blinded Evaluator, No-treatment Control, Multicenter, Prospective Clinical Study of RHA[redacted] for the Treatment of Moderate to Severe Tissue Volume Deficiencies in the Infraorbital Regions), [redacted]. The reference document for this statistical plan is the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved before any unblinded inferential or descriptive analysis of data pertaining to [redacted].

1.1. Rationale for Study

RHA[redacted] is an investigational device which was initially assessed for the perioral lines indication in a previous clinical investigation conducted by [redacted] and whose premarket approval was approved by the FDA on 22 December 2021.

The purpose of this study is to inject RHA[redacted] into the infraorbital regions to achieve volume correction in the infraorbital area and to demonstrate that it is superior to no treatment in subjects aged 22 years and older to support a premarketing authorization application to United States (US) FDA for RHA[redacted].

To date, no soft tissue dermal fillers have been approved by the US FDA for use in the infraorbital regions. Therefore, the options for treatment of this area are limited to surgery, injection of one's own fat tissue, or off-label use of the medical devices marketed for different indications. Data about the effectiveness and/or safety are available from retrospective studies and case reports. The majority of the risks from RHA[redacted] are expected to be similar to those associated with other hyaluronic acid (HA) dermal fillers used as off-label treatment in the infraorbital. These include risks associated with all skin injection procedures, with the use of anesthetic agents, or with the use of RHA[redacted]. In the light of the potential risks and benefits, a prospective clinical study of RHA[redacted] HA dermal filler to assess the effectiveness and safety of the RHA[redacted] in the infraorbital area is justified.

1.2. Hypothesis

The RHA[redacted] group will be superior to the No-treatment control group for the correction of volume deficiencies in the infraorbital regions as determined by the Teoxane Infraorbital Hollows Scale (TIOHS – 5-point scale from grade 0 to 4) at 12 weeks after the initial treatment or randomization (for the No-treatment control group). An improvement in the TIOHS of ≥1 grade compared to pre-treatment for both eyes will be considered clinically meaningful.

Additionally, the change from Baseline in selected questions of the FACE-Q "Appraisal of lower eyelids" domain score (converted to a 0-100 scale – Rasch conversion) at 12 weeks for subjects treated with RHA[redacted] will be statistically superior (by at least 12 points) to the subjects of the No-treatment control group. The average of the raw score for the [redacted] FACE-Q "Appraisal of lower eyelids" will be also improved by 3 points or more for subjects randomized in the RHA[redacted] treatment group at 12 weeks to confirm that the statistical superiority is clinically significant.

2. Study Objectives and Endpoints

2.1. Study Objectives

The study is designed to achieve a series of objectives outlined below.

2.1.1. Primary Effectiveness Objective

To assess the effectiveness of RHA[redacted] (as judged by clinicians and subjects) for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions at 12 weeks after the initial treatment.

2.1.2. Secondary Effectiveness Objectives

To assess the effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment.

[redacted]

[redacted]

2.1.4. Safety Objective

- To assess the safety of RHA[redacted] in subjects treated for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment

[redacted]

2.2. Study Endpoints

2.2.1. Effectiveness Endpoints

2.2.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study is the responder rate after 12 weeks.

The effectiveness of RHA[redacted] will be demonstrated if the responder rate for subjects treated with RHA[redacted] is statistically superior to the responder rate for subjects of the No-treatment control group 12 weeks (Visit 5) after randomization as assessed by the Blinded Live Evaluator (BLE) using the live-validated TIOHS. [redacted]

[redacted]

Additionally, the following 2 conditions must be met:

- The responder rate for RHA[redacted] is ≥70%
- The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group is ≥50%.

A responder will be defined as a subject with a ≥1-grade improvement in both eyes on the TIOHS as assessed by the BLE from before initial treatment and 12 weeks after the initial treatment (Visit 5).

The co-primary endpoint will be the change from Baseline in selected questions of the FACE-Q "Appraisal of lower eyelids" domain score at 12 weeks. The effectiveness of RHA[redacted] will be demonstrated if the modified FACE-Q "Appraisal of lower eyelids" change from Baseline score (converted to a 0-100 scale – Rasch conversion) for subjects treated with RHA[redacted] is statistically superior (by at least 12 points) to the subjects of the No-treatment control group 12 weeks (Visit 5) after randomization [redacted]

[redacted]

Additionally, the following 2 conditions must be met:

- The mean change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is ≥ 3
- The difference between the modified FACE-Q "Appraisal of lower eyelids" change from Baseline for subjects treated with RHA[redacted] and the No-treatment control group is ≥12.

[redacted] Subjects randomly assigned to the No-treatment control group will receive treatment in Phase 1b, but these data will not be pooled for the primary endpoint analysis.

Superiority will be declared if:

- the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and
- the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and
- the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and
- the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12.

2.2.1.2. Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are:

- Proportion of subjects with both eyes with ≥1-grade improvement on the TIOHS as assessed:
    - By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/ initial treatment) = rate of responders at the given time point

[redacted]

[redacted]

- Proportion of subjects who were "improved" or "much improved" using the Global Aesthetic Improvement Scale (GAIS) as assessed:
    - By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/ initial treatment)

[redacted]

- Proportion of subjects "satisfied" or "very satisfied" with the effect of the study treatment, using the Subject satisfaction scale as assessed by the subject at each site visit from Visit 3/Visit 3b (4 weeks after initial treatment)
- FACE-Q assessment by the subject through the "Appraisal of lower eyelids" (all questions) scale of the FACE-Q at each site visit starting from Baseline (except for Visit 2)

[redacted]

2.2.2. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse events (AEs), with a focus on treatment related AEs based on the TI assessment, and AEs reported from the Common Treatment Response (CTR) diary, from randomization

[redacted]

[redacted]Post-injection CTR, [redacted]

Each AE will be coded to a Preferred Term (PT) and associated System Organ Class (SOC) according to an established and validated adverse reaction dictionary (Medical Dictionary for Regulatory Activities [MedDRA], latest available version) before the randomized treatment code is broken.

3. Overall Study Design and Plan

3.1. Overall Design

Enrollment:

This is a multicenter, blinded evaluator, randomized, prospective, no treatment control clinical study to identify whether RHA[redacted] is superior to no treatment for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions. The study [redacted] will include at least 20% of subjects with Fitzpatrick skin types IV-VI: including minimum of 10% subjects presenting with Fitzpatrick skin types V or VI of which ≥3% will have Fitzpatrick skin type V [redacted] and ≥3% will have Fitzpatrick skin type VI [redacted].

The TI and the BLE will evaluate the subject's infraorbital hollows independently of each other using the TIOHS at Screening (Visit 1) for eligibility. If the assessments of the TI and the BLE are the same or differ exactly by 1 point on the scale, the difference will be considered acceptable. The TI and the BLE must agree that the subject meets the inclusion criterion number 4 (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline of the primary endpoint. If the TI and the BLE do not agree on eligibility, or if their assessments differ by 2 points or more on the scale, the subject will not be eligible.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Subjects enrolled [redacted] will be randomly assigned in a ratio of 3:1 at Screening (Visit 1) to receive RHA[redacted] or to receive no treatment (No-treatment control group). Subjects receiving RHA[redacted] will be further divided by the method of administration (i.e., injection with a needle or a cannula), which will be defined for each site before the beginning of the study. Depending on the site, RHA[redacted] will be administered with a 30G ½" needle [redacted] or with a 25G 1 ½" cannula [redacted] Site selection will aim to achieve approximately 1:1 distribution between the subgroups. The BLE will be blinded to the study groups (RHA[redacted] group or No-treatment control group).

Phase 1a: Up to 12 weeks after the initial treatment for the RHA[redacted] group or after randomization for the No-treatment control group; primary endpoint

Subjects who will be randomly assigned to the RHA[redacted] group at Screening [redacted] will receive their injection at Visit 1. The TI or designee will call subjects 72 hours post-treatment (Visit 1 Call). Subjects will come to the site [redacted] 12 weeks (Visit 5, primary endpoint) after the initial treatment. Afterwards, subjects will proceed directly to Phase 2. Phase 1b is not applicable for subjects randomly assigned to the RHA[redacted] group.

Subjects randomly assigned to the No-treatment control group [redacted] at Screening will receive

no treatment in Phase 1a of the study. They will come to the site [redacted] 12 weeks (Visit 5, primary endpoint) after randomization. After completing all assessments for Visit 5, subjects will immediately begin Phase 1b (Visit 1b is on the same day as Visit 5) and will receive their initial treatment with RHA[redacted].

[redacted]

Phase 1b: after the primary endpoint assessment up to 12 weeks after the initial treatment for the No-treatment control group

Phase 1b is only applicable to subjects initially randomly assigned to the No-treatment control group. Once all evaluations applicable for Visit 5 are completed, subjects will proceed directly to Visit 1b (on the same day). Evaluations completed at Visit 5 will be used for Visit 1b and will become the new Baseline for Phase 1b.

Subjects will receive their initial treatment with RHA[redacted] at Visit 1b.

Subjects will follow the same schedule as those initially randomly assigned to the RHA® 1 group: RHA® 1 will be administered on the same day (Visit 1b). The TI or designee will call the subject 72 hours post-treatment (Visit 1b Call). Subjects will come to the site [redacted] 12 weeks (Visit 5b) after their initial treatment. Afterwards, subjects will proceed to Phase 2.

Phase 2 and Exit visit: 12 weeks after the initial treatment up to the end of the study for the RHA[redacted] group and the No-treatment control group

Phase 2 will occur 12 weeks after receiving initial treatment with RHA[redacted] for subjects in the RHA[redacted] and the No-treatment control group (after Phase 1b).

All these subjects will come to the site 24 weeks (Visit 6), [redacted] and 52 weeks (Visit 8) after their initial treatment. All subjects will be followed for 52 weeks after their initial treatment with RHA[redacted].

Subjects will be offered retreatment at Visit 8 (52 weeks after their initial treatment). Retreatment will be administered if the TI deems it to be appropriate and the subject agrees. If the subject does not receive retreatment, Visit 8 (52 weeks after initial treatment) will become the Exit visit.

If the subject receives retreatment at Visit 8, the TI or designee will call him or her after 72 hours (Visit 8 Call). The subjects will come to the site [redacted] 12 weeks (Visit 11) after retreatment for follow-up and safety assessments. Visit 11 will be the Exit Visit.

Assessments throughout the study: RHA[redacted] and No-treatment control group

The TI will conduct safety and effectiveness evaluations at each study visit until the Exit visit (Visit 8 or 12). Subjects with an ongoing adverse device effect (ADE) will be followed until the

event(s) has resolved or resolved with sequelae, or deemed no longer necessary as per TI judgment, or if follow-up is no longer possible.

Subjects will report their CTRs in a subject diary for 30 days after any injection (initial or retreatment).

The BLE will conduct assessments of effectiveness at all visits starting at Visit 5 (12 weeks after randomization). The primary endpoint assessment will be at Visit 5 (12 weeks after randomization) only. The primary endpoint will include data from subjects assigned to the RHA[redacted] and the No-treatment control group before receiving initial injection. Data from subjects randomly assigned to [redacted] the No-treatment control group after they receive treatment in Phase 1b will not be considered for the primary endpoint.

[redacted]

[redacted]

3.3. Study Population

A potential subject will be included in the study if they meet the inclusion criteria described in the protocol. Subjects shall be 22 years of age or older, seeking treatment of moderate to severe tissue volume deficiencies in the infraorbital region with a grade of 2 to 3 (moderate to severe) on the TIOHS for both eyes.

If the subject meets any of the exclusion criteria, such as the exclusion of subjects with known hypersensitivity or previous allergic reaction to any component of the study device, or known history of multiple severe allergies, or history of anaphylactic shock, or any other criteria for exclusion, the subject is excluded from the study as per protocol.

Full list of inclusion/exclusion criteria is described in the protocol.

A total of 258 subjects (maximum 259) will be enrolled in the study, at least 20% subjects with Fitzpatrick skin types IV-VI (minimum 20% of the global study population) including at least 10% with Fitzpatrick skin types V/VI of which ≥3% will have Fitzpatrick skin type V (≥8 subjects) and ≥3% will have Fitzpatrick skin type VI (≥ 8 subjects).

[redacted]

[redacted]

3.4.1. Injection of Study Device

Method of administration will be either with a 30G ½" needle (included with the product) or a 25G 1½" cannula [redacted]).

Injection area and depth: RHA[redacted] is injected from the sub-dermis to the periosteum in the infraorbital hollow.

Amount of filler to be administered: Up to 1.0 mL per eye at each treatment (max: 2.0 mL per treatment).

[redacted]

3.5. Method of Assigning Subjects to Treatment Groups

[redacted]

Randomization numbers will be assigned sequentially as subjects are entered into the study. The randomization will be stratified by site.

Needle and cannula subgroups are intended to be determined at the site level: the method of administration of RHA[redacted] (i.e., injection with a needle or a cannula) will be defined for each site

at the beginning of each stage of the study. The sites will be selected with an aim to achieve 1:1 distribution of subjects between the subgroups. [redacted]

If consent has been obtained, but the subject does not meet the entry criteria, they will be considered a screen failure and will not be enrolled.

3.6. Blinding and Unblinding

The TI, unblinded to allocation to groups, will be asked to minimize the number of people who will have the allocation information or who will have any form of access to such information. [redacted]

The BLE and study personnel not involved with the site (e.g., data management, medical monitor) will be blinded to assignment to groups and, if possible, to subgroups. [redacted]

Subjects will not be blinded.

Unblinding in case of medical emergency is not applicable since the TI, who is in charge of safety follow-up of subjects, will be aware of the treatment administered.

Overall unblinding will take place at the end of the study only after database lock has occurred.

[redacted]

[redacted]

[redacted]

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using Statistical Analysis Software (SAS) release 9.4 or higher. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, the number of missing values, mean, 95% confidence interval (CI) (as applicable), SD, median, minimum, and maximum, unless otherwise specified.

Categorical (qualitative) variable summaries will include the frequency and proportion of subjects who are in a particular category, or for each possible value.

For non-visit based data point proportions (AEs, CTRs, medications), the denominator for the percentage calculation will be based upon the total number of subjects in the study population. For visit based data point proportions, like response rates and categorical proportions at visits, calculation will be based upon the total number of subjects with non-missing data for the observation at the specific visit.

95% CIs of proportions will be also presented where indicated in this SAP.

The number of missing values will be calculated as difference of the total number of values in the study population minus the number of non-missing values.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median), and CI will be reported to 1 more decimal place than the observed data, and SD will be reported to 2 more decimal places than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

[redacted]

[redacted]

[redacted]

[redacted]

4.2.3. Data Monitoring Committee

Not applicable.

5. Analysis Populations

The following 4 analysis populations are planned for this investigation:

- **Screening population:** All subjects who provide informed consent and demographic and/or Baseline Screening assessment results, regardless of their randomization and treatment status in the investigation. The untreated control group will only be included in the Screening population as they will not receive RHA[redacted] treatment throughout the clinical study.
- **Safety population (SAFT):** All subjects who are assigned to either the RHA[redacted] group or the No-treatment control group and complete Visit 1 [redacted]. Subjects will be

analyzed according to their actual arm received.

- **Intent-to-Treat population (ITT):** All subjects who are randomly assigned to either the RHA[redacted] or the No-treatment control group and complete Visit 1. Subjects will be analyzed according to their initial arm assignment regardless of whether or not they received RHA[redacted].
- **Per Protocol population (PP):** All subjects in the ITT population who completed up to Visit 5 (primary endpoint visit at 12 weeks) with no major CIP deviations that could affect effectiveness assessments. The sponsor will identify major CIP deviations per Protocol Deviation Guidance Plan (PDGP) prior to the database lock.

[redacted]

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For all effectiveness and safety endpoints (for which a Baseline data is applicable), Baseline is defined as the last non-missing measurement preceding the initial treatment for subjects assigned to RHA[redacted] and randomization date/time for subjects assigned to control groups. For the No-treatment control group, a new Baseline will be defined as the last non-missing measurement at or before Visit 5 (12 weeks after randomization) before continuing to Phase 1b. This new Baseline will be used when applicable for secondary effectiveness analysis.

If the subject is eligible, the BLE's assessment will be used for the Baseline of the primary

endpoint.

[redacted]

If the time of an assessment done the day of initial treatment is missing, the assessment will be considered performed as per protocol to define timing comparing to the treatment.

6.1.2. Multiple Comparisons

Not applicable, there is no multiple comparison in the study.

6.1.3. Handling of Dropouts or Missing Data

6.1.3.1. Multiple Imputation for TIOHS and FACE-Q Data

Any subject who withdraws from the study will be considered as a study discontinuation. Subjects who discontinue study should be assessed in accordance with the assessments/tests specified normally for the end of the study visit.

For subjects in the ITT lost-to-follow-up (LTFU) before Visit 5 or not present at the primary endpoint visit for the TIOHS assessment, the multiple imputation will be performed for missing values. The method assumes data are MAR. Thus, subjects with missing values will have imputed values similar to other subjects with comparable observed profiles in the regression variables. Only Visit 5 TIOHS data will be imputed using regression method within FCS, SAS proc mi, using treatment group as the independent variable, TIOHS as the dependent variable, and age, sex and TIOHS at Baseline (BLE) for the eye as covariates. One data will be imputed per eye. Subjects will be then considered as responder or not based on this imputed value. [redacted]

For subjects in the ITT lost-to-follow-up (LTFU) before Visit 5 or not present at the primary endpoint visit for the FACE-Q assessment, the multiple imputation will be performed for missing values. The method assumes data are MAR. Thus, subjects with missing values will have imputed values similar to other subjects with comparable observed profiles in the regression variables. Only Visit 5 modified FACE-Q Rasch converted score data will be imputed using regression method within FCS, SAS proc mi, using treatment group as the independent variable, modified FACE-Q Rasch converted score as the dependent variable, and age, sex, Fitzpatrick skin type (I-III / IV-VI) and modified FACE-Q Rasch converted score at Baseline as covariates. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.4. Analysis Visit Windows

Statistical analyses will be based on scheduled visit as collected in the eCRF without further realignment.

[redacted]

6.1.6. Derived Variables

The following derived and computed variables have been initially identified as important for the analysis of effectiveness.

It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary or secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the

analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

6.1.6.1. Responder Rate

Definition of responder: a subject with an absolute ≥1-grade improvement in both eyes on the TIOHS as assessed by the BLE from before initial treatment (Baseline) to 12 weeks after the initial treatment (Visit 5). A negative change from the Baseline value is considered as an improvement.

6.1.6.2. FACE-Q Scores

For FACE-Q "Appraisal of lower eyelids" domain, the outcome of all the question, described below, will be pooled and data will be transformed so that higher scores reflected superior (positive) outcome and adapted to a scale of 100 units (i.e., worst/lowest score = 0, best/highest score = 100). Transformation of scores will be done according to FACE-Q manual.

The Rasch converted scores will be calculated based on the following domain and questions.

Domain "Appraisal of lower eyelids":

a. Excess fat under your eyes?
b. Excess skin under your eyes?
c. Puffiness under your eyes?
d. How noticeable the lines under your eyes are?
e. Crepey (wrinkled) skin under your eyes?
f. How old the area under your eyes makes you look?
g. How tired the area under your eyes makes you look?

Raw score will be derived as follow:

- Not at all: 4
- A little: 3
- Moderately: 2
- Extremely: 1

The converted raw scores for items that make up a scale are added to provide a total score. The total score is converted to a score from 0 to 100. If missing data is less than 50% of the scale's items, insert the mean of the completed items to calculate the total score and round it to the nearest integer. [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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6.1.6.3. Adverse Device Effect

An ADE is any AE with a relationship to the study procedure or study device recorded in the eCRF as 'Possibly related' or 'Probably related' or 'Causal relationship'. An AE with missing or not assessable relationship will be considered as 'treatment related (probably related)'. AEs will be tabulated by all relationship categories recorded in eCRF.

6.1.6.4. CTRs

A CTR is a predefined known clinical sign or symptom occurring during the 30 days after injection and reported by the subject for each of the 30 days. [redacted]

[redacted]

[redacted]

6.1.6.5. Prior and Concomitant Medications

Medications that started prior to the initial treatment for subjects assigned to RHA[redacted] and randomization date/time for subjects assigned to control groups will be considered prior medications.

A concomitant medication is defined as any medication that was administered during the treatment period. This includes medications that started before the treatment period and continued while on treatment and medications that started during the treatment period. [redacted]

If the start/stop dates of medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

6.1.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. According to this plan, data not subject to analysis will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs, it will be shown in tables as < 0.0001.

For missing AEs onset dates, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial AE start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month and day are unknown, then:
  - If the year matches the year of injection date, and the end date (if present) is after injection date, then impute as the month and day of the injection date.
  - Otherwise, assign January.
- If the month only is unknown, then:
  - If the year matches the year of injection date and day is on or after day of injection, then assign the month of injection. If this produces a date after the AE end date, assign the month before.

- If the year matches the year of injection date and day is before day of injection, then assign the month after injection. If this produces a date after the AE end date, assign the month of injection.
- Otherwise, assign January.

- If the day is unknown, then:
  - If the month and year match the month and year of the injection date, then impute as the day of injection date. If this produces a date after the AE end date, assign 01.
  - Otherwise, assign 01.

For partial AE end dates:

- If the year is unknown, then do not impute the date but assign as a missing value. At the time of the analysis, an AE with a complete missing end date will be considered ending at the cut-off date of the analysis in order to derive the duration.
- If the month is unknown, then assign December. If this produces a date after the last contact date, assign this date.
- If the day is unknown, then assign the last day of the month. If this produces a date after the last contact date, assign this date.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

The total number of subjects for each of the following categories will be presented overall for the enrolled population:

- Screening Population
  [redacted]
- Safety population (SAFT)
- Intent-to-treat Population (ITT)
- Per Protocol Population (PP)
- Subjects enrolled by site

[redacted]

The total number of screening failures and the reasons for screen failure will be presented overall.

7.2. Protocol Deviations

Protocol deviations will be identified and classified at the data review meeting before defining the analysis populations for the interim and the final analyses.

Only subjects with potentially important deviations as defined in the PDGP, will be discussed.

Important protocol deviations leading to exclusion of the PP population, i.e., major deviations, will be summarized by type of deviations for the ITT and SAFT populations. Deviations directly linked to COVID-19 will be reported and summarized separately.

All protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographics (age, sex, height, body weight, childbearing potential, ethnicity, race, Fitzpatrick skin type) will be completed for each of the following populations: ITT, SAFT, and PP.

For the continuous variables, the number of non-missing values and the mean, SD, minimum, median, and maximum will be tabulated.

Descriptive summaries of the medical/surgical history and prior medications will be completed for the Safety population.

Medical/surgical history will be coded with MedDRA dictionary. Incidences of findings in medical history will be summarized by SOC and PT, unless otherwise specified.

The frequency and percentage of prior medications for subjects in RHA[redacted] and No-treatment control groups will be summarized using the latest version available at time of the database lock of the World Health Organization Drug Dictionary (WHO-DD) by Anatomical Therapeutic Chemical (ATC) level 2 within level 1. [redacted]

7.4. Exposure and Compliance

Data will be tabulated for Safety population.

Number of treatment sessions will be tabulated in a frequency table for RHA[redacted] and No-treatment control groups.

[redacted]

Number of device malfunction reported by visit will be tabulated in a frequency table by treatment group.

All exposure data will be listed.

8. Effectiveness Analysis

All effectiveness analysis will be based on the ITT population. Primary endpoint and TIOHS responder as assessed by BLE analyses will be repeated for the PP population.

8.1. Primary Effectiveness Analysis

Primary endpoint:

Primary endpoint is the responder rate after 12 weeks.

A responder is defined as a subject with an absolute ≥1-grade improvement in both eyes on the TIOHS as assessed by the BLE from before initial treatment to 12 weeks after the initial treatment (Visit 5). A negative change from Baseline value is considered as an improvement. Subject with missing assessment for at least one eye at Visit 5 will be considered as a non-responder.

Responder rate at Visit 5 as assessed by the BLE will be tabulated by treatment group: frequency of responders, percentage of responders along with 95% CI will be tabulated. Fisher's exact test will be performed to compare responder rates between RHA[redacted] and the No-treatment control group. Test will be one-sided with a Type I error rate at 0.025. To achieve superiority, the observed *P* value must be ≤0.025.

[redacted]

Missing data will be handled as described in section 6.1.3.1.

Additionally, the following 2 conditions must be met:

- At least 70% of the subjects treated with RHA[redacted] must be responders
- The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group must be ≥50% points.

Co-primary endpoint:

The co-primary endpoint will be the change from Baseline in the modified FACE-Q "Appraisal of lower eyelids" domain score [redacted] and the average change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" converted raw score at 12 weeks. Missing data will be handled as described in section 6.1.3.1.

[redacted]

[redacted]

Superiority will be declared if:

- the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and
- the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and
- the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and
- the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12.

[redacted]

Normality, homogeneity of variance, and random independent samples are required for performing the analysis. ANCOVA requires the following additional assumptions:

- For each independent variable, the relationship between the dependent variable (y) and the covariate (x) is linear
- The lines expressing these linear relationships are all parallel (homogeneity of regression slopes)
- The covariate is independent of the treatment effects (i.e., the covariant and independent variables are independent)

Normality is tested via proc univariate in SAS, Shapiro-Wilk test. [redacted]

If assumptions for ANCOVA model are not fulfilled, the Wilcoxon-Mann-Whitney non parametric model will be used to test the Rasch converted mean score difference between RHA[redacted] and No-treatment control group. A bootstrap estimate of the mean difference will be used with 1000

samples with replacement of the observations. The 95% CI of the mean difference will be estimated with the percentile interval. In this case, baseline score, site and RHA[redacted] subgroups will be analyzed in the subgroup analyses.

Only data from the Phase 1a [redacted] will be taken into account. Data from subjects randomly assigned to the No-treatment control group after treatment received in the Phase 1b [redacted] will not be pooled for the primary endpoint analysis.

Overall superiority can be declared if all superiority criteria are met both for primary and co-primary endpoints.

[redacted]

[redacted]

8.3. Secondary Effectiveness Analysis

[redacted]

Secondary endpoints will be analyzed [redacted]

[redacted]

- Analysis of data from Visit 1/Visit 1b to Visit 11 with all subjects pooled together.

[redacted]

8.3.1. TIOHS Assessed by BLE, [redacted]

Summary statistics (mean, minimum, maximum, SD, and 95% CI of the mean, change from Baseline) will be calculated and presented per eye for each study visit. [redacted]

The TIOHS is a subjective 5-grade static scale as detailed below, will be assessed by TI and BLE.

Grade description:

Grade 0 - None

Grade 1 - Minimal

Grade 2 - Moderate

Grade 3 – Severe

Grade 4 - Very severe.

Relative frequency will be based upon the total number of subjects with non-missing data for the observation at the specific visit.

[redacted]

8.3.2. Responder Rate Based on TIOHS by BLE

Responder rate defined as both eyes with an absolute ≥1-grade improvement from Baseline on the TIOHS will be tabulated by treatment group: frequency of responders, percentage of responders along with 95% CI will be tabulated. Fisher's exact test will be performed to compare responder rates at each applicable visit.

The following categories are used:

- Responder
- Non-responder

Responder rate calculation will be based upon the total number of subjects with non-missing data for the observation at the specific visit.

A figure will be created by treatment arm for TIOHS grade responder rate assessed by BLE and TI as well. The figure will represent responder rate at each time point along with 95% confidence intervals for each treatment arm.

8.3.3. FACE-Q

For FACE-Q "Appraisal of lower eyelids", the outcome of all the question will be pooled and data will be transformed so that higher scores reflected superior (positive) outcome and adapted to a scale of 100 units (i.e., worst/lowest score = 0, best/highest score = 100) as per section 6.1.6.2. Total raw score, total converted raw score and Rasch converted score will be presented.

Only 7-item FACE-Q "Appraisal of lower eyelids" will be presented.

Mean, SD, 95% CI of the mean, median, min-max, change from Baseline, 95% CI for change from Baseline will be summarized by treatment arm. FACE-Q scale score change from Baseline values at each visit will be compared between treatment arms by t test or, in case normality assumption is not met, Wilcoxon-Mann-Whitney test. *P* values will be presented in the summary table.

A summary table with number of subjects answering each possibility by question will also be provided by visit.

[redacted]

8.3.4. GAIS Assessed by [redacted] BLE and Subject

The GAIS is a subjective 5-grade dynamic scale as detailed below and will be assessed by

Investigators and subjects.

Grade description:

1. Much improved
2. Improved
3. No change
4. Worse
5. Much worse.

GAIS grade frequencies and percentages will be calculated and presented for each scheduled study visit.

Additionally, proportions of "improved" and "much improved" (GAIS responder rate) will be presented, along with the 95% CI of the proportion at each applicable study visit and for each evaluators.

For GAIS assessed by BLE, [redacted] and subject, Fisher's exact test will be performed to compare responder rates at each applicable visit .

Relative frequency and responder rate calculation will be based upon the total number of subjects with non-missing data for the observation at the specific visit.

A figure will be created by treatment arm for GAIS responder rate assessed by BLE, [redacted] and subject as well. The figure will represent responder rate at each time point along with 95% confidence intervals, for each treatment arm.

8.3.5. Subject Satisfaction Score

Subject Satisfaction will be assessed by subjects using the following static 5-grade scale.

Grade description:

1. Very satisfied
2. Satisfied
3. Neither satisfied nor dissatisfied
4. Dissatisfied
5. Very dissatisfied.

Satisfaction grade frequencies and percentages will be calculated and presented for each scheduled study visit.

For subject satisfaction, proportions of "satisfied" and "very satisfied" (subject satisfaction responder rate) will be presented, along with the 95% CI of the proportion at each applicable study visit. Fisher's exact test will be performed to compare responder rates at each applicable visit.

[redacted]

[redacted]

9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

All AEs will be coded using the MedDRA dictionary.

Number of all AEs, ADEs, [redacted] and number and percentage of subjects having the specific AEs will be presented. 2-sided exact 95% CIs will be calculated for the proportion of subjects having the specific AEs.

All AEs reported during the study will be described by SOC and PT.

Incidence rates defined as number of subjects presenting the AE divided by the number of subjects in the treatment group with 2-sided exact 95% CIs will be calculated for the overall incidence of AEs, ADEs, [redacted]

The causal relationship of the AE to the study treatment is determined by the investigator by relationship to the study procedure and relationship to the study device [redacted]

[redacted]

[redacted]

Individual listings of all AE data will also be given.

9.1.1. Deaths

All deaths occurring during the study will be listed.

9.2. CTRs

Number of all CTRs and number and percentage of subjects having the specific CTR will be presented for each injection. [redacted]

CTRs to be reported are the following;

- Redness
- Pain
- Tenderness
- Firmness
- Swelling
- Lumps/Bumps
- Bruising
- Itching
- Discoloration

[redacted]

[redacted]

9.3. Clinical Laboratory Evaluations

Urine Pregnancy Test (UPT) for women of childbearing potential will be listed.

[redacted]

[redacted]

10. COVID-19 Impact

Visits and assessments impacted by the COVID-19 pandemic will be listed.

[redacted]

[redacted]

11. Changes from Protocol

Not applicable.

12. Changes from Planned Analysis

Not applicable.

[redacted]

14. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (eCRF page or listing number).

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figure 1: Standardized Layout

<*Sponsor Name*> Page xx of xx

Protocol: <*protocol id*> Version

<*Table, Listing, Figure*> xx.x.x

<*Title of Table Listing or Figure*>

<*Study Population and if applicable subgroup Description*>

Body of Table, Listing or Figure

<*Note: If directly Applicable*>

Footnote 1 <*if applicable*> Recommendation is to keep footnotes to a minimum

Footnote 2 <*if applicable*>

Footnote n <*if applicable*>

Footnote n+1 <*pgm path and name*>, <*date*>

15.2. Planned Table Shells

Will be provided in separate document.

15.3. Planned Listing Shells

Will be provided in separate document.

15.4. Planned Figure Shells

Will be provided in separate document.

[redacted]

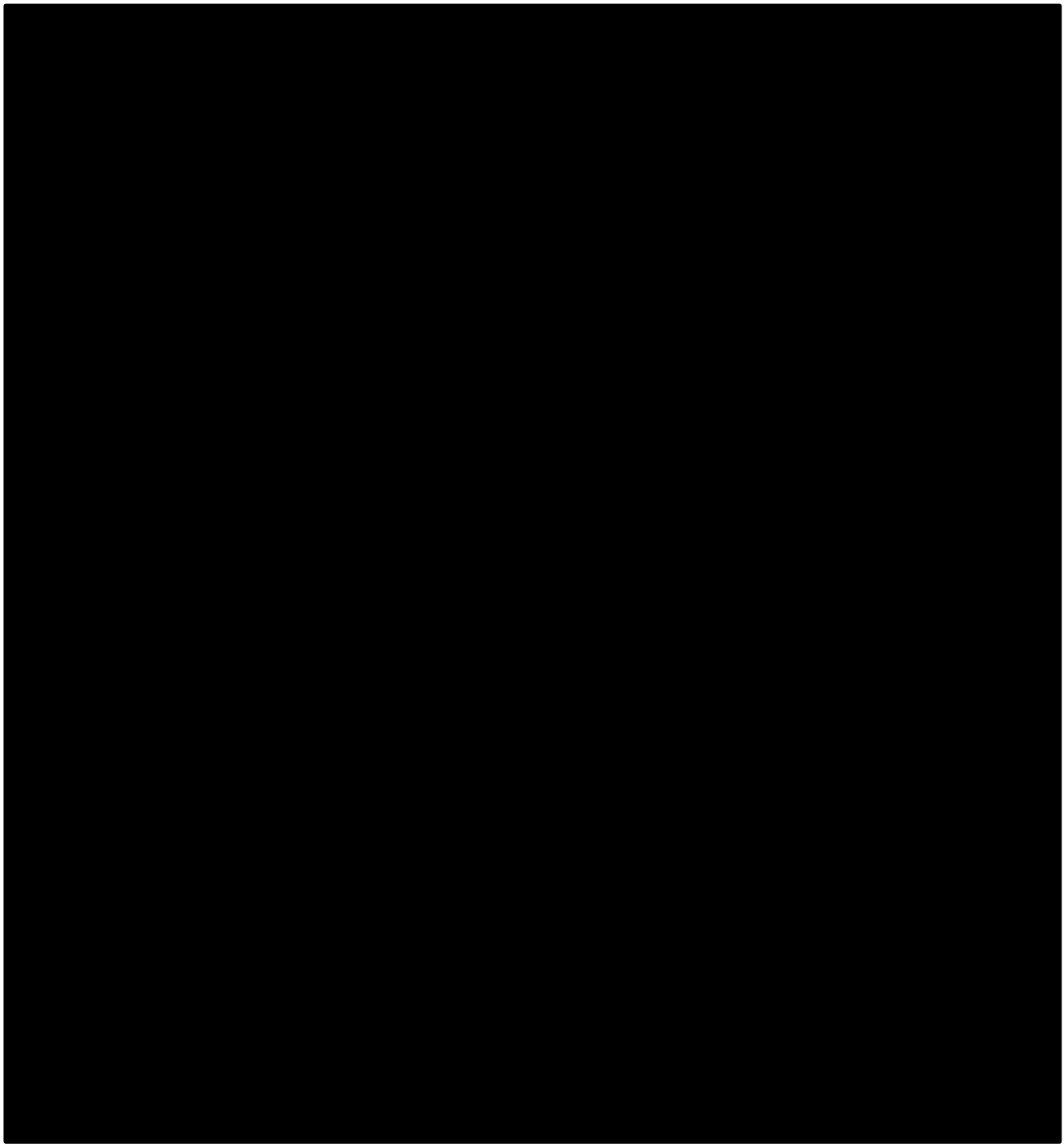
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]