Statistical Analysis Plan

Sponsor	[redacted]
Protocol Title:	A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation
Protocol Number:	[redacted]
[redacted]	[redacted]
Document Version:	[redacted]
Document Date:	16-Nov-2021

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	Print Name: [redacted] Sign Name:	
[redacted]	Print Name: [redacted] Sign Name:	

Table of Contents

List of Tables and Figures

[redacted]

1. Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for [redacted] (A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation), dated 22-MAR-2021 version #[redacted]. The reference document for this SAP is the protocol. 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 submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining [redacted]

1.1. Rationale for Study

In the United States (US), RHA® 3 is FDA approved for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs), in adults 22 years or older.

Assuming a similar volumizing effect, the purpose of this study is to inject RHA® 3 into the lips to achieve lip augmentation and demonstrate that it is non-inferior to [redacted] for this indication in subjects aged 22 years or older. The goal is to show that treatment with RHA® 3 will result in added volume and fullness to the lips 12 weeks after the last treatment.

1.2. Hypothesis

The Teoxane Lip Fullness Scale (TLFS) change from Baseline for subjects treated with RHA® 3 will be statistically non-inferior to the change from Baseline for subjects treated with [redacted] for the assessment of lip augmentation and fullness as determined by the Blinded Live Evaluator (BLE) using the TLFS at Week 12 after the last treatment (initial or touch-up). [redacted]

[redacted]

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 Objective

To assess the effectiveness (non-inferiority) of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation, 12 weeks after the last treatment (initial or touch-up).

2.1.2. Secondary Objectives

Secondary effectiveness objectives are:

- To assess the effectiveness of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation up to 52 weeks
- To assess the responder rate of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks
- To assess the subject satisfaction and patient-reported outcome of the aesthetic procedure (FACE-Q) with RHA® 3 versus [redacted] after lip augmentation up to 52 weeks
- To assess the Global Aesthetic Improvement Scale (GAIS) of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks

[redacted]

2.1.4. Safety Objective

To assess the safety of RHA® 3 in subjects after lip augmentation.

2.2. Study Endpoints

2.2.1. Effectiveness Endpoints

2.2.1.1. Primary Effectiveness Endpoint

The primary endpoint of the study is the difference in the TLFS change from Baseline to 12 weeks after the last day of treatment between subjects treated with RHA® 3 and those treated with [redacted]

The effectiveness of RHA® 3 will be demonstrated if the change from Baseline for subjects treated with RHA® 3 is statistically non-inferior to the change from Baseline for subjects treated with [redacted] at 12 weeks after the last treatment as assessed by the BLE using the TLFS. The difference in the TLFS change from Baseline to 12 weeks will be used to establish non-inferiority, [redacted].

A change in the TLFS ≥1 grade compared to pretreatment will be considered clinically meaningful.

[redacted]

2.2.1.2. Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are:

- TLFS change from Baseline assessed:
  - By the BLE at each visit at the study from Visit 4 [redacted]
- Responder rate calculated using TLFS assessed:
  - By the BLE at each visit at the study from Visit 4 [redacted]

  A responder will be defined as a subject who has a ≥1 grade improvement on the TLFS.
- Subject satisfaction using the Subject Satisfaction Scale at each visit at the study site starting at Visit 2

[redacted] FACE-Q scores for each module (satisfaction with lips and satisfaction with outcome) assessed by the subject at each visit [redacted]
- GAIS as assessed:
  - By the BLE starting at each visit at the study from Visit 4

[redacted]

[redacted]

2.2.2. Safety Endpoints

The safety endpoints are:

- Adverse Events (AEs)
- Post-injection Common Treatment Response (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

This is a multicenter, double-blinded, randomized, prospective, controlled clinical study to identify whether RHA® 3 is non-inferior to [redacted] for lip augmentation at Week 12 after the last treatment (initial or touch-up).

The TI will evaluate the subject's lip fullness using the live validated 5-grade TLFS grade 1 to 5 at Screening (Visit 1, 0 Week) for eligibility of the subject for the study.

The BLE will evaluate the subject's lip fullness using the TLFS at Screening (Visit 1, 0 Week) to confirm eligibility and to establish a pretreatment score for assessment of effectiveness. This will be done independently of the TI. [redacted]

[redacted]

Enrolled subjects will be randomly assigned in a 3:1 ratio to either the RHA® 3 or the [redacted] treatment group. Subjects will be blinded to the study treatment. The TI will administer the fillers, and if necessary, subjects will receive a touch-up treatment 4 weeks after the initial treatment to optimize the results. If the touch-up treatment is administered, the subject will be asked to come to the site for an additional visit ([redacted]) 4 weeks after the touch-up injection.

Subjects will be followed for 52 weeks after their last treatment (initial treatment or touch-up), at which point, they will be offered retreatment with RHA® 3, regardless of their original treatment, provided that the TI deems the treatment to be appropriate and the subject agrees. Reasons for not administering the retreatment will be documented. The subject will then be followed for an additional 4 weeks before exiting the study. If the subject or the TI declines retreatment, this visit [redacted] 52 weeks after the last treatment) will be considered the study Exit visit. For subjects with retreatment, the Exit visit will be at [redacted] 4 weeks after the retreatment.

The TI will conduct safety and effectiveness evaluations at each study visit, which will occur at 4 weeks after the initial and touch-up treatment [redacted] 36 weeks [redacted] and 52 weeks [redacted] after the last treatment, and 4 weeks [redacted]) after retreatment or until all treatment-related ongoing AEs have resolved or resolved with sequelae as per TI judgment or if follow-up is no longer possible.

A follow-up telephone call for safety will be performed 3 days after each treatment [redacted] initial, touch-up, and retreatment, respectively). Subjects will report their CTRs in a subject diary for [redacted] days after each injection. The diary will also include a list of selected AEs potentially associated with injection of dermal fillers for subjects to report if applicable. [redacted]

Subjects who had entered the study under earlier versions of the Clinical Investigation Plan (CIP) (version [redacted] and earlier) and who do not agree with the extension of their participation in the study as per CIP version 5.0, to 52 weeks after last injection, will be allowed to continue with the visits as originally planned. They will exit the study at [redacted] 36 weeks after last injection) or, if

they receive retreatment [redacted] they will have a follow-up telephone call [redacted] and will exit the study [redacted], 4 weeks after retreatment. Further details are described in the CIP.

A BLE will conduct assessments of effectiveness during the study, including assessment of the primary endpoint [redacted] 12 weeks after the last treatment). The BLE will conduct effectiveness evaluations at [redacted] 36 weeks after the last treatment), [redacted] 52 weeks after the last treatment), and [redacted] 4 weeks after the retreatment, if applicable).

For full details of the study design, please refer to the protocol.

3.2. Sample Size and Power

The primary endpoint of the study is the difference in the TLFS change from Baseline to 12 weeks after the last day of treatment between subjects treated with RHA® 3 and those treated with [redacted]

A modified intent-to-treat (mITT) analysis set will be used for the effectiveness analysis. [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 lip augmentation [redacted]

[redacted]

[redacted]

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

A total of 200 subjects will be enrolled in the study, [redacted]

3.4. Treatment Allocation, Randomization and Blinding

The randomization schedule will be computer generated using a permuted block algorithm and randomly allocate the investigational product in a 3:1 ratio. Subject will be randomized to one of the following groups:

- RHA® 3 study device
- [redacted] control device.

Randomization numbers with specific treatment assignments will be assigned sequentially in a 3-digit subject number, as subjects are entered into the study. [redacted]

[redacted]

[redacted]

3.5. Injection of Study Device

[redacted]

Injection areas: The TI will inject each device into the vermillion body, vermillion border, and oral commissures, as needed, to achieve optimal aesthetic outcome.

Amount of filler to be administered: Up to 1.5 mL per lip (upper and lower) at each treatment (initial, touch-up, and retreatment).

[redacted]

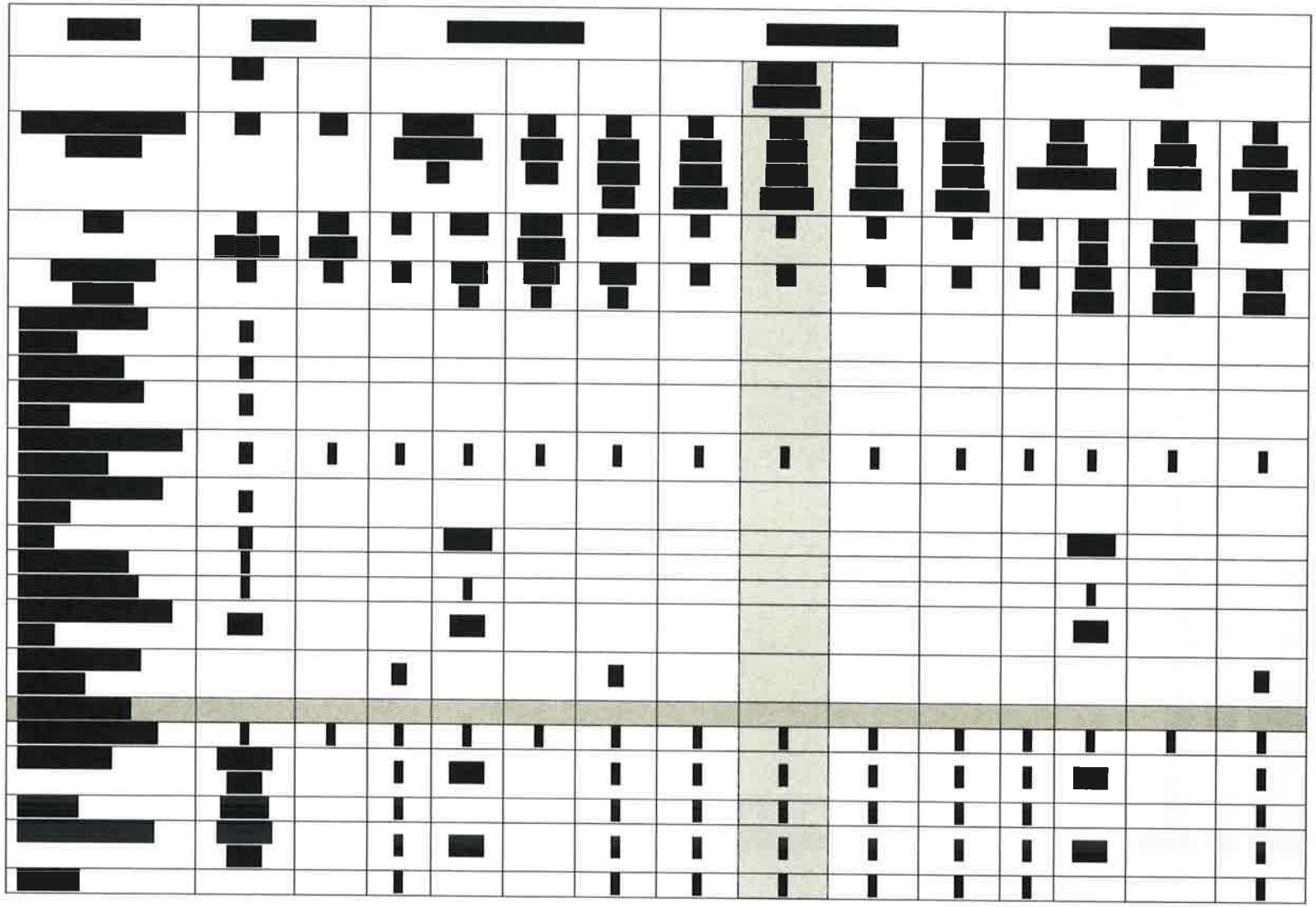
[redacted]

[redacted]

[redacted]

[redacted]

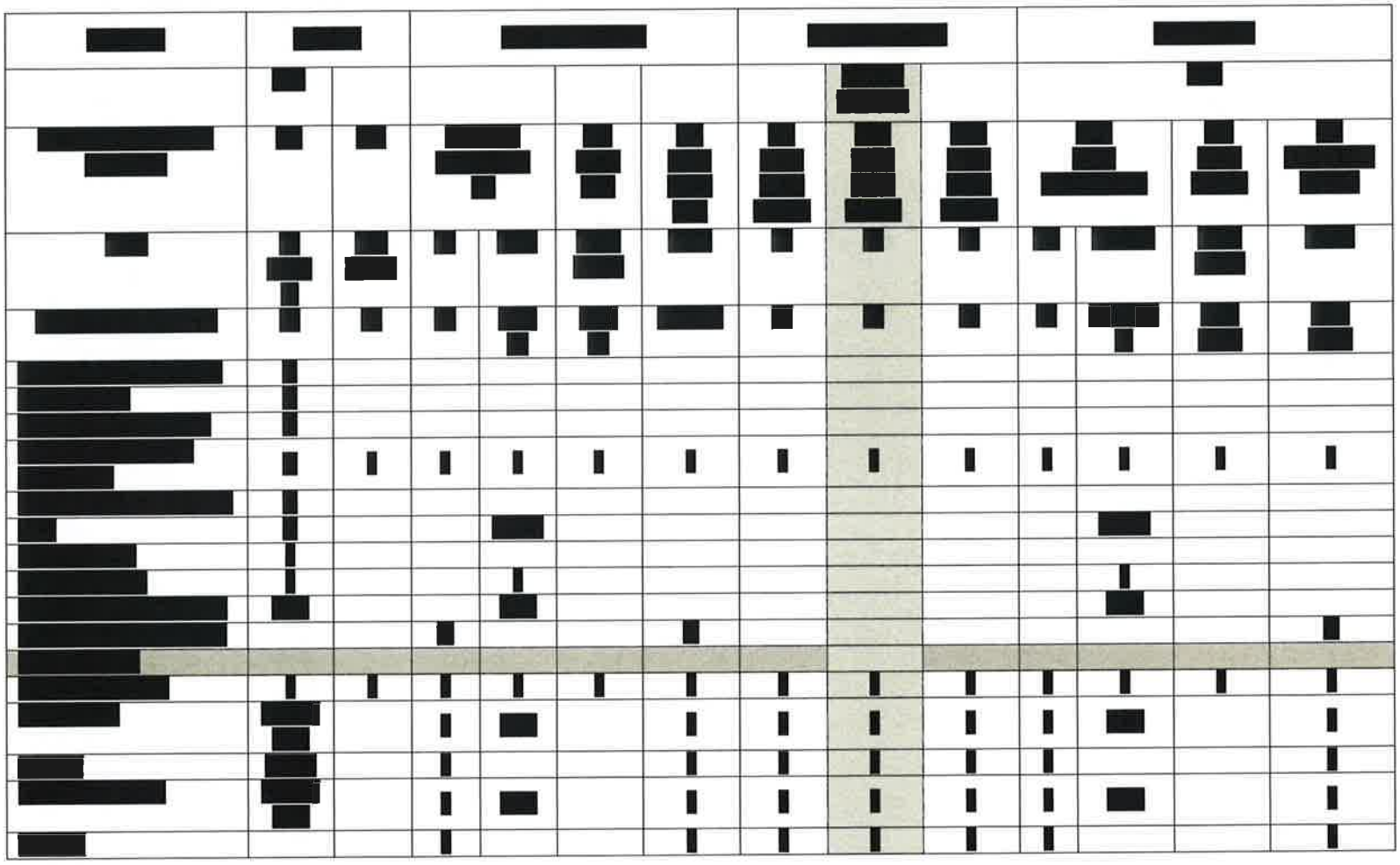
[redacted]



[redacted]

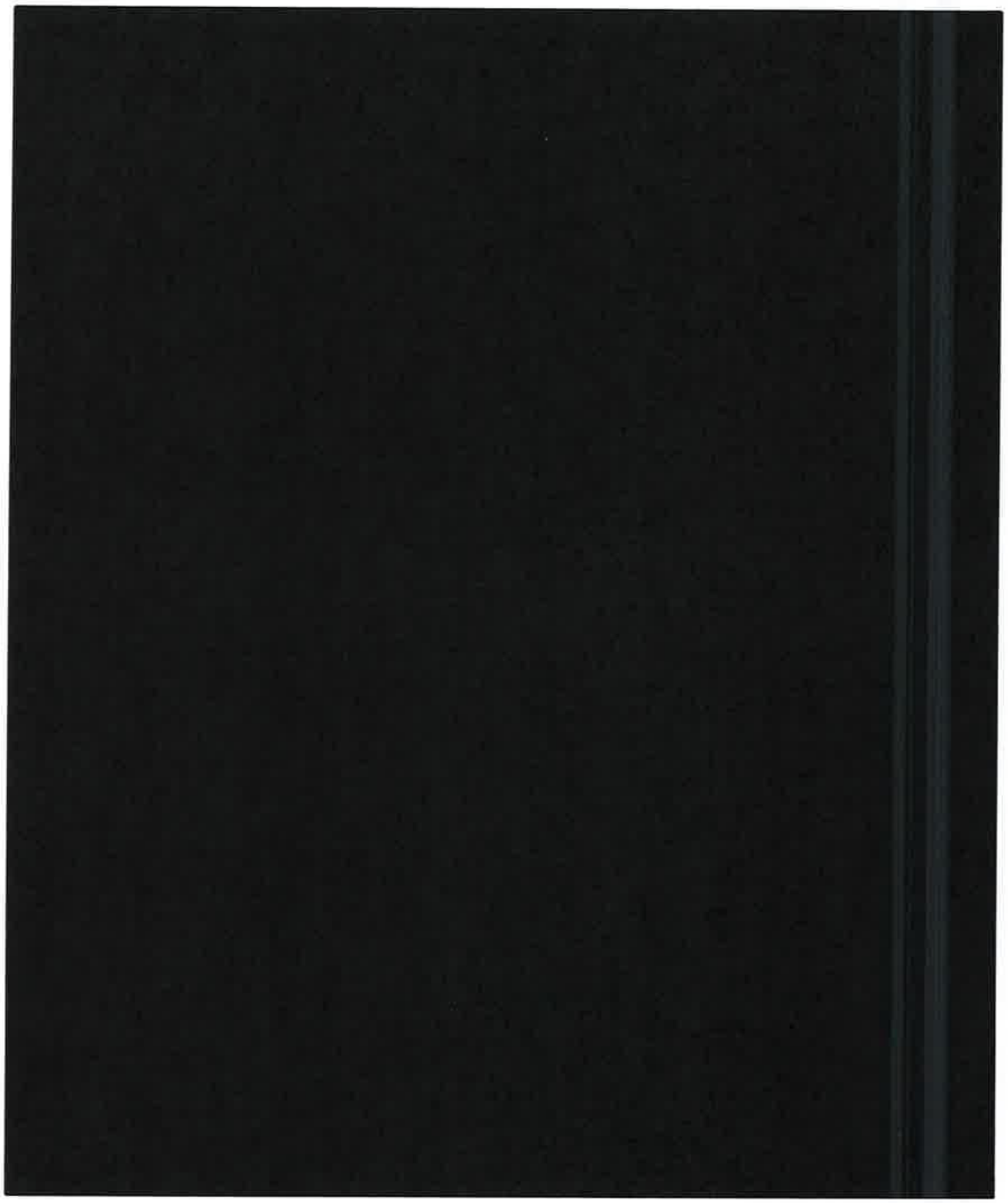
[redacted]

[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 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% 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.

[redacted]

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

[redacted]

5. Analysis Populations

The following [redacted] analysis populations are planned for this investigation:

- **Screening:** All subjects who provide informed consent and demographic and/or Baseline screening assessment results, regardless of the subject's randomization and treatment status in the investigation.
- **Safety (SAFT):** All subjects who receive at least 1 treatment with RHA® 3 or [redacted]
- **Modified intent-to-treat (mITT)** analysis set will be used for effectiveness analysis. The mITT set is based on the conventional intent-to-treat (ITT) analysis set:

  [redacted]

- [redacted]**Per Protocol (PP):** All subjects in the mITT population who receive treatment and do not have any major CIP deviations. [redacted]

[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), the last non-missing observation recorded prior to first study treatment administration will be used as the Baseline observation for all calculations. If no observation is available prior to first study treatment administration, then Baseline value is considered missing and protocol deviation is recorded.

[redacted]

6.1.4. Analysis Visit Windows

Statistical analyses will be based on scheduled visit as collected in the electronical Case Report Form (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: ≥1-grade point on the TLFS 12 weeks after the last treatment when compared to pretreatment (Baseline). A positive change from Baseline value is considered as improvement.

6.1.6.2. FACE-Q Scores

For FACE-Q (Satisfaction with Lips and Satisfaction with Outcome), the outcome of all the question of each domain, 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.

[redacted]

[redacted]

As per the FACE-Q manual, there is no overall or total FACE-Q© score, only scores for each independent scale. The 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[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]	[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]	[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]

6.1.6.3. Adverse Device Effect

An adverse device effect (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 [redacted] after injection and reported by the subject [redacted]

[redacted]

6.1.6.5. Prior and Concomitant Medications

Medications that started prior to the first study treatment 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.

If the start/stop dates of a 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.

Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All P values will be displayed in 4 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 adverse events onset dates and times, 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.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of the first dose the time assigned is 12:00;
- if the date is the same as the date of the first dose and the only hour is missing the hour assigned is 12 or the hour of the first dose, whichever is later, and if the date is the same as the date of the first dose and only the minute is missing the minute assigned is 30 or the minute of the first dose, whichever is later. Otherwise, the hour assigned is 12 if the hour is missing and the date is not the same as the date of the first dose, and the minute assigned is 30 if the date is not the same as the date of first dose.

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
- Safety Analysis Set (SAFT)
- Intent-to-treat Population (ITT)
- Modified Intent-to-treat Population (mITT)
- Per Protocol Population (PP)

[redacted]

[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 final analysis.

[redacted]

All protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

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

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 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.

7.4. Exposure and Compliance

Data will be tabulated for Safety population (SAFT).

Number of treatment sessions will be tabulated in a frequency table for both treatment groups.

Volume to obtain an OCR (initial treatment and touch-up) and volume injected at retreatment will be tabulated in a summary table by treatment group.

Injection technique will be tabulated in a frequency table by treatment group and treatment occasion.

All exposure data will be listed.

8. Effectiveness Analysis

The primary and secondary effectiveness analyses will be based on the mITT population. The analyses will be repeated for the PP population.

For categorical variables, the 2 groups will be compared using independent-testing based on a 2-group, 2-sided, Fisher's exact test. For continuous variables, ANCOVA or applicable non-parametric method will be used.

8.1. Primary Effectiveness Analysis

Poolability analysis for study sites will be performed before the main analysis. If sites do have an effect on primary outcome, then site as covariate will be included in main model for primary analysis.

Non-inferiority Analysis (Main Analysis):

To demonstrate non-inferiority of RHA® 3 compared to [redacted] at 12 weeks after the last treatment, the difference in the TLFS grade change between Baseline and 12 weeks will then be tested between groups (RHA® 3 minus [redacted]).

[redacted]

Normality, homogeneity of variance and random independent samples are required for performing the analysis. [redacted]

[redacted]

If non-inferiority is achieved, the TLFS grade difference as rated by the BLE at 12 weeks after Baseline will be analyzed in terms of superiority.

A 2-sided 95% CI, based on an analysis such as [redacted], will be computed for the difference in RHA® 3 minus [redacted]

- If the lower bound of the CI is >-0.5, then non-inferiority is demonstrated.
- Else, if the lower bound is ≤-0.5, non-inferiority is not demonstrated.
- If the lower bound of the CI is ≥0.5, then RHA® 3 superiority is demonstrated.

[redacted]

8.3. Secondary Effectiveness Analysis

8.3.1. TLFS Assessed by [redacted] BLE

Summary statistics (mean, minimum, maximum, SD, and 95% CI of the mean, change from Baseline) will be provided/presented for each study visit for TLFS grade overall [redacted].

The following categories are used:

- Grade 1 - Very Thin
- Grade 2 - Thin
- Grade 3 - Moderate
- Grade 4 - Full
- Grade 5 - Very Full

[redacted]

8.3.2. Responder Rate Based on TLFS

Responder rate 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.

[redacted]

8.3.3. GAIS Assessed by [redacted] BLE [redacted]

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

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

Grade description:

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

[redacted]

8.3.4. Subject Satisfaction Score

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

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

Grade description:

1. Very satisfied

[redacted]

5. Very dissatisfied

[redacted]

[redacted]

8.3.8. FACE-Q

For FACE-Q, the outcome of all the question of each domain 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). Total raw score and Rasch converted score will be presented.

Mean, SD, 95% confidence interval of the mean, median, min-max, change from Baseline (only for "Satisfaction with Lips" domain), 95% CI for change from Baseline will be summarized by treatment arm. [redacted]

[redacted]

[redacted]

[redacted]

9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

Adverse events will be recorded either directly by the TI or will come from CTR diary per their duration ([redacted]

All AEs will be coded using the MedDRA dictionary.

Number of all AEs, ADEs, [redacted]

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 [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]

The same analyses will be performed for ADEs including also tabulation by SOC and PT.

[redacted]

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]

The CTR incidence rates will be presented by Fitzpatrick skin type subgroups (I-III and IV-VI) and by treatment groups.

[redacted]

Individual data listings of all CTR symptoms and events data will also be given.

[redacted]

[redacted]

9.4. Further Safety Evaluations

9.4.1. Injection Site Pain

Assessment of injection site pain immediately after each injection and at 5, 15 and 30 minutes after injection (0-100 mm VAS) will be described with summary statistics (mean, minimum, maximum, SD, and 95% CI).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. COVID-19 Impact

COVID-19 impacted visits and assessments will be listed.

[redacted]

12. References

[redacted]

13. Tables, Listings, and Figures

All tables, listings, and figures 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 (listing number).

[redacted]

Table 5: Planned tables

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

[redacted]

Table 6: [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]
[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]
[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]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

13.3. Planned Figure Descriptions

[redacted]

Table 7: [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]	[redacted]

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for All Tables, Listings, and Figures

[redacted]

Appendix 1: Abbreviations

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

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