Statistical Analysis Plan

Sponsor	[redacted]
Protocol Title:	A Prospective, Randomized, Blinded Evaluator, Multicenter, Between-subjects Clinical Study to Evaluate Safety and Effectiveness of RHA® 4 versus [redacted] for Treatment of Midface Volume Deficiency
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[redacted]

List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BLE	Blinded Live Evaluator
BMI	body mass index
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
ICF	Informed Consent Form
ICH	International Conference on Harmonization

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

1.2. Hypothesis

The RHA4 group will be statistically non-inferior to the [redacted] group for the treatment of midface volume deficiency as determined by the Teoxane Midface Volume Deficit Scale (TMVDS – 5-point scale [redacted]) 8 weeks after the last treatment (initial or touch-up).

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

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 (non-inferiority) of RHA4 versus [redacted] on adding volume in the midface region in subjects seeking treatment of midface volume deficiency 8 weeks after the last treatment (initial or touch-up).

2.1.2. Secondary Effectiveness Objectives

The secondary objectives are:

- To assess the effectiveness of RHA4 versus [redacted] on adding volume in the midface region in subjects seeking treatment of midface volume deficiency up to 52 weeks after last treatment and 12 weeks after retreatment

[redacted]

2.1.3. Safety Objective

- To assess the safety of RHA4 versus [redacted] in subjects undergoing treatment of midface volume deficiency up to 52 weeks after last treatment and 12 weeks after retreatment

[redacted]

- [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

- 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

At Screening (Visit 0), the TI will evaluate the subject's midface using the 5-grade Teoxane Midface Volume Deficit Scale (TMVDS) for eligibility of the subject

The BLE will evaluate the subject's midface using the TMVDS at Screening to confirm eligibility. This will be done independently of the TI. If the assessments of the TI and the BLE are the same or differ exactly by 1 point of the scale, the difference will be considered acceptable.

Subjects who are eligible to participate in the main study will be enrolled and randomly assigned in a 3:1 ratio to receive RHA4 or .

Administration and Evaluation

At Visit 1, continuous eligibility will be assessed. All evaluations performed at Visit 1 before the injection will be considered for the Baseline.

The TI will inject the device at Visit 1.

Administration of will follow the instructions for use (IFU), the TI can use an FDA-approved needle and/or cannula as per their choice, at each injection.

RHA4 can be injected with a needle, and/or with a cannula; this will be left to the choice of the

[redacted]

The primary endpoint of the study is the difference in the TMVDS change from Baseline to 8 weeks after the last day of treatment between subjects treated with RHA4 and those treated with [redacted].

A Per Protocol (PP) and Intent-to-treat (ITT) analysis sets will be used for the effectiveness analysis.

[redacted]

The devices used for administration must be approved for the use by the US FDA.

Injection area: The TEOXANE SA midface treatment area will focus on the anteromedial and lateral malar regions. The treatment area is delimited using the following triangle: its base line is parallel to the nasolabial fold (at least 0.4″ [1 cm] lateral to the fold), the superior side of the triangle is a line from the superior part of the nasal alar crease to the superior root of the helix of the ear and the inferior side of the triangle is a line running from the lateral oral commissure to the superior root of the helix of the ear.

Treatment of nasolabial folds, temples, pre-auricular and periorbital regions are prohibited.

Amount of device to administer: The maximum volume per administration of RHA4 and [redacted] into the midface area is 6.0 mL per treatment session (total for both sides of the face, i.e., 3.0 mL maximum per side).

3.5. Method of Assigning Subjects to Treatment Groups

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® 4 study device
- [redacted] control device.

[redacted]

3.6. Blinding and Unblinding

The TI, unblinded to treatment allocation, will be asked to minimize the number of people who will have treatment allocation information or who will have any form of access to such information. Access will only be given to personnel who must have it to, for example, administer the filler, call the subjects, or schedule visits.

The BLE and study personnel not involved with the site (e.g., data management, medical monitor) will be blinded to treatment assignment. All evaluations performed by the BLE will be

[redacted]

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

[redacted]

5. Analysis Populations

The following 4 analysis populations are planned for this investigation:

- **Screening population (SCR):** 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 population (SAFT):** All subjects who receive at least 1 treatment with RHA4 or [redacted]. Subjects will be analyzed according to their actual arm.
- **Intent-to-treat population (ITT):** All subjects who are randomly assigned to either the RHA4 group or the [redacted] control group. Subjects will be analyzed according to their initial arm assignment regardless of whether or not they received the planned treatment.
- **Per Protocol population (PP):** All subjects in the ITT population who receive treatment and do not have any major CIP deviations. [redacted].

Analysis of the primary effectiveness endpoints will be based on the PP population [redacted]

[redacted]

[redacted]

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

[redacted]

6.1.6.5. Prior and Concomitant Medications

Medications that started prior to the initial 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.

Subjects retreated with an unexpected treatment at Visit 7 will have their assessments performed after retreatment excluded from the analysis and only listed.

All *P* values will be displayed in 4 decimals and rounded using standard scientific notation (eg, 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:

[redacted]

All protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographics (age, sex, height, body weight, calculate body mass index (BMI), ethnicity, race, Fitzpatrick skin type) will be completed for each of the following populations: ITT, Safety 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 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.

Number of treatment sessions will be tabulated in a frequency table by treatment group.

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

Method of administration, injection technique, depth of injection where device was injected will be tabulated in a frequency table by treatment group.

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

Primary effectiveness analysis will be based on the PP population [redacted] Secondary effectiveness analyses will be based on the ITT population. TMVDS responder rate as assessed by BLE secondary analyses will be repeated for the PP population.

[redacted]

[redacted]

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

[redacted]

8.2.2. Responder Rate Based on TMVDS Assessed by BLE[redacted]

Responder rate will be tabulated by treatment group [redacted]: frequency of responders, percentage of responders along with 95% CI will be tabulated. [redacted]

The following categories are used:

- Responder
- Non-responder

[redacted]

[redacted]

8.2.5. Subject Satisfaction Score

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

Grade description:

1. Very satisfied

[redacted]

5. Very dissatisfied.

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

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.

[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

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,

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]

9.1.1. Deaths and Serious Adverse Events

All deaths occurring during the study will be listed.

All SAEs 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]

10. COVID-19 Impact

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

15. Tables, Listings, and Listing Shells

15.1. Standard Layout for all Tables, Listings, and Figures

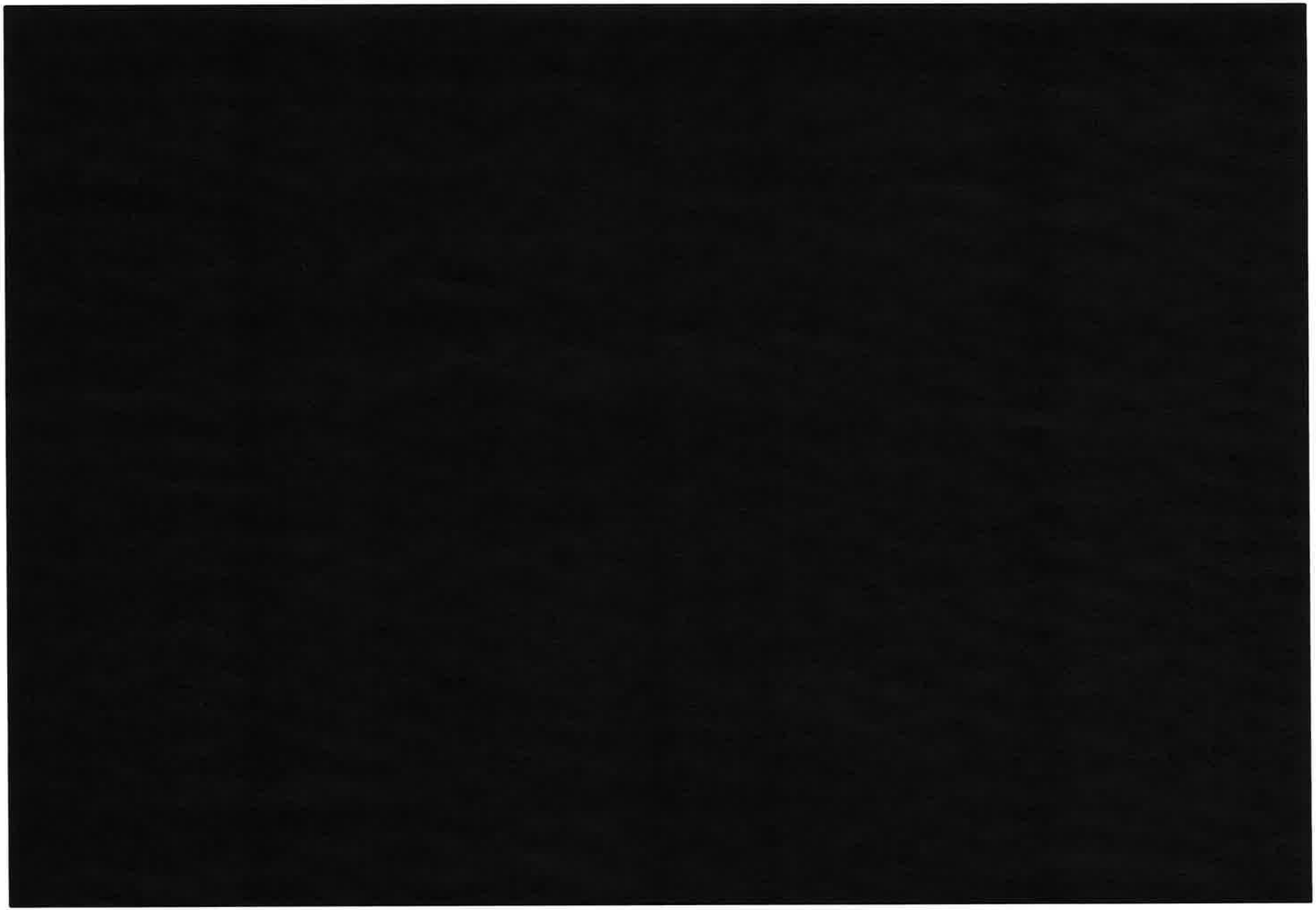
The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each tables, listings and figures (TLF) shell.

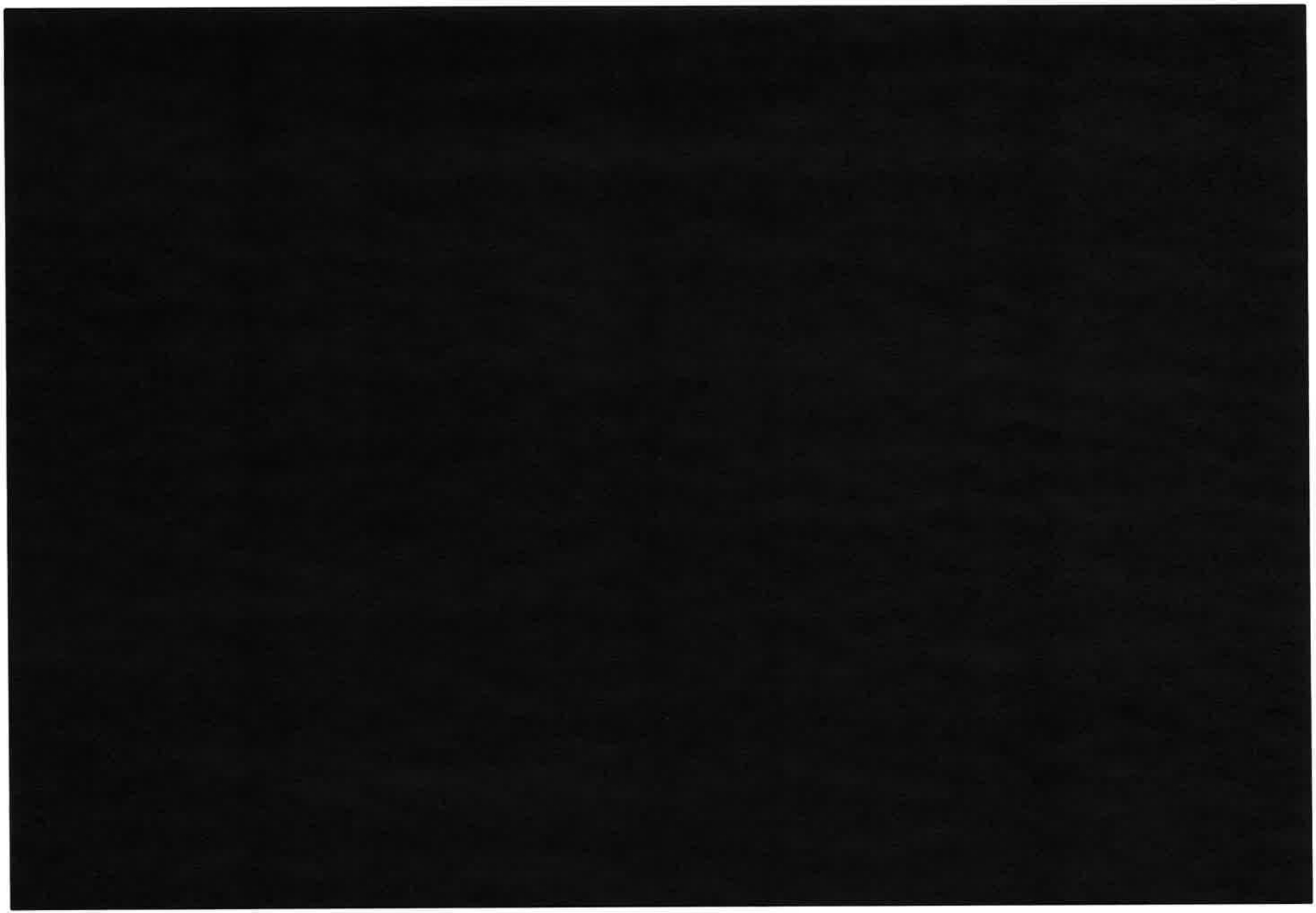
15.2. Planned Table Shells

Will be provided in separate document.

15.4. Planned Figure Shells

Will be provided in separate document.





Appendix 2: Clinical Investigation Design