1. TITLE PAGE

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

Clinical Investigation Plan

INVESTIGATIONAL PRODUCT:	RHA® 4
CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
INVESTIGATIONAL DEVICE EXEMPTION NUMBER:	G210086
DEVELOPMENT PHASE:	Pivotal
INDICATION:	Treatment of midface volume deficiency
METHODOLOGY:	Controlled, randomized, blinded evaluator, multicenter, between subjects, prospective
PROTOCOL VERSION:	[redacted]
PROTOCOL DATE:	12-Jul-2023
INITIAL PROTOCOL:	Original Protocol Version 1.0, 08-Mar-2021
PROTOCOL WRITTEN BY:	[redacted]
SPONSOR:	TEOXANE SA Rue de Lyon 105 CH – 1203 Geneva, Switzerland
SPONSOR CONTACT PERSON:	[redacted]
UNITED STATES SPONSOR:	[redacted]

APPROVAL SIGNATURES

CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
CLINICAL INVESTIGATION PLAN TITLE:	A Prospective, Randomized, Blinded Evaluator, Multicenter, Between-subjects Clinical Study to Evaluate Safety and Effectiveness of RHA® 4 versus [redacted] XC for Treatment of Midface Volume Deficiency

I, the undersigned, have read this clinical investigation plan and confirm that, to the best of my knowledge, it accurately describes the planned conduct of the investigation.

SIGNATURE **DATE**

[redacted]
Sr Clinical Project Manager
[redacted]

[redacted]
Clinical Program Manager
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[redacted]
Clinical Development and Medical Affairs Director
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Regulatory Affairs Director
[redacted]

[redacted]

SIGNATURE **DATE**

[redacted]
Biostatistician
[redacted]

[redacted]

AMENDED PROTOCOL

Revision history:

TITLE:	A Prospective, Randomized, Blinded Evaluator, Multicenter, Between-subject Clinical Study to Evaluate Safety and Effectiveness of RHA® 4 versus [redacted] for Treatment of Midface Volume Deficiency
CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
PROTOCOL VERSION:	[redacted]
ORIGINAL PROTOCOL DATE:	Original Protocol Version 1.0, 08-Mar-2021
AMENDMENT 1 DATE:	[redacted]
AMENDMENT 2 DATE:	[redacted]
AMENDMENT 3 DATE:	[redacted]
AMENDMENT 4 DATE:	[redacted]
AMENDMENT 4.1 DATE:	[redacted]
AMENDMENT 5 DATE:	[redacted]
AMENDMENT 5.1 DATE	[redacted]
AMENDMENT 5.2 DATE	[redacted]
AMENDMENT 6 DATE:	[redacted]
AMENDMENT 7 DATE:	[redacted]
AMENDMENT 8 DATE:	Amended Protocol Version [redacted], 12-Jul-2023

The following are the amended protocol and appendices, including all revisions specified in the REASONS FOR AMENDMENT and SUMMARY OF AMENDED SECTIONS.

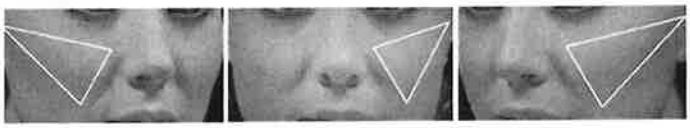
2. CLINICAL INVESTIGATION PLAN SUMMARY

2.1. Summary

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
TITLE OF INVESTIGATION	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
SPONSOR/ MANUFACTURER	TEOXANE SA, Rue de Lyon 105, CH – 1203 Geneva, Switzerland
DEVELOPMENT PHASE:	Pivotal
CONTROL DEVICE NAME	[redacted]
INDICATION FOR USE	RHA® 4 (further referred to as "RHA4") injectable gel is intended to be used for injection into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies in subjects aged 22 or older.
CLINICAL INVESTIGATION PURPOSE	The purpose of the clinical investigation is to evaluate the safety and effectiveness of RHA4 when compared to [redacted] in the treatment of midface volume deficiency.
TREATMENT GROUPS	This study plans to enroll at least 200 subjects (≥20% of subjects with Fitzpatrick skin types IV-VI, including 10% of subjects with types V/VI with at least 5 subjects with type V and 5 subjects with type VI) with a maximum of 210 subjects. At least 10% of subjects will be male. Subjects will be randomly assigned (3:1 ratio) at Screening to the following groups: • RHA4 group – approximately 150 subjects • [redacted] – approximately 50 subjects [redacted]
STUDY CENTERS AND LOCATION	8 to 10 investigative sites in the United States (US) will participate [redacted]
STUDY DURATION	Individual study participation: The minimum and maximum anticipated duration of subject participation [redacted] are 52 and 71 weeks, respectively. [redacted]

[redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
OBJECTIVES	• Primary effectiveness objective: ○ To assess the effectiveness 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) • Secondary effectiveness objectives: ○ 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] • 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]
DEVICE TREATMENT	The Treating Investigator (TI) is recommended to follow the injection guideline for RHA4 administration and [redacted] Instructions for Use (IFU) for [redacted] injection. Briefly: <u>Injection depth</u> Study and control devices (RHA4 and [redacted]) will be injected in the subcutaneous and/or supraperiosteal layers. [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] Injection area The TEOXANE SA midface treatment area will focus on the anteromedial and lateral malar regions. A schematic of the treatment area is delimited using the triangle below. 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. [redacted]  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). [redacted]
INVESTIGATION DESIGN	Enrollment This is a prospective, randomized, controlled, blinded evaluator, multicenter, between subjects clinical study to identify whether RHA4 is non-inferior to [redacted] for treatment of midface volume deficiency 8 weeks after the last treatment (initial or touch-up). [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] The Blinded Live Evaluator (BLE) will evaluate the subject's midface as a whole using the TMVDS at Screening to confirm eligibility. This will be done independently of the TI. [redacted] Subjects who are eligible to participate [redacted] will be enrolled and randomly assigned in a 3:1 ratio at Visit 1 to receive RHA4 or [redacted]. [redacted] 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.

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	Administration of [redacted] will follow the IFU, the TI can use an FDA-approved needle and/or cannula as per their choice at each injection. Administration method and injection technique at each injection will be recorded. RHA4 can be injected with a needle and/or with a cannula; this will be left to the choice of the TI at each injection. Administration method and injection technique at each injection will be recorded. If necessary, subjects will receive a touch-up treatment to optimize the results 4 weeks after the initial treatment with the same product that they received at Visit 1. The TI will conduct safety and effectiveness evaluations at each study visit occurring [redacted] weeks after the initial or touch-up treatment ([redacted]). Additionally, the TI or designee will call the subjects 3 days after each treatment to ask questions about their health status and AEs [redacted] and will conduct safety evaluations 2 weeks after each treatment session [redacted]. All subjects, regardless of whether they received RHA4 or [redacted] at Visit 1 and regardless of whether they received touch-up treatment or not, will be offered a retreatment with RHA4 [redacted]. Retreatment will be administered if the TI deems it appropriate and if the subject agrees. [redacted] The subject will then be followed for 12 weeks after retreatment [redacted] before exiting the study or until all treatment-related adverse events (AEs) have resolved or until the TI determines that follow-up is no longer necessary. Subjects not receiving retreatment will exit the study [redacted] (52 weeks after the last treatment). Subjects will report their common treatment responses (CTRs) in a subject diary for 30 days after each injection. The diary will also include a list of selected AEs that are potentially associated with dermal filler injections, and subjects who experience such AEs will be required to immediately report them to the TI or seek medical attention if they experience them. [redacted] The TI will follow up on the subject until the Exit visit [redacted] or until all treatment-related ongoing AEs have resolved or until the TI determines that follow-up is no longer necessary. BLE assessments The BLE will conduct assessments of effectiveness [redacted] primary endpoint, and all visits [redacted]. If the subject receives retreatment, the BLE will conduct additional assessments [redacted] In case of premature termination, the BLE will also conduct the assessment at the Exit visit. [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] For further details on procedures and timing of the events please refer to the Schedule of Events table.
BLINDING	The BLE will be blinded to allocation to groups (RHA4 group or [redacted] group). Furthermore, to ensure that they remain blinded and unbiased when making their assessments throughout the study, the BLE, TI, and subjects will not be allowed to refer to each other's effectiveness assessments. All subjects will be instructed to not discuss their study treatment, AEs, or CTRs with the BLE.
ASSESSMENTS	• TMVDS: A validated proprietary 5-point scale [redacted] assessing the volume deficit in the midface region • Global Aesthetic Improvement Scale (GAIS): A balanced, 5-point scale assessing aesthetic improvement • FACE-Q scale (satisfaction with cheeks): A subject-reported outcome measure, assessed by the subject using the satisfaction with cheeks scale. This assessment will be performed at rest and when smiling. • Subject satisfaction scale: A balanced, 5-point scale assessing subject satisfaction with study treatment [redacted] • Adverse Events: with the focus on AEs related to treatment (ADEs), Unanticipated Adverse Device Effects (UADEs), Serious AEs (SAEs), Adverse Events of Special Interest (AESIs), AEs from CTRs, causality, duration, and severity as per TI assessment

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] • Post-injection CTRs: through 30-day subject CTR diary, which also includes vision disturbances • [redacted]
ELIGIBILITY CRITERIA	Inclusion Criteria [redacted]: A potential subject will be enrolled in the study if the subject meets all of the following inclusion criteria: 1. Is outpatient, male or female of any race, 22 years of age or older 2. If female, is not pregnant, not breastfeeding, and either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or must have a negative urine pregnancy test (UPT) at Visit 1 and prior to each injection and must agree to practice 1 of the following medically acceptable methods of birth control throughout the study: [redacted] 3. Seeks treatment of midface volume deficiency (realistic and achievable as per TI opinion) [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 7. Is able to follow study instructions and complete all required visits 8. Is willing to sign the institutional review board-approved ICF, photographic release form, and the authorization for use and release of health and research study information (Health Insurance Portability and Accountability Act) form and, if applicable, the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed. Exclusion Criteria [redacted]: A potential subject will be excluded from the study if the subject meets any of the following exclusion criteria: [redacted] 2. Has known hypersensitivity or previous allergic reaction to any component of the study or the control device 3. Has known sensitivity to local anesthetics of the amide type, including known or suspected lidocaine hypersensitivity, history of multiple severe allergies, or history of anaphylactic shock 4. Has known susceptibility to keloid formation, hypertrophic scarring, or clinically significant skin pigmentation disorders as judged by the TI 5. Has a history of severe chronic systemic diseases, including but not limited to, poorly controlled diabetes mellitus (all types), congestive heart failure, severe liver disease, severe kidney disease, and others that are likely to interfere with the measured parameters or to put the subjects to an undue risk as judged by the TI [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 15. Has medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or

INVESTIGATIONAL PRODUCT NAME	RHA® 4
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	compliance of the subject and would make the subject inappropriate for entry into this study, as judged by the TI 16. Has clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability, as judged by the TI [redacted]

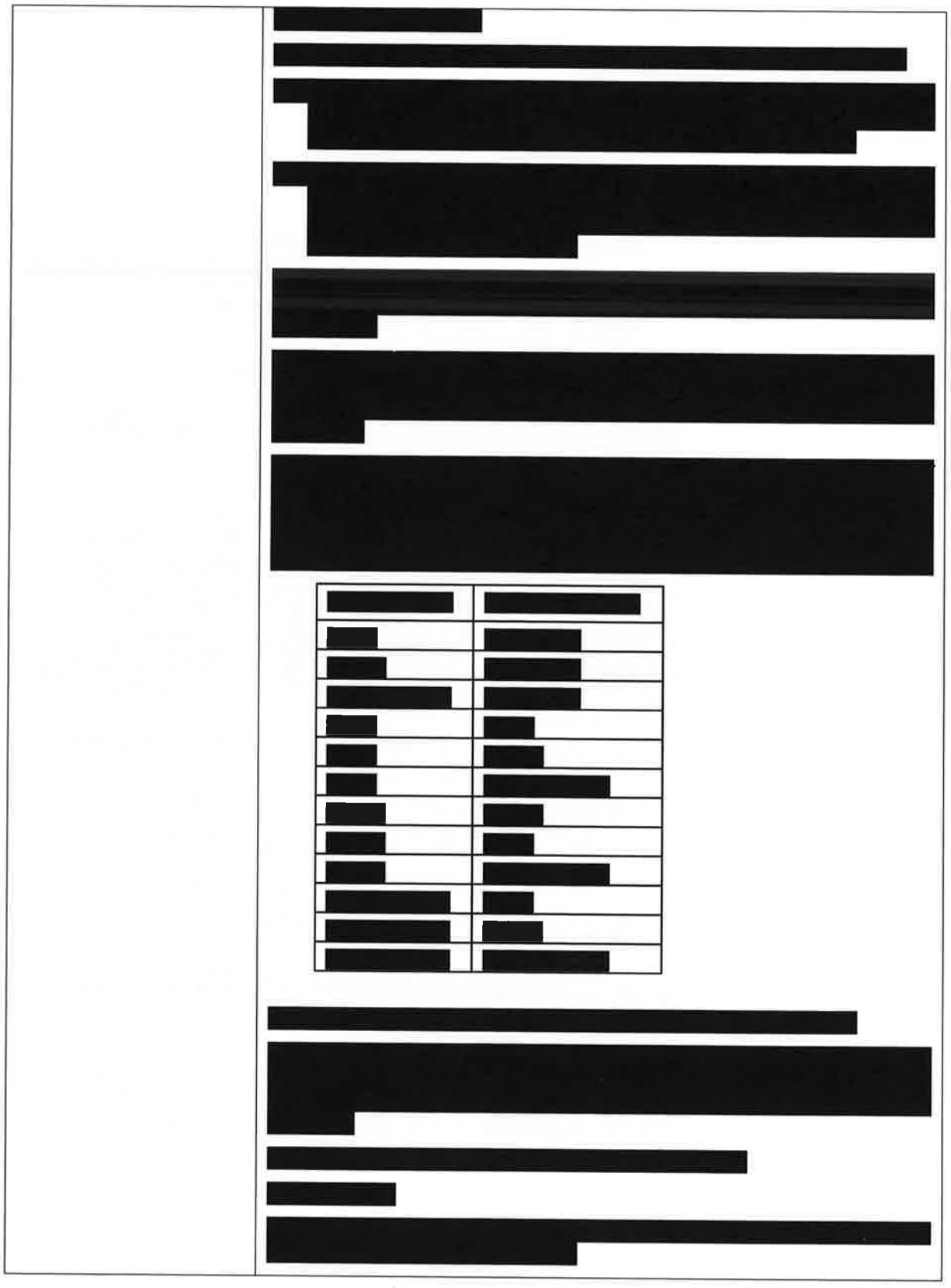
INVESTIGATIONAL PRODUCT NAME	RHA® 4
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
[redacted]	[redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 12. [redacted]
PRIMARY EFFECTIVENESS ENDPOINT	The effectiveness of RHA4 will be demonstrated if the change from Baseline for subjects treated with RHA4 is statistically non-inferior to the change from Baseline for subjects treated with [redacted] 8 weeks after the last treatment (at Visit 3) as assessed by the BLE using the TMVDS. Non-inferiority margin is set as 0.5. A change in the TMVDS ≥1 grade compared to pretreatment will be considered clinically meaningful. [redacted]
SECONDARY EFFECTIVENESS ENDPOINTS	• TMVDS change from Baseline assessed: [redacted]By the BLE at each visit [redacted] • Responder rate for TMVDS (≥1 grade improvement on the TMVDS compared to Baseline): [redacted]By the BLE at each visit [redacted] • GAIS as assessed: [redacted]By the BLE at each visit [redacted] • FACE-Q scores assessed by the subject [redacted]

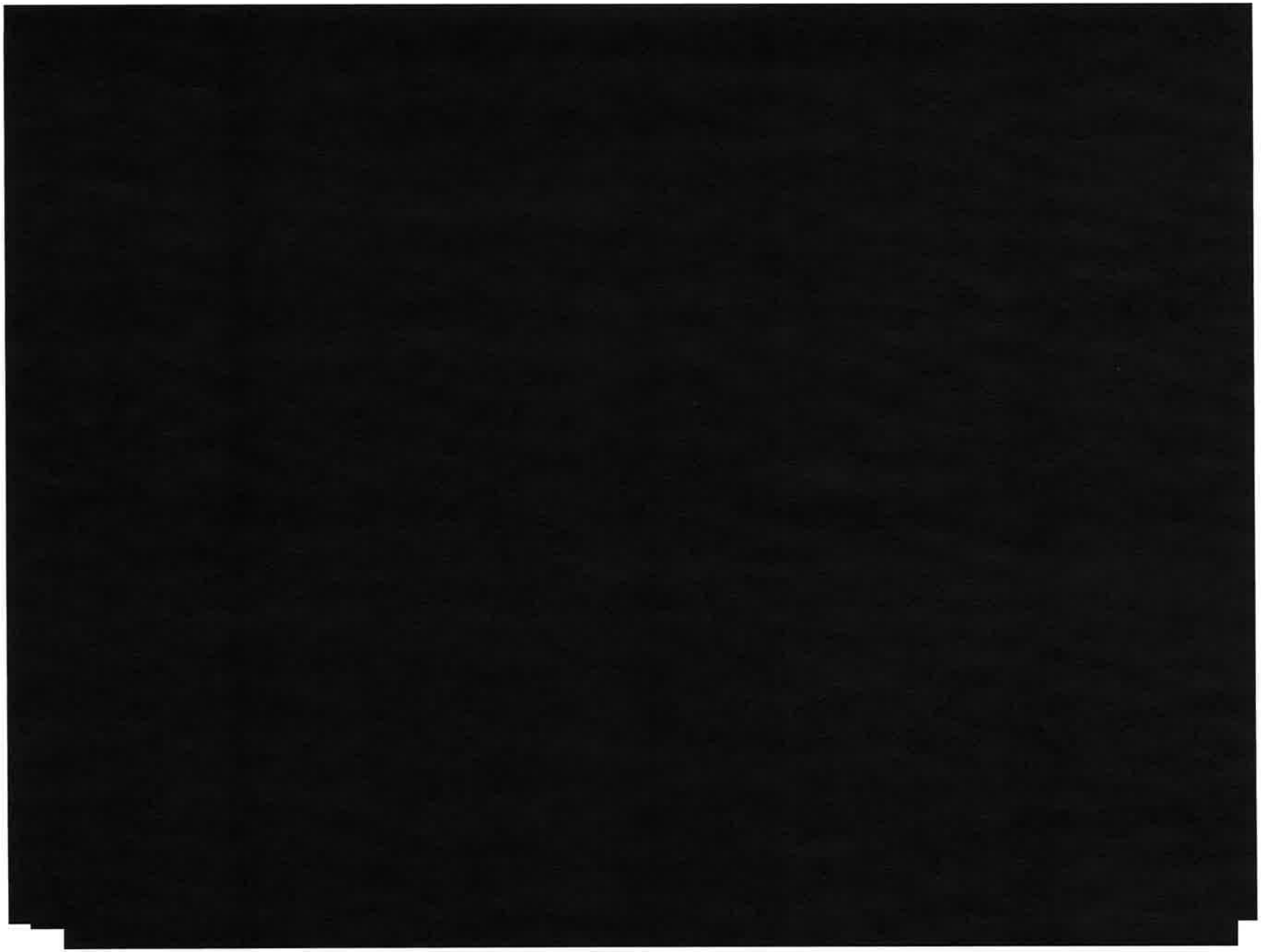
INVESTIGATIONAL PRODUCT NAME	RHA® 4
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] Subject satisfaction assessed by the subject [redacted]
SAFETY ENDPOINTS	• Adverse events with a focus on treatment-related AEs based on the TI assessment, and AEs reported from the CTR diary [redacted] • Post-injection CTR, including vision disturbances, through 30-day subject CTR diary [redacted] • [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
[redacted]	[redacted]
SAMPLE SIZE	[redacted]
STATISTICAL METHODS AND ANALYSIS SUMMARY	All data will be recorded in an electronic case report form. [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 4**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted]

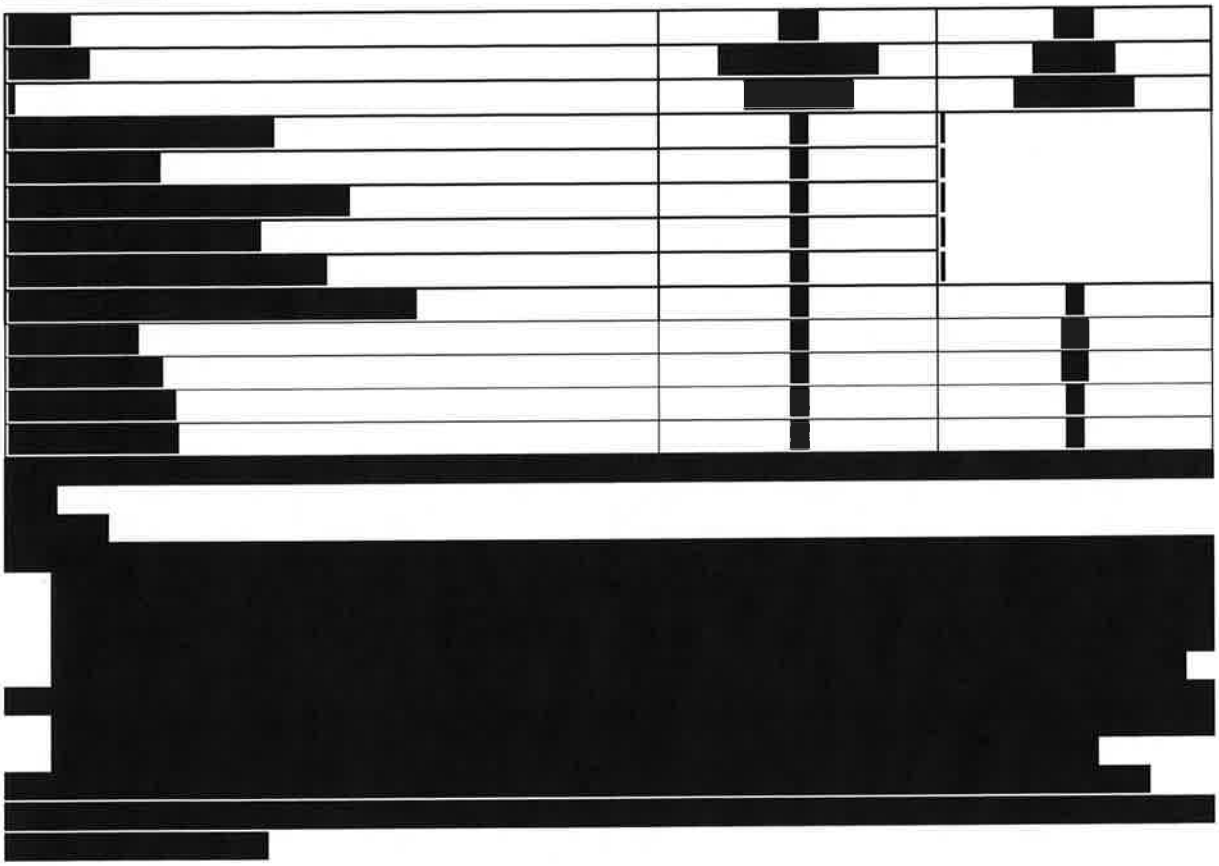


INVESTIGATIONAL PRODUCT NAME	RHA® 4
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted]



[redacted]

[redacted]



3. TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5. INTRODUCTION TO THE CLINICAL INVESTIGATION

5.1. Background

The cheeks or midface area represent a key feature of the face, and together with the eyes, nose, and lips, are associated with youth and attractiveness. The shape and fullness of the cheeks are influenced by a multitude of internal and environmental factors that can dramatically change the cheek's appearance over time.[1] In recent years, a greater cultural value on youth and health along with improved techniques have resulted in an increase in cosmetic procedures, and the cheeks have become an area of choice for facial rejuvenation.

Loss of subcutaneous fullness is one of the key factors that contributes to the aging of the cheeks.[1] With age, depletion of subcutaneous fullness in the malar prominence and progressive buccal hollowing causes suboptimal facial proportion, while the loss of infraorbital subcutaneous tissue gives rise to more prominent orbicularis oculi and results in "crow's feet" (rhytids). In addition, ptotic cheek fat can descend over time to form nasolabial folds (NLFs), resulting in a cheek concavity that is further highlighted by gradually reduction of malar fullness.

The cheek is the facial injection site that can benefit the most from rejuvenation.[2] Treatment in the midface includes surgical (such as cheek implants) and nonsurgical procedures (such as injection of soft tissue fillers).[3] Injection of such fillers for facial volume restoration and contour enhancement has shown to be a favorable treatment as the procedure can be performed quickly, cause little down time, and yield a high rate of patient satisfaction.[2] Soft tissue fillers are most frequently used in the form of hyaluronic acid (HA) and in general were the second most frequently used medical devices for minimally invasive cosmetic procedures in 2019.[4] Fillers consisting of HA that are approved by the United States (US) Food and Drug Administration (FDA) include Juvéderm® [redacted] and Restylane® Lyft for cheek augmentation.[5]

Hyaluronic acid, also known as hyaluronan, is the most abundant glycosaminoglycan found in the human dermis. Used as a dermal filler, HA has a long record of data confirming its safe use. The persistence of HA in the tissues and its resistance to degradation can be obtained by chemical crosslinking, which allows modification of the rheological and physical properties of the HA, while maintaining the biocompatibility of the basic polymer.[6] The injection of an HA gel dermal fillers, as a minimally invasive procedure, has been the method of choice for the augmentation and enhancement of the cheeks. This clinical investigation will evaluate the use of the HA dermal filler RHA4 for the treatment of midface volume deficiency.

5.2. Study Device Name

RHA® 4 (further only "RHA4"). RHA stands for Resilient Hyaluronic Acid.

5.3. Intended Purpose Statement

RHA4 is intended to be used for cheek augmentation and/or correction of age-related midface contour deficiencies in subjects aged 22 years or older.

5.4. Investigational Product Description

The device under clinical investigation is RHA4 manufactured by TEOXANE SA.[7]

[redacted]

[redacted]

5.4.1. Delivery System and Implantation

RHA4 is supplied in individual blister packages containing a 1.2 mL treatment syringe with two 27G ½" needles. The contents of the syringe are sterile and non-pyrogenic. They should not be resterilized or used if the blister package has been opened or damaged.

[redacted]

5.4.2. Nonclinical Testing and Previous Clinical Experience

All information regarding preclinical testing and previous clinical experience with RHA4 is included in the current IB.[6]

5.5. Control Device

The control device is [redacted]

[redacted] is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenous gel implant. It consists of HA produced by *Streptococcus equi* species of bacteria, which is crosslinked with BDDE. It is formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

[redacted] is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults over the age of 21.

[redacted]

[redacted] should be used according to its IFU.[8]

5.6. Injection of RHA4 or [redacted]

The TI is recommended to follow the injection guideline for RHA4 administration and [redacted] IFU[8] for [redacted] injection. Briefly:

Injection depth: Study and control devices (RHA4 and [redacted]) will be injected in the subcutaneous and/or supraperiosteal layers.

[redacted]

Administration method: For RHA4, the needle that could be used is the one provided in the box (27G ½" needle [TSK]) and/or the cannula [redacted]

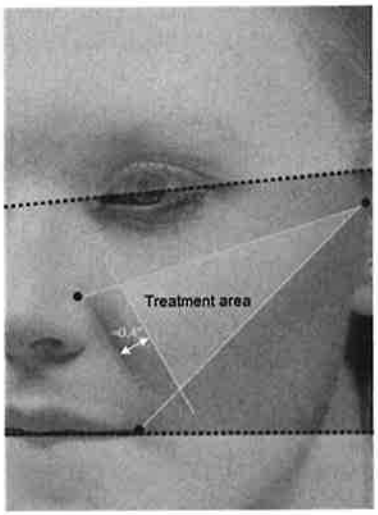
[redacted]

[redacted]

Injection area: The TEOXANE SA midface treatment area will focus on the anteromedial and lateral malar regions. A schematic of the treatment area is delimited using the following triangle (Figure 5-1): 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.

Figure 5-1: Midface Treatment Area



Amount of device to administer: The maximum volume per administration of the 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).

[redacted]

5.7. Justification for the Clinical Investigation

In the US, RHA4 is FDA-approved for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as NLFs, in adults 22 years or older. Assuming a similar volumizing effect, the purpose of this investigation is to inject RHA4 into the subcutaneous and/or supraperiosteal for cheek augmentation and/or correction of age-related midface contour deficiencies. Assuming a similar volumizing effect, the investigation is also designed to demonstrate that RHA4 is non-inferior to [redacted] for this indication in subjects aged 22 years or older. The goal is to show that treatment with RHA4 will result in added volume to the cheeks 8 weeks after the last treatment.

[redacted]

5.7.1. Justification for the Clinical Investigation Design

The investigation is designed to prospectively evaluate RHA4 in treatment of midface volume deficiency, and to compare its safety and effectiveness to that of [redacted]. The clinical investigation design was selected to minimize bias by using subject randomization and blinding of the independent evaluator (Blinded Live Evaluator [BLE]), whose assessments will be used for the primary and secondary endpoint analyses. The comparison of the safety and effectiveness of RHA4 against [redacted] will be done between subjects and will include subjects from multiple sites.

[redacted]

6. CLINICAL INVESTIGATION PURPOSE, OBJECTIVES, AND ENDPOINTS

6.1. Clinical Investigation Purpose

The purpose of this clinical investigation is to evaluate the safety and effectiveness of RHA4 when compared to [redacted] for the treatment of midface volume deficiency.

6.2. Objectives

6.2.1. Primary Effectiveness Objective

- To assess the effectiveness 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) (Table 6-1)

6.2.2. Secondary Effectiveness Objective

- 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]

6.2.3. Safety Objective

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

[redacted]

Table 6-1: Objectives Mapped to Endpoints

Objectives	Endpoints
Primary effectiveness	
• To assess the effectiveness 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)	• The effectiveness of RHA4 will be demonstrated if the change from Baseline for subjects treated with RHA4 is statistically non-inferior to the change from Baseline for subjects treated with [redacted] 8 weeks after the last treatment (at Visit 3) as assessed by the BLE using the TMVDS. Non-inferiority margin is set as 0.5. • A change in the TMVDS ≥1 grade compared to pretreatment will be considered clinically meaningful. • [redacted]
Secondary effectiveness[a]	
• 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	• TMVDS change from Baseline assessed: [redacted] By the BLE at each visit [redacted] • Responder rate for TMVDS (≥1 grade improvement on the TMVDS compared to Baseline): [redacted] By the BLE at each visit [redacted] • GAIS as assessed: [redacted] By the BLE at each visit [redacted] [redacted] FACE-Q scores assessed by the subject at each visit ([redacted] [redacted] Subject satisfaction assessed by the subject at each visit [redacted] • [redacted]
• [redacted]	[redacted]

[redacted]

	○ [redacted]
[redacted]	[redacted]
Safety	
• To assess the safety of RHA4 versus [redacted] in subjects undergoing treatment of midface volume deficiency to 52 weeks after last treatment and 12 weeks after retreatment	• Adverse events with a focus on treatment-related AEs based on the TI assessment, and AEs reported from the CTR diary [redacted] Post-injection CTR, [redacted] • [redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	

6.3. Hypothesis

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

[redacted]

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

6.4. Risks and Anticipated Adverse Device Effects

The safety of the study and control devices has not been established during pregnancy or in breastfeeding females.

The following risks have been associated with the use of HA dermal fillers in general, not just RHA4. There are various types of risks associated with the injection of an HA dermal filler on the face:

- Risks associated with all skin injection procedures
- Risks associated with the anesthetic agent (lidocaine) or other allergens
- Risks that are typically associated with RHA4, [redacted], and HA dermal fillers in general
- Other risks that are not typical but have been reported in the literature

6.4.1. Risks Associated with All Skin Injection Procedures

The following are risks associated with all skin injection procedures:

- Infection
- Bleeding
- Blistering
- Bruising (ecchymosis)
- Increased bleeding or bruising at the injection site if using medications that reduce the ability to clot (such as aspirin, ibuprofen [e.g. Motrin® or Advil®], vitamin E and prescription anticoagulants)
- Pain at and around the injection site that could induce lightheadedness or fainting

6.4.2. Risks Associated with the Anesthetic Agent (Lidocaine) or Other Allergens

Subjects with known history of allergy to lidocaine or Gram-positive bacterial proteins should not receive any injection as both study and control devices contain them and they risk anaphylactic shock. Reported anaphylactic shocks are very rare.

The concentration of lidocaine is low and the risk of other types of allergic reactions is low. Those allergic reactions may include skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and temporary loss of skin color.

6.4.3. Risks That Are Typically Associated with RHA4, [redacted], and HA Dermal Fillers in General

The following have been associated with the use of HA dermal fillers. Although RHA4 has shown some differences compared to some of the HA dermal fillers currently available, they are expected to share a similar safety profile.[6,9] The following risks are anticipated adverse device events when using an HA dermal filler:

- There are common treatment reactions such as: redness (erythema), inflammation, pain, tenderness, firmness (induration), swelling, lumps/bumps, bruising (ecchymosis), edema, itching, discoloration/hyperpigmentation.
- Other, less frequent risks have also been reported such as paresthesia, rash, telangiectasia, dermatitis, scarring, scab, peeling/shedding, urticaria, abscess formation, papules, blister, product migration, nausea, headache, reactivation of herpes, malaise, hypersensitivity, lack of effect, injection site inflammation, injection site abscess, injection site cellulitis, gingival pain, and acne cyst.

[redacted]

[redacted]

For further and most recent information about RHA4, refer to the most recent version of the IB[6] and the IFU.[7]

7. CLINICAL INVESTIGATION DESIGN

Enrollment

This is a prospective, randomized, controlled, blinded evaluator, multicenter, between subjects clinical study to identify whether RHA4 is non-inferior to [redacted] for treatment of midface volume deficiency 8 weeks after the last treatment (initial or touch-up).

[redacted]

[redacted]

[redacted]

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 [redacted] will follow the IFU, the TI can use an FDA-approved needle and/or cannula as per their choice at each injection. [redacted]

[redacted]

If necessary, subjects will receive a touch-up treatment to optimize the results 4 weeks after the initial treatment with the same product that they received at Visit 1. The TI will conduct safety and effectiveness evaluations at each study visit [redacted] after the initial or touch-up treatment [redacted]. Additionally, the TI or designee will call the subjects 3 days after each treatment to ask questions about their health status and [redacted] and will conduct safety evaluations 2 weeks after each treatment session [redacted].

All subjects, regardless of whether they received RHA4 or [redacted] at Visit 1 and regardless of whether they received touch-up treatment or not, will be offered a retreatment with RHA4 [redacted] (52 weeks after the last treatment). Retreatment will be administered if the TI deems it appropriate and if the subject agrees. [redacted] The subject will then be followed for 12 weeks after retreatment [redacted] before exiting the study or until all treatment-related adverse events (AEs) have resolved or until the TI determines that follow-up is no longer necessary. Subjects not receiving retreatment will exit the study [redacted] 52 weeks after the last treatment).

Subjects will report their common treatment responses (CTRs) in a subject diary for 30 days after each injection. The diary will also include a list of selected AEs that are potentially associated with dermal filler injections, and subjects who experience such AEs will be required to immediately report them to the TI or seek medical attention if they experience them. All efforts should be made by the TI or designee to schedule the applicable visits [redacted] to allow completion of the CTR diary. [redacted]

The TI will follow up on the subject until the Exit visit [redacted] or until all treatment-related ongoing AEs have resolved or until the TI determines that follow-up is no longer necessary.

[redacted]

BLE assessments

The BLE will conduct assessments of effectiveness [redacted] all visits [redacted]. If the subject receives retreatment, the BLE will conduct additional assessments [redacted]. In case of premature termination, the BLE will also conduct the assessment at the Exit visit.

[redacted]

Figure 7-1: Investigation Design

7.1. Clinical Investigation Duration

Individual study participation: The minimum and maximum anticipated duration of subject participation are 52 and 71 weeks, respectively. [redacted]

[redacted]

[redacted]

7.2. Clinical Investigation Enrollment

[redacted]

This study plans to enroll at least 200 [redacted] with a maximum of 210 subjects. [redacted]

Subjects will be randomly assigned (3:1 ratio) at Screening to 1 of the following groups:

- RHA4 group – approximately 150 subjects
- [redacted] group – approximately 50 subjects

[redacted]

The TI and the subject will not be blinded, while the BLE will be blinded to allocation to groups (RHA4 group or [redacted] group). All evaluations performed by the BLE will be conducted completely separately from the TI, and the BLE must not have any access to subject documents, records, notes, or any other sources of information that might indicate the allocated treatment. The BLE must have a separate eCRF account that will not allow him/her to access any data about the subject.

[redacted]

Subjects who do not meet all inclusion criteria or meet any of the exclusion criteria will not be enrolled.

7.3. Clinical Investigation Sites

The clinical study is to be conducted at 8 to 10 investigational sites in the US. [redacted]

[redacted]

[redacted]

[redacted]

7.4. Selection of Clinical Investigation Subject Population

Subjects who seek treatment of midface volume deficiency are possible candidates for the clinical investigation and will be screened for eligibility based on the inclusion and exclusion criteria below.

[redacted]

Vulnerable subjects:

Part 21 Code of Federal Regulations (CFR)/Good Clinical Practice (GCP)/International Organization for Standardization (ISO) regulations, and IRBs stipulate that additional protections should be included for individuals who are deemed vulnerable:

- Prisoners
- Pregnant women and fetuses
- Children
- Cognitively impaired persons and adult subjects who cannot consent for themselves, in which case, a legally authorized representative would provide consent

Individuals who are deemed vulnerable are excluded from the clinical investigation.

7.4.1. Inclusion Criteria

A potential subject will be enrolled to the main study if the subject meets all of the following inclusion criteria:

1. Is outpatient, male or female of any race, 22 years of age or older
2. If female, is not pregnant, not breastfeeding, and either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or must have a negative urine pregnancy test (UPT) at Visit 1 and prior to each injection and must agree to practice 1 of the following medically acceptable methods of birth control throughout the study:

[redacted]

[redacted]

3. Seeks treatment of midface volume deficiency (realistic and achievable as per TI opinion)

[redacted]

7. Is able to follow study instructions and complete all required visits
8. Is willing to sign the IRB-approved ICF, photographic release form, and the authorization for use and release of health and research study information (Health Insurance Portability and Accountability Act) form and, if applicable, the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed.

7.4.2. Exclusion Criteria

A potential subject will be excluded from the main study if the subject meets any of the following exclusion criteria:

[redacted]

2. Has known hypersensitivity or previous allergic reaction to any component of the study or the control device
3. Has known sensitivity to local anesthetics of the amide type, including known or suspected lidocaine hypersensitivity, history of multiple severe allergies, or history of anaphylactic shock
4. Has known susceptibility to keloid formation, hypertrophic scarring, or clinically significant skin pigmentation disorders as judged by the TI
5. Has a history of severe chronic systemic diseases, including but not limited to, poorly controlled diabetes mellitus (all types), congestive heart failure, severe liver disease, severe kidney disease, and others that are likely to interfere with the measured parameters or to put the subjects to an undue risk as judged by the TI

[redacted]

[redacted]

[redacted]

15. Has medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or compliance of the subject and would make the subject inappropriate for entry into this study, as judged by the TI
16. Has clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability, as judged by the TI

[redacted]

[redacted]

[redacted]

[redacted]

8. INVESTIGATION PROCEDURES

8.1. Procedures by Visit

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

[redacted]

8.1.1. Visit 0 (Week up to -3)

Visit 0 is the Screening visit. [redacted]

The screening procedures will include the following assessments:

1. Obtain written informed consent
2. Collect demographic information
3. Record medical history, including current therapies (e.g., prescription and nonprescription medications) and previous surgeries
4. Measure height, weight, calculate body mass index (BMI)
5. Collect prior and concomitant medications
6. Perform the TMVDS assessment (both the TI and the BLE)

[redacted]Assess inclusion/exclusion criteria [redacted]

[redacted]

8.1.2. Visit 1 (Week 0)

Visit 1 is the first day of the study, Week 0 for all subjects.

[redacted]

Subjects who are eligible [redacted] at Visit 0 [redacted] will have following assessments performed **before the injection**:

1. TI
    a. UPT for female subjects of childbearing potential
    [redacted]
    c. TMVDS (does not need to be repeated if Visit 0 is on the same day as Visit 1)
    d. Review continuous eligibility
    e. Photography of the subject's midface area
2. BLE
    a. TMVDS (does not need to be repeated if Visit 0 is on the same day as Visit 1)
    [redacted]
3. Subject
    [redacted] FACE-Q questionnaire [redacted]

All these assessments represent Baseline [redacted]

[redacted]

The TI will **administer the allocated filler** maintaining the blinding described in Section 9.3 and according to the IB, IFUs and Section 9.7. [redacted]

[redacted]

[redacted]

8.1.3. Visit [redacted] (Telephone Call, +3 Days After the Initial Treatment)

Visit [redacted] is a telephone call 3 ± 2 days after the initial treatment (3 days from the last treatment) for all subjects.

The TI or designee will collect information about potential AEs [redacted]

[redacted] **Visit** [redacted]

Visit 1B is performed at the site 2 weeks ± 3 days after the initial treatment.

The TI or designee will collect information about potential AEs, review the partially completed 30-day CTR diary and perform vision assessments.

[redacted]

[redacted]

[redacted]

8.1.9. Visit [redacted] (Primary Endpoint, 8 Weeks After the Last Treatment)

Visit [redacted] is at the site and will be scheduled 8 weeks ±3 days after the last treatment, either initial or touch-up. The assessments performed at this visit will be used for the primary endpoint evaluation.

[redacted]

2. BLE:
    a. TMVDS
    [redacted]
    d. GAIS
3. Subject:
    [redacted] FACE-Q questionnaire [redacted]
    b. GAIS
    c. Subject satisfaction
    [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Assessments

8.2.1. Urine Pregnancy Test

A UPT for women of childbearing potential only will be conducted at the site prior to each application of the filler (Section 2.2).

[redacted]

8.2.2. Safety Assessments

Safety assessments will include the evaluation of AEs, [redacted]

8.2.2.1. Adverse Events

The definition and management of AEs, and any special considerations for AEs, are provided in Section 10.

[redacted]

[redacted]

[redacted]

8.2.2.4. Common Treatment Response

The subject will receive a diary booklet and instructions for recording their observations of the CTRs of the study treatments [redacted]

[redacted]

[redacted]

[redacted]

8.2.3.1. Teoxane Midface Volume Deficit Scale

Midface volume deficiency will be assessed by the TI and the BLE at time points in the Schedule of Events (Section 2.2) using the 5-point TMVDS provided in Appendix B. [redacted]

For eligibility purposes only: if the TI and BLE assessment differ by exactly 1 point on the TMVDS, this is considered acceptable. [redacted] 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 more than 1 point of the scale, the subject will not be eligible.

[redacted]

8.2.3.2. Global Aesthetic Improvement

Global aesthetic improvement assessment will be assessed by the [redacted], BLE, and subjects at time points in the Schedule of Events (Section 2.2) using a 5-grade GAIS (Table 8-1). [redacted]

[redacted]

Table 8-1: Global Aesthetic Improvement Scale

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

8.2.3.3. FACE-Q

The subject-reported outcome measure FACE-Q scale[15] will be assessed as in the Schedule of Events (Section 2.2). Only one selected scale (satisfaction with cheeks scale) from the FACE-Q will be used for the purpose of this study. This scale measures the appearance of the midface area with items that ask about the symmetry, smoothness, attractiveness, contours and youthful fullness of the cheeks. The subject will be asked to complete FACE-Q questionnaire at rest and when smiling This scale is provided in Appendix C.

8.2.3.4. Subject Satisfaction

Subject satisfaction will be measured by using a 5-point balanced scale [redacted] The subject will be instructed to "Rate your level of satisfaction with the effect of study treatment in the treated area by using the following scale" (provided in Table 8-2).

Table 8-2: Subject Satisfaction Scale

Grade	Description
1	Very satisfied
2	[redacted]
3	[redacted]
4	[redacted]
5	Very dissatisfied

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. CLINICAL INVESTIGATION TREATMENT AND FOLLOW-UP

9.1. Subject Informed Consent

While the enrollment for the main study is ongoing, the following will apply:

All suitable candidates being considered for enrollment in the clinical investigation [redacted] will meet with the TI or designee and have the investigation explained in detail. This will include, but will not be limited to, the potential risks and benefits of participation [redacted]

Each subject will be provided with a written copy of the informed consent in a language they can comprehend and will be given ample opportunity to read and pose questions they may have about the investigation. If, after review, the subject agrees to participate, they will sign the ICF. [redacted]

If the subject subsequently fails to meet eligibility criteria for the main study, they will be considered a screen failure and will not receive treatment with the study device or the control device under the clinical investigation. [redacted]

Information regarding changes in the clinical investigation or new information obtained that could significantly affect a subject's future health and/or medical care must be provided to all subjects in written format. Subjects should be asked to reaffirm their continuing informed consent.

Failure to obtain signed informed consent prior to the use of the study device constitutes a major CIP deviation and noncompliance with 21 CFR Parts 50.20 and/or ISO 14155. If informed consent is not obtained, the subject's participation will be terminated, and his/her data will not be used. The TI will provide a written report to the sponsor indicating the failure to obtain signed informed consent within the reporting timelines required by the central IRB and other local/national laws. The sponsor or designee will then inform the appropriate agencies/committees according to applicable national regulations.

9.2. Randomization

The randomization schedule will be computer generated using a permuted block algorithm and randomly allocate the investigational product in a 3:1 ratio. [redacted]

[redacted]

9.3. Blinding/Unblinding Clinical Investigation Plan

9.3.1. General Blinding

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 [redacted]

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

[redacted]

9.3.2. Blinded Procedures

All evaluations performed by the BLE will be performed separately from the TI. The BLE must not have any access to subject documents, records, notes, or any other sources of information that might indicate the allocated treatment (such as the randomization schedule or the randomization ratio). The BLE must also have a separate eCRF account that will not allow them access to any subject data.

Furthermore, to ensure that the BLE remains blinded and unbiased when making their assessments during the study, the BLE, the TI, and the subject will not be allowed to discuss each other's study assessments. All subjects will be instructed to not discuss their study treatment, AEs, or CTRs with the BLE.

9.3.3. Unblinding Procedures

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]

9.4. Pretreatment Procedures and Tests

The procedures and tests to be performed prior to randomization are described for Visit 1 (Section 8.1.1).

[redacted]

9.5. Baseline Evaluations and Data Collection

All of the data collected at Visit 1 prior to randomization will be defined as Baseline for the purpose of the study and further analysis.

[redacted]

All evaluations performed by the BLE will be considered as Baseline for the purpose of the primary endpoint analysis.

[redacted]

9.7. Clinical Investigational Product Treatment

The TI will inject the filler (RHA4 or [redacted]) in all subjects at the initial treatment (Visit 1). Four weeks later (Visit 2), the TI will decide whether touch-up treatment is necessary to achieve OCR. If necessary, the same filler that was injected during the initial treatment will be administered as touch-up treatment.

[redacted]

9.7.1. Study Device

The study device is RHA4 [redacted]. Please see Section 5.4 and the IB[6] for further information.

9.7.2. Control Device

[redacted] will be used as the active treatment control for the initial treatment and touch-up treatment, if applicable, in subjects randomized to [redacted] treatment. [redacted] is approved for deep (subcutaneous and/or supraperiosteal) injection for cheek [redacted] in the US and will be used according to the IFU.[8]

9.7.3. Injection of RHA4 or [redacted]

The TI is recommended to follow the injection guideline for RHA4 administration and [redacted] IFU[8] for [redacted] injection.

For administration of [redacted], the TI can use a US FDA-approved needle and/or cannula as per the IFU (i.e., needle 27G ½″, needle 25G 1″ and cannula 25G 1 ½″). Injection technique and administration method (needle and/or cannula) at each injection will be recorded.

RHA4 can be injected with a needle, and/or with a cannula; this will be left to the choice of the TI at each injection. Injection technique and administration method (needle and/or cannula) at each injection will be recorded.

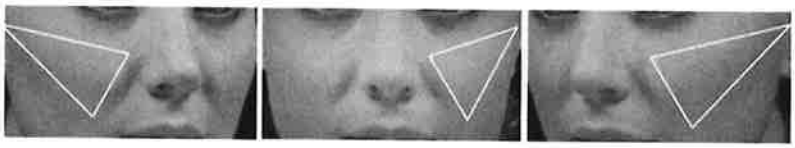
Injection depth: Study and control devices (RHA4 and [redacted]) will be injected in the subcutaneous and/or supraperiosteal layers.

[redacted]

Injection area: The TEOXANE SA midface treatment area will focus on the anteromedial and lateral malar regions. A schematic of the treatment area is delimited using the following triangle (Figure 9-1): 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.

Figure 9-1: Midface Treatment Area



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).

[redacted]

[redacted]

10. ADVERSE EVENTS

Subjects will be monitored carefully during the investigation for possible safety events. Safety events include the CTRs, AEs, ADEs, [redacted]

All events will be reported and documented on the appropriate eCRF (AE report). Adverse event information will be recorded in the eCRF Adverse Event Form.

[redacted]

All observations and clinical findings, including the nature, seriousness, severity, and relationship to the study or to the control device and/or the procedure, will be assessed by the TI or designee and documented on the eCRF. Documentation will also include a detailed description of the event, treatments rendered in response to the event, and outcomes of the treatment.

Assessment and reporting of safety events will follow all national and local laws and requirements for the conduct of clinical studies, including ISO 14155 and US 21 CFR 812.150.

[redacted]

10.1. Definitions

10.1.1. Adverse Events

An AE is untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, whether or not related to the study device, the control device, or the study procedures and whether anticipated or unanticipated.

10.1.2. Adverse Device Effects

An ADE is any adverse event related to the use of the study device, the control device, or the study procedures. This definition includes AEs resulting from insufficient or inadequate IFUs, deployment, implantation, installation, or operation, or any malfunction of the study or the control device. This definition also includes any event resulting from use error or from intentional misuse of the study or the control device.

[redacted]

10.1.6. Device Malfunction

Device malfunction is a failure of the device to perform in accordance with its intended purpose when used in accordance with the IFU/IB or CIP. A device malfunction may or may not be associated with an AE. If it is, the AE or ADE should be reported separately.

[redacted]

10.2. Evaluation and Assessment

For the purposes of this investigation, any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs that occurs in a subject after randomization is considered an

[redacted]

AE, regardless of the investigation group to which the subject is assigned; [redacted]

Any medical conditions, problems, signs, symptoms, and findings that occur prior to randomization are to be reported as pre-existing conditions. Such conditions should be documented and reported on the medical history eCRF as a pre-existing condition. If a pre-existing condition worsens after randomization (frequency increases and/or severity grade increases), it should be documented as an AE.

[redacted]

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

10.2.1. Relationship to Device

For each AE identified in the investigation, the TI or designee must assess its relationship to the study and the control device and/or to the procedure. The TI must determine whether there is a reasonable possibility that these caused or contributed to an AE.

If an AE occurs after randomization but before the first dose of the study device, the relationship to the study device and/or the injection will be considered "not applicable". However, such AEs still need to be recorded.

The relationship assessment, based on clinical judgment, often relies on the following categories:

- A temporal relationship between the event and application of the study or the control device
- A plausible biological mechanism for the study or the control device to cause the AE

[redacted]Another possible etiology [redacted]

[redacted]

[redacted]

10.3. Safety Reporting

It is TI's responsibility to oversee the safety of the investigation at his/her site. This safety monitoring will include careful assessment by the TI and appropriate reporting of all safety events as noted previously.

The site should follow all applicable governance, including FDA regulations, FDA guidance, and IRB requirements for notification of all types of AEs.

[redacted]

[redacted]

10.3.4. Device Malfunctions Reporting

Device malfunctions will be reported using the Device Malfunction Report Form and supply information relevant to the event.

[redacted]

[redacted]

10.4. Pregnancy

All female subjects of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Female subjects of childbearing potential should be instructed to contact the TI or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the study or the control device on every female subject of childbearing potential. A subject who is found to be pregnant at Visit 1 will be excluded from the study and considered to be a screen failure for the main study.

A subject who becomes pregnant during the study after the first injection will not receive further injections and will be followed for safety purposes. The assessments scheduled for the Exit visit are required to be performed as soon as possible after learning of the pregnancy.

The TI must report the pregnancy to [redacted] safety representative within 48 hours of learning of it using the specific Pregnancy Report Form and send it to the same email address as for SAE reporting.

[redacted]

10.5. Data Monitoring Committee

Not applicable.

10.6. Clinical Events Committee

Not applicable.

11. STATISTICAL METHODS

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted as well as all statistical assumptions will be written and approved prior to database lock.

[redacted]

11.1. Analysis Populations

The following 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: All subjects who receive at least 1 treatment with RHA4 or [redacted]
- Intent-to-treat (ITT): All subjects who are randomly assigned to either the RHA4 group or the [redacted] control group.
- Per-protocol (PP): All subjects in the ITT population who receive treatment and do not have any major CIP deviations. The sponsor will identify major CIP deviations prior to database lock.

[redacted]

[redacted]

11.2. Sample Size Determination

This study will randomize at least 200 subjects [redacted] with a maximum of 210 subjects. [redacted]

[redacted]

11.3. Subjects and Demographics

[redacted]

11.3.2. Clinical Investigation Plan Deviations

A CIP deviation is any noncompliance with the clinical investigation CIP or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP requirements. The noncompliance may be either on the part of the subject, the TI, or study site staff. Corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site TI to report any CIP deviations after identification. All deviations must be addressed in study source documents and reported to the sponsor. Clinical investigation plan deviations must be sent to the reviewing IRBs as per local regulations. The site TI is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of CIP deviations will be included in the CIP deviation guidance plan.

[redacted]

Demographic variables will include age, sex, height, and weight [redacted]

11.4. Effectiveness Analyses

Primary effectiveness analysis will be based on the PP population as requested by the US FDA and will be repeated for the ITT population. [redacted]

[redacted]

[redacted]

11.4.1. Primary Effectiveness Analysis

The primary analysis will be performed as follows: to demonstrate non-inferiority of RHA4 compared to [redacted] at 8 weeks after the last treatment, the difference in the TMVDS grade change between Baseline and 8 weeks will then be tested between groups (RHA 4 minus [redacted]).

[redacted]

[redacted]

11.4.2. Secondary Effectiveness Analysis

[redacted]

Teoxane Midface Volume Deficit Scale change from Baseline ([redacted] BLE, [redacted]):

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

[redacted]

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

[redacted]

Responder rate for TMVDS ([redacted], BLE, [redacted]):

Number and proportion of responders, along with 95% CI of responder rate will be calculated for each visit by treatment arm ([redacted] BLE), [redacted]

[redacted]

Global Aesthetic Improvement Scale ([redacted] BLE, [redacted]):

Frequencies and proportion of subjects with GAIS score categories and rates of GAIS responders (who have improved or much improved score) along with 95% CIs will be presented by treatment arm.

FACE-Q scores:

[redacted]

Subject satisfaction score:

Subject satisfaction frequencies and percentages for satisfied/very satisfied response will be tabulated for each visit [redacted]

[redacted]

11.5. Safety Analyses

[redacted]

All AEs will be coded using the MedDRA dictionary. All AEs reported during the study will be described by system organ class (SOC) and preferred term (PT). [redacted]

[redacted]

[redacted]

[redacted]

12. INVESTIGATOR AND SPONSOR RESPONSIBILITIES

Steps to ensure the accuracy and reliability of data include the selection of qualified TIs and appropriate investigation sites, review of CIP procedures with the TI and associated personnel before the investigation, periodic monitoring visits, and meticulous data management.

12.1. Investigator Responsibilities

The TI is responsible for the conduct of the investigation at the site. **Prior** to shipment of the first study device and first procedure, the TI must do the following:

- Read and understand the CIP
- Sign and complete the Investigator's Agreement (see Attachment 17.1)
- Provide an accurate financial disclosure and file an update annually and 1 year after the completion of the investigation
- Ensure appropriate IRB and institutional approvals are in place prior to completing any portion of the informed consent process or permitting subject participation
- Complete and file a fully executed clinical trial agreement between sponsor or sponsor's designee, TI, and institution (as applicable)
- Provide assurance of completed training on the study device and procedures being studied under the CIP
- Handle and store the RHA4 and [redacted] as per the CIP and their respective IFUs and IBs

[redacted]

12.1.1. Deviations from Clinical Investigation Plan

A CIP deviation is defined as an event where the TI or site personnel deviate from the CIP or investigation procedures. It is the TI's responsibility to ensure that there are no deviations from the CIP.

[redacted]

A TI may deviate from the CIP without prior written approval from the sponsor or sponsor's designee in cases of medical emergencies to protect the life or physical well-being of a subject in an emergency. In that event, the TI is required to notify the sponsor and the applicable IRB as soon as possible, but no later than 5 working days after the emergency occurred, of the deviation from the CIP.

[redacted]

12.1.2. Maintaining Records

The TI will maintain the following accurate, complete, and current records relating to the TI's participation in an investigation:

- Correspondence with another TI, an IRB, the sponsor, a monitor, or the FDA
- [redacted]Records of each subject's case history and exposure to the study or control device, [redacted]

[redacted]

[redacted]

12.1.4. Prohibition of Promotion

The IDE regulations prohibit the promotion of any investigational device. Therefore, no TI (or any person acting on behalf of a TI) may promote the investigational use or represent that the device is safe or effective for the purposes for which it is being investigated, or imply safety or effectiveness (or lack thereof) by discussing individual site experiences in any forum.

Prohibition of promotion does not apply to promotion of the clinical investigation by the sponsor to facilitate recruitment.

[redacted]

12.2. Sponsor Responsibilities

12.2.1. General Duties

The sponsor has the overall responsibility for the conduct of the investigation, including assurance that the investigation satisfies the regulatory requirements of the appropriate regulatory agencies, ensuring IRB approvals, selecting TIs, ensuring proper monitoring, and ensuring that informed consent is obtained. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.2.4. Changes in the Clinical Investigation Plan

The sponsor will obtain FDA approval for any change to the CIP that may affect the scientific soundness of the investigation or the rights, safety, and/or welfare of the subjects.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.1. Data Management

The standard procedures for handling and processing records will be followed per GCP [redacted]

[redacted]

The TI/institution will permit direct access to source data and documents for investigation-related monitoring, audits, IRB reviews, event adjudication, and regulatory inspections to be performed. The TI will obtain, as part of the informed consent process, permission for authorized sponsor employees, investigation monitors, or regulatory authorities to review, in confidence, records that identify subjects in this investigation.

13.2. Confidentiality of Data

Information about investigation subjects will be kept confidential and managed according to the requirements and regulations of the local and national governing bodies.

All data and information collected during this investigation will be considered confidential by the sponsor and their delegates. All data used in the analysis and summary of this investigation will be anonymous and without reference to specific subject names. Access to subject files will be limited to authorized personnel of the sponsor and sponsor's designee, the TI, clinical site research staff, and authorized regulatory authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this investigation.

The photography will include the subject's face. Should photographs of a subject's face be used for potential publication, promotions or other purposes, it must only include parts of the face that are necessary to illustrate or document the effect of the dermal filler used as per this study. The subject will need to sign a specific photography release form to specify whether they allow use of the image for other purposes such as publication or promotion. The subject's decision will be tracked in a site-specific photography release log. [redacted]

13.3. Source Documents

Source data is all information, original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the investigation. Source data are contained in source documents (original records or certified copies). Examples of these original documents and data records include, but are not limited to, the following: medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy and at the laboratories involved in the clinical investigation.

[redacted]

13.4. Electronic Case Report Forms

This investigation will use an eCRF as the primary data collection instrument and will record data by electronic capture. All data requested on the eCRF must be entered. All missing data must be explained. If an entry on the eCRF is left blank because the procedure was not done or the question was not asked, a query will be generated for the site data entry staff. If any entry error has been made, correct and enter the correct data in the eCRF. All such changes are recorded in the audit and queries report. All electronic data capture systems must be 21 CFR Part 11 and/or ISO14155-compliant.

The eCRFs contain confidential material. Specific instructions to complete the eCRFs will be provided to the TI and other site personnel, as appropriate. The TIs or designees are responsible for reporting clinical investigation-requested information in the eCRFs.

[redacted]

13.5. Record Retention

The TI will retain investigation essential documents for a minimum of 2 years after the date a marketing application is approved for the device for the indication for which it is being investigated, or 2 years after formal closure of the investigation, whichever is longer. These documents must be retained for a longer period if required by an agreement with the sponsor or sponsor's designee or defined by local or national regulations. The sponsor or sponsor's designee will inform the TI/institution as to when these documents no longer need to be retained. All clinical sites will maintain all records pertaining to this investigation for a minimum of 2 years after the investigation is discontinued. The sponsor or sponsor's designee will notify the clinical sites of the date of discontinuation.

13.6. Clinical Data Monitoring Procedures

Clinical research associates will conduct site visits at the investigation facilities to monitor the investigation in compliance with the CIP, SOPs, GCP, ISO 14155, and the clinical monitoring plan (CMP). Monitoring visits will occur as defined in the CMP and/or as required to conduct the investigation. The clinical investigation center agrees to allow these monitors and other authorized [redacted] personnel access to information and clinical supplies related to the investigation. The CRAs will verify data entered into the eCRFs against hospital records or other source documents to ensure accuracy and completeness of the eCRFs for each subject. Treating investigators and their staff agree to assist the monitors in their activities. Requests may be made to review subject charts by the sponsor or sponsor's designee so that CIP adherence and source documentation can be verified.

[redacted]

14. ETHICS AND REGULATORY COMPLIANCE

14.1. Conduct of the Clinical Investigation

Conduct of the clinical investigation will follow [redacted], as well as CFR/ISO 14155, the Declaration of Helsinki, ICH Harmonized Tripartite Guideline for GCP, and other national and local laws. Each TI must sign and date the Investigator's Agreement prior to the start of this investigation. With the signature, the TI agrees to perform all investigation procedures according to the governing local and national regulations, and the CIP.

14.2. Conflict of Interest

The FDA reviews the financial interests of TIs (or subinvestigators and their spouses and/or dependent children) in an IDE investigation. If the FDA believes that the financial interests of any TI raise serious questions about the integrity of the data, the FDA may take any action it deems necessary to ensure the reliability of the data, including the following:

- Initiating agency audits of the data derived from the TI in question
- Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the TI's data on the overall investigation outcome
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned investigation

Therefore, any TI (or subinvestigator), his/her spouses, and/or dependent children who has a potential conflict of interest with this investigation (e.g., patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must have the conflict evaluated by the sponsor. If a financial interest appears to exist, a management plan should be generated to minimize bias and must be approved by the investigation sponsor prior to participation in this investigation.

14.3. Institutional Review Board/Competent Authority Approval

A properly constituted, valid IRB must review and approve the CIP, the ICFs, and related subject information and recruitment materials before the start of the investigation. It is the responsibility of the TI to obtain approval of the CIP from the institution's IRB and to keep the IRB informed of any UADE as per IRB requirements and SMP. Additional requirements imposed by the IRB or other regulatory authority will be followed if appropriate. All correspondence with the IRB should be filed by the TI and copies sent to the sponsor or sponsor's designee(s).

14.4. Clinical Investigation Informed Consent Approval

Informed consent will be obtained in writing and documented before a subject is enrolled in the clinical investigation in accordance with the principles of informed consent according to the Declaration of Helsinki, GCP, 21 CFR Part 50, the Medical Devices Directive 93/42/EEC, and ISO 14155.

It is the responsibility of the TI to ensure that written informed consent is obtained from the subject (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care. Information obtained during the conduct of the clinical investigation that may impact the subject informed consent may require revisions to the ICFs. If so, revisions and

reapprovals of such changes by the appropriate regulating authority are required. Documentation of the current versions of the ICFs will be documented in the clinical trial master file.

14.5. Subject Identification and Confidentiality

Subject identification and confidentiality will be ensured according to the terms and definitions in 21 CFR Parts 50, 56 and 812/ISO14155. This includes, but is not limited to, the following:

- Subjects will be identified on all eCRFs and source documents by a unique identification reference that may include the subjects' initials
- Electronic case report forms are confidential documents and will only be made available to the sponsor or sponsor's designee, the TI, the biostatistician, and if requested, to advisory committees and regulatory authorities (including FDA)
- Data will be stored and analyzed by computer following national regulations for handling of computerized data

Each investigation center will maintain (anonymous to [redacted]) a list identifying all subjects entered into the investigation. The list will be maintained as part of the investigation file.

This investigation will be conducted according to the US FDA standards of GCP (FDA Title 21 CFRs Part 11, 50, 54, 56 and 812), ISO 14155, the Declaration of Helsinki, and the ICH guidelines.

This investigation is to be conducted according to and other applicable national, state, and local government regulations and institutional research policies and procedures.

[redacted]

Should photograph(s) of a subject's face be used for potential publication, promotions, or other purposes, it must only include parts of the face that are necessary to illustrate or document the effect of the dermal filler used as per this study. The subject will be asked whether they agree to use their photographs for use outside the study, such as publication or promotion using a separate photography release form. Their decision will be stored at the site in a separate photography release log.

[redacted]

[redacted]

14.8. Insurance

The sponsor will maintain insurance coverage for this investigation. Pertinent information regarding the coverage will be made available to the site upon request.

14.9. Site Audit Plan

Participation as a TI in this investigation implies acceptance of potential inspection by government regulatory authorities, and applicable compliance and quality assurance offices. The TI and/or designee must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. The TI must provide the sponsor or sponsor's designee with copies of all correspondence that may affect the review of the current investigation or his/her qualification as a TI in clinical studies conducted by the sponsor.

14.9.1. Internal Audits by Sponsor or Sponsor's Designee

In accordance with local and national regulations and the sponsor's or sponsor's designee's SOPs, the sponsor or sponsor's designee may request access to all investigation records, including source documents, for inspection. The TI will ensure the capability for inspections of applicable investigation-related facilities (e.g., catheterization laboratory, surgery suite, diagnostic laboratory).

Internal quality assurance audits will be conducted at selected investigation sites during the investigation. Selection of sites to undergo auditing will be determined by the sponsor per a pre-established audit plan.

14.9.2. External Audits

Regulatory agencies may also request to inspect investigation sites. The TI or designee is required to report to the sponsor or sponsor's designee as soon as possible after receiving a request from a regulatory authority to perform an inspection. The TI agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.10. Investigational Product Traceability

Investigational products will be stored at each site according to the IB and records will be kept to document product storage and management; sponsor-provided unique identification numbers and labeling identifying them as IDE products will be clearly visible. All sites will maintain a device accountability log that will match subjects to a particular study device by a unique manufacturer number. At the conclusion of the investigation, all study and control devices will be either returned to the sponsor or to the central pharmacy or destroyed at site level if the appropriate site SOP are in place.

14.11. Public Domain Access to the Clinical Investigation

A description of this clinical investigation will be available on http://www.ClinicalTrials.gov, as required by US law. Information regarding public access will be presented in the ICF, as required by US law.

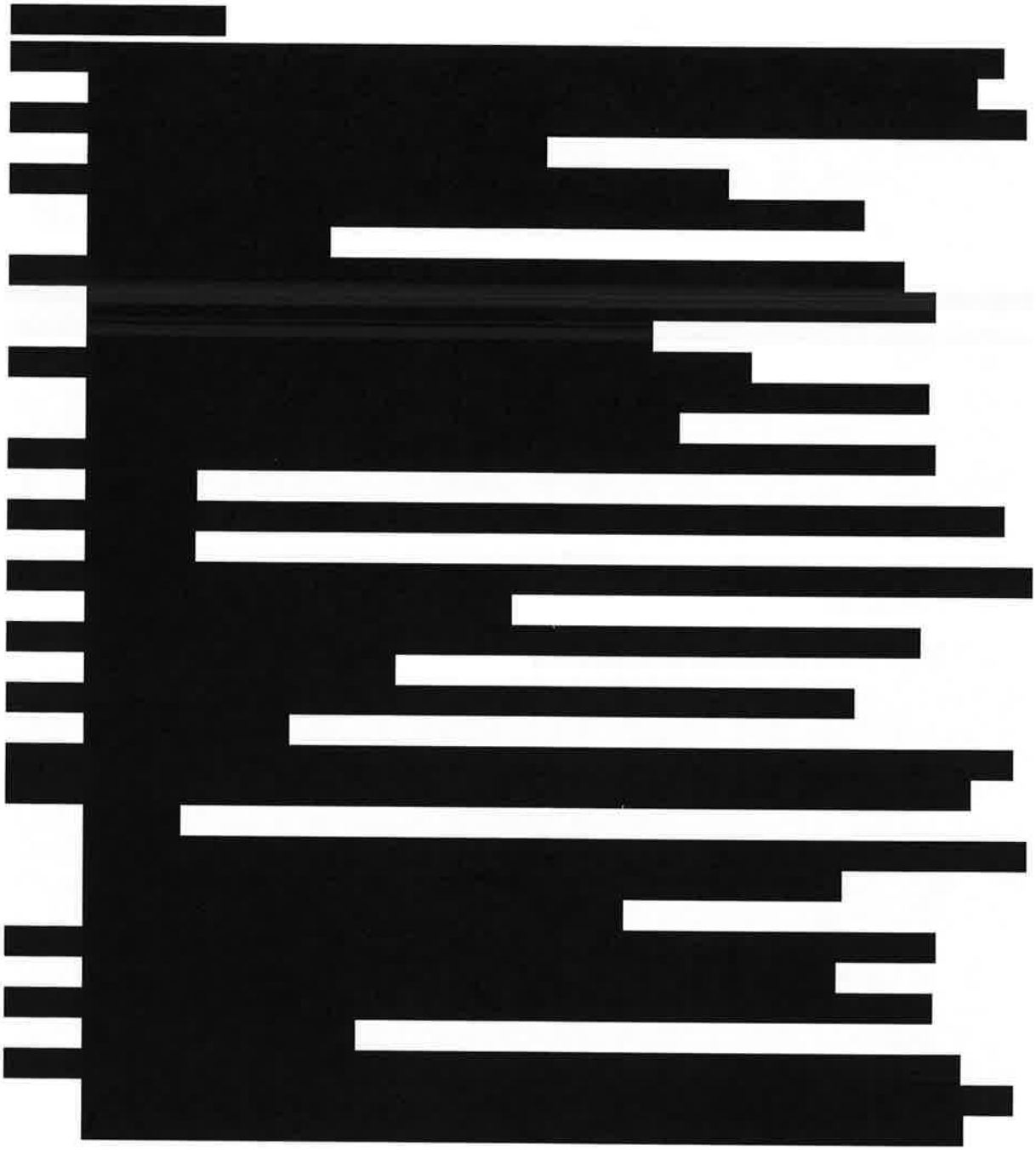
15. GENERAL CONSIDERATIONS

15.1. Discontinuation of the Investigation

Discontinuation of individual subjects is described in Section 7.4.5.

[redacted]

[redacted]



17. ATTACHMENTS

17.1. Investigator's Agreement

CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
CLINICAL INVESTIGATION PLAN 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
AMENDED CLINICAL INVESTIGATION PLAN:	[redacted] 12-Jul-2023

I have read this CIP and agree to conduct this clinical investigation as outlined herein. [redacted]

Treating Investigator:

Printed Name:

_____

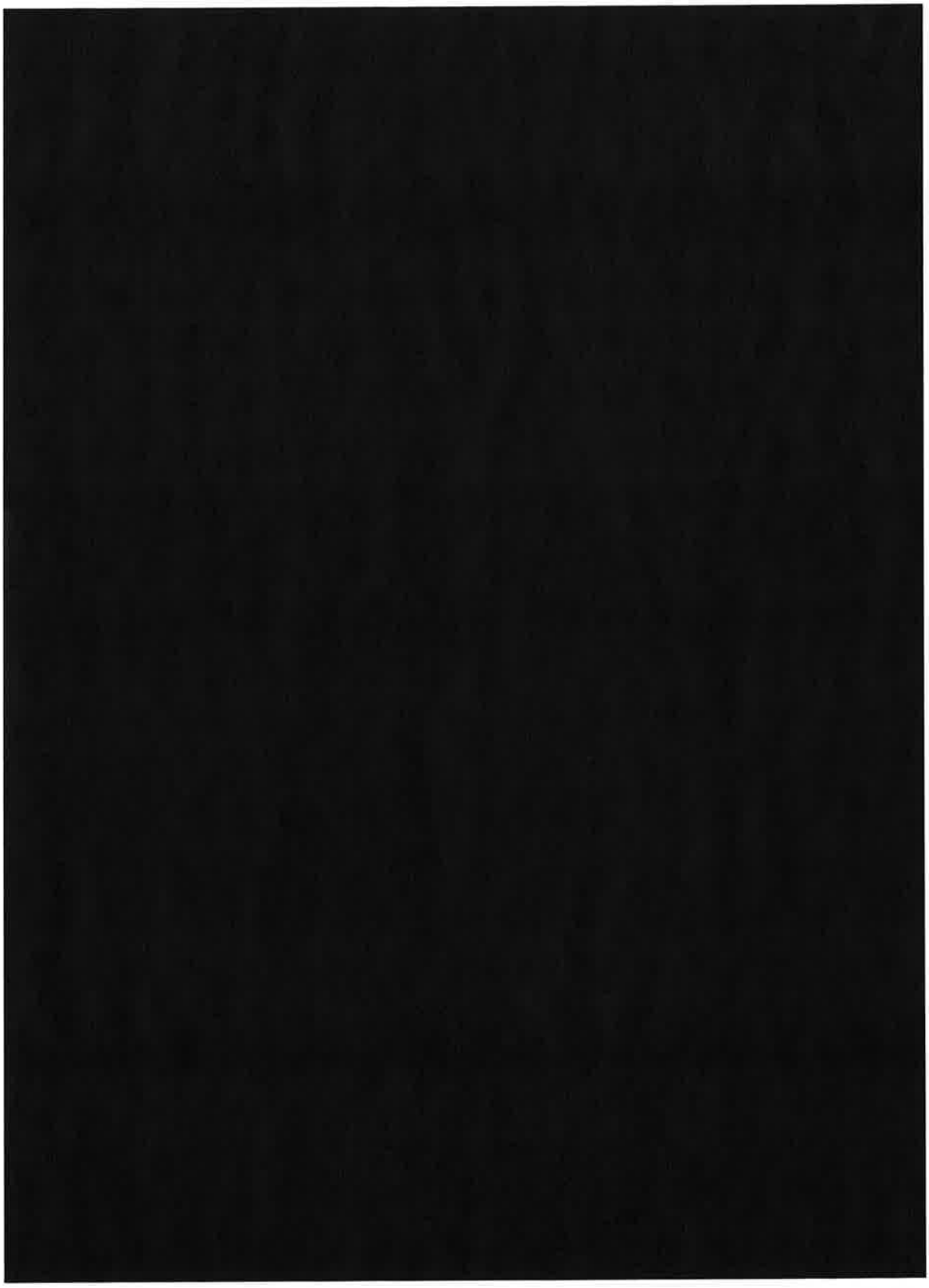
Signature:

_____

Date:

_____

[redacted]



[redacted]

[redacted]

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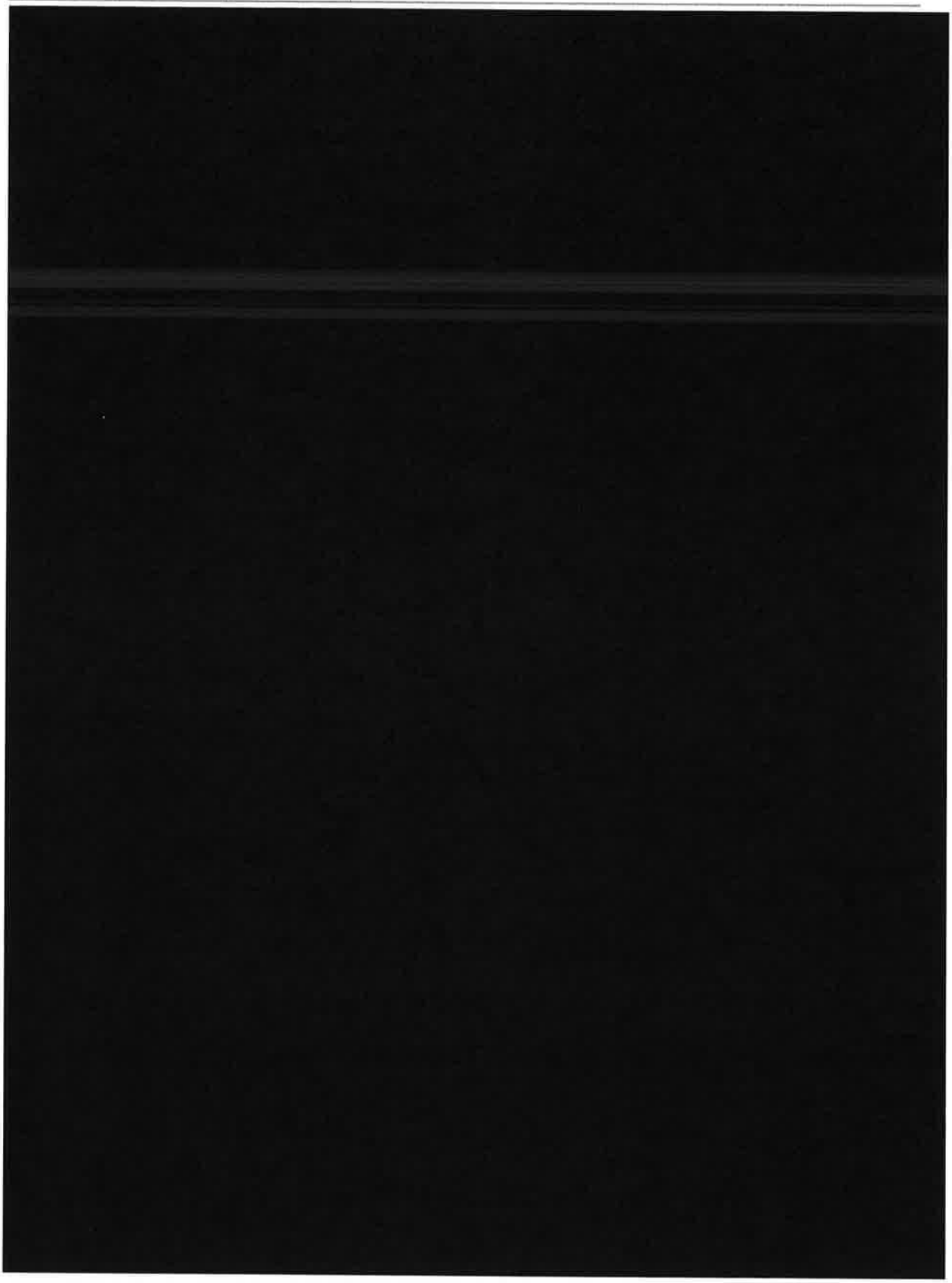
[redacted]



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