A randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective clinical study to evaluate the effectiveness and safety of using the dermal filler RHA®4 injected with a cannula or with a sharp needle for the treatment of moderate to severe nasolabial folds

IDE Pivotal Study

Protocol: [redacted]

Date: 06-May-2021

Study Sponsor:
TEOXANE SA
Rue de Lyon 105
CH - 1203 Genève, Switzerland
+41 (0) 22.344.96.36

US Sponsor:
[redacted]

Clinical Research Organization:
[redacted]

Confidentiality Statement

PROTOCOL APPROVAL SIGNATURE PAGE

The following individuals approve this version of Protocol [redacted]. All changes to this version of the protocol must have a prior written approval and require an amendment or administrative letter.

Accepted for the Sponsor – TEOXANE SA:

[redacted] Clinical Project Manager DATE

[redacted] Clinical Development and Medical Affairs Director DATE

[redacted] QA/RA Director DATE

Accepted for the Clinical Research Organization - [redacted]:

[redacted] Managing Director DATE

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol. I will ensure that all subinvestigators and other investigation staff members have read and understand all aspects of the protocol.
- Maintain all information supplied by [redacted] in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.
- Cooperate fully with [redacted] and [redacted] during the investigation. I will adhere to all Food and Drug Administration (FDA), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), International Organization for Standardization (ISO) 14155, Good Clinical Practice (GCP), Declaration of Helsinki, and other applicable regulations and guidelines regarding clinical investigations during and after investigation completion.

I have read this protocol in its entirety and I agree to all aspects.

Principal Investigator *(Print Name)*	Signature	DATE

SYNOPSIS

Protocol Version	Version [redacted] 06-May-2021	**Investigational Device**	RHA®4 injected with a ([redacted]) cannula into the NLF. The brand of cannula ([redacted]) used for injection is up to the discretion of the Treating Investigator (TI), providing the cannula is registered for use by the US FDA and that the cannula bore is [redacted]. The injection technique is left to the discretion of the TI.
Study Number	[redacted]		
Phase	IDE Pivotal	**Control Device**	Approved RHA® 4 injected with the provided TSK 27G x ½" sharp needle.
Indication	Injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds.	**Study Sites**	Multicenter, 3 to 4 US sites
Title	A randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective clinical study to evaluate the effectiveness and safety of using the dermal filler RHA®4 injected with a cannula or with a sharp needle for the treatment of moderate to severe nasolabial folds.		
Sponsor	TEOXANE SA, Rue de Lyon 105, CH - 1203 Geneva, Switzerland		
Study Duration	[redacted]	**Number of Subjects**	At least 50 subjects treated with cannula and sharp needle with at least 20% of subjects presenting Fitzpatrick skin type IV to VI including 10% of subjects presenting Fitzpatrick skin type V and VI.
Treatment Groups	Each enrolled subject will receive injections of RHA®4 with a cannula into the nasolabial fold (NLF) of the left or right side of the face, and injections of the control device (sharp needle) into the contralateral NLF.		
Study Design	This is a randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA®4 injected in NLFs with a cannula ([redacted]) is non-inferior to RHA®4 injected in NLFs with a sharp needle ([redacted]) for the correction of moderate to severe NLFs as determined by the Blinded Live Evaluator (BLE) using the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) [redacted]. At screening, the Treating Investigator (TI) and Blinded Live Evaluator (BLE) will evaluate subjects' NLF severity to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement (i.e., moderate to severe bilateral nasolabial folds; grade 3 or 4 on the five-point NLF-WSRS; symmetrical in terms of grade). BLE and TI must independently agree that the criterion is met; however, strict concordance of severity is not required. [redacted]		

	[redacted]
Hypothesis	RHA®4 injected in NLFs with a cannula is non-inferior to RHA®4 injected in the NLFs with a sharp needle for the correction of moderate to severe NLFs as determined by the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) [redacted].
Objectives	1. Demonstrate the non-inferiority of RHA®4 injected in the NLFs with a cannula versus the control (RHA®4 injected in NLF with a sharp needle) [redacted] for the correction of moderate to severe NLFs. Assessment of non-inferiority will be based on the change from Baseline in NLF-WSRS [redacted] as rated by the Blinded Live Evaluator (BLE) at each investigative site. 2. Evaluate the safety of RHA®4 injected in NLF with a cannula versus the control [redacted]
Inclusion Criteria	1. Outpatient, male or female of any race, 22 years of age or older. 2. Female subjects of childbearing potential must have a negative UPT at Visit 1 and practice a reliable method of contraception throughout the study. [redacted] 3. Moderate to severe bilateral nasolabial folds (grade 3 or 4 on the five-point NLF-WSRS). BLE and TI must independently agree that the criterion is met; however, strict concordance of severity not required [redacted]

	[redacted] 4. Nasolabial folds of the same NLF-WSRS grade on the left and right sides of the face. [redacted] 6. Able to follow study instructions and complete all required visits. 7. Sign the IRB-approved ICF, Photographic Release Form, the Authorization for Use and release of Health and Research Study Information (HIPAA) form, and if applicable, the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed.
Exclusion Criteria	1. Known hypersensitivity or previous allergic reaction to any component of the study devices. [redacted] 3. Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, or history of anaphylactic shock. 4. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion). 5. Clinically significant active skin disease or infection in the NLF regions within 6 months prior to study entry (TI discretion). [redacted] 9. History of connective tissue disease. 10. Malignancy (excluding non-melanoma skin cancer) within the past 5 years. 11. History of skin cancer in the treatment area. [redacted] 18. 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, in the judgment of the Investigator, would make the subject inappropriate for entry into this study. 19. Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability.

	20. Exposure to any other investigational drug/device within 90 days of entering the study or planning to participate in another investigation during the course of the study. 21. [redacted]
Device Administration	[redacted] **Injection technique:** The injection technique (e.g., linear threading (retrograde or anterograde), cross hatching, fan like administration, multiple puncture) will be at the discretion of the TI and will be recorded in the eCRF. [NOTE: Cross-hatching is a "needle only" injection technique] [redacted]
Blinding	Due to the visual and sensory differences between the cannula and sharp needle, it is not feasible to mask the TI or the subject. However, the **BLE will be blinded to the treatment allocation.** Furthermore, to ensure that the BLE remains masked and that all assessors remain unbiased when making their assessments, the BLE, TI and subject will not be allowed to refer to each other's efficacy assessments. All subjects will be instructed to not discuss their study treatment, AEs, or CTRs with the BLE.
Randomization	A randomization algorithm will provide equal balancing for the side of the face and the order of injection (i.e., left or right / 1st or 2nd order).
Visit Procedures	[redacted] *Refer to the Study Summary Tables and the Study Schematic for a schedule of activities.*
Aesthetic Effectiveness Evaluations	[redacted]

	[redacted] 12. [redacted]
Primary Effectiveness Endpoint	The primary effectiveness endpoint will be aesthetic improvement from pre-injection as assessed by the NLF-WSRS (BLE) [redacted] following last treatment (initial or touch-up). The primary hypothesis is that RHA®4 used in conjunction with cannula is non-inferior to RHA®4 with sharp needle. An NLF-WSRS change from Baseline of ≥1 grade will be considered clinically significant. A non-inferiority margin of 0.5 grade difference in change from Baseline between cannula and needle will be used to test the primary hypothesis. [redacted]
Secondary Effectiveness Endpoints	[redacted] 14. [redacted]
Safety Endpoints	1. AEs across the duration of the study (incidence, intensity, and duration) 2. [redacted] [redacted]Post-injection Common Treatment Response [redacted] [redacted] 5. [redacted]
Statistical Methods	[redacted]

	[redacted]
Sample Size	[redacted]

[redacted]

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

[redacted]

FIGURE 1. STUDY SCHEMATIC

TABLE OF CONTENTS

CONTACT LIST

Medical Monitor

[redacted]

Sponsor Clinical Program Manager

[redacted]

Sponsor US Legal Representant

[redacted]

CRO Clinical Project Manager

[redacted]

24-Hour Emergency Phone Number

[redacted]

NOTE: Changes in the names, addresses or telephone numbers of these contacts will be considered administrative and will not require a protocol amendment before being implemented.

[redacted]

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

1 INTRODUCTION

1.1 Background

Hyaluronic acid (HA) is a long-chain, repeated dimer, N-acetyl glucosamine and D-glucuronic acid polymer and is a major component of the extracellular matrix. HA is widely present in all animal species and does not differ from one species to another. Due to this extended compatibility, non-human HA can be used in humans without unacceptable adverse effects. Due to its natural viscoelastic and hydrogel properties, HA is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction.

It was demonstrated that by chemically crosslinking the molecule, HA becomes resistant to degradation and its persistence in tissues is increased.[1,2] This does not affect the carboxylic and N-acetyl functions of the molecule and allows modification of the rheological and physical properties of HA while maintaining the biocompatibility of the basic polymer.[3]

Dermal fillers in general, and hyaluronic acid (HA) fillers specifically, are aesthetic devices that are not used for the diagnosis or treatment of any specific disease state. Rather, they are used for the treatment of age-related wrinkles/folds and facial volume loss. Specific use data are published on the American Society of Plastic Surgeons (ASPS) website. Based on Teoxane's knowledge of the aesthetic industry, it is likely that most HA dermal filler procedures are performed by dermatologists, aesthetic nurses, and/or physician assistants rather than by plastic surgeons. However, as use statistics are not available from the various dermatological societies, the data provided below are likely an underestimation of the total number of dermal filler procedures performed in the U.S. It is not expected that the demographics of this indication would be substantially different from the ASPS data.

The following data for 2019 were extracted from the ASPS website in August 2020 (https://www.plasticsurgery.org/news/plastic-surgery-statistics):

- 16.3 M cosmetic minimally invasive procedures, up 2% from previous year
- 2.72 M procedures with any dermal filler, up 1% from previous year
- 2.16 M procedures with HA, up 1% from previous year
- 36% of all HA filler procedures were in patients ≥ 55 years old
- 3% of all HA filler procedures were in males

While data are not available from ASPS regarding race or ethnic-specific subgroups, data from various HA dermal fillers clinical trials indicate that the majority of subjects are Caucasian females. Historically, approximately 20-25% of subjects enrolled in dermal filler studies have been Fitzpatrick skin types IV-VI (as per FDA requirements for minimum enrollment of darker skin type subjects in these studies). As such, the percentage of darker skin types treated in dermal filler studies is not necessarily representative of real world experience for patients seeking many dermal filler aesthetic procedures/indications.

RHA®4 dermal filler is a device containing colorless, biodegradable, sterile, biocompatible, crosslinked HA of non-animal origin (i.e., bacterial fermentation using *Streptococcus zooepidemicus*). Crosslinking is performed using 1,4-butanediol diglycidyl ether (BDDE) to form a gel. RHA®4 contains 0.3% w/w of lidocaine hydrochloride, a drug substance widely used for its anesthetic properties (i.e., it blocks the origin and transmission of nervous influx at the point of injection by stabilizing the neuronal membrane).

RHA®4 is intended for injection into the deep dermis to superficial subcutaneous tissue of the face to correct moderate to severe dynamic facial wrinkles and folds, such as NLFs. RHA®4 has received PMA approval for this indication per P170002 in October 2017.

[redacted]

1.3 Hypothesis

RHA®4 injected in NLFs with a cannula is non-inferior to RHA®4 injected in the NLFs with a sharp needle for the correction of moderate to severe NLFs as determined by the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) [redacted]

[redacted]

2 STUDY OBJECTIVES

The study is designed to achieve the following objectives:

1. Demonstrate the non-inferiority of RHA®4 injected in the NLFs with a cannula versus the control (RHA®4 injected in NLF with a sharp needle) [redacted] for the correction of moderate to severe NLFs. Assessment of non-inferiority will be based on the change from Baseline in NLF-WSRS [redacted] as rated by the Blinded Live Evaluator (BLE) at each investigative site.
2. Evaluate the safety of RHA®4 injected in NLF with a cannula versus the control [redacted].

3 COMPLIANCE STATEMENT

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), the Declaration of Helsinki, and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312). In addition, the study will be conducted in compliance with all applicable laws and regulatory requirements relevant to the use of new medical devices in the United States.

The sites' Principal Investigator (also referred to as the Treating Investigator [TI], both terms are used interchangeably) is responsible for ensuring the privacy, safety and welfare of the subjects during and after the study, and must ensure that personnel are trained and immediately available in case of a medical emergency. The TI must be familiar with the background and requirements of the study and with the properties of the study device as described in the Investigator's Brochure and package inserts. The Principal Investigator at each site has the overall responsibility for the conduct and administration of the study at their site, and for contact with study site management, and local authorities [redacted] will facilitate and manage all interactions between the site and the IRB.

3.1 Variations to the Protocol

No changes from the final approved (signed) protocol will be initiated without the prior approval of the FDA and the IRB except 1) when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration, or 2) minor administrative or typographical corrections. The sites' Principal Investigators and the Sponsor must sign any protocol amendments.

3.2 Investigational Sites

Three (3) to Four (4) U.S. investigational sites will participate in this study. Each site will obtain written approval from a Central IRB prior to recruitment and enrollment of any subject into the study. Any changes to the study procedures must be made with the mutual agreement of the Principal Investigator and the Sponsor, documented in an amendment to the protocol, and approved by the reviewing IRB.

[redacted]

3.3 Training and Certification on the NLF Wrinkle Severity Rating Scale (NLF-WSRS)

[redacted]

[redacted]

3.4 Medical Monitor

A Medical Monitor will provide safety oversight for this clinical study. The Medical Monitor, in consultation with the Sponsor's team, will review and evaluate AEs/SAEs/UADEs/[redacted] on a regular basis, review safety reports, and will provide consultation and recommendations with regard to inclusion/exclusion criteria, concomitant medications/treatments, and subject discontinuations. The Medical Monitor will follow the Safety Management Plan and report the trends of AEs, and address specifically SAE, UADE, [redacted] with the Sponsor.

3.5 Photography

Set-up of photographic equipment, as well as training and quality control processes, will be provided and will be managed by a dedicated professional third party [redacted]

4 OVERVIEW OF STUDY DESIGN

4.1 Study Design

This is a randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA®4 injected in NLFs with a cannula ([redacted]) is non-inferior to RHA®4 injected in NLFs with a sharp needle ([redacted]) for the correction of moderate to severe NLFs as determined by the Blinded Live Evaluator (BLE) using the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) [redacted].

At screening, the Treating Investigator (TI) and Blinded Live Evaluator (BLE) will evaluate subjects' NLF severity to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement (i.e., moderate to severe bilateral nasolabial folds; grade 3 or 4 on the five-point NLF-WSRS; symmetrical in terms of grade). BLE and TI must independently agree that the criterion is met; however, strict concordance of severity is not required.

[redacted]

4.2 Study Design Rationale

4.2.1 Study Population

At least 50 subjects will be enrolled and receive study treatment. [redacted]

the inclusion and exclusion criteria.

4.2.2 Primary Endpoint

The primary effectiveness endpoint will be aesthetic improvement from pre-injection as assessed by the NLF-WSRS (BLE) [redacted] The primary hypothesis is that RHA®4 used in conjunction with cannula is non-inferior to RHA®4 with sharp needle. An NLF-WSRS change from Baseline of ≥1-grade will be considered clinically significant. A non-inferiority margin of 0.5 grade difference in change from Baseline between cannula and needle will be used to test the primary hypothesis.

[redacted]

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Outpatient, male or female of any race, 22 years of age or older.

[redacted]

[redacted]Moderate to severe bilateral nasolabial folds (grade 3 or 4 on the five-point NLF-WSRS. BLE and TI must independently agree that the criterion is met; however, strict concordance of severity is not required. [redacted]

4. Nasolabial folds of the same NLF-WSRS grade on the left and right sides of the face.
5. Willing to abstain from facial aesthetic procedures/therapies that could interfere with the study evaluations (e.g., other fillers, botulinum toxin injections, laser or chemical resurfacing, facial plastic surgery, etc.) for the duration of the study (see Section 7.5.1 for prohibited/restricted medication/procedures).
6. Able to follow study instructions and complete all required visits.
7. Sign the IRB-approved ICF, Photographic Release Form, the Authorization for Use and release of Health and Research Study Information (HIPAA) form, and if applicable the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed.

5.2 Exclusion Criteria

1. Known hypersensitivity or previous allergic reaction to any component of the study devices.
2. Use of a prohibited treatment/procedure within time periods defined in Section 7.5.1.
3. Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, or history of anaphylactic shock.
4. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion).

[redacted]

6 TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

All subjects who are randomized will receive a 3-digit subject number, starting at 001. Subject numbers will be assigned in ascending order and will be coupled with the site identification number for unique identification of each subject. The subject number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number; new subjects will be allocated a new subject number. Screen Failures will be entered in the eCRF.

Upon qualifying for treatment, subjects will be randomized for the side of the face and the order of injection of study devices (i.e., left or right / 1st or 2nd order).

Subjects will be considered "enrolled" at the time of consent, and will be considered "enrolled and randomized" at the time of randomization. The required sample size is based on "enrolled and randomized" subjects. If an enrolled subject withdraws from the study prior to being randomized, he/she may be replaced.

[redacted]

[redacted]

7 DEVICE APPLICATION

7.1 Study Devices

RHA® 4: A sterile, biodegradable, biocompatible, viscoelastic, clear, colorless, homogenized gel implant. It consists of crosslinked hyaluronic acid produced by fermentation of *Streptococcus zooepidemicus*, formulated to a concentration of 23 mg/g and 0.3% w/w lidocaine in a physiologic buffer. It is supplied in individual treatment syringes with 27G ½ inch disposable sterile needles.

Cannulas for Injection:

7.2 Injection of Study Devices

At Visit 1, each randomized subject will receive injections of RHA®4 injected with cannula into the NLF of the left or right side of the face, and injections of the control device (i.e. RHA®4 injected with a sharp needle) into the contralateral NLF.

7.2.1 Injection Depth

7.2.2 Injection Technique

The injection technique (e.g., linear threading (retrograde or anterograde), cross hatching, fan like administration, multiple puncture, etc.) will be at the discretion of the TI. Technique(s) used for

each side will be recorded in the eCRF. [NOTE: Cross hatching is a "needle only" injection technique].

Devices will be injected using the needle that is provided within the standard packaging of the device on the left or right side of the face. The TI is not permitted to use a needle of different gauge, length or brand. On the contralateral side, devices will be injected using a small cannula ([redacted]).

7.2.3 Supplementary Anesthesia

RHA®4 contains lidocaine. Additional anesthesia is prohibited (e.g., EMLA, dental blocks, ice, etc.). Ice may be used at the discretion of the TI for post-injection treatment for pain or discomfort, but only after all injection pain assessments for both sides of the face have been completed (i.e., at 60 minutes post-injection).

[redacted]

[redacted]

7.3 Labeling, Packaging and Storage

Supplies of RHA®4 will be provided to the sites in bulk (i.e., individual kits per subject will not be provided). External packaging (carton) will be labeled with study information (i.e., study number, study Sponsor, name and address of [redacted], quantity, "CAUTION: Investigational device. Limited by US Federal law to investigational use", etc.). There may be one or two blisters inside each carton. Each blister will contain one syringe and two needles. Each blister is unique to a subject and must not be used for more than one subject. The Tyvek lid on the blister will include:

[redacted]

- Name and address of the Sponsor/Manufacturer (i.e., [redacted]
- Quantity of syringes (n=1)
- Quantity [redacted] needles (n=2)
- Batch number and Manufacturing date
- Expiry date
- The CAUTION statement mentioned above

The Investigator Brochure will provide all relevant contraindications, hazards, adverse effects, warnings and precautions.

The study device is to be stored at room temperature (2°C to 25°C) in a secure restricted area.

It is the responsibility of the TI to verify that a device is within its expiry date before being used.

7.4 Study Device Supply and Accountability

The study Sponsor will ensure that participating sites are provided with a sufficient supply of study devices and cannulas for all treatments. It is forbidden to use a study device for purposes other than defined in this protocol. Syringes are single use and must not be shared between subjects.

Study devices must be kept in a locked area with access restricted to designated study personnel. The Principal Investigator or designee will inventory and acknowledge receipt of all study device shipments, and ensure that the integrity of study devices is not jeopardized prior to use.

Accurate accountability records will be maintained that include batch numbers, quantities received/returned/destroyed, as well as dates and volumes administered, and the site monitor will be provided access to the study devices and records for periodic review.

Unused syringes and **cannulas** will be returned to the Sponsor at the end of the study unless other arrangements are agreed upon in writing. **Used syringes** and **cannulas** will be destroyed as per each site's standard procedures.

7.4.1 Other Study Supplies

Supplies that are unique to the study will be provided by [redacted] (e.g., UPTs, photographic equipment, source document worksheets, etc.). The site is responsible for routine supplies related to pre-/post-injection care (e.g., alcohol wipes, gauze, etc.).

7.5 Concomitant Medications and Procedures

All treatment/procedures received by the subject within 30 days prior to the Baseline visit and throughout the treatment period, including the name of the treatment/procedure, must be recorded in the eCRF with end dates, if applicable. Use of prohibited treatment/procedures must be recorded in the eCRF up to the extent of the prohibited time period indicated above. Furthermore, previous use of facial aesthetic treatment/procedures must be recorded for up to 1 year prior to the Baseline visit.

In the event such prohibited therapies are administered during the study period, the Medical Monitor will be contacted to discuss the details of the event. Subject participation will not automatically be discontinued. At a minimum, the event will be documented by the site staff as a protocol deviation, as instructed by the Medical Monitor. Depending upon the nature of the prohibited therapy and the timing relative to the determination of the primary endpoint, the Medical Monitor may make a decision to discontinue the subject.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. If the permissibility of a specific medication/treatment is in question, the Medical Monitor should be contacted before the prohibited medication/treatment is administered.

7.5.1 Prohibited Treatment and Procedures

Subjects must not undergo any type of facial or cosmetic procedure below the orbital rim, including but not limited to dental, plastic or reconstructive surgery; non-ablative procedures; botulinum toxin injections; laser resurfacing; dermabrasion; lipo-injection; or chemical peel at any time during this study. Other necessary therapies that will not interfere with the response to treatment may be provided to the subject at the discretion of the TI.

The following medications/procedures have either restrictions for usage, or are prohibited during the course of the study and appropriate washout periods noted below must be respected:

[redacted]

8 DATA COLLECTION

8.1 Electronic Case Report Form

Treatment and follow-up of subjects will be recorded in a 21 CFR part 11 compliant eCRF. Data will be first recorded into the medical record and study specific source document worksheets prior to entry into the eCRF. The study coordinator will refer to these worksheets in conjunction with the medical record in order to complete data entry into the eCRF.

In order to review and electronically sign the eCRF, the TI and BLE will each have an individual login password that will allow them to view only the data that they have generated. The TI and BLE must ensure that they electronically sign for completed eCRFs on a timely basis.

8.2 Subject Diaries and Questionnaires

[redacted]

8.3 Photography

Calibrated photographs will be taken at Visit 1 (pre- and post-injection) and at Visits [redacted] according to a standardized protocol incorporating appropriate quality control processes [redacted]

[redacted]

9 STUDY EVALUATIONS

9.1 Informed Consent

The TI (or designate) will explain the benefits and risks of study participation to each subject. Written informed consent must be obtained prior to any study related procedure.

9.2 Visit Procedures

9.2.1 Visit 1 (Screening / Enrolment / Treatment)

Procedures that can be completed up to 14 days before V1 are indicated by "+"

- Written informed consent+
- UPT (if female subject of childbearing potential) +
- Inclusion / exclusion criteria+
- Medical history and demographics+
- Concomitant medications/treatments+
- [redacted]
- Randomization to study treatment (i.e., left side/right side; 1st/2nd order)
- Photography (pre- and post-injection)
- Injection of study devices
- TI Assessments
  - [redacted]
- BLE Assessments
  - [redacted]
- Subject Assessments
  - [redacted]
- CTR Diary
  - *Train subject on proper use and completion*
  - *Train subject in recognizing potentially rare events of injection into the vascular system (as described in the CTR diary), and to contact their doctor immediately if an event is suspected*
- Adverse Event evaluation

9.2.2 Visit 1a Phone Follow-up (3 days post initial injection ± 1 day)

- CTR diary review
- Concomitant medications/treatments review
- AE review

9.2.3 Visit 2 ([redacted])

- Concomitant medications/treatments
- Adverse Event evaluation (including CTR Diary review)

- Photography (if T/U, taken pre-treatment)
- TI Assessments
- Subject Assessments
- Touch-up Injections (TI discretion)

9.2.4 Visit 2a Phone Follow-up Phone (3 Days post-T/U injection ± 1 day)

9.2.5 Visit 2b ( )

Visit only for subjects receiving T/U at V2

- Concomitant medications/treatments
- Adverse Event evaluation (including CTR Diary review)
- Photography
- TI Assessments

- Subject Assessments

- **Study Exit**

[redacted]

9.3 Efficacy

9.3.1 Aesthetic Effectiveness Evaluations

9.3.1.1 Nasolabial Fold Wrinkle Severity Rating Scale

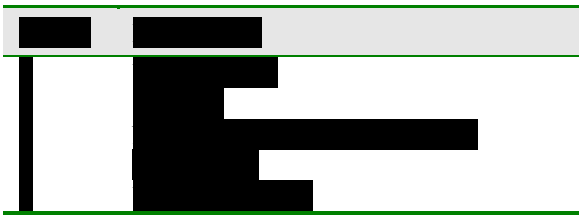
The NLF-WSRS will be assessed **at rest** by the TI and BLE using the validated 5-grade WSRS photo-numeric scale [redacted]

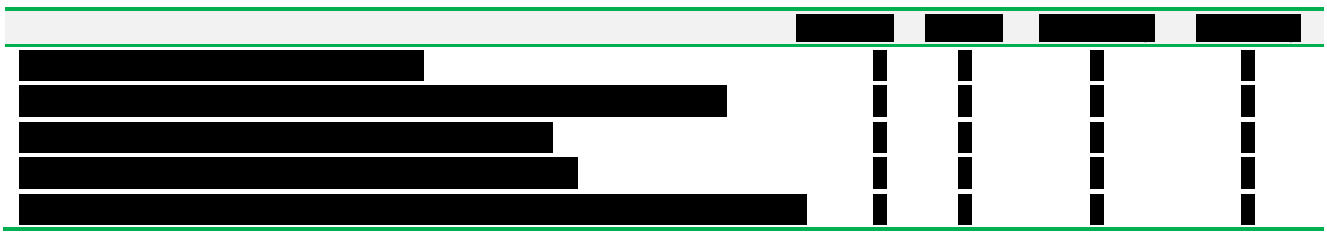
[redacted]

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

[redacted]

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





9.4 Safety

Safety will be evaluated through a 4-week patient Common Treatment Response (CTR) diary that captures post-injection signs/symptoms, measures of injection site pain and AE reporting based on phone follow-ups and clinic visits.

9.4.1 Patient Common Treatment Response Diary

The study coordinator will provide subjects with instructions for daily recording of his/her observations of the CTRs of the study treatments into an electronic diary for the first 4 weeks after each treatment. The diary will be activated after treatment and will be discussed during the 3-day post-injection telephone follow-up. Subjects should complete the diary at approximately the same time each day (i.e., AM or PM).

The subject diary will capture the following CTRs that typically occur following the injection of a dermal filler; specifically, redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and "other". The CTR diary will include a detailed glossary describing all signs/symptoms listed in the diary. Subjects will record the presence and the severity of each observed sign/symptom as: none, mild, moderate, or severe.

9.4.2 3-Day Telephone Follow-up

The subject will be contacted by telephone by the investigational site approximately 3 days following study injections and will be queried regarding health status and AEs. Information gathered will be documented in the progress notes and upon confirmation at the next clinic visit, data will be entered into the eCRF. The investigational site must attempt at least twice to contact the subject. All failed attempts will also be documented in the study notes.

[redacted]

9.4.5 Pregnancy and Contraception

All women 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 by using effective birth control methods (e.g., oral contraceptive, condom, IUD, injectable contraceptive, diaphragm or vasectomized partner). Male subjects have no contraceptive restrictions. Women 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 device on every woman of childbearing potential. A woman who is found to be pregnant at Visit 1 will be excluded from the study and considered to be a screen failure.

A woman 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.

Pregnancies will be recorded using the Pregnancy Form and will not be considered as an AE.

9.4.6 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study device(s) will be recorded in the eCRF. Subjects will be questioned for the occurrence of any new or worsening signs or symptoms at each visit by the following methods:

- Information volunteered by the subject
- Open ended and non-leading questions such as: Have you had any health problems since your last visit?
- Observation by the investigational team, other care providers or relatives

9.4.6.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject administered the study device and which may, but does not necessarily, have a causal relationship with the device. An AE can therefore be any unfavorable or unintended sign (for example an abnormal laboratory finding), symptom or disease temporally associated with the use the study device, whether or not considered related to that device.

AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, solicited via the diary and subject interviews, uncovered by review of concomitant medications or therapies, and/or observed by the study site staff. The TI will determine the description (sign, symptom, or diagnosis), onset, resolution, seriousness, severity, cause and action taken for any event.

[redacted]

[redacted]

9.4.9 Serious Adverse Events (SAEs) and Unexpected Adverse Device Effects (UADEs)

A **SAE** is defined as any unfavorable medical occurrence that meets any of the following:

1. Results in death.
2. Is life-threatening: "Life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization: Planned and routine hospital admissions for pre-existing conditions are not considered SAEs and do not require reporting as an AE unless the condition has worsened beyond what would reasonably be expected for that subject. If a subject experiences an additional AE that prolongs a pre-planned hospitalization this is considered to be an SAE and should be reported as an SAE. Pre-planned admissions must be recorded in the subject's source documentation.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly or birth defect resulting from a pregnancy that occurred during the study.

6. Is an important medical event: Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should usually be considered serious.

A **UADE** is defined as any device-related AE that meets any of the following:

1. Is not identified in nature, severity or frequency in current literature on the product.
2. Is life threatening, even if temporary in nature.
3. Results in permanent impairment of a body function or permanent damage to a body structure.
4. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
5. Any device malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

9.4.10 Causality Assessment

The TI's assessment of an AE's relationship to the study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. The TI will assign the causality assessment according to his/her clinical experience and the subject's description of the event. The Sponsor will be responsible for the final causality judgment. The causal relationship should be classified according to the following criteria (not all variables need to be present to be indicative of relationship to the device):

Definitely related:

- The temporal sequence of AE onset relative to injection of study device is reasonable.
- The AE is more likely explained by the study device or procedure than by another cause.
- The AE shows a pattern consistent with previous knowledge of the study device.

Probably related:

- The temporal sequence of AE onset relative to injection of study device is reasonable.
- The AE is more likely explained by the study device or procedure than by another cause.

Possibly related:

- The temporal sequence of AE onset relative to injection of study device is reasonable.
- The AE could have been due to another equally likely cause.

Probably not related:

- There is another more likely cause of the AE.

Definitely not related:

- The temporal sequence of AE onset relative to injection of study device is not reasonable.
- There is another obvious cause of the AE.

9.4.11 Severity Assessment

For events reported on the AE eCRF, the TI will determine the severity classification based on his/her clinical experience and by using the following definitions of severity (note: a "severe" AE is not the same as a SAE):

- Mild: Symptoms are barely noticeable or do not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: Symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.
- Severe: Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

The maximal severity for the AE will be recorded, even if the AE presented as being less severe at some point during the event.

[redacted]

9.4.13.1 All Adverse Events

All AEs, whether serious or not, will be recorded from the time of informed consent until the last study visit, or until 30 days following the last study treatment. The TI will assess all AEs and

record details of seriousness, severity, duration, and action taken with study device, and relationship to the study device.

If an AE occurs, the first concern will be the safety of the study participants. All Device Related AEs occurring after study device administration will be followed until the event has resolved or stabilized or until follow-up is no longer possible or the TI deems it unnecessary.

The Sponsor is responsible for reporting AEs to the relevant governing authorities in the time frame applicable according to international and local law.

9.4.13.2 Serious Adverse Events (SAEs) and Unexpected Adverse Device Effects (UADEs)

All SAEs and UADEs that occur after the time of informed consent through 7 days after subject completion of the study, or within 4 weeks following the last study treatment, must be reported to [redacted] within 24 hours of awareness. Initial reports must be made by contacting [redacted] as per the following: [redacted]

- Obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
- Provide [redacted] with a complete, written case history, including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement as to whether the event was or was not related to the use of the study device.
- With the assistance of [redacted], notify the governing IRB of the SAE or UADE in accordance with the requirements of SAE reporting stipulated by the governing IRB.

<u>Serious Adverse Event Reporting</u>

The TI will report SAEs on the (S)AE report form within 24 hours of awareness and complete the eCRF within 48 hours of awareness. [redacted]

[redacted]

[redacted]

<u>Unanticipated Adverse Device Effect Reporting</u>

The TI will report UADEs on the SAE/UADE report form within 24 hours of awareness and complete the eCRF within 48 hours of awareness.

[redacted]

[redacted]

[redacted]

Study Hold Due to UADEs

If the Medical Monitor determines that an UADE(s) presents an unreasonable risk to subjects, the Sponsor shall put on hold all investigation or parts of investigations presenting that risk as soon as possible. The study hold shall occur no later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect. The Sponsor will not resume an on hold investigation without IRB and FDA approval.

[redacted]

9.4.13.4 Device Malfunctions Reporting

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

[redacted]

9.4.14 MDR Reportable Events

[redacted]

[redacted]

9.4.14.1 Pregnancy

The TI must report pregnancy to [redacted] within 48 hours of learning of it using the specific pregnancy form and send it to the same e-mail address as for SAE reporting.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion due to a congenital abnormality, or a complication of pregnancy or a congenital abnormality diagnosed at any time during the pregnancy or postpartum are considered SAEs and must be reported as such. An elective abortion of a normal pregnancy without complications is not considered an SAE.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the TI to obtain this information within 28 calendar days after the initial notification and approximately 28 calendar days postpartum. The need for safety follow-up until birth will not hold up the study database lock. If the study is completed and/or the study database is locked before the postpartum follow-up is expected, the TI will notify [redacted] of the outcome of the pregnancy only via e-mail: [redacted] and the pregnancy notification will be processed accordingly outside the eCRF.

In addition to the above, if the TI determines that the pregnancy meets seriousness criteria, it must be reported also as an SAE (in addition to reporting the pregnancy itself).

10 SUBJECT COMPLETION / WITHDRAWAL / STOPPING RULES

10.1 Completion

A subject will be considered to have completed the study if he or she has completed all the assessments or has experienced an event that precludes further participation in the study.

10.2 Withdrawal

A subject **will be** withdrawn from the study for any of the following reasons:

- Lost to follow-up;
- Withdrawal of consent;
- The Principal Investigator believes that for safety reasons (e.g., AE, concurrent illness) that it is in the best interests of the subject to be withdrawn from study participation;
- The subject's attending physician requests that the subject be withdrawn from the study;
- The Principal Investigator or the Sponsor, for any reason, stops the study or stops the subject's participation in the study.

Protocol deviations will not lead to automatic withdrawal unless they indicate a significant risk to the subject's safety. All major protocol deviations must be discussed promptly with the Medical Monitor.

A subject **may be** withdrawn from the study, in consultation with the Medical Monitor, for any of the following reasons:

- Lack of compliance to study procedures;
- A major protocol deviation or violation;
- Poor visit attendance.

Should a subject decide to withdraw after administration of a study device(s), or should the Principal Investigator decide to withdraw the subject, the Principal Investigator (or designate) will complete and report the observations up to the time of withdrawal.

All subjects who are withdrawn from the study will be requested to come in to complete their next scheduled clinic visit. The next scheduled visit may be brought forward to facilitate this. A complete evaluation at the time of the subject's withdrawal should be made. Additionally, subjects who withdraw from the study will be requested to allow continued safety monitoring, either via telephone interviews or clinic visits, whichever is more appropriate.

The reason and date of withdrawal must be noted on the eCRF. If the reason for withdrawal is an AE or an abnormal laboratory test result, monitoring will continue until resolution or until an appropriate medical judgment concerning the cause or importance has been made. The specific event or test result(s) must be recorded on the eCRF.

[redacted]

11 STATISTICAL METHODS

11.1 Primary Endpoint

The primary effectiveness endpoint will be aesthetic improvement from pre-injection as assessed by the NLF-WSRS (BLE) The effectiveness of RHA®4 will be demonstrated if RHA®4 used in conjunction with cannula is statistically non-inferior to RHA®4 with sharp needle as assessed by the BLE

11.3 Safety Endpoints

The following safety endpoints will be explored:

1) AEs across the duration of the study (incidence, intensity, and duration).

3) Post-injection Common Treatment Response (4-week CTR diary; incidence, intensity, and duration).

5) Injection Site pain immediately after treatment, and at 5, 30, and 60 minutes post-treatment.

11.4 Analysis Populations

Three subject analysis populations are defined: Intent-to-Treat (ITT) Population, Per Protocol (PP) Population, and Safety (SAFT) Population. All analysis populations will be defined and determined prior to database closure and unblinding for the final analysis.

[redacted]

[redacted]

11.6 General Considerations

Data will be listed by treatment group and subject number. Safety and efficacy data will be summarized by treatment group. Descriptive statistics will consist of mean, standard deviation, minimum/maximum for continuous variables, and frequency and percent for discrete variables.

A full description of the statistical methods planned for this study will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized and approved by the study Sponsor prior to the last subject's last visit. All programs for data output and analyses will be written in SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

[redacted]

[redacted]

11.7 Effectiveness Analysis

11.7.1 Primary Endpoint

The primary endpoint of NLF-WSRS change from Baseline [redacted] as rated by the BLE will be analyzed in a non-inferiority statistical model using the PP population with a 0.5 margin for the difference between cannula and needle. [redacted]

11.7.2 Secondary Endpoints

All statistical inference tests will be performed at the same significance level (α) of 0.05. For categorical and continuous variables, the two groups will be compared using two-sided parametric or non-parametric tests for paired data, as appropriate. For continuous variables, the Shapiro-Wilk test will be used to assess normality. If data appear normally distributed, testing will be conducted using the Student t-test, while testing will be conducted with the Wilcoxon signed-rank test if not normally distributed.

11.8 Safety Analysis

The SAFT Population will be used to summarize the safety of the study devices and will consist of all treated subjects. The primary safety analysis is the calculation of the incidence of CTRs and adverse events in the study period. Point estimates for all CTRs, AEs and SAEs will be presented and two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs. Tables will be generated which summarize AEs by investigator assessments of both relationship to treatment and severity.

11.8.1 Adverse Events (AEs)

Safety outcomes will be incidence rate of AEs, including UADEs, types of AEs and their severity and relationship to study treatment.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. These events, irrespective of relationship to study medication, will be summarized by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The number of subjects reporting an AE, the number of AEs, and percentages of subjects in each category will be summarized. AEs by severity and relationship to study will be summarized in a similar way. Serious AEs will be summarized separately. [redacted]

[redacted]

12 ETHICAL ASPECTS

12.1 Informed Consent

This study will be conducted in compliance with 21 CFR Part 50 for informed consent. Written informed consent will be obtained from each subject before any procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. It will also be explained to the subject that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the subject will be given to all subjects. The information provided must include an adequate explanation of the aims, methods, anticipated benefits, potential hazards, compensation and/or honoraria, and insurance arrangements in force.

The subject's willingness to participate in the study will be documented in writing on a consent form, which will be signed by the subject with the date and time of that signature indicated. The site will keep the original consent forms and copies will be given to the subjects.

See also Section 9.1.

12.2 Health Authorities and IRBs

The Principal Investigator will ensure that the conduct of the study conforms to the Declaration of Helsinki, the Belmont Report, and with national laws and regulations for clinical research.

Before starting this study, the protocol will be submitted to the FDA and central IRB for evaluation. As required, the study will not start before the IRB and the FDA give approval.

12.3 Confidentiality Regarding Study Subjects

The Principal Investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (e.g., subject or screen number).

The site monitor, properly authorized persons on behalf of the Sponsor's quality assurance unit, or competent authorities may scrutinize personal medical information for the purpose of verifying data recorded on the eCRF. Personal medical information will always be treated as confidential, according to local privacy regulations.

13 STUDY MANAGEMENT & ADMINISTRATION

13.1 Protocol Amendments

No amendments to the protocol will be implemented without the prior written consent of the Sponsor. Should an amendment be necessary, the reviewing IRB and FDA may require review and approval prior to its implementation.

13.2 Monitoring and Quality Assurance

13.2.1 Information to Study Personnel

The Principal Investigator, [redacted] is responsible for ensuring that all study personnel are qualified for their designated roles and for providing information about the study to all staff members involved in the study or in any element of subject management, both before starting the practical performance of the study and during the course of the study (e.g., when new staff become involved).

The [redacted] site monitor is responsible for initiating the site, conducting interim monitoring visits, ensuring site compliance with the protocol and closing out the site at the end of the study. Additional information available during the study should be given as agreed upon, either by the Principal Investigator or the site monitor, and always when new staff members become involved in the study.

13.2.2 Study Monitoring

[redacted] clinical monitors will conduct approximately 2-3 on-site or remote interim monitoring visits at each study site in order to ensure compliance to the protocol, applicable regulations, and ICH-GCP, and to ensure safety of the subjects and maintenance of adequate and accurate clinical records. A dedicated close-out visit will also be conducted at each site.

Monitoring functions will be performed in compliance with GCP and the study specific Monitoring Plan. The Principal Investigator agrees to allow the site monitors, and other authorized Sponsor personnel, access to the clinical supplies, the investigational agent dispensing and storage area, subject medical records, laboratory data, and other source documentation of the study subjects.

Source Document worksheets for all subjects and eCRFs will be reviewed in detail by the site monitor to ensure data integrity. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the eCRFs and/or worksheets in question will be corrected by the study coordinator and confirmed/signed for by the TI or BLE, as appropriate. Data clarification or query forms may be generated for omissions or clarifications, to be completed and returned to the site monitor.

The dates of monitoring visits will be recorded by the site monitor in a sign-in log to be kept at the site. The Sponsor expects that, during monitoring visits, the study coordinator and Principal Investigator will be available, the source documentation will be available, and a suitable environment for on-site visits will be provided for review of study-related documents.

The TI and assisting staff must agree to cooperate with the site monitor to resolve any problems, errors, or possible misunderstandings concerning any data discrepancies detected in the course of these monitoring visits.

As part of the supervision of the study progress other Sponsor personnel may accompany the site monitor on visits to the study site.

13.2.3 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor (or its designate) may audit the investigational site to compare raw data, source data, and associated records with the interim (if applicable) or final report of the study to assure that data have been accurately reported.

The Principal Investigator must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP. The Principal Investigator should notify the Sponsor and [redacted] no later than 24 hours upon notification of being audited by the FDA or IRB.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the Principal Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to use continuous vigilance to identify and promptly report deviations to [redacted]

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the [redacted] must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the IRB per its guidelines.

The protocol must be rigorously adhered to; however, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of an Investigator.

[redacted]

14 DATA HANDLING AND RECORD KEEPING

14.1 Source Data

The site is required to maintain adequate and accurate medical records designed to record all observations and other data pertinent to the study for each study subject. Source documentation is generally considered to be the document on which the information or data point was first recorded. Source documentation may include a subject's medical records, hospital charts, clinic charts, and the site's study files as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms.

[redacted]

Pertinent records related to the study (e.g., the subject's medical chart) will be made available to the Sponsor representative on request with due precaution to protect the privacy of the subject. If applicable (i.e., SAE reporting), personal identifying information (except subject initials) will be redacted on any photocopies of relevant medical records and replaced with the unique subject number before submission to the Sponsor. The TI will protect the confidentiality of all subjects' records within applicable federal, state and local laws.

A subject identification code list will be maintained in order to allow unambiguous identification of each subject included in the study. This list should contain the subject's full name, date of birth, dates of participation and identification number as per local regulations.

The Principal Investigator must agree to supply all details to Sponsor auditor(s) and/or regulatory authorities, ensuring the data is held confidentially at the site after completion of the study. A note will be made in the hospital or clinical medical records, if appropriate, that the subject is participating in a clinical study.

The eCRF and subjects' medical records will be reviewed [redacted], representatives from [redacted], the IRB, and/or the FDA to the extent permitted by regulations.

14.2 Case Report Form

In this study the case report form will be an eCRF. The study coordinator must complete the eCRF for each subject within a timely manner of the visit occurring.

The site monitor will review the completed eCRF for accuracy, completeness and consistency with source documentation (i.e., medical records, source document worksheets, etc.). The site monitor will submit requests for correction/clarification of data (e.g., queries) to the study coordinator when inconsistencies are identified during monitoring and source data verification or during the edit check process.

All corrections and alterations of eCRF data must be made by the study coordinator in a timely manner and according to the instructions provided. Completed eCRFs for each visit (i.e., those reviewed by [redacted] and with no remaining queries) should then be reviewed and electronically signed by the TI. In order to review and electronically sign the eCRF, the TI will each have his/her own login that will allow them to view only the data that they have generated.

A full audit trail detailing corrections and alterations made to the eCRF will be maintained.

Upon study completion, a softcopy of the eCRF for each subject will be provided to the site.

14.3 Archiving of Study Documentation

Essential documents are any records that demonstrate the compliance of the subject, Investigators, Sponsor, and site monitor with the study protocol, with standards of GCP, and with all applicable regulatory requirements. Essential documents (including but not limited to study-related correspondence (including emails), subject records, subject privacy documentation, records of the distribution and use of study devices, and copies of eCRFs should be retained and available for audit by the Sponsor's auditor and regulatory authorities until at least 2 years after the latest among the following scenarios: completion or termination of the study, the last approval of a marketing application, no pending or contemplated marketing applications, or formal discontinuation of clinical development of RHA®4. These documents should be retained for a longer period, however, if mandated by the applicable regulatory requirements, by conditions imposed by the IRB, or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Principal Investigator when these documents no longer need to be retained.

The Sponsor must be notified in writing if the Principal Investigator chooses to store the records at a different physical address than the site address or if the Principal Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

15 FINANCING AND INSURANCE

A separate financial agreement (Clinical Trial Agreement) will be made between the Sponsor and the Principal Investigator at each site.

The study is covered under a [redacted] liability insurance policy. The certificate of insurance will be provided upon request.

16 REPORTING AND PUBLICATION OF RESULTS

[redacted] as the Sponsor, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation among multiple Principal Investigators and sites and [redacted]. Authorship will be established prior to the writing of the manuscript. As this study involves multiple sites, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with [redacted].

All information, including but not limited to information regarding RHA®4 or the Sponsor's operations supplied by the Sponsor to the Principal Investigator and not previously published, along with any data generated as a result of this study are considered confidential and remain the sole property of the Sponsor. The Principal Investigator agrees to maintain this information in confidence, and will use the information only to perform the study.

The Sponsor or its designee is responsible for preparing a clinical study report.

The Sponsor or its designee is responsible for publicly registering this study on http://www.clinicaltrials.gov/ prior to initiating enrolment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

18 APPENDICES

APPENDIX A: ADJUSTMENTS OF VISITS AND ASSESSMENTS DUE TO PUBLIC HEALTH EMERGENCY OF COVID-19

1. General Guidance

Subject safety and preserving the integrity of the data are of the highest priority. Any federal, state and local rules, guidances, or laws shall be followed.

Study visits and procedures should be followed per-protocol whenever possible. Any specific changes in study conduct that deviate from the protocol should be communicated to the sponsor via reporting to the site's Clinical Research Associate (CRA), Clinical Project Manager (CPM), and IRB, as applicable. All protocol deviations which occur as a result of COVID-19 disruptions (including remote visits), will be differentiated from other deviations and must be documented on the appropriate reporting forms/source document, and clearly annotated "protocol deviations due to COVID-19 illness/restrictions/etc.". If the subject is unable or unwilling to come to the site due to COVID-19, the TI needs to ask for the reasons and document them in the source documents.

The TI is responsible for ensuring subjects' safety and for monitoring all active subjects per protocol. TI must ensure that study subjects are kept informed of changes to the study and monitoring plans that could impact them.

Should a subject develop any symptoms that could be related to COVID-19 or any other acute infection disease, the subject will be instructed to:

- Contact the TI as soon as possible
- Contact their general physician to be examined and determine the course of action according to the standard of care.

The TI or designee will follow-up with the subject as needed but at least within 72 hours of awareness to obtain an update on the subject's health and to obtain information on whether COVID-19 has been diagnosed or not. If the subject has been diagnosed with COVID-19, the event will be reported as an AE.

[redacted]

[redacted]

[redacted]

[redacted]

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