A randomized, controlled, double-blinded, within-subject (split-face), multicenter, prospective clinical study to compare the level of pain using the dermal filler RHA® [redacted] formulated with two different anesthetics in the treatment of perioral rhytids

IDE Pivotal Study

Protocol: [redacted]

Date: 10-Sep-2019

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 Operations Manager 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, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by TEOXANE SA 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.

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

Principal Investigator *(Printed Name)*	Signature	Date

SYNOPSIS

Protocol Version	Version [redacted] 10-Sep-2019	**Investigational Device**	RHA® [redacted] with [redacted] (RHA® [redacted])
Study Number	[redacted]		
Phase	IDE Pivotal	**Control Device**	RHA® [redacted] with lidocaine (RHA® [redacted])
Indication	Injection in the dermis and superficial dermis of the face for correction of moderate to severe perioral rhytids	**Study Sites**	Multicenter, maximum 3 US sites
Title	A randomized, controlled, double-blinded, within-subject (split-face), multicenter, prospective clinical study to compare the level of pain using the dermal filler RHA® [redacted] formulated with two different anesthetics in the treatment of perioral rhytids		
Sponsor	TEOXANE SA, Rue de Lyon 105, CH - 1203 Geneva, Switzerland		
Study Duration	Approximately 60 days	**Number of Subjects**	Maximum 30 subjects treated with RHA® [redacted] and RHA® [redacted] with at least 20% of subjects presenting Fitzpatrick skin type IV to VI including at least 10% of subjects presenting Fitzpatrick skin type V to VI.
Treatment Groups	Each enrolled subject will receive injections of RHA® [redacted] with [redacted] into the perioral rhytids of the left or right side of the mouth, and injections of the control device (i.e., RHA® [redacted] with lidocaine) into the perioral rhytids of the contralateral side of the mouth.		
Study Design	This is a randomized, controlled, double-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA® [redacted] with [redacted] is non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection. At screening, the Treating Investigator (TI) will evaluate subjects' perioral rhytid severity (using the Perioral Rhytid Severity Rating Scale; PR-SRS) to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement. At Visit 1, RHA® [redacted] with [redacted] will be administered in a random sequence (first or second injection) and side of the mouth (left or right) and RHA® [redacted] with lidocaine will be administered to the other side. Study subjects and the TI injecting study devices will be blinded. [redacted] Immediately <u>after</u> injection of an upper perioral quadrant, subjects will rate injection site pain experienced **during injection** using a 100 mm Visual Analog Scale (VAS). Injection site pain in each side of the mouth will also be assessed at 15, 30, 45 and 60 minutes after the upper quadrant was injected. [redacted]. Safety evaluation will consist of AE assessments, a 30-day CTR (Common Treatment Response) diary, [redacted]		

	[redacted] and a follow-up call performed by the study site at 72 hours after injection. Subjects will attend Visit 2 (30 days post-injection) where efficacy and safety assessments will be conducted. Subjects who present with an unresolved clinically significant device related AE at Visit 2 will receive the optional follow-up phone call no later than 30 days after Visit 2. If the clinically significant AE remains unresolved, the Investigator will request that the subject to attend the optional in-clinic follow-up visit (i.e., Visit 3) within 5 working days. Follow-up of the clinically significant AE will continue until the AE is resolved or the TI determines that additional follow-up is not necessary. [redacted]
Hypothesis	The anesthetic effect of RHA® [redacted] with [redacted] will be non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection into the upper perioral rhytids assessed immediately after injection of each upper quadrant using a 100 mm Visual Analog Scale (VAS).
Objectives	Demonstrate the non-inferiority of RHA® [redacted] with [redacted] versus the control (RHA® [redacted] with lidocaine) in terms of reducing pain during device injection into the upper perioral rhytids. Injection pain during injection will be based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each upper perioral quadrant.
Inclusion Criteria	1. Outpatient, male or female of any race, 22 years of age or older. Female subjects of childbearing potential must have a negative UPT at Visit 1 and practice a reliable method of contraception throughout the study. 2. Moderate to severe bilateral perioral rhytids (grade 2 or 3 on the four point PR-SRS). 3. Perioral rhytids of the same PR-SRS grade on the left and right sides of the mouth. [redacted] 5. Able to follow study instructions and complete all required visits. 6. 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. Female subjects who are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control. 2. Known hypersensitivity or previous allergic reaction to any component of the study devices. 3. [redacted]. 4. Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, or history of anaphylactic shock. [redacted] 7. History of active chronic debilitating systemic disease that, in the opinion of the investigator, would make the subject a poor candidate in the study. 8. History of connective tissue disease. 9. Malignancy (excluding non-melanoma skin cancer) within the past 5 years.

	10. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to Visit 1. [redacted] 13. History of skin cancer in the treatment area. 14. Elective, clinically significant facial procedures that may confound the interpretation of the results in the perioral region (TI discretion), prior to study enrollment. 15. Clinically active disease or infection in the perioral area or mouth (e.g., dental abscess). [redacted] 17. Medical or psychiatric conditions that may increase the risk associated with study participation or 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. [redacted] 20. Exposure to any other investigational drug/device within 90 days of entering the study. 21. Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability.
Device Administration	[redacted] **Injection area:** For the purposes of this study, the lip will be defined as the structures within the vermilion border. The focus of this study is to treat perioral rhytids, [redacted]
Blinding	This is a double-blinded study. Subjects and TI will be blinded to treatment allocation.
Randomization	A randomization algorithm will provide equal balancing for the side of the mouth and the order of injection of study devices [redacted]
Visit Procedures	*Refer to the Study Summary Tables and the Study Schematic for a schedule of activities.*
Anesthetic Effectiveness	• Injection Site Pain during injection in the upper perioral quadrants (primary endpoint) • Injection Site Pain at 15, 30, 45 and 60 minutes post-injection in each side of the mouth

Evaluations	• [redacted]
Aesthetic Effectiveness Evaluations	[redacted] • [redacted]
Safety Evaluations	• Adverse Events. • Post-injection Common Treatment Response [redacted] (30-day patient CTR diary). [redacted] • [redacted]
Primary Endpoint	Injection site pain felt <u>during</u> injection of the upper perioral quadrant assessed by the subject immediately following injection with RHA® [redacted] with [redacted] compared to the injection site pain felt <u>during</u> injection into the contralateral upper perioral quadrant assessed immediately following injection with RHA® [redacted] with lidocaine.
Secondary Endpoints	[redacted] • [redacted]
Sample Size	[redacted] [redacted] the Sponsor increased the sample size of the study [redacted] to 30.
Statistical Methods	[redacted]

[redacted]

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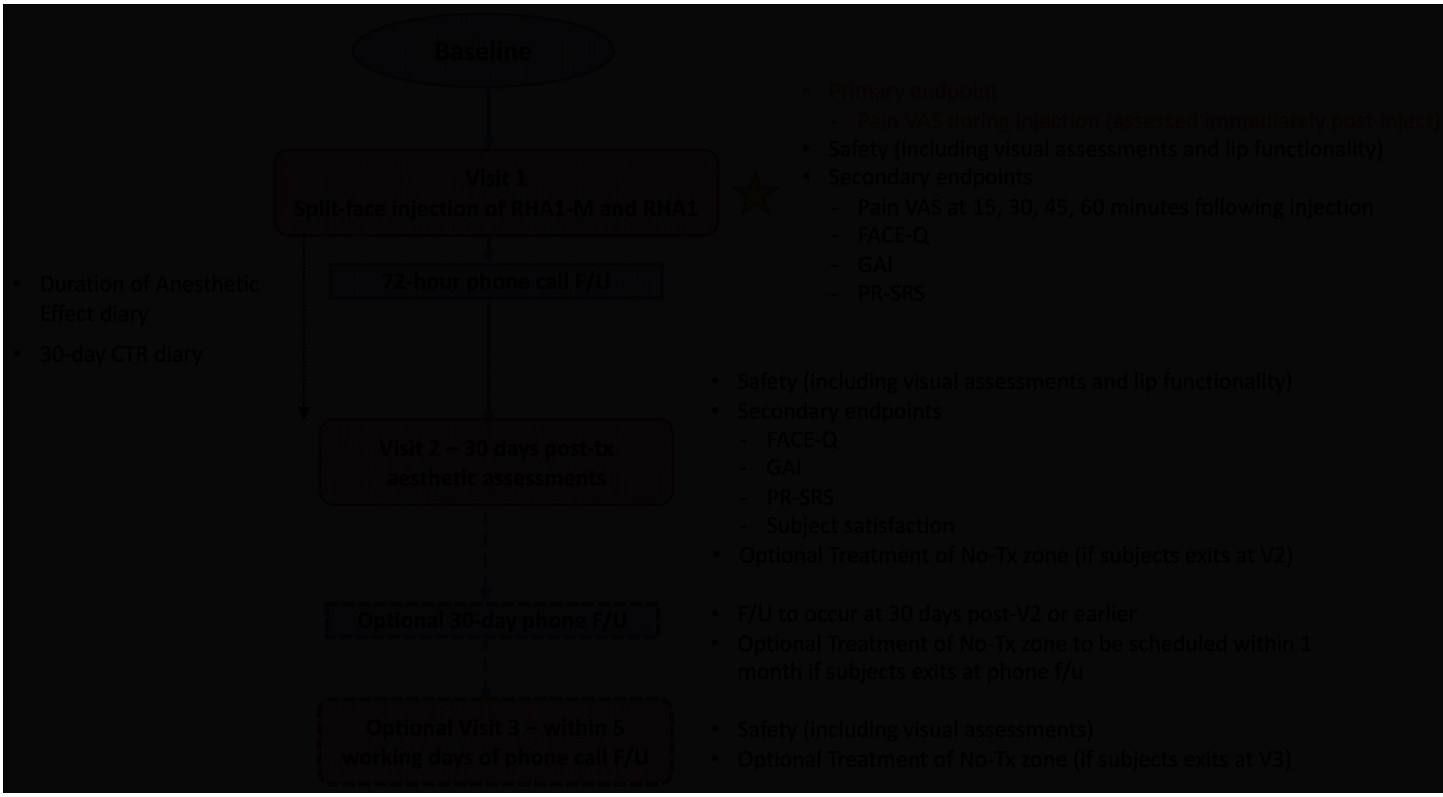
[redacted]

FIGURE 1. STUDY SCHEMATIC



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CONTACT LIST

Medical Monitor

[redacted]

Sponsor Contacts

[redacted]

[redacted]

CRO 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.

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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 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 2018 were extracted from the ASPS website in June 2019 (https://www.plasticsurgery.org/news/plastic-surgery-statistics):

- 15.9 M cosmetic minimally invasive procedures, up 2% from previous year
- 2.68 M procedures with any dermal filler, up 2% from previous year
- 2.13 M procedures with HA, up 2% 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, such as lip augmentation.

RHA® [redacted] and RHA® [redacted] dermal fillers are devices 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® [redacted] product contains 0.3% w/w of lidocaine hydrochloride, and RHA® [redacted] contains 0.3% w/w of [redacted] hydrochloride. Both lidocaine and [redacted] are drug substances widely used for their anesthetic properties (i.e., they block the origin and transmission of nervous influx at the point of injection by stabilizing the neuronal membrane).

RHA® [redacted] and RHA® [redacted] are intended for injection in the dermis and superficial dermis of the face to correct moderate to severe perioral rhytids. RHA® [redacted] is an investigational device that has not yet been approved by the FDA. TEOXANE S.A. has recently completed a pivotal clinical study (IDE number G160123) investigating RHA® [redacted] for the treatment of perioral rhytids that is intended to secure a Premarket Approval (PMA) from the FDA for this device. All subjects in this study have completed their final visits, there were no UADEs or Treatment-Related SAEs, and data analysis is in progress. The primary endpoint was achieved.

[redacted]

[redacted]

1.3 Hypothesis

The anesthetic effect of RHA® [redacted] with [redacted] will be non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection into the upper perioral rhytids assessed immediately after injection of each upper quadrant using a 100 mm Visual Analog Scale (VAS).

2 STUDY OBJECTIVE

The study objective is to demonstrate the non-inferiority of RHA® [redacted] with [redacted] versus the control (RHA® [redacted] with lidocaine) in terms of reducing pain during device injection into the upper perioral rhytids. Injection pain during injection will be based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each upper perioral quadrant.

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

Maximum three (3) 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.

Each site will have one TI who will be responsible for administering all study treatments, assessing safety, and conducting subject assessments. TIs will be specialists in the fields of cosmetic dermatology or plastic surgery and will have extensive experience with dermal fillers. The TI will function as the site's Principal Investigator. Additionally, each site will have a study coordinator.

[redacted]

3.3 Training and certification on the Perioral Rhytids Severity Rating Scale (PR-SRS)

[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 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] AEs 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, double-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA® [redacted] with [redacted] is non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection.

At screening, the Treating Investigator (TI) will evaluate subjects' perioral rhytid severity (using the Perioral Rhytid Severity Rating Scale; PR-SRS) to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement.

At Visit 1, RHA® [redacted] with [redacted] will be administered in a random sequence (first or second injection) and side of the mouth and RHA® [redacted] with lidocaine will be administered to the other side. Study subjects and the TI injecting study devices will be blinded.

[redacted]

Immediately <u>after</u> injection of an upper perioral quadrant, subjects will rate injection site pain experienced **during injection** using a 100 mm Visual Analog Scale (VAS). Injection site pain in each side of the mouth will also be assessed at 15, 30, 45 and 60 minutes after the upper quadrant was injected.

[redacted]

Safety evaluation will consist of AE assessments, [redacted] a 30-day CTR diary, and a follow-up call performed by the study site at 72 hours after injection.

Subjects will attend Visit 2 (30 days post-injection) during which efficacy and safety assessments will be conducted. Subjects who present with an unresolved clinically significant device related AE at Visit 2 will receive the optional follow-up phone call no later than 30 days after Visit 2. If the clinically significant AE remains unresolved, the Investigator will request that the subject attend the optional in-clinic follow-up visit (i.e., Visit 3) within 5 working days. Follow-up of the clinically significant AE will continue until the AE is resolved or the TI determines that additional follow-up is not necessary.

[redacted]

[redacted]

4.2 Study Design Rationale

4.2.1 Study Population

Maximum 30 subjects will be enrolled and receive study treatment. [redacted]

4.2.2 Primary Endpoint

The primary endpoint is injection site pain during injection into the upper perioral rhytids assessed immediately following injection with RHA® [redacted] with [redacted] (using a 100 mm VAS) compared to the injection site pain felt during injection into the contralateral upper perioral rhytids assessed immediately following injection(s) with RHA® [redacted] with lidocaine.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Outpatient, male or female of any race, 22 years of age or older. Female subjects of childbearing potential must have a negative UPT at Visit 1 and practice a reliable method of contraception throughout the study.

[redacted]

2. Moderate to severe bilateral perioral rhytids (grade 2 or 3 on the four point PR-SRS).
3. Perioral rhytids of the same PR-SRS grade on the left and right sides of the mouth.

[redacted]

5. Able to follow study instructions and complete all required visits.
6. 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. Female subjects who are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control.
2. Known hypersensitivity or previous allergic reaction to any component of the study devices.

[redacted]

4. Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, or history of anaphylactic shock.
5. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion).

[redacted]

7. [redacted].
8. History of connective tissue disease.
9. Malignancy (excluding non-melanoma skin cancer) within the past 5 years.
10. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to Visit 1.

[redacted]

13. History of skin cancer in the treatment area.
14. Elective, clinically significant facial procedures that may confound the interpretation of the results in the perioral region (TI discretion), prior to study enrollment.

[redacted]

17. 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.

[redacted]

20. Exposure to any other investigational drug/device within 90 days of entering the study.
21. Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability.

6 TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

All subjects who have signed an ICF 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.

Upon qualifying for treatment, subjects will be randomized for the side of mouth and the order of injection of study devices [redacted] If needed to improve cosmetic results, the lower perioral quadrant of a side will be injected only after both upper perioral quadrants have been injected.

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.

This is a double-blinded study in which subjects and TIs will be blinded to treatment allocation.

Designated site personnel will secure the randomization/treatment allocation information and any other record of study treatment from potential discovery by the TI or the subject. Any instance where the blind is opened to the TI or subject will be documented in writing.

If it is medically imperative to know what device was injected into the left and right perioral rhytids, the TI or study coordinator will contact [redacted] to confirm the rationale for unblinding. If appropriate, [redacted] and/or the Sponsor will approve unblinding and treatment assignments for that particular subject will be disclosed. The rationale for breaking the code must be recorded in subjects' medical record and eCRF.

7 DEVICE APPLICATION

7.1 Study Devices

RHA® with : A sterile, biodegradable, biocompatible, viscoelastic, clear, colorless, homogenized gel implant. It consists of cross-linked hyaluronic acid produced by fermentation of *Streptococcus zooepidemicus*, formulated to a concentration of 15 mg/g and 0.3% w/w in a physiologic buffer

RHA® with lidocaine: A sterile, biodegradable, biocompatible, viscoelastic, clear, colorless, homogenized gel implant. It consists of cross-linked hyaluronic acid produced by fermentation of *Streptococcus zooepidemicus*, formulated to a concentration of 15 mg/g and 0.3% w/w lidocaine in a physiologic buffer

For additional information regarding RHA , please refer to Investigator's Brochure.

7.2 Injection of Study Devices

At Visit 1, each enrolled and randomized subject will receive injections of RHA® with into the perioral rhytids of the upper left quadrant or the upper right quadrant, and injections of the control device (i.e., RHA® with lidocaine) into the contralateral upper quadrant. Using the same device as the upper quadrant for that side, the lower perioral quadrant of a side will be injected only after both upper perioral quadrants have been injected and only if needed.

7.2.1 Injection Depth

7.2.2 Injection Technique

The injection technique (e.g., linear threading, cross hatching, fan like administration, multiple puncture, etc.) will be at the discretion of the TI, and will be recorded. The same injection technique will be used on both sides of the mouth.

For the purposes of this study, the lip will be defined as the structures within the vermilion border. The focus of this study is to treat perioral rhytids, and there will be no augmentation of the lips, but the vermilion border may be treated to ensure a satisfactory result of the treatment of the perioral rhytids.

Devices will be injected using the needle that is provided within the standard packaging of the device; the TI is not permitted to use a needle of different gauge or length.

7.2.3 Supplementary Anesthesia

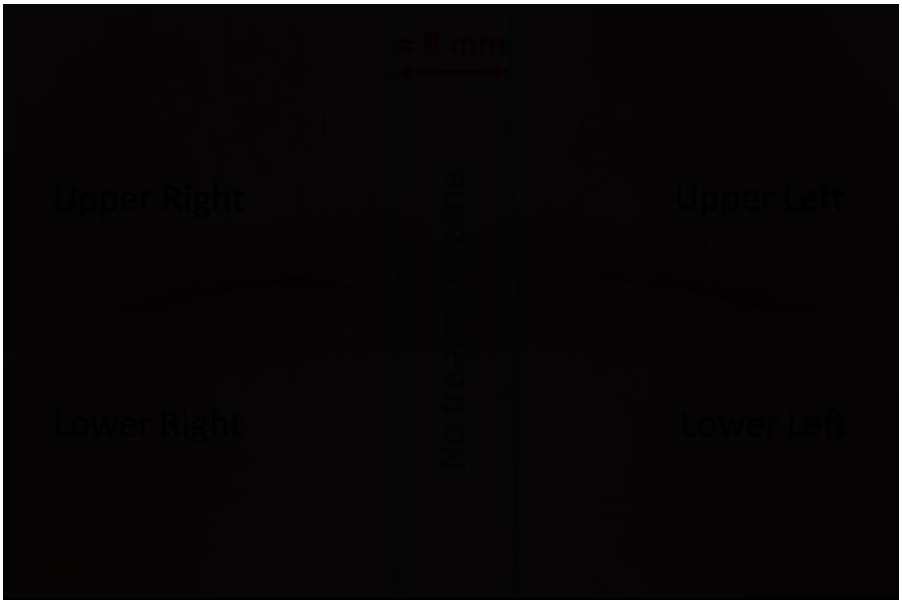
Both study devices contain an anesthetic. Additional anesthesia is prohibited (e.g., EMLA, dental blocks, ice, etc.). Ice may be used at the discretion of the TI for post-injection treatment for pain or discomfort, but only after all injection pain assessments for both sides of the mouth have been

completed (i.e., at 60 minutes post-injection).

[redacted]

[redacted]

[redacted]



[redacted]

7.3 Labeling, Packaging and Storage

Supplies of RHA® [redacted] with [redacted] and RHA® [redacted] with lidocaine 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 TEOXANE, 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. The Tyvek lid on the blister will include:

[redacted]

- Name and address of the Sponsor/Manufacturer (i.e., TEOXANE S.A.)
- Quantity of syringes (n=1)
- Quantity of [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.

7.3.1 Relabeling

Real-time aging testing is in progress for the study devices. As new test data will become available throughout the course of the study, the shelf life of the study devices may be extended through the course of the study. The site monitor and/or study coordinator will be responsible for relabeling the Tyvek lid with the new expiry date. The site monitor and/or study coordinator will follow a specific procedure to perform and verify the product relabeling with the extended expiry date (to be provided in a separate guidance document). The relabeling process will be documented. The study devices may also be returned to the Sponsor to be relabeled. When the study devices have reached the expiry date as indicated on its label, the TI should segregate them and follow the instructions from the site monitor as to relabeling by the site monitor and/or study coordinator or for returning the devices to the Sponsor.

It is the responsibility of the TI to verify that a device is within its expiry date before being used. The initial shelf life of the study devices will be approximately 9 months; however, as devices being subjected to real time aging are being tested periodically, the shelf-life could be extended.

7.4 Study Device Supply and Accountability

The study Sponsor will ensure that participating sites are provided with a sufficient supply of study devices 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 will be returned to the Sponsor at the end of the study unless other arrangements are agreed upon in writing. **Used syringes** 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, paper study diaries, 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

Any medication or procedure, including over-the-counter preparations, that the subject takes during the study protocol period is considered concomitant medication and will be captured on the Concomitant Medications and Procedures page of the eCRF.

[redacted]

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.

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 will have an individual login password that will allow them to view only the data that they have generated. The TI must ensure that they electronically sign for completed eCRFs on a timely basis.

8.2 Subject Diaries

Subjects will record Common Treatment Responses (CTRs) for 30 days post-injection using paper-based diaries. Data recorded in this diary will be entered into the eCRF by the study coordinator.

[redacted]

Subjects will also record "duration of anesthetic effect" using paper-based diaries. Data recorded in this diary will be entered into the eCRF by the study coordinator.

8.3 Photography

Calibrated photographs will be taken at Visit 1 (pre-injection and post-injection) and Visit 2 according to a standardized protocol incorporating appropriate quality control processes (i.e., [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)
- Photography (pre-injection and post-injection)
- Injection of study devices
- TI Assessments
  - [redacted]
- Subject Assessments
  - [redacted]
- CTR Diary and "Duration of Anesthetic Effect" Diary
  - *Dispense diaries to subject and train subject on proper completion*
  - *Train subjects 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*

9.2.2 Follow-up Phone Call (72 hours post-injection)

- CTR diary review
- Anesthetic effect duration diary review
- Concomitant medications/treatments review
- AE review

9.2.3 Visit 2 (30 days from V1; ±3 days)

- Concomitant medications/treatments
- Photography
- [redacted]

- TI Assessments
- Subject Assessments
- Collect and review CTR Diary and "Duration of Anesthetic Effect" Diary
- Next Study Visit
  - *If Subject presents with an unresolved device related clinically significant AE, proceed to Follow-up Phone Call.*
  - *If Subject does not present with an unresolved device related clinically significant AE, the subject will **exit** the study and optional treatment with a commercially available product approved for injection into the perioral rhytids will be offered to subjects with remaining lines and/or wrinkles in the no-treatment zone.*

9.2.4 Follow-up Phone Call – Optional (no later than 30 days from V2)

- Concomitant medications/treatments review
- AE review
  - *Confirm if subject is still experiencing the unresolved clinically significant device related AE(s)*
    - *If yes, the site will request that the subject attend the optional in-clinic within 5 working days.*
    - *If no, the subject will **exit** the study*
- **Study Exit**

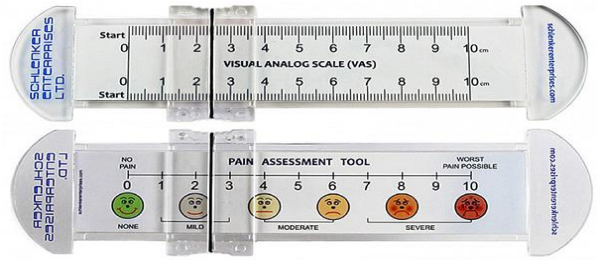
9.3 Effectiveness Variables

9.3.1 Anesthetic Effectiveness Variables

9.3.1.1 Injection Site Pain - Primary Effectiveness Variable

Injection pain will be self-assessed by the subject using a Visual Analog Scale (VAS) Pain Scale Ruler (see Figure 3 below). The VAS Pain Scale Ruler has two sides. Using the side that shows faces and is labeled "Pain Assessment Tool", subjects will move the slider to the location that represents their level of pain. The site will use the other side of the ruler to determine the VAS score (expressed in units of mm).

Figure 3. VAS Ruler



Immediately <u>after</u> injection of an upper perioral quadrant, subjects will rate injection site pain **during injection**. Injection site pain in each side of the mouth will also be assessed at 15, 30, 45 and 60 minutes after the upper quadrant for that side was injected.

The occurrence of injection site pain is not to be considered an AE unless it is in excess to that typically observed following injection of a dermal filler (as determined by the TI).

[redacted]

[redacted]

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

[redacted]

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

[redacted]

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

9.3.2.5 Treatment Volume

The total volume injected in each upper quadrant will be collected for each study device. Additionally, total volume required injected in each lower quadrant will be collected. Treatment volume will be measured to an accuracy of 0.1 mL.

9.4 Safety

Safety will be evaluated through a 30-day patient Common Treatment Response (CTR) diary that captures post-injection signs/symptoms and AE reporting based on phone follow-ups and clinic visits. [redacted]

9.4.1 30-Day Patient Common Treatment Response Diary

The subject will receive a diary booklet and instructions for recording his/her observations of the CTRs of the study treatments for the first 30 days after treatment. The diary will be dispensed after treatment and will be discussed during the 72-hour 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". Subjects will record the presence and the severity of each observed sign/symptom as: none, mild, moderate, or severe.

[redacted]

The 30-day patient CTR diary will capture the daily occurrence of each CTR. The 30-day patient CTR diary will include a detailed glossary describing all signs/symptoms listed in the diary.

9.4.2 72-Hour Telephone Follow-up

The subject will be contacted by telephone by the investigational site approximately 72 hours 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

A female of childbearing potential must present a negative UPT prior to injection of the study device. Subjects who are pregnant are excluded from the study.

Female subjects of childbearing potential are expected to prevent pregnancy occurring whilst on treatment by using effective birth control methods (e.g., oral contraceptive, condom, IUD, injectable contraceptive, diaphragm or vasectomized partner). Male subjects have no contraceptive restrictions.

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.

CTRs will not be considered AEs unless the duration and/or severity exceed what is typically observed following injection of a dermal filler, and are clinically significant as determined by the TI. CTRs will be reviewed by TI to ensure that CTRs are elevated to the status of an AE as appropriate, and will determine AE severity and the relationship to the study devices. CTRs that are present on day 30 of the diary (or on the last recorded day of the diary) will by default be elevated to the status of an AE, regardless of TI assessment.

Disease signs and symptoms that existed prior to the study injections are not considered AEs. Recurring symptoms associated with pre-existing conditions are not considered AEs unless they have a clinically significant increase in severity and/or frequency, as determined by the TI.

Clinically significant abnormal laboratory tests (if applicable) must be recorded as an AE.

Changes resulting from normal growth and/or development occurring at a physiologically appropriate time that do not vary significantly from the frequency or severity expected, for example, the onset of menses or menopause, are not to be considered AEs.

[redacted]

9.4.8 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.

9.4.9 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.

9.4.10 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.

9.4.11 Adverse Event Reporting

9.4.11.1 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 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.

9.4.11.2 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 30 days following the study treatment, must be reported to [redacted]. Initial reports must be made by contacting [redacted] as per the following: Contact the [redacted] by telephone and **complete the**

SAE/UADE Form and submit by [redacted] or by email. [redacted]. It is the site's responsibility to perform the following:

- 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.

Reporting Timelines

UADEs: The site must report UADEs [redacted] within 24 hours of awareness of the event. Within 24 hours of receiving the UADE report from the site, [redacted] must report the UADE to the Sponsor. As per 21 CFR 812.46 (US), the Sponsor must investigate the UADE and report the results to the FDA and IRB within 10 working days of receiving the report from [redacted].

- **SAEs:** The site must report the SAE to the [redacted] within 24 hours of becoming aware of the event. Within 24 hours of receiving the SAE report from the site, [redacted] must report the SAE to the Sponsor. Sponsor must investigate the SAE and, if it is device related, will report the results to the FDA and IRB within 10 working days of receiving the report from [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]

9.4.11.4 Pregnancy

Pregnancy is not considered an SAE or AE. The site will inform [redacted] immediately of any case of pregnancy and collect information on any subject who becomes pregnant during the study using the *Unexpected Problems Report Form.*

Subjects who become pregnant will continue to be followed up for scheduled efficacy and safety assessments for the duration of the study.

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 significant 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]

[redacted]

[redacted]

[redacted]

11 STATISTICAL METHODS

11.1 Primary Endpoint

The primary endpoint will be the injection site pain felt during injection of the upper perioral quadrants assessed by the subject immediately following injection with RHA® with , compared to the injection site pain felt during injection of the contralateral upper perioral quadrant assessed immediately following injection with RHA® with lidocaine.

The effectiveness of RHA® with will be demonstrated if the injection site pain during injection of the upper perioral quadrant assessed by subjects immediately following injection with RHA® with is statistically non-inferior to the injection site pain felt during injection of the contralateral upper perioral quadrant assessed by subjects immediately following injection with RHA® with lidocaine.

The primary endpoint will use a paired design and will be analyzed using hypothesis test.

For achieving non-inferiority, the observed p value must be ≤0.05, taking account of the non-inferiority margin.

In case of non-inferiority, for achieving superiority of RHA® with over RHA® with lidocaine in terms of reducing pain, the observed p-value must be ≤0.05.

11.2 Secondary Endpoints

11.3 Safety Endpoints

The following safety endpoints will be explored:

1) Occurrence of Common Treatment Responses (CTRs)
2) Occurrence of Adverse Events (AEs)

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]

11.6 General Considerations

Data will be listed by treatment group and subject number. The safety and efficacy data will be summarized by treatment allocation. Descriptive statistics will consist of mean, standard deviation, minimum and 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]

11.7 Effectiveness Analysis

11.7.1 Primary Endpoint

Effectiveness of RHA® [redacted] with [redacted] versus control will first be analyzed in a non-inferiority statistical model using the pain felt by the subject during injection. If non-inferiority is achieved, pain felt by the subject during injection will be tested for superiority (i.e., to confirm if RHA® [redacted] is superior to RHA® [redacted] for reducing pain).

[redacted] Wilcoxon signed-rank test

[redacted]

[redacted]

[redacted]

[redacted]

Wilcoxon signed-rank test

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 relationship to study treatment. Severity and relationship to study treatment will be assessed and recorded.

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. Specifically, the following AE incidence tables will be provided:

- All and possibly* related AEs sorted by SOC
- All and possibly* related AEs sorted by decreasing frequency
- SAEs: All and possibly* related SAEs sorted by seriousness criterion
- SAEs: All and possibly* related SAEs sorted by SOC
- UADEs: All and possibly* related UADEs sorted by SOC
- Death: All and possibly* related deaths sorted by SOC

** definitely probably, possibly*

Incidence rates with two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs

Statistical analysis will also be performed to evaluate the potential impact of the injection technique on the safety data.

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 two 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.

Monitoring functions will be performed in compliance with recognized GCP and as per 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. Approximately two on-site interim monitoring visits will be conducted at each site, and a dedicated close-out visit will also be conducted at each site.

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, 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 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.

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 by [redacted] representatives from TEOXANE SA, 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 hardcopy 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® [redacted] with [redacted] or RHA® [redacted] with lidocaine. 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 Study Agreement) will be made between the Sponsor and the Principal Investigator at each site.

The study is covered under a TEOXANE SA liability insurance policy. The certificate of insurance will be provided upon request.

16 REPORTING AND PUBLICATION OF RESULTS

TEOXANE SA, 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 TEOXANE SA personnel. 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 TEOXANE SA.

All information, including but not limited to information regarding RHA® [redacted] with [redacted], RHA® [redacted] with lidocaine, 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 www.clinicaltrials.gov prior to initiating enrolment.

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