A Randomized, Blinded, No-Treatment Control, Multicenter, Prospective Clinical Study of TEOSYAL® RHA Redensity for the Treatment of Moderate to Severe Perioral Rhytids

IDE Pivotal Study

Protocol: TEO-RHA-1501

Version: v.1.2

Date: 27-Oct-2017

[redacted]

Study Sponsor:
TEOXANE SA
[redacted]

US Sponsor:
[redacted]

Clinical Research Organization:
[redacted]

Confidentiality Statement

The information contained in this document is provided in confidence. It is understood that this information will not be disclosed to others without prior agreement with the Sponsor, except to other study personnel and to the extent necessary to obtain informed consent from participating subject.

PROTOCOL APPROVAL SIGNATURE PAGE

The following individuals approve this version of Protocol TEO-RHA-1501. 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:

Printed Name	Title
Signature	Date

Accepted for the Clinical Research Organization - [redacted]:

Printed Name	Title
Signature	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

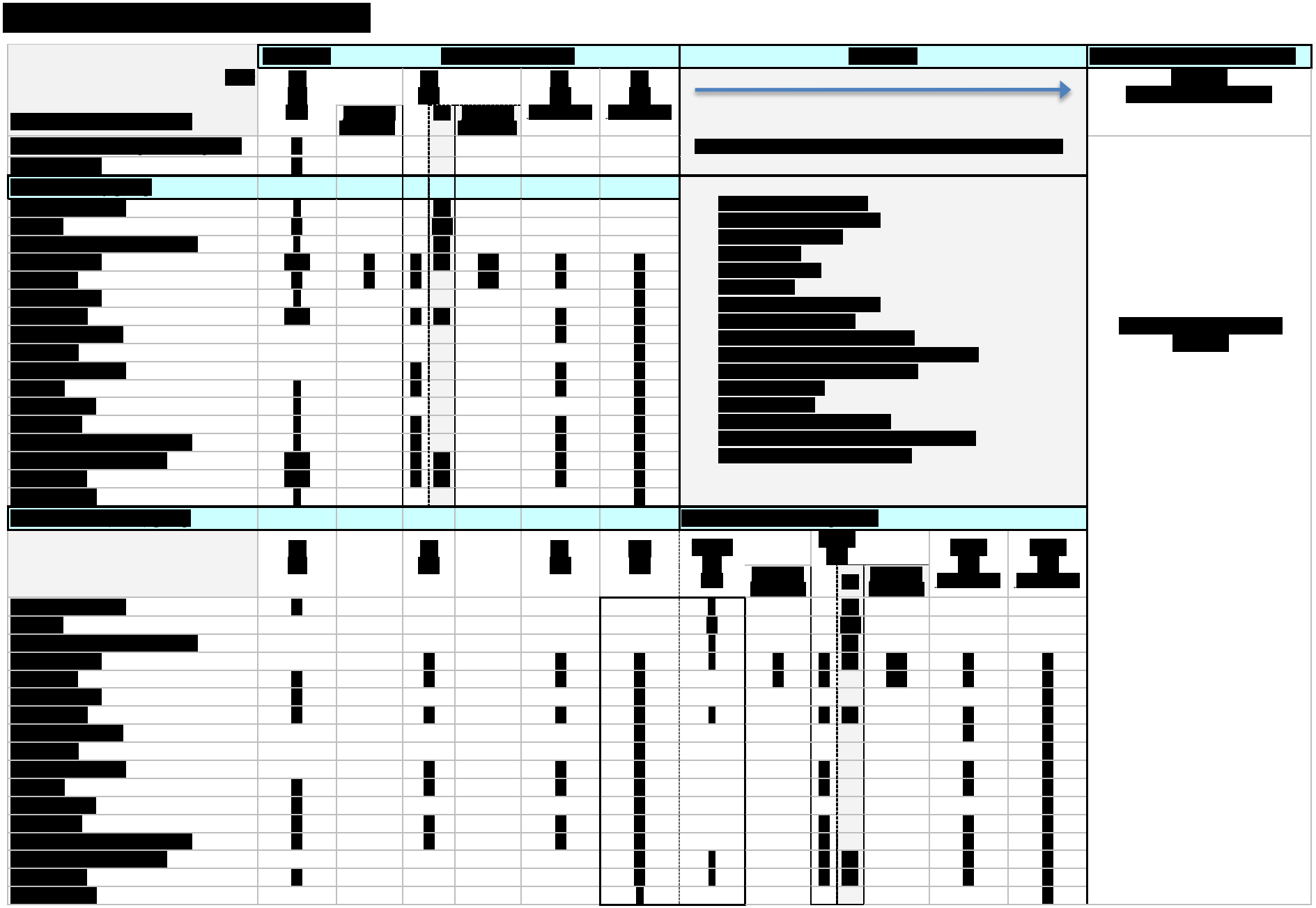
Protocol Version	Version 1.2 27-Oct-2017	**Investigational Device:**	TEOSYAL® RHA Redensity
Study Number	TEO-RHA-1501		
Phase	IDE Pivotal	**Control Device:**	No-Treatment
Indication	Injection in the dermis and superficial dermis of the face for correction of moderate to severe perioral rhytids	**Study Sites:**	Multicenter, up to 10 sites 2 Canadian sites with the remainder being US sites
Title	A Randomized, Blinded, No-Treatment control, Multicenter, Prospective Clinical Study of TEOSYAL® RHA Redensity for the Treatment of Moderate to Severe Perioral Rhytids		
Sponsor	TEOXANE SA, Rue de Lyon 105, CH - 1203 Genève, Switzerland.		
Study Duration	52 to 58 weeks for subjects randomized to TEOSYAL® RHA Redensity treatment group, and 60 to 66 weeks for subjects randomized to the "No-Treatment" control group	**Number of Subjects**	At least 200 subjects, 150 treated and 50 No-Treatment controls
Treatment Groups	Subjects will be randomized (3:1 ratio) to one of the following groups: • TEOSYAL® RHA Redensity • No-Treatment control		
Study Design	This is a randomized, blinded, No-Treatment control, multicenter, prospective clinical study, to identify whether TEOSYAL® RHA Redensity is more effective than No-Treatment in the correction of moderate to severe perioral rhytids at Week 8 after last treatment. The Treating Investigator (TI) at screening will evaluate the subject's perioral rhytids severity using the Perioral Rhytids Severity Rating Scale (PR-SRS) for eligibility of the subject for the study. The Blinded Live Evaluator (BLE) at screening will evaluate the subject's perioral rhytids severity using the PR-SRS in order to confirm eligibility and to establish a pre-treatment score for assessment of effectiveness. This will be done independently of the TI, and exact concordance between the BLE and the TI is not necessary for eligibility of the subject for the study. Enrolled subjects will be randomized to either the TEOSYAL® RHA Redensity treatment group or the "No-Treatment" control group. The TI will administer study device, and if necessary, subjects will receive a touch-up treatment 14 days following the initial treatment to optimize the results. The TI will conduct safety and effectiveness evaluations at study visits, which will occur at Week 4, 8, 12, 16, 24, 36, and 52 after the last treatment, and 4 weeks after a repeat treatment. A Blinded Live Evaluator (BLE) will conduct assessments of efficacy during the trial, including assessment of the primary endpoint at Week 8 after the last treatment. The BLE will conduct effectiveness evaluations at Week 8, 12, 16, 24, 36, and 52 after the last treatment. All subjects will be followed for 52 weeks after initial treatment or touch-up, at which point they will be offered retreatment (provided that the TI deems the treatment to be appropriate and the subject agrees) and will then be followed for 4 weeks after retreatment before exiting the study. If a subject has returned to his pre-treatment PR-SRS score at Week 12 or Week 16 or Week 24 or Week 36 after initial treatment or touch up (as assessed by the TI), subject will be eligible for optional early retreatment if necessary at 12 or 16 or 24 or 36 weeks after baseline (provided that the TI deems the treatment to be appropriate, and the subject agrees). The subject will then be		

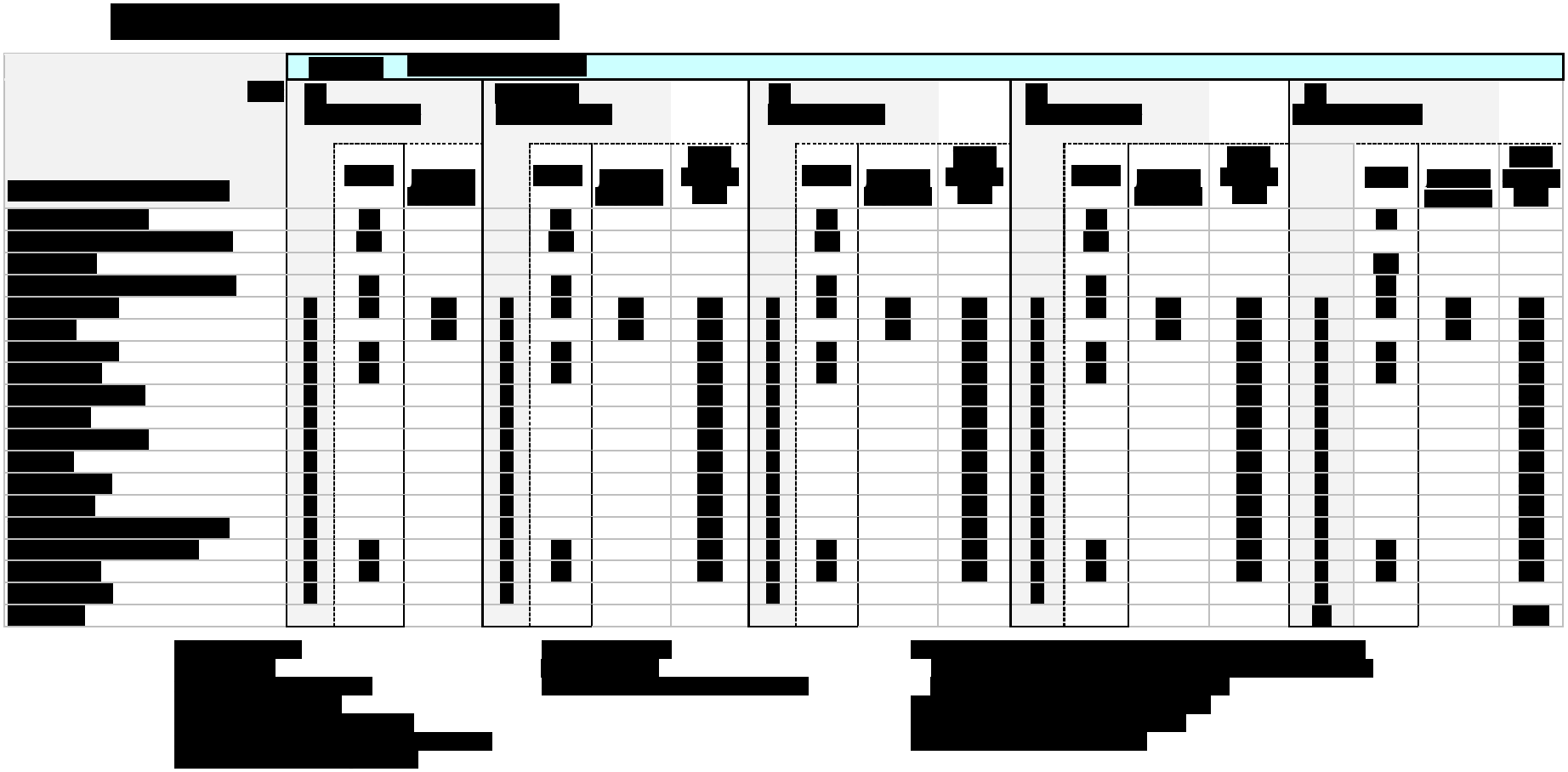
	followed for an additional 4 weeks after repeat treatment and for all subsequent scheduled visits. Subjects receiving optional early retreatment at Week 12 or Week 16 or Week 24 or Week 36 after the after initial treatment or touch-up, will be offered retreatment at Week 52. Subjects randomized to the "No-Treatment" control group will receive their first treatment after the primary endpoint evaluation (Week 8 after randomization) and will then follow the same schedule as the initial treatment group.
Hypothesis	TEOSYAL® RHA Redensity will be superior to No-Treatment control for the correction of moderate to severe perioral rhytids as determined by the PR-SRS at Week 8 after the last treatment. An improvement in the PR-SRS of ≥1-grade compared to pre-treatment will be considered clinically meaningful.
Objectives	To establish the safety and effectiveness of TEOSYAL® RHA Redensity in the treatment of moderate to severe perioral rhytids.
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] 3. Willing to abstain from facial aesthetic procedures/therapies that could interfere with study evaluations (e.g., other fillers, botulinum toxin injections, laser or chemical resurfacing, etc.) for the duration of the study [redacted] 4. Able to follow study instructions and complete all required visits. 5. Sign the IRB-approved ICF, Photographic Release Form and the Authorization for Use and release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed.
Exclusion Criteria	1. Female subjects that 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. [redacted] 6. Clinically significant active skin disease within 6 months prior to study entry (TI discretion). [redacted] 8. History of connective tissue disease. [redacted] 10. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to Visit 1. [redacted] 12. Herpes simplex lesion flare-ups greater than 6 per year. [redacted] 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] 16. Subjects with known prolonged bleeding times because of disease or medication. If on a drug or supplement that prolongs bleeding times (eg non-steroidal anti-inflammatory, anti-coagulant, fish oil), wait 14 days or until bleeding times return to normal before injecting. [redacted] 18. Have dentures or any device covering all or part of the upper palate, and/or severe malocclusion, dentofacial or maxillofacial deformities, or significant asymmetry of the perioral area (TI discretion). [redacted] 20. Exposure to any other investigational drug/device within 90 days of entering the study. 21. [redacted]
Device Administration	[redacted]
Blinding	The BLE will be blinded to the treatment allocation. Furthermore, to ensure that they remain masked and unbiased when making their assessments throughout the study, 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.
Visit Procedures	[redacted]
Efficacy Evaluations	[redacted] • [redacted]
Safety Evaluations	• Adverse Events. • Post-injection common treatment response [redacted]

	• Assessments of lip function; [redacted] • Assessment of Injection Site Pain [redacted]
Primary Endpoint	The primary endpoint will be a co-primary endpoint. A responder will be defined as a subject who has a ≥1-grade improvement on the PR-SRS as assessed by the BLE before initial treatment and at Week 8 after initial treatment or touch-up. Only data from the first 8-week phase will be taken into account. The No-Treatment control group after treatment will not be pooled for the primary endpoint. The effectiveness of TEOSYAL® RHA Redensity will be demonstrated if: • The responder rate for subjects treated with TEOSYAL® RHA Redensity is statistically superior to the responder rate for the No-Treatment control, and; • The responder rate for subjects treated with TEOSYAL® RHA Redensity is ≥70%, and; • The difference between the responder rate for subjects treated with TEOSYAL® RHA Redensity and the No-Treatment group must be ≥50 points.
Secondary Endpoints	For the Secondary Endpoints, like for the Primary Endpoint, only data from the first 8-week phase will be taken into account, and will compare TEOSYAL® RHA Redensity to No-Treatment (the No-Treatment control group after treatment will not be pooled): [redacted] • [redacted]
Sample Size	[redacted] In order to have the study able to detect any AE that has an incident rate of 2.5% or more in the sub-population of subjects of Fitzpatrick skin type IV to VI, at least 160 subjects should be enrolled and treated with the investigational device in the two pooled arms. With an anticipated 20% drop-out rate throughout the entire study, a minimum total sample of 200 subjects (160 / 0.8 = 200), who will each receive TEOSYAL® RHA Redensity are required in order to detect a sufficient AE rate. [redacted]
Statistical Methods	**Primary Endpoint:** The primary endpoint will be analyzed in a superiority statistical model using the PR-SRS as rated by the BLE. A responder is defined as a subject with a ≥1-grade improvement on the PR-SRS as assessed by the BLE at Week 8 after initial or touch-up compared with the pre-treatment assessment (baseline) by the BLE. Only data from the first 8-week phase will be taken into account (the No-Treatment control group after treatment will not be pooled for the primary endpoint). [redacted]

	[redacted]





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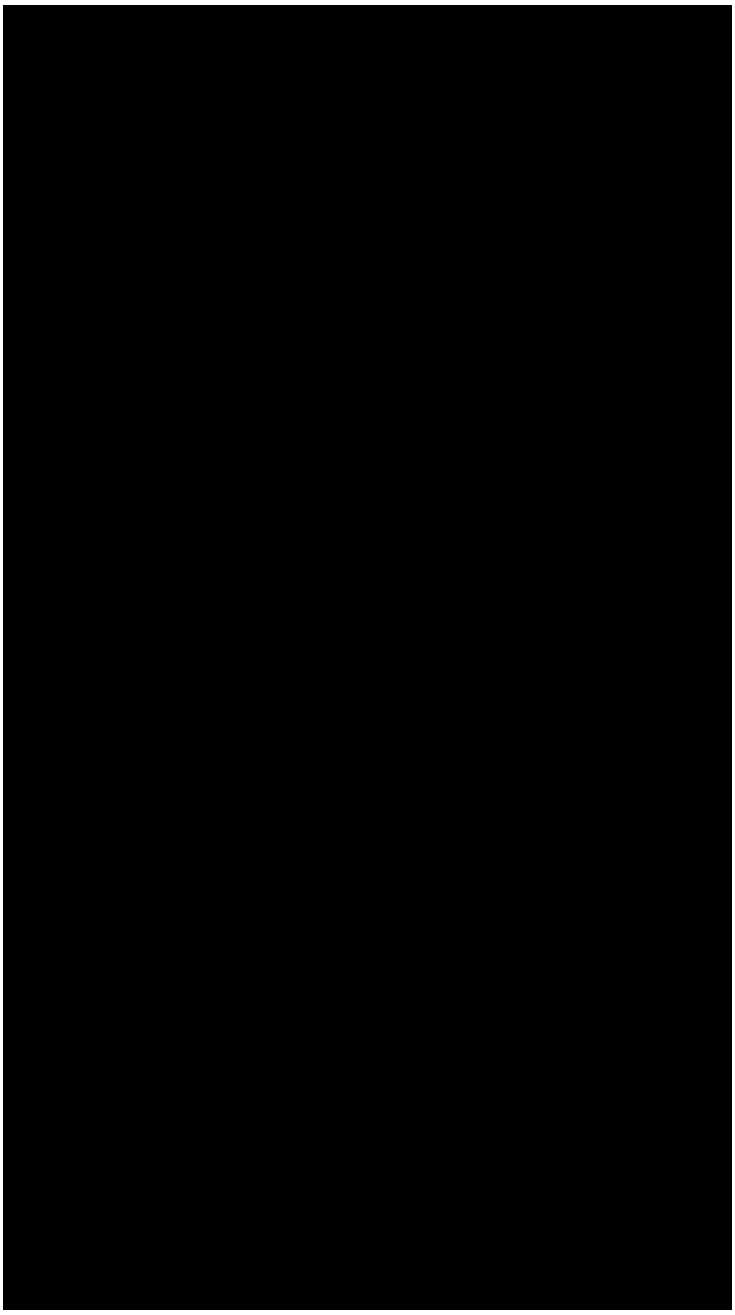

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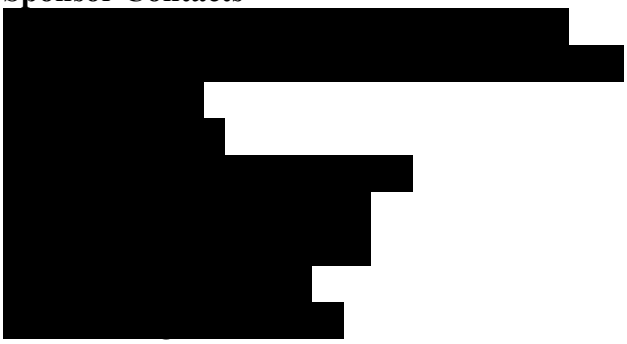
CONTACT LIST

Medical Monitor

Sponsor Contacts



CRO Project Manager

24-Hour Emergency Phone Number

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.

ABBREVIATIONS

[redacted]	[redacted]

1 INTRODUCTION

1.1 Background

[redacted]

1.2 Rationale for Study

[redacted]

1.3 Hypothesis

TEOSYAL® RHA Redensity will be superior to No-Treatment control for the correction of moderate to severe perioral rhytids as determined by the PR-SRS at 8 weeks after initial or touch-up treatment. An improvement in the PR-SRS of ≥1-grade from pre-treatment will be considered clinically meaningful.

2 STUDY OBJECTIVES

The study objectives are to establish the safety and effectiveness of TEOSYAL® RHA Redensity in the treatment of moderate to severe perioral rhytids:

1. To demonstrate the superiority of TEOSYAL® RHA Redensity versus the No-Treatment control at 8 weeks for the correction of moderate to severe perioral rhytids. Assessment of superiority will be based on the Perioral Rhytids Severity Rating Scale (PR-SRS) as rated by the Blinded Live Evaluator (BLE) at each investigative site.

2. To evaluate the safety of TEOSYAL® RHA Redensity for the treatment of moderate to severe perioral rhytids. Safety will be determined by the rates of Adverse Events (AEs) associated with the use of the study device. Subjects will be observed for up to approximately 52 weeks following initial treatment or touch-up treatment with the study device. Safety will also be evaluated for 4 weeks following any retreatment.

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, 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 and in Canada.

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 trained in its proper use are immediately available in case of a medical emergency. The Investigators (BLE and 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]

3.1 Variations to the Protocol

[redacted]

3.2 Investigational Sites

Up to ten (10) U.S. and Canadian 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 protocol, and approved by the reviewing IRB.

[redacted]

[redacted]

3.4 Independent Panel Review (Photographs)

Three independent experts, that are not Investigators in the clinical study, will be selected and trained to conduct PR-SRS assessments on photographs. Prior to conducting the Independent Panel Review (IPR), each member of the panel will be certified regarding the conduct of PR-SRS assessments as described in Section 3.3.

3.5 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 monthly, 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 with the Sponsor.

3.6 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, blinded, No-Treatment control, multicenter, prospective clinical study, to identify whether TEOSYAL® RHA Redensity is more effective than No-Treatment in the correction of moderate to severe perioral rhytids at Week 8 after initial or touch-up treatment.

The **Treating Investigator** (TI) will evaluate subjects for eligibility of the subject for the study. The **Blinded Live Evaluator** (BLE) at screening will evaluate the subject's perioral rhytids severity using the Perioral Rhytids Severity Rating Scale (PR-SRS) in order to confirm eligibility and to establish a pre-treatment score. This will be done independently of the TI, and exact concordance between the BLE and the TI is not necessary.

Enrolled subjects will be randomized to either the TEOSYAL® RHA Redensity treatment group or the "No-Treatment" control group. The TI will administer study device, and if necessary, subjects will receive a touch-up treatment 14 days following the initial treatment to optimize the results. The TI will conduct safety and effectiveness evaluations at study subject visits, which will occur at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, and 4 weeks after a repeat treatment.

The BLE will conduct assessments of efficacy during the trial, including assessment of the primary endpoint at Week 8 after initial or touch up treatment. The BLE will conduct effectiveness evaluations at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment.

Subjects will be followed for 52 weeks from initial or touch up treatment, at which point they will be offered a repeat treatment (provided that the TI deems the treatment to be appropriate, and if the subject agrees). The subject will then be followed for an additional 4 weeks after the treatment before exiting the study.

Should a subject return to his/her pre-treatment PR-SRS level before Week 52, as assessed by the TI, he/she will be eligible to receive an early repeat treatment (provided that the TI deems the treatment to be appropriate, and if the subject agrees) at Week 12, or Week 16, or Week 24, or Week 36 after initial or touch-up treatment. .

Subjects randomized to the "No-Treatment" control group will receive their first treatment after the primary endpoint evaluation (8 weeks after randomization) and will then follow the same schedule as the initial treatment group.

4.2 Study Design Rationale

4.2.1 Study Population

At least 200 subjects will be enrolled and randomized. At least 150 subjects will receive treatment with TEOSYAL® RHA Redensity, and at least 50 subjects will be enrolled as No-Treatment controls.

[redacted]

[redacted]

[redacted]

4.2.2 Primary Effectiveness Outcome Measurement

The primary endpoint will be a co-primary endpoint. A responder will be defined as a subject who has a ≥1-grade improvement on the PR-SRS as assessed by the BLE before initial treatment (baseline) and at Week 8 after initial or touch-up treatment. The effectiveness of TEOSYAL® RHA Redensity will be demonstrated if:

- The responder rate for subjects treated with TEOSYAL® RHA Redensity is statistically superior to the responder rate for the No-Treatment control, and;
- The responder rate for subjects treated with TEOSYAL® RHA Redensity is ≥70%, and;
- The difference between the responder rate for subjects treated with TEOSYAL® RHA Redensity and the No-Treatment group must be ≥50 points.

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]

3. Willing to abstain from facial aesthetic procedures/therapies below the orbital rim that could interfere with study evaluations (e.g., other fillers, lip augmentation, botulinum toxin injections, laser or chemical resurfacing, etc.) for the duration of the study (see Section 7.5.1 for the medications/procedures have either restrictions for usage, or are prohibited during the course of the study).
4. Be able to follow study instructions and likely to complete all required visits;
5. Sign the IRB-approved ICF, Photographic Release Form and the Authorization for Use and release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed.

5.2 Exclusion Criteria

1. Female subjects that are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control.

[redacted]

3. Use of a prohibited treatment/procedure within time periods [redacted]

[redacted]

5. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion).

[redacted]

[redacted]

8. History of connective tissue disease.

[redacted]

10. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to Visit 1.

[redacted]

12. Herpes simplex lesion flare-ups greater than 6 per year.

[redacted]

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]

16. Subjects with known prolonged bleeding times because of disease or medication. If on a drug or supplement that prolongs bleeding times (eg non-steroidal anti-inflammatory, anti-coagulant, fish oil), wait 14 days or until bleeding times return to normal before injecting.

[redacted]

18. Have dentures or any device covering all or part of the upper palate, and/or severe malocclusion, dentofacial or maxillofacial deformities, or significant asymmetry of the perioral area (TI discretion).

[redacted]

20. Exposure to any other investigational drug/device within 90 days prior to study entry.

[redacted]

6 TREATMENT ALLOCATION AND RANDOMIZATION

All subjects who have signed an ICF will receive a 4-digit subject number, starting at 0001. 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 to a study group utilizing a randomization algorithm embedded into the electronic Case Report Form (eCRF).

Subjects will be randomized (3:1 ratio) to one of the following groups:

- TEOSYAL® RHA Redensity;
- No-Treatment (untreated control).

The TI will secure the treatment allocation and any other record of study treatment from potential discovery by the BLE. Any instance where the blind is opened to the BLE will be documented in writing.

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.

7 DEVICE APPLICATION

[redacted]

[redacted]

7.3 Labeling, Packaging and Storage

Open-label packaged supplies of TEOSYAL® RHA Redensity 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:

- Study number: TEO-RHA-1501
- IDE number: e.g., G160123
- Name and address of the Sponsor/Manufacturer (i.e., TEOXANE S.A.)
- Name of product (i.e., TEOSYAL® RHA Redensity)
- Batch number
- Manufacturing date
- Expiry date
- The CAUTION statement mentioned above

There will be no study specific labeling applied directly to the device syringe. 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 area with restricted access.

7.3.1 Relabeling

Real-time aging testing is in progress for TEOSYAL® RHA Redensity. As new test data will become available throughout the course of the study, the shelf life of TEOSYAL® RHA Redensity may be extended through the course of the study. The site monitor will be responsible for relabeling the Tyvek lid with the new expiry date. The site monitor 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. TEOSYAL® RHA Redensity may also be returned to the Sponsor to be relabeled. When TEOSYAL® RHA Redensity has reached the expiry date as indicated on its label, the PI should segregate them and follow the instructions from the site monitor as to awaiting for relabeling by the site monitor or 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 TEOSYAL® RHA Redensity will be approximately 6 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 initial treatments, touch-up treatments, and for retreatments. It is forbidden to use a study device for purposes other than defined in this protocol.

Study devices must be kept in a locked area with access restricted to designated study personnel. The Principal Investigator or designate will inventory and acknowledge receipt of all study device shipments, and to 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 disposed of according to each site's standard procedures.

7.4.1 Other Study Supplies

[redacted]

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.

7.5.1 Prohibited Treatment and Procedures

[redacted]

[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.

A paper CRF will be used to capture additional demographics and social history.

Two sets of worksheets will be used to capture study specific information (i.e., efficacy assessments, injection volumes, injection technique, etc.); one set for the BLE and study coordinator, and one set for the TI and study coordinator. This will allow the BLE and TI to remain blinded to each other's assessments. The study coordinator will refer to these worksheets in conjunction with the medical record in order to complete data entry into the eCRF. Study Investigators will not disclose their opinion regarding treatment outcomes with subjects in order to, 1) prevent subjects from sharing such opinions between the TI and the BLE, and 2) avoid biasing subject reported outcomes.

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

8.2 Subject Diary and Questionnaires

Subjects will complete paper-based subject 14-day diaries and questionnaires. Data recorded in these documents will be entered into the eCRF by the study coordinator.

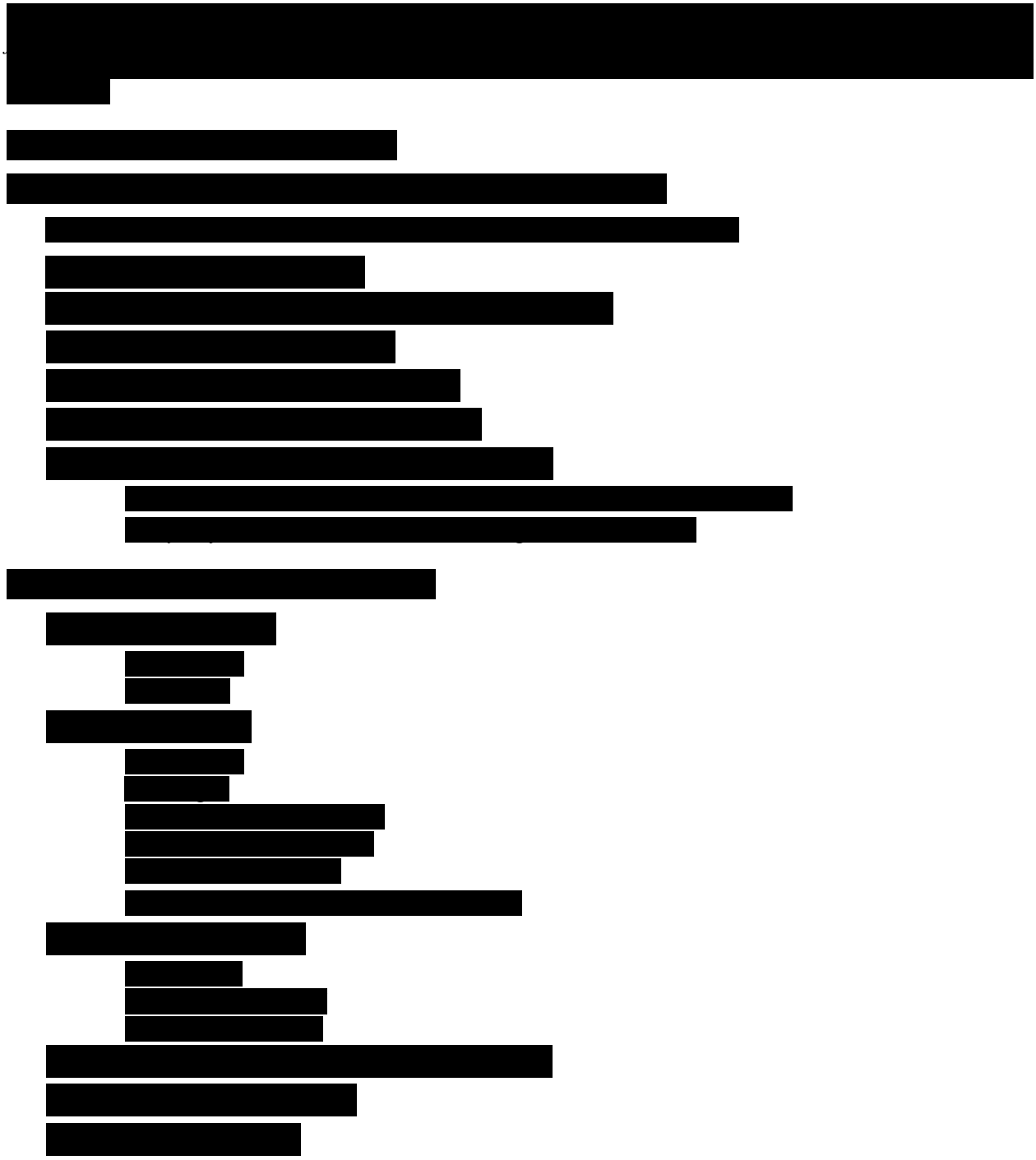
8.3 Photography

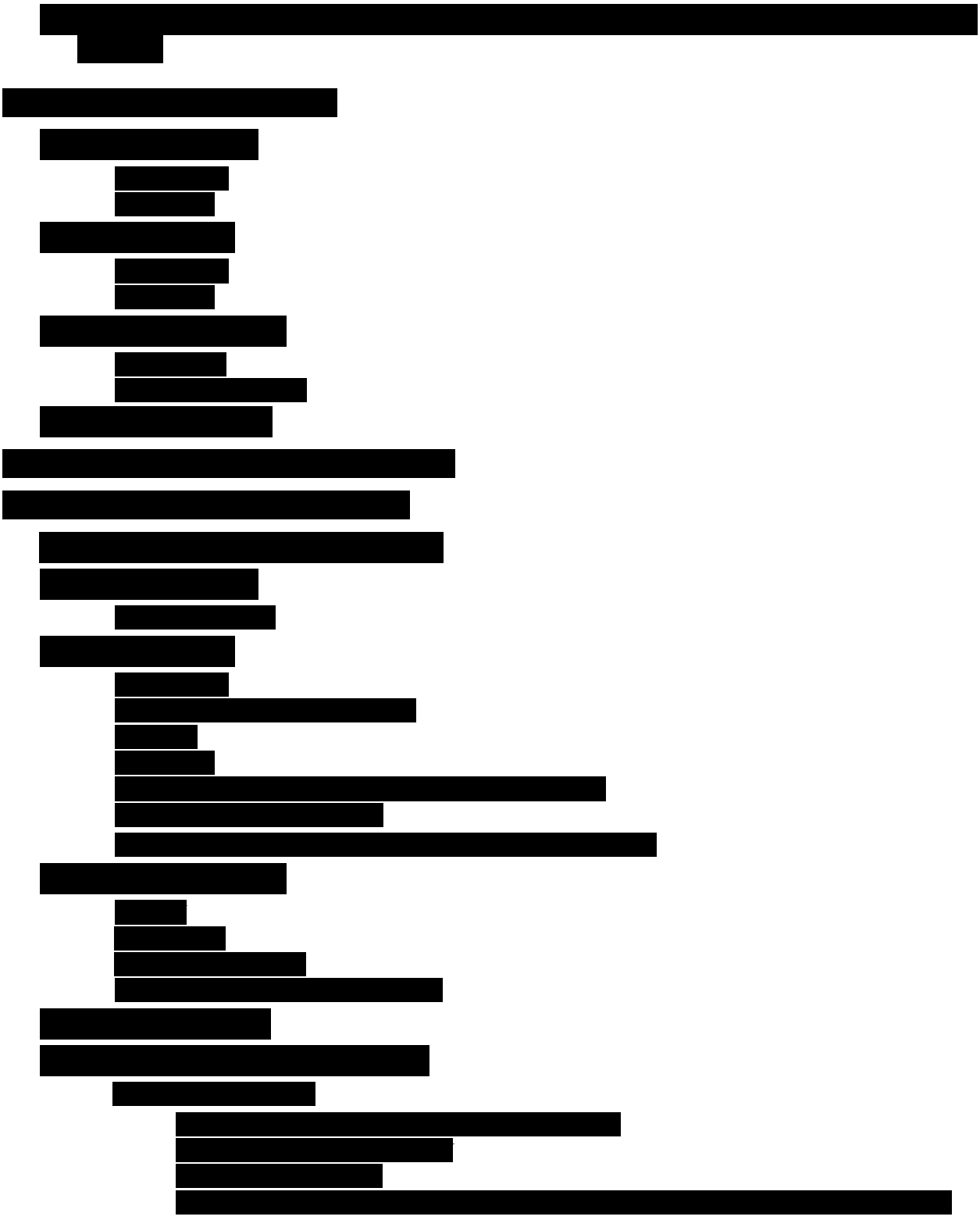
[redacted]

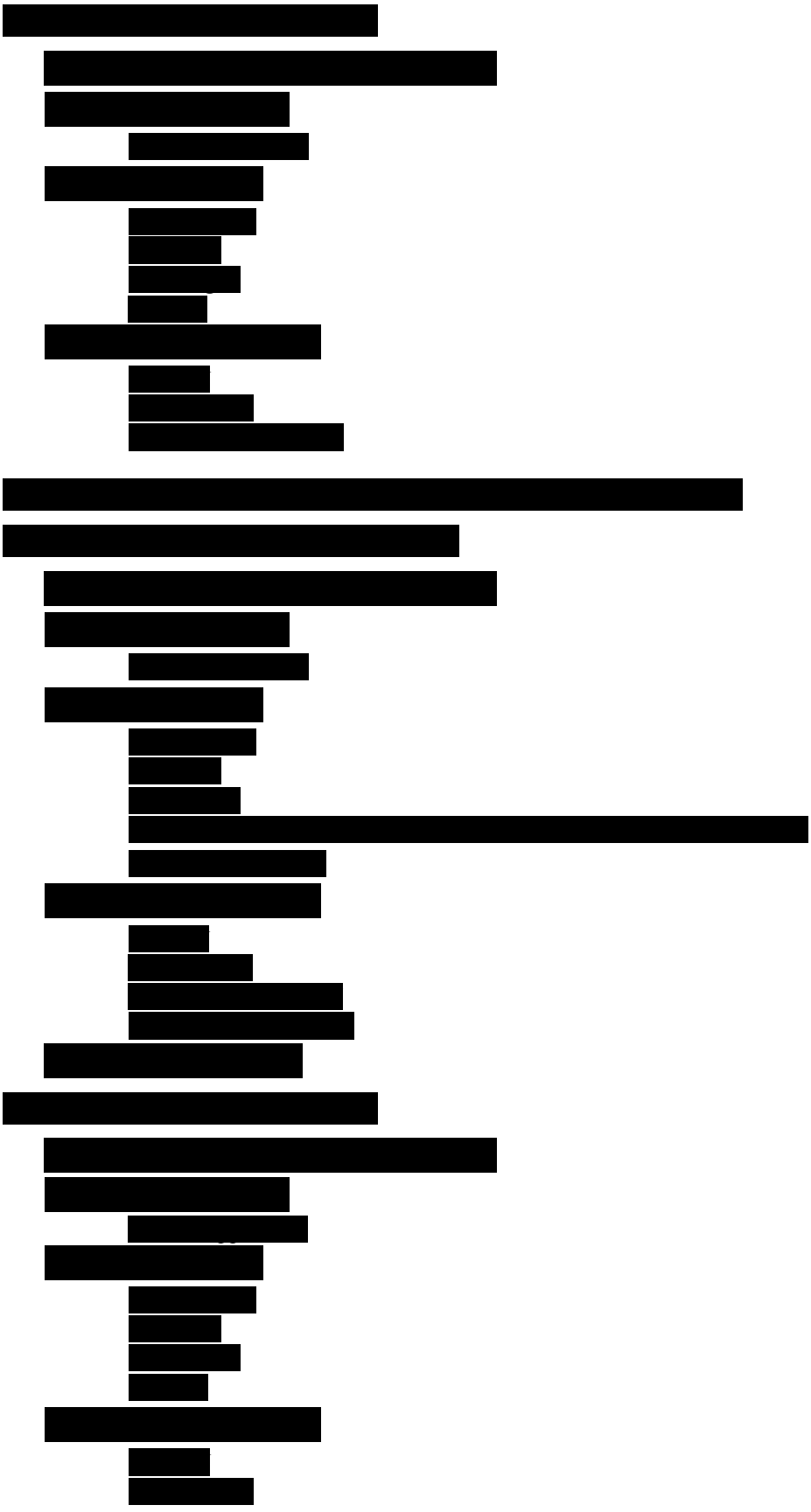
9 STUDY EVALUATIONS

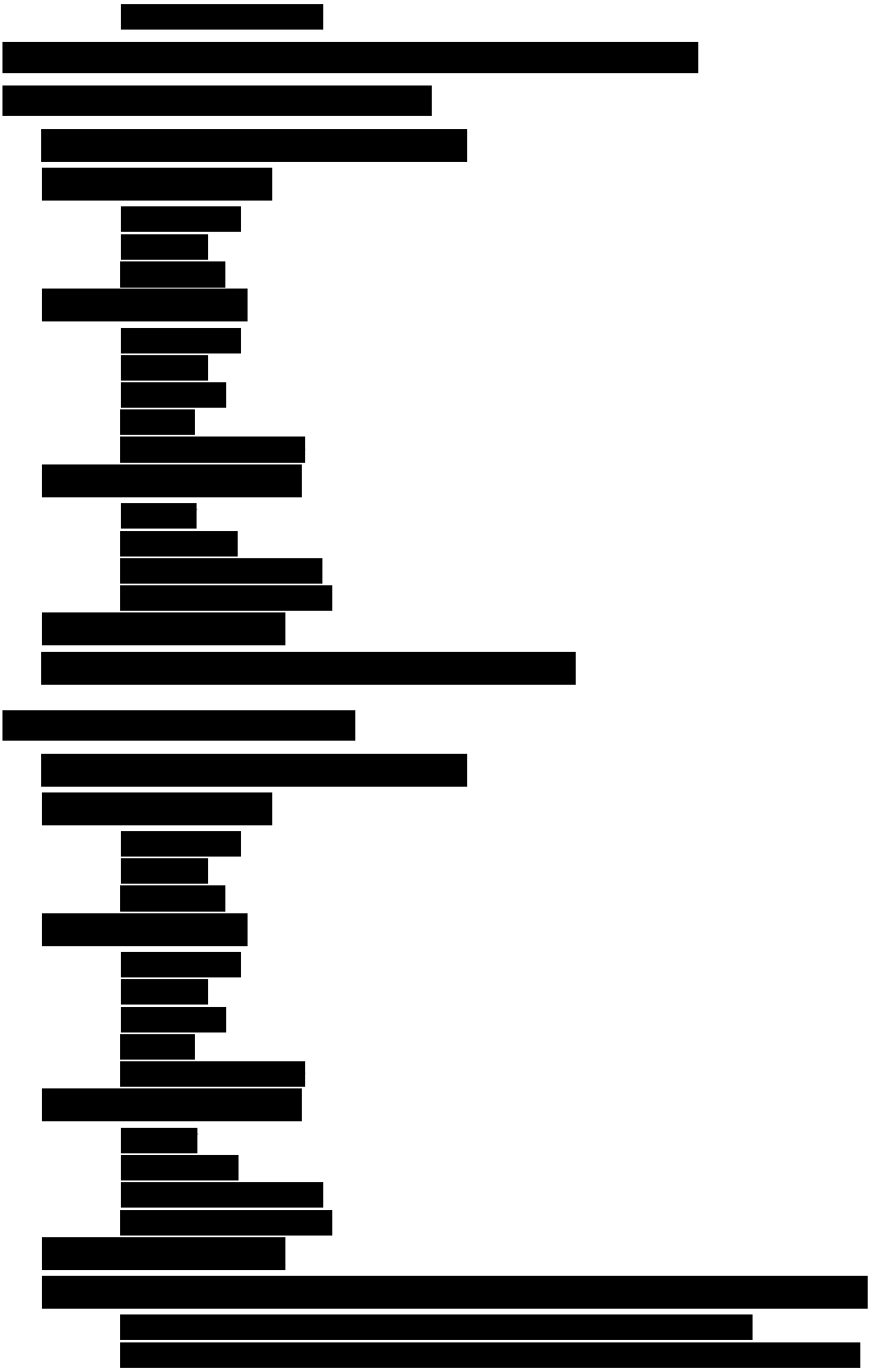
9.1 Informed Consent

The Principal Investigator (or designate) will explain the benefits and risks of participation in the study to each subject and will obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study related procedure and injection of study devices).









[redacted]

[redacted]

9.5 Efficacy

9.5.1 Primary Efficacy Variable

[redacted]

[redacted]

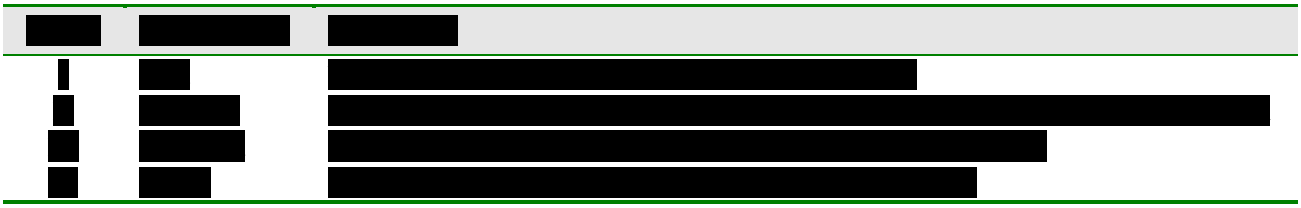
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

9.5.2 Secondary Efficacy Variables

[redacted]

[redacted]



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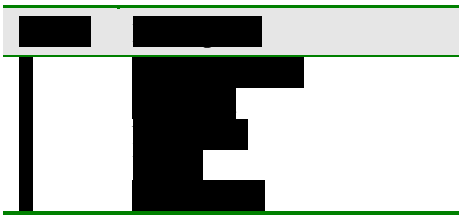

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

9.6 Safety

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.6.5 Pregnancy

A female of childbearing potential must present a negative UPT prior to any injection (initial, touch-up, retreatment) 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, or diaphragm). Male subjects have no contraceptive restrictions.

9.6.6 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

9.6.6.1 Adverse Event Reporting

Throughout the course of the study, all AEs will be monitored and reported through the AE eCRF. 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.

If a Device Related AE(s) is ongoing at the final study visit, the TI will determine which action should be taken and should schedule a clinic visit (if appropriate; i.e., if the event is clinically significant) within 4 weeks to verify that the AE has resolved.

9.6.6.2 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered the study device and which does not necessarily have to have a causal relationship

with the device. An AE can therefore be any unfavorable or unintended sign (for example an abnormal laboratory finding), a 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]

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.

Clinically significant abnormal clinical 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.

9.6.6.3 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.
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.

9.6.6.4 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.

9.6.6.5 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.

9.6.7 Adverse Event Reporting

9.6.7.1 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 1 month 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. The Sponsor is responsible for reporting AEs to the relevant governing authorities in the time frame applicable according to international and local law.

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

All SAEs and UADEs that occur after the time of informed consent through to 7 days after a subject's completion of study participation, or within 1 month following the last study treatment, must be reported [redacted]. within 24 hours of awareness. [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] 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.
- [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 the UADE [redacted] within 24 hours of becoming aware of the event. Within 24 hours of receiving the UADE report from the site [redacted] must report the UADE to the Sponsor. As required by 21 CFR 812.46 (US) and Subsection 59(1) of the Medical Device Regulations (SOR/98-282) (Canada), the Sponsor

must investigate the UADE and report the results to the FDA, Health Canada and IRB within 10 working days† of receiving the report [redacted]

- **SAEs:** The site must report the SAE [redacted] within 24 hours of becoming aware of the event. Within 24 hours of receiving the SAE report from the site, [redacted] should report the SAE to the Sponsor. The Medical Monitor will investigate the SAE. SAEs will be reported to the IRB as per the regulations of the IRB. SAEs will be reported to FDA in study annual and final reports.

[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, Health Canada and FDA approval.

9.6.7.3 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 not receive further treatments with the study device(s), but will continue to be followed up for scheduled efficacy and safety assessments for the duration of the study. All pregnancies should be followed to term and the outcome reported [redacted] to determine the outcome of pregnancy.

10 SUBJECT COMPLETION / WITHDRAWAL

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 Discontinuation of Treatment

A subject **will be** discontinued from further applications of the study devices if they become pregnant; however, they will continue all other assessments as per protocol.

10.3 Withdrawal

[redacted]

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.

11 STATISTICAL METHODS

11.1 Primary Endpoint

The primary endpoint will be a co-primary endpoint. A responder will be defined as a subject who has a ≥1-grade improvement on the PR-SRS as assessed by the BLE at Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE. Only data from the first 8-week phase will be taken into account. The No-Treatment control group after treatment will not be pooled for the primary endpoint.

The effectiveness of TEOSYAL® RHA Redensity will be demonstrated if:

- The responder rate for subjects treated with TEOSYAL® RHA Redensity is statistically superior to the responder rate for the No-Treatment control, and;
- The responder rate for subjects treated with TEOSYAL® RHA Redensity is ≥70%, and;
- The difference between the responder rate for subjects treated with TEOSYAL® RHA Redensity and the No-Treatment group is ≥50 points.

11.2 Secondary Endpoints

For the Secondary Endpoints, like for the Primary Endpoint, only data from the first 8 week phase will be taken into account, and will compare TEOSYAL® RHA Redensity to No-Treatment (the No-Treatment control group after treatment will not be pooled for the secondary endpoints):

- FACE-Q at Week 4 and Week 8 after initial or touch-up treatment.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by subject at Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by BLE at Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.
- Proportion of subjects "satisfied" or "very satisfied" at Week 8 after initial or touch-up treatment, using the 5-point scale assessing subjects' satisfaction with study treatment.

11.3 Exploratory Endpoints

For the following Exploratory Endpoints, like for the Primary Endpoint, only data from the first 8 week phase will be taken into account and will compare TEOSYAL® RHA Redensity to No-Treatment (the No-Treatment control group after treatment will not be pooled for these exploratory endpoints):

- Proportion of subjects with ≥1-grade improvement from pre-treatment on the PR-SRS as assessed by the Treating Investigator, at Week 4 and Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by Treating Investigator at Week 4 and Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.

- Proportion of subjects with ≥1-grade improvement from pre-treatment of dynamic perioral rhytids on the 1-4 Modified Glogau classification of wrinkling as assessed by the BLE at Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.
- Proportion of subjects with ≥1-grade improvement from pre-treatment of dynamic perioral rhytids on the 1-4 Modified Glogau classification of wrinkling as assessed by the Treating Investigator at Week 4 and Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Proportion of subjects with ≥1-grade improvement from pre-treatment on the PR-SRS, as evaluated by the Independent Photographic Reviewers (IPR) at Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the IPR. For a given subject to be considered a responder, at least 2 of the 3 readers must have confirmed a 1-point improvement for that subject.

For the following Exploratory Endpoints, unlike for the Primary and Secondary Endpoints, data from the TEOSYAL® RHA Redensity group and from the No-Treatment control group after treatment will be pooled (if deemed comparable).

- Proportion of subjects with ≥1-grade improvement of their dynamic perioral rhytids on the 1-4 Modified Glogau classification of wrinkling as assessed by the BLE at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.
- Proportion of subjects with ≥1-grade improvement of dynamic perioral rhytids on the 1-4 Modified Glogau classification of wrinkling as assessed by the Treating Investigator at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Subject satisfaction at Weeks 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-point scale assessing subjects' satisfaction with study treatment.
- FACE-Q at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment
- Proportion of subjects with a ≥1-grade improvement based on the PR-SRS assessed by the Treating Investigator at Weeks 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Proportion of subjects with a ≥1-grade improvement based on the PR-SRS assessed by the BLE at Weeks 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.
- Proportion of subjects with a ≥1-grade improvement, based on the PR-SRS as evaluated by the Independent Photographic Reviewers (IPR) at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the IPR. For a given subject to be considered a responder, at least 2 of the 3 readers must have confirmed a 1-point improvement for that subject
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by subjects at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.

- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by Treating Investigators at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by BLE at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (GAI) scale.
- Proportion of subjects with a natural look ≥7, and proportion of subjects with a natural feel ≥7, both assessed by subjects at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using a 11-point scale.

11.4 Analysis Populations

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

11.4.1 Intent-to-Treat (ITT) Population

[redacted]

11.4.2 Per Protocol (PP) Population

[redacted]

11.4.3 Safety (SAFT) Population

The SAFT Population will consist of all study subjects that were randomized and received at least one treatment with the study device.

11.5 Sample Size Considerations

[redacted]

The study will ensure that enrolled subjects are representative of U.S. population ethnicity and will be comprised of at least 25% subjects of Fitzpatrick skin IV to VI. In order to be able to detect a sufficient AE rate (i.e., maximum 2.5% in the sub-population of subjects of Fitzpatrick skin type IV to VI), the number of subjects must be increased beyond that required for achieving statistical power for the primary efficacy outcome; specifically:

[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 values, tables, 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). All programs for data output and analyses will be written in SAS version 9.3 or higher (SAS Institute, Inc., Cary, NC).

Missing Values

For subjects lost-to-follow-up (LTFU), or not present at a visit, missing data will be imputed using last observation carried forward (LOCF) for the primary endpoint (PR-SRS, ITT population). Various statistical procedures to confirm the impact of missing data (e.g., Tipping Point Analysis) will be detailed in the Statistical Analysis Plan. No imputations will be performed for secondary endpoints; analyses will utilize available data as observed.

Discontinuation and Drop-Outs

Dropouts will not be replaced. All available data from dropouts will be included in the ITT analysis. Subject disposition will be summarizing the number of subjects enrolled in the study and those that discontinued the study and their reason.

Interim Analysis

There will be no interim efficacy analysis.

Poolability Between Countries

Due to the potential impact on safety and effectiveness, the variation in data across baseline demographics will be accounted, and heterogeneity across the two countries (US and Canada) will be investigated to establish if the data for safety and effectiveness can be combined.

To assess the homogeneity of the baseline characteristics across the two countries, and to determine if data from both countries could be pooled, statistical hypothesis tests will be performed with their null hypotheses as the absence of difference between US and Canada. All observed two-sided p-value must be >0.05 to pool data from the two countries. If the two-sided p-value is less or equal to 0.05, then, data collected from subjects of both countries will not be pooled. Percentages of each characteristic of the demographics will be compared using a Fischer's Exact test, and continuous data will be compared using a Student t test. The full details will be provided in the Statistical Analysis Plan.

11.7 Efficacy Analysis

[redacted]

[redacted]

[redacted]

11.8 Safety Analysis

[redacted]

[redacted]

The study will be able to detect any AE that has an incident rate of <1.0% (0.625%) or more (assuming 200 subjects will be treated with the investigational device in the two pooled arms and taking [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.8.1 Adverse Events (AEs)

[redacted]

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

[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.

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.

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.

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, Health Canada and to the central IRB for evaluation. As required, the study will not start before the IRB, and the local Health Authority (FDA for US sites and Health Canada for Canadian sites) 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 & ADMINISTRATIVE REQUIREMENTS

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, Health Canada 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, with the assistance of [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, for ensuring site compliance with the protocol and for 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

Clinical monitors of [redacted]. will visit the study site periodically to ensure adherence to the protocol and applicable regulations, to ensure compliance with ICH-GCP, to ensure safety of the subjects, and to ensure 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 seven 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 BLE or 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, Health Canada 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, the Blinded Live Evaluator, 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]. Protocol Deviation Form 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 (i.e., BLE or TI).

14 DATA HANDLING AND RECORD KEEPING

14.1 Source Data

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.

The site is required to prepare and maintain adequate and accurate medical records designed to record all observations and other data pertinent to the study for each study subject. Source Document Worksheets will be prepared [redacted] for this purpose and serve as part of the source record for a subject's study-related data. [redacted]

Two sets of worksheets will be used to capture study specific information [redacted] one set for the BLE and study coordinator, and one set for the TI and study coordinator. This will allow the BLE and TI to remain blinded to each other's assessments. The study coordinator will refer to these worksheets in conjunction with the medical record in order to complete data entry into the eCRF.

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 Principal Investigator will protect the

confidentiality of all subjects' records within applicable federal, state, provincial 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 the subject's medical records pertinent to the study will be reviewed by [redacted] representatives from TEOXANE SA, the IRB and regulatory bodies such as the FDA and Health Canada 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 appropriate Investigator (i.e., BLE or TI). In order to review and electronically sign the eCRF, the BLE and TI will each have their 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 all TEOSYAL® RHA Redensity, and copies of eCRFs should be retained and available for audit by the Sponsor's auditor and regulatory authorities until at least 2 years (US Sites) or 25 years (Canadian Sites) 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 TEOSYAL® RHA Redensity. 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 TEOSYAL® RHA Redensity 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 designate is responsible for preparing a clinical study report.

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

17 REFERENCES

1. Weiss C, et al. The role of Na-hylan in reducing postsurgical tendon adhesions. Bull Hosp Jt Dis Orthop Inst. 1986, Vol. 46, 1, pp. 9-15.

2. Weiss C, et al. The role of Na-hylan in reducing postsurgical tendon adhesions: Part 2. Bull Hosp Jt Dis Orthop Inst. 1987, Vol. 47, 1, pp. 31-39.

3. Balaz EA, et al. Biocompatible viscoelastic gel slurries, their preparation and use. 0 466 300 A2 European, 1992.

18 APPENDICES

Appendix A: Protocol Version History

APPENDIX A: PROTOCOL VERSION HISTORY

Version and Date	Description
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]