1. TITLE PAGE

A RANDOMIZED, BLINDED EVALUATOR, NO-TREATMENT CONTROL, MULTICENTER, PROSPECTIVE CLINICAL STUDY OF RHA[redacted] FOR THE TREATMENT OF MODERATE TO SEVERE TISSUE VOLUME DEFICIENCIES IN THE INFRAORBITAL REGIONS

Clinical Investigation Plan

INVESTIGATIONAL PRODUCT:	RHA[redacted]
CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
INVESTIGATIONAL DEVICE EXEMPTION NUMBER:	G200191
DEVELOPMENT PHASE:	Pivotal
INDICATION:	Moderate to severe tissue volume deficiencies in the infraorbital regions
METHODOLOGY:	No-treatment controlled, randomized, blinded evaluator, multicenter, prospective
PROTOCOL VERSION:	[redacted]
PROTOCOL DATE:	Original Protocol Version 1.0, 22-Jun-2020
AMENDMENT DATE:	Amended Protocol [redacted] 24-Apr-2024
PROTOCOL WRITTEN BY:	[redacted]
SPONSOR:	TEOXANE SA Rue de Lyon 105 CH – 1203 Geneva, Switzerland
SPONSOR CONTACT PERSON:	[redacted]
UNITED STATES SPONSOR:	[redacted]

APPROVAL SIGNATURES

CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
CLINICAL INVESTIGATION PLAN TITLE:	A Randomized, Blinded Evaluator, No-treatment Control, Multicenter, Prospective Clinical Study of RHA[redacted] for the Treatment of Moderate to Severe Tissue Volume Deficiencies in the Infraorbital Regions

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

SIGNATURE **DATE**

[redacted]
Head of Clinical Development Market Expansion
[redacted]

[redacted]
Regulatory Affairs Director
[redacted]

[redacted]
Senior Clinical Project Manager
[redacted]

SIGNATURE	**DATE**
[redacted] Senior Medical Director [redacted]	
[redacted] Manager, Biostatistics [redacted]	

AMENDED PROTOCOL

Revision history:

TITLE:	A Randomized, Blinded Evaluator, No-treatment Control, Multicenter, Prospective Clinical Study of RHA[redacted] for the Treatment of Moderate to Severe Tissue Volume Deficiencies in the Infraorbital Regions
CLINICAL INVESTIGATION PLAN NUMBER:	TEO-RHA-1902
PROTOCOL VERSION:	[redacted]
ORIGINAL PROTOCOL DATE:	Original Protocol Version 1.0, 22-June-2020
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The following are the amended protocol [redacted] and appendices, including all revisions specified in the REASONS FOR AMENDMENT and SUMMARY OF AMENDED SECTIONS.

2. CLINICAL INVESTIGATION PLAN SUMMARY

2.1. Summary

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
TITLE OF INVESTIGATION	A Randomized, Blinded Evaluator, No-treatment Control, Multicenter, Prospective Clinical Study of RHA[redacted] for the Treatment of Moderate to Severe Tissue Volume Deficiencies in the Infraorbital Regions
MANUFACTURER/ SPONSOR	TEOXANE SA, Rue de Lyon 105, CH – 1203 Geneva, Switzerland
DEVELOPMENT PHASE:	Pivotal
CONTROL DEVICE NAME	No treatment
INDICATION FOR USE	RHA[redacted] is intended to be used for correction of moderate to severe tissue volume deficiencies in the infraorbital regions
CLINICAL INVESTIGATION PURPOSE	The purpose of the study is to evaluate the safety and effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions
TREATMENT GROUPS	[redacted]. A 3:1 ratio between the RHA[redacted] group and the No-treatment control group is planned for the overall study [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] [redacted]: [redacted] [redacted] [redacted] A total of 248 subjects in the safety study population will be able to detect any adverse event (AE) in the subpopulation of subjects with Fitzpatrick skin type IVVI with an incidence rate of at least 2.5% (and any AE with an incidence rate of at least 0.5% in the overall population). At least 248 subjects will be enrolled in the safety study population to maintain sufficient power for the safety and effectiveness analysis. [redacted]
STUDY CENTERS AND LOCATION	[redacted] up to 12 investigative sites in the United States will participate in [redacted] this study.
STUDY DURATION	Individual study participation: The minimum and maximum anticipated duration of subject participation are [redacted] to 19 months ([redacted] to 76 weeks), respectively. [redacted] [redacted]
OBJECTIVES	• Primary effectiveness objective: o To assess the effectiveness of RHA[redacted] (as judged by clinicians and subjects) for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions at 12 weeks after the initial treatment.

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	• Secondary effectiveness objectives: o To assess the effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment. • Safety Objective: o To assess the safety of RHA[redacted] in subjects treated for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment. [redacted] o [redacted]
DEVICE TREATMENT	Method of administration will be either with a 30G ½″ needle (included with the product) or a 25G 1½″ cannula [redacted]. Injection area and depth: RHA[redacted] is injected from the sub-dermis to the periosteum in the infraorbital hollow. Amount of filler to be administered: Up to 1.0 mL per eye at each treatment (max: 2.0 mL per treatment). [redacted]
INVESTIGATION DESIGN	<u>Enrollment</u> This is a multicenter, blinded evaluator, randomized, prospective, no-treatment control clinical study to identify whether RHA[redacted] is superior to no treatment for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions. The study [redacted] will include at least 20% of subjects with Fitzpatrick skin types IV-VI: including minimum of 10% subjects presenting with Fitzpatrick skin types V or VI, [redacted] The TI and the Blinded Live Evaluator (BLE) will evaluate the subject's infraorbital hollows independently of each other using the Teoxane Infraorbital Hollows Scale (TIOHS) at Screening (Visit 1) for eligibility. [redacted] The TI and the BLE must agree that the subject meets the inclusion criterion number 4 (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline of the primary endpoint. If the TI and the BLE do not agree on eligibility

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	or if their assessments differ by 2 points or more on the scale, the subject will not be eligible. [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] <u>Phase 1a: Up to 12 weeks after the initial treatment for the RHA[redacted] group or after randomization for the No-treatment control group; primary endpoint</u> Subjects who will be randomly assigned to the RHA[redacted] group at Screening [redacted] will receive their injection at Visit 1. The TI or designee will call subjects 72 hours post-treatment (Visit 1 Call). Subjects will come to the site

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 12 weeks (Visit 5, primary endpoint) after the initial treatment. Afterwards, subjects will proceed directly to Phase 2. Phase 1b is not applicable for subjects randomly assigned to the RHA[redacted] group. Subjects randomly assigned to the No-treatment control group [redacted] at Screening will receive no treatment in Phase 1a of the study. They will come to the site 2 weeks (Visit 2), 4 weeks (Visit 3), 8 weeks (Visit 4), and 12 weeks (Visit 5, primary endpoint) after randomization. After completing all assessments for Visit 5, subjects will immediately begin Phase 1b (Visit 1b is on the same day as Visit 5) and will receive their initial treatment with RHA[redacted]. [redacted] <u>Phase 1b: after the primary endpoint assessment up to 12 weeks after the initial treatment for the No-treatment control group</u> Phase 1b is only applicable to subjects initially randomly assigned to the No-treatment control group. Once all evaluations applicable for Visit 5 are completed, subjects will proceed directly to Visit 1b (on the same day). Evaluations completed at Visit 5 will be used for Visit 1b and will become the new Baseline for Phase 1b. Subjects will receive their initial treatment with RHA[redacted] at Visit 1b. Subjects will follow the same schedule as those initially randomly assigned to the RHA[redacted] group: RHA[redacted] will be administered on the same day (Visit 1b). The TI or designee will call the subject 72 hours post-treatment (Visit 1b Call). Subjects will come to the site [redacted], and 12 weeks (Visit 5b) after their initial treatment. Afterwards, subjects will proceed to Phase 2. <u>Phase 2 and Exit Visit: 12 weeks after the initial treatment up to the end of the study for the RHA[redacted] group and the No-treatment control group</u> Phase 2 will occur 12 weeks after receiving initial treatment with RHA[redacted] for subjects in the RHA[redacted] group [redacted] and the No-treatment control group (after Phase 1b). All these subjects will come to the site 24 weeks (Visit 6), [redacted] and 52 weeks (Visit 8) after their initial treatment. All subjects will be followed for 52 weeks after their initial treatment with RHA[redacted]. Subjects will be offered retreatment at Visit 8 (52 weeks after their initial treatment). Retreatment will be administered if the TI deems it to be appropriate and the subject agrees. If the subject does not receive retreatment, Visit 8 (52 weeks after initial treatment) will become the Exit visit. If the subject receives retreatment at Visit 8, the TI or designee will call him or her after 72 hours (Visit 8 Call). The subjects will come to the site [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 12 weeks (Visit 11) after retreatment for follow-up and safety assessments. Visit 11 will be the Exit Visit. Assessments throughout the study: RHA[redacted] group [redacted] and No-treatment control group The TI will conduct safety and effectiveness evaluations according to the schedule of events until the Exit Visit (Visit 8 or 11). Subjects with an ongoing adverse device effect (ADE) will be followed until the event(s) has resolved or resolved with sequelae, or deemed no longer necessary as per TI judgment, or if follow-up is no longer possible. Subjects will report their Common Treatment Responses (CTRs) in a subject diary for 30 days after any injection (initial or retreatment). The BLE will conduct assessments of effectiveness at all visits starting at Visit 5 (12 weeks after randomization). The primary endpoint assessment will be at Visit 5 (12 weeks after randomization) only. The primary endpoint will include data from subjects assigned to the RHA[redacted] group [redacted] and the No-treatment control group before receiving initial injection.
BLINDING	The BLE will be blinded to allocation to groups (RHA[redacted] group, [redacted] No-treatment control group) and to randomization ratio. Furthermore, to ensure that they remain blinded and unbiased when making their assessments throughout the study, the BLE, TI, and subjects will not be allowed to refer to each other's effectiveness assessments. All subjects will be instructed to not discuss their study treatment, AEs, or CTRs with the BLE.
PRIMARY EFFECTIVENESS ENDPOINT	The primary endpoint will be the responder rate after 12 weeks. The effectiveness of RHA[redacted] will be demonstrated if: [redacted] The responder rate for subjects treated with RHA[redacted] is statistically superior to the responder rate for subjects of the No-treatment control group 12 weeks (Visit 5) after randomization as assessed by the BLE using the live-validated TIOHS. [redacted] [redacted] [redacted] [redacted] Additionally, the following 2 conditions must be met: • The responder rate for RHA[redacted] is ≥70% • The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group is ≥50% A responder will be defined as a subject with ≥1-grade improvement in each of the eyes on the TIOHS as assessed by the BLE before initial treatment and 12 weeks after the initial treatment (Visit 5). Improvement of the right eye and the left eye

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	will be assessed individually (one eye at a time). A responder will be defined when the right eye improves by ≥1-grade and when the left eye improves by ≥1 grade. The co-primary endpoint will be the change from Baseline in selected questions of the FACE-Q Appraisal of lower eyelids domain score (converted to a 0-100 scale – Rasch conversion) at 12 weeks. The effectiveness of RHA[redacted] will be demonstrated if the modified FACE-Q Appearance of lower eyelids change from Baseline score for subjects treated with RHA[redacted] is statistically superior (by at least 12 points) to the subjects of the No-treatment control group 12 weeks (Visit 5) after randomization (including subjects who received RHA[redacted]). [redacted] [redacted] [redacted] Additionally, the following 2 conditions must be met: • The mean change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is ≥ 3 • The difference between the modified FACE-Q "Appraisal of lower eyelids" change from Baseline for subjects treated with RHA[redacted] and the No-treatment control group is ≥12. [redacted] Only data from Phase 1a [redacted] will be taken into account. Data from subjects randomly assigned to the No-treatment control group after treatment received in the Phase 1b will not be pooled for the primary endpoint analysis. Superiority will be declared if: • the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and • the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and • the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and • the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
SECONDARY EFFECTIVENESS ENDPOINTS	The secondary endpoints will consist of the following: • Proportion of subjects with both eyes with ≥1-grade improvement on the TIOHS as assessed: o By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/initial treatment) = rate of responders at the given time point o [redacted] • Proportion of subjects who were "improved" or "much improved" using the Global Aesthetic Improvement Scale (GAIS) o By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/initial treatment) o By the subject at each site [redacted] [redacted]Proportion of subjects "satisfied" or "very satisfied" with the effect of the study treatment, using the Subject satisfaction scale as assessed by the subject at each site visit [redacted] • FACE-Q assessment by the subject through the Appraisal of lower eyelids (all questions) scale of the FACE-Q at each site visit starting from Baseline [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] • [redacted]
SAFETY ENDPOINTS	The safety endpoints: • Adverse events with a focus on treatment related AEs (ADEs) based on the TI assessment, and AEs reported from the CTR diary from randomization [redacted] • [redacted]
[redacted]	[redacted]
ELIGIBILITY CRITERIA	<u>Inclusion Criteria:</u> A potential subject will be included in the study if he/she meets all of the following inclusion criteria: 1. Outpatient, male or female of any race, 22 years of age or older 2. Subject, if female, is not pregnant, not breastfeeding, and either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]); or must have a negative urine pregnancy test at Visit 1 and prior to each injection, and must agree to practice 1 of the following medically acceptable methods of birth control throughout the study: [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] [redacted] [redacted] 3. Subject is seeking treatment of moderate to severe tissue volume deficiencies in the infraorbital region (realistic and achievable as per TI opinion) 4. Has a grade of 2 to 3 (moderate to severe) on the TIOHS for both eyes Note: If the assessments of the TI and the BLE are the same or differ exactly by 1 point on the scale, the difference will be considered acceptable. The TI and the BLE need to agree that the subject meets the eligibility criterion (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline for the primary endpoint. If the TI and the BLE do not agree on eligibility, or if their assessments differ by 2 points or more on the scale, the subject will not be eligible. 5. Able to follow study instructions and complete all required visits 6. Willing to sign the institutional review board-approved informed consent form, photographic release form, and the authorization for use and release of health and research study information (Health Insurance Portability and Accountability Act) form and, if applicable, the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed <u>Exclusion Criteria:</u> A potential subject will be excluded from the study if he/she meets any of the following exclusion criteria: 1. Known hypersensitivity or previous allergic reaction to any component of the study device, including local anesthetics of the amide type (e.g., mepivacaine, lidocaine), including known or suspected lidocaine hypersensitivity, or allergy to Gram-positive bacterial proteins 2. Known history of multiple severe allergies, or history of anaphylactic shock [redacted] 4. Prior lower eyelid surgery, including orbital or midface surgery, or has a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments or plans to have it during the study 5. Is planning to undergo during the study or has undergone any type of facial, plastic, nonablative, or reconstructive surgery (e.g., blepharoplasty, face lift, or rhinoplasty) within 6 months before randomization. Subject is also excluded if

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	residual swelling is present or complete healing has not occurred within at least 6 months of the treatment received. [redacted] 10. Known susceptibility to keloid formation, hypertrophic scars, hyperpigmentation, or compromised healing that would compromise the effectiveness outcome 11. Ongoing cutaneous infection at the site of injection at randomization [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 19. [redacted]
ASSESSMENTS	• TIOHS: A live-validated 5-point scale (from grade 0 to 4) for assessing infraorbital hollows depression as assessed by [redacted] BLE • GAIS: A subjective, balanced, 5-point scale assessing aesthetic improvement as assessed by the subject, [redacted] and BLE • FACE-Q scale: Validated Subject-Reported Outcome Measure, assessed at each study visit by the subject using the Appraisal of lower eyelids scale • Subject satisfaction scale: A subjective, balanced, 5-point scale assessing subject satisfaction with study treatment [redacted] [redacted] Adverse events: with the focus on AEs related to treatment (ADEs), [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	• Post-injection CTRs: through 30-day subject CTR diary, which also includes vision disturbances • [redacted]
STATISTICAL METHODS AND ANALYSIS SUMMARY	All data will be recorded in eCRFs. The following 4 analysis populations are planned for this investigation: • Screening population: All subjects who provide informed consent and demographic and/or Baseline Screening assessment results, regardless of their randomization and treatment status in the investigation. [redacted] • Safety population (SAFT): All subjects who are assigned to either the RHA[redacted] group or the No-treatment control group and complete Visit 1 • Intent-to-Treat population (ITT): All subjects who are assigned to either the RHA[redacted] group [redacted] or the No-treatment control group and complete Visit 1. Subjects will be analyzed according to their initially assigned arm assignment, regardless of whether or not they received RHA[redacted] • Per-Protocol population (PP): All subjects in the ITT population who completed up to Visit 5 (primary endpoint visit at 12 weeks) with no major CIP deviations that could affect effectiveness assessments. The sponsor will identify major CIP deviations per Protocol Deviation Guidance Plan (PDGP) prior to the database lock. Analysis of the primary effectiveness endpoints will be based on the ITT population and will be repeated for the PP population. Analysis of the secondary effectiveness endpoints will be based on the ITT population. [redacted] For the ITT analysis of the primary effectiveness endpoint, multiple imputations will be used for missing observations. [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] Primary Effectiveness Analysis: The rate of responders 12 weeks after randomization in the RHA[redacted] group [redacted] will be compared with the rate of responders in the No-treatment control group using an independent testing based on a 2-group, 1-sided, Fisher's exact statistic test. To achieve superiority, the observed p-value must be ≤0.025. Additionally, to be able to declare superiority: • At least 70% of the subjects treated with RHA[redacted] must be responders • The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group must be ≥50% points The co-primary endpoint, change from Baseline in modified FACE-Q Appearance of lower eyelids score (converted to a 0-100 scale using Rasch conversion) at 12 weeks, will be evaluated. [redacted] The modified FACE-Q Appearance of lower eyelids change from Baseline score for subjects treated with RHA[redacted] will be compared with FACE-Q Appearance of lower eyelids for subjects of the No-treatment control group at 12 weeks (Visit 5) after randomization using t-test or non-parametric equivalent like Wilcoxon rank-sum test. Superiority will be declared if: • the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	• the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and • the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and • the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12 Overall superiority can be declared if all superiority criteria are met both for primary and co-primary endpoints. [redacted] Secondary Effectiveness Analysis: No imputation will be performed for secondary (or pooled secondary) effectiveness endpoints, or safety outcomes; all analyses will utilize available data as observed. For each treatment group, descriptive summary statistics (mean, minimum, maximum, standard deviation [SD], and 95% confidence interval [CI] of the mean) and change from Baseline (absolute and relative) will be presented by study visit. Baseline is defined as the measurement preceding the initial treatment. For the No-treatment control group, Baseline is defined as the last measurement at Visit 5 (12 weeks after randomization) before continuing to Phase 1b. For endpoints with qualitative results, frequencies and percentages will be calculated and presented for each visit by treatment group. A Fisher's exact test will be used to compare proportions at each time point between the RHA[redacted] group [redacted] and the No-treatment control group in Phase 1a. [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA[redacted]
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	For the FACE-Q, the answers to all questions of the scale will be pooled and data will be transformed and adapted to a scale of 100 units (i.e., worst/lowest score = 0; best/highest score = 100) as per FACE-Q user manual. The highest score will reflect positive outcome. [redacted] For the GAIS (all evaluators), proportions of "improved" and "much improved" will be presented, along with the number of subjects and 95% CI of the proportion at each applicable study visit. For subject satisfaction, proportions of "satisfied" and "very satisfied" will be presented, along with the number of subjects and 95% CI of the proportion at each applicable study visit. [redacted] Safety Analyses: [redacted] All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs reported during the study will be described by system organ class and preferred term. The number and percentage of subjects experiencing at least 1 AE that are treatment related (ADE) will be presented. [redacted] Further analyses will be performed for the AEs and ADEs as described in the statistical analysis plan. [redacted]

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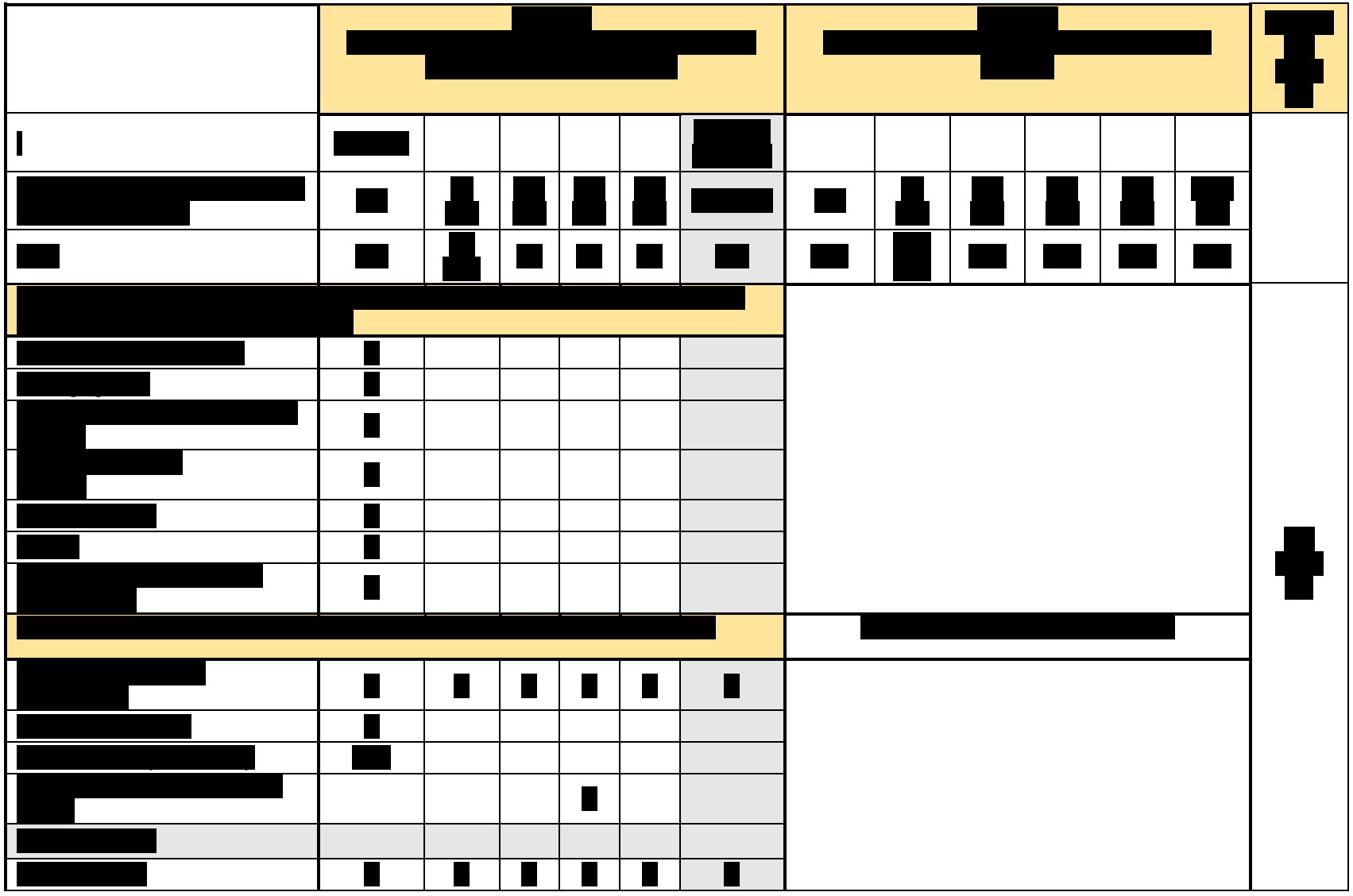

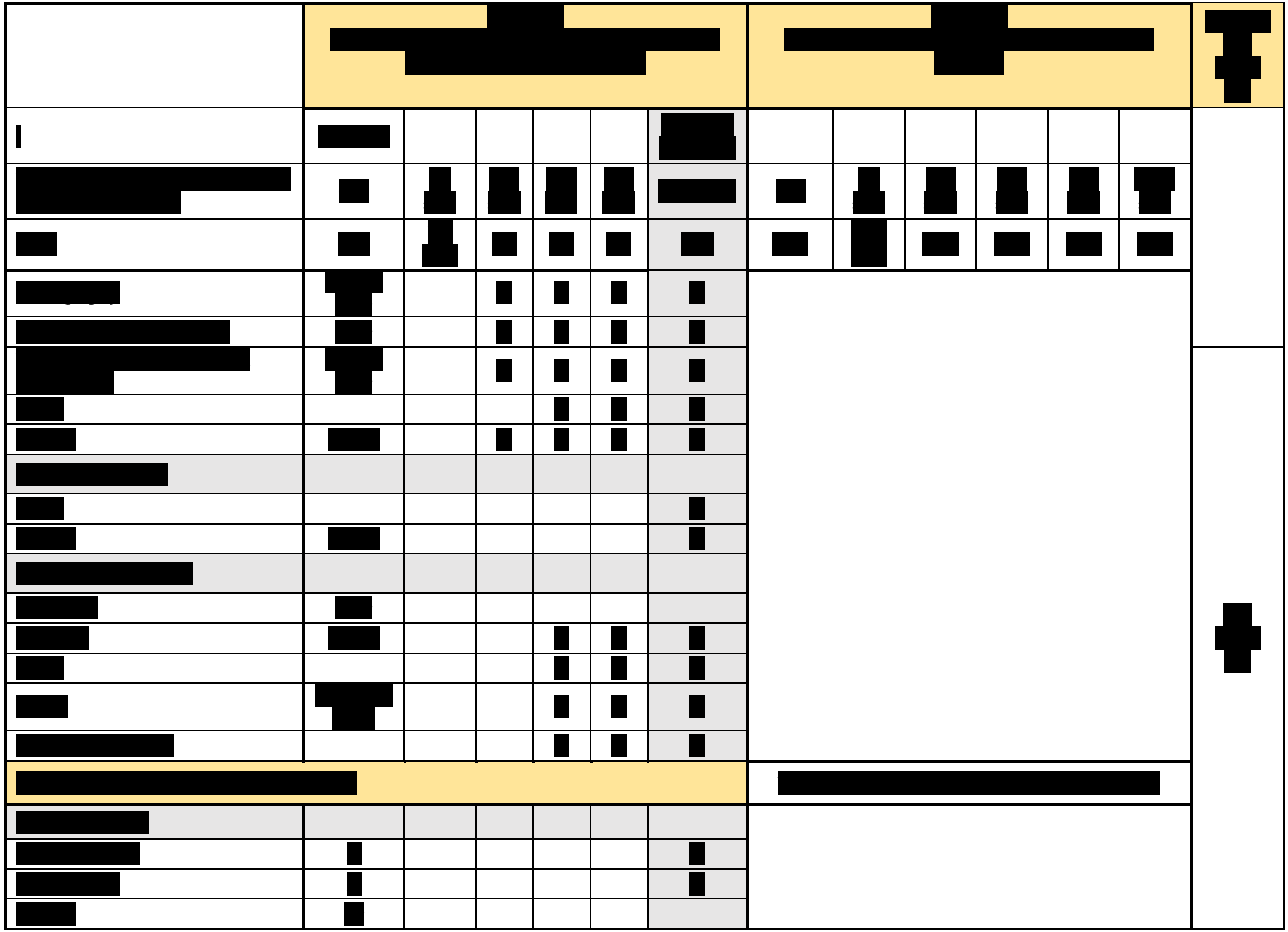

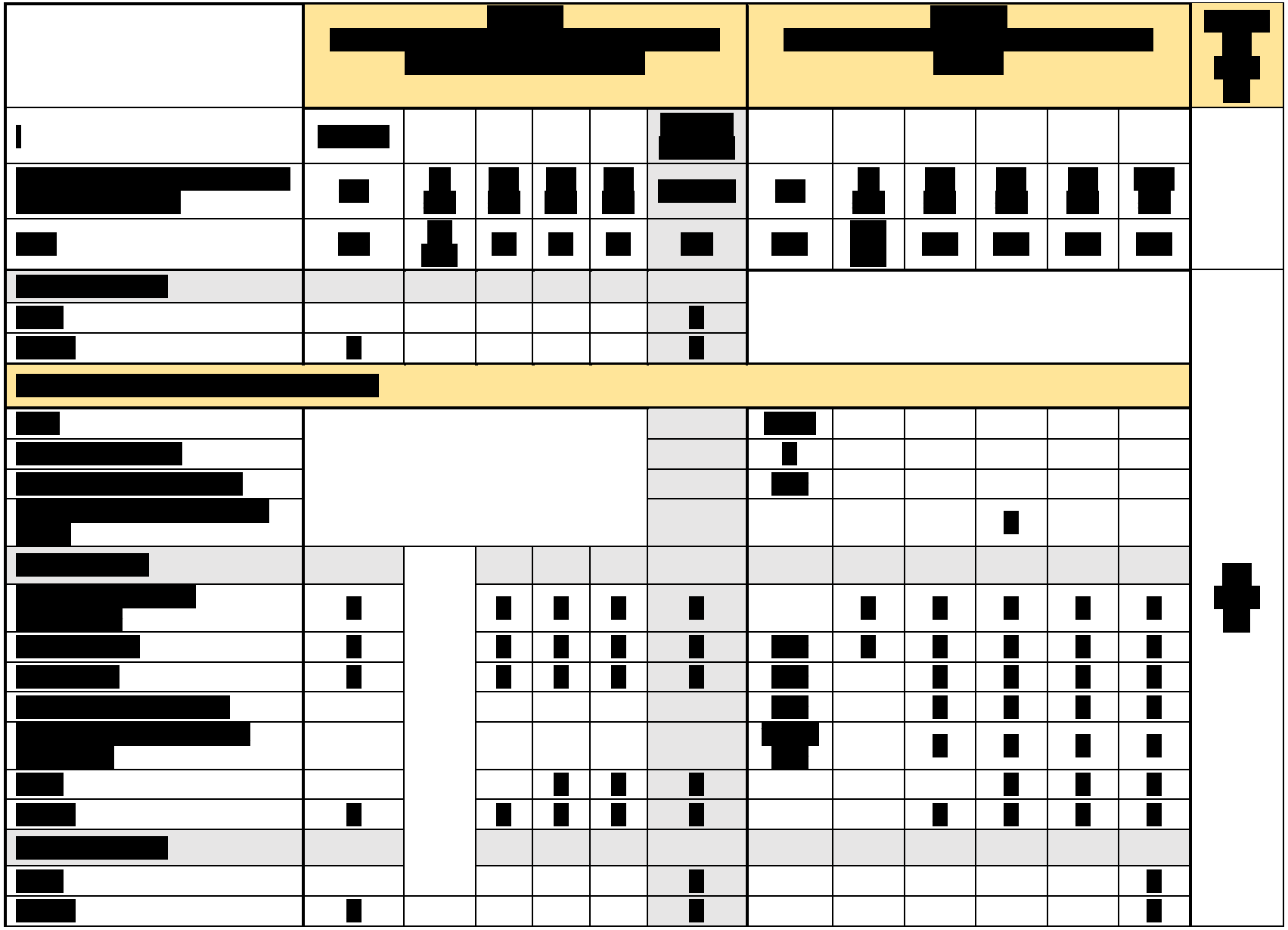

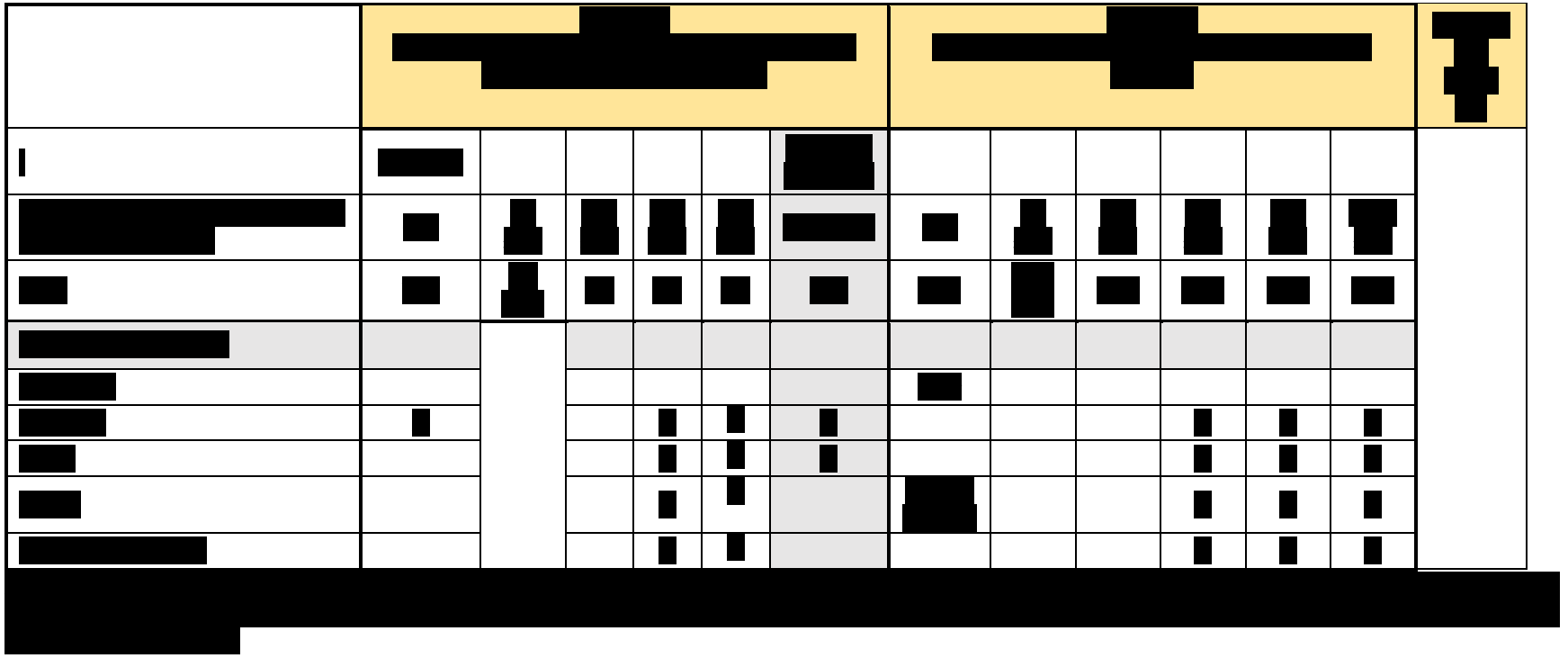

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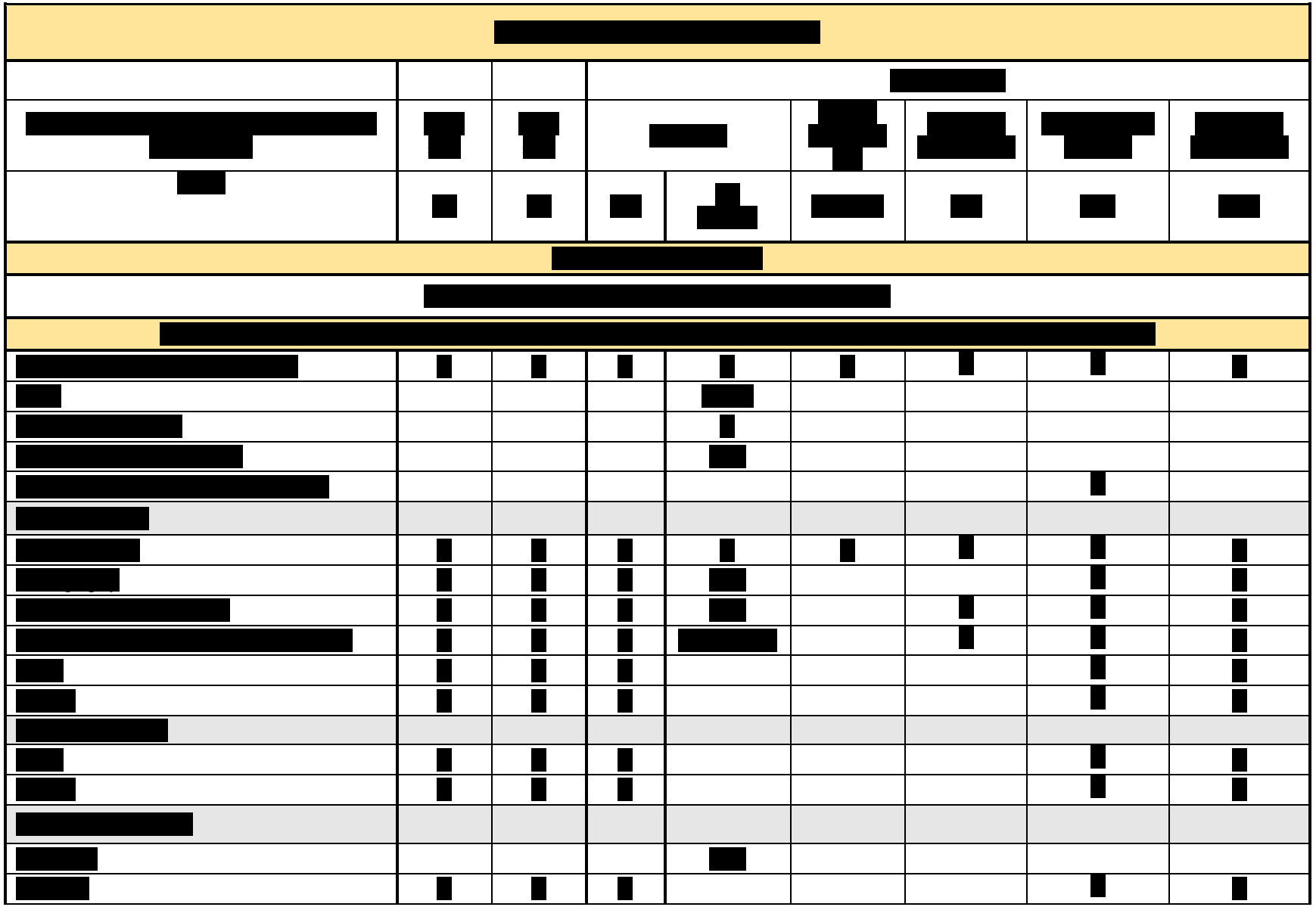

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADE	Adverse Device Effect
AE	Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
BDDE	1,4-butanediol diglycidyl ether
BLE	Blinded Live Evaluator
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Plan
CMP	Clinical Monitoring Plan
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTR	Common Treatment Response
DMP	Data Management Plan
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic Acid
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IPR	Independent Panel Review
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NaHA	sodium hyaluronate
[redacted]	[redacted]
PP	Per-Protocol
PSAQ	Periorbital Subject Assessment Questionnaire
[redacted]	[redacted]
SAFT	Safety Population

ABBREVIATION	EXPLANATION
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMP	Safety Management Plan
SOP	Standard Operating Procedure
TI	Treating Investigator
TIOHS	Teoxane Infraorbital Hollows Scale
[redacted]	[redacted]
UPT	Urine Pregnancy Test
US	United States
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

5. INTRODUCTION TO THE CLINICAL INVESTIGATION

5.1. Background

The eyes represent a key feature of the face. Their color, shape, surrounding area, and their expressivity immediately draw our attention. The effects of aging are particularly visible in the periorbital area due to delicate periorbital skin and subcutaneous tissue. Over the past decade, this area has become an area of choice for facial rejuvenation. According to a cross-sectional research survey, aesthetically oriented women consider infraorbital grooves as one of the most troublesome areas of the face.[1]

Grooves in the infraorbital region include the tear trough deformities (located between the palpebral and orbital parts of the orbicularis oculi), the nasojugal grooves (inferior border of the orbicularis oculi), and the palpebromalar grooves (overlying the inferomedial orbital rim). Several factors such as the herniation of intraorbital fat, the atrophy of the skin and subcutaneous fat, the contraction of the orbital part of the orbicularis oculi muscle or squinting, and the malar bone resorption may cause the grooves. Relatively broad depressions in the infraorbital area, referred to as infraorbital hollows, may occur with or without grooves and in some cases, if the soft tissue atrophies inferior to the arcus marginalis, the hollow can manifest as a groove and may require treatment.[2,3]

Treatment in the infraorbital region includes surgical and nonsurgical methods. Nonsurgical methods include injection of one's own harvested fat tissue or injection of soft tissue fillers. Soft tissue fillers used in cosmetic surgery are generally registered as medical devices. There are various types of fillers and their effect can be permanent (e.g., polymethylmethacrylate), semi-permanent (e.g., calcium hydroxylapatite, poly-L-lactic acid), or temporary (e.g., collagen, hyaluronic acid).[4] To date, there is no medical device approved by the US Food and Drug Administration (FDA) for injection into the periorbital area and treatment of infraorbital hollows; the use of soft tissue fillers is currently off-label in that area.

Hyaluronic acid (HA), also known as hyaluronan, is the most abundant glycosaminoglycan found in the human dermis. Used as a dermal filler, HA has a long record of data confirming its safe use. The persistence of HA in the tissues and its resistance to degradation can be obtained by chemical crosslinking, which allows modification of the rheological and physical properties of the HA, while maintaining the biocompatibility of the basic polymer.[5] The injection of a HA gel dermal fillers, as a minimally invasive procedure, is becoming the method of choice for the treatment of the infraorbital hollows. This clinical investigation will evaluate the use of the HA dermal filler RHA® 1 for the treatment of the infraorbital area.

5.2. Study Device Name

RHA[redacted]. RHA® stands for Resilient Hyaluronic Acid.

5.3. Intended Purpose Statement

RHA[redacted] is intended to be used for the correction of moderate to severe tissue volume deficiencies in the infraorbital hollows in subjects 22 years old or older.

5.4. Investigational Product Description

The device under clinical investigation is RHA[redacted] manufactured by TEOXANE SA.

[redacted]

[redacted]

5.4.1. Delivery System and Implantation

RHA[redacted] is supplied in individual blister packages containing a 1 mL treatment syringe with two 30G x ½″ needles (only for the sites selected to be "needle" sites). The contents of the syringe are sterile and nonpyrogenic. They should not be resterilized or used if the blister package has been opened or damaged.

[redacted]

5.4.2. Nonclinical Testing and Previous Clinical Experience

All information regarding the nonclinical testing and the previous clinical experience with RHA[redacted] is included in the current IB.[5]

5.4.3. Injection of RHA[redacted]

Injection area and depth: RHA[redacted] is injected from the sub-dermis to the periosteum in the infraorbital hollow.

Amount of filler to be administered: Up to 1.0 mL per eye at each treatment (max: 2.0 mL per treatment).

[redacted]

5.5. Justification for the Clinical Investigation

RHA[redacted] is an investigational device, which has not yet been approved by the FDA. It has been assessed for the perioral lines indication in a previous clinical investigation conducted by TEOXANE SA, which has been completed and shortly submitted to the FDA.

The purpose of this study is to inject RHA[redacted] into the infraorbital regions to achieve volume correction in the infraorbital area and to demonstrate that it is superior to no treatment in subjects

[redacted]

aged 22 years and older to support a premarketing authorization application to US FDA for RHA[redacted].

[redacted]

5.6. Justification for the Clinical Investigation Design

The study is designed to prospectively evaluate RHA[redacted] in the treatment of tissue volume deficiencies in the infraorbital regions and show that it is superior to no treatment. The study design was selected to minimize bias by using subject randomization and blinding of the independent evaluator (Blinded Live Evaluator [BLE]), whose assessment will be used for the primary endpoint analysis. The comparison of the safety and effectiveness of RHA[redacted] against no treatment will be done between subjects and will include subjects from multiple sites, [redacted]

6. CLINICAL INVESTIGATION PURPOSE, OBJECTIVES, AND ENDPOINTS

6.1. Clinical Investigation Purpose

The purpose of the study is to evaluate the safety and effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions.

6.2. Objectives and Endpoints

Objectives mapped to endpoints are displayed in Table 6-1.

6.2.1. Primary Effectiveness Objective

To assess the effectiveness of RHA[redacted] (as judged by clinicians and subjects) for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions at 12 weeks after the initial treatment.

6.2.2. Secondary Effectiveness Objectives

To assess the effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment.

6.2.3. Safety Objective

- To assess the safety of RHA[redacted] in subjects treated for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment

[redacted]

Table 6-1 Objectives Mapped to Endpoints

Objectives	Endpoints
Primary effectiveness	
To assess the effectiveness of RHA[redacted] (as judged by clinicians and subjects) for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions at 12 weeks after the initial treatment	The primary endpoint will be the responder rate after 12 weeks. The effectiveness of RHA[redacted] will be demonstrated if: • The responder rate for subjects treated with RHA[redacted] is statistically superior to the responder rate for subjects of the No-treatment control group 12 weeks (Visit 5) after randomization as assessed by the BLE using the live-validated TIOHS Additionally, the following 2 conditions must be met: • The responder rate for RHA[redacted] is ≥70% • The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group is ≥50% A responder will be defined as a subject with a ≥1-grade improvement in both eyes on the TIOHS as assessed by the BLE before initial treatment and 12 weeks after the initial treatment (Visit 5). The co-primary endpoint will be the change from Baseline in the modified FACE-Q Appraisal of lower eyelids domain score (converted to a 0-100 scale – Rasch conversion) at 12 weeks. The effectiveness of RHA[redacted] will be demonstrated if the modified FACE-Q Appearance of lower eyelids change from Baseline score for subjects treated with RHA[redacted] is statistically superior (by at least 12 points) to the subjects of the No-treatment control group 12 weeks (Visit 5) after randomization (including subjects who received RHA[redacted] during Stage 1). Additionally, the following 2 conditions must be met: • The mean change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is ≥ 3 • The difference between the modified FACE-Q "Appraisal of lower eyelids" change from Baseline for subjects treated with RHA[redacted] and the No-treatment control group is ≥12

Objectives	**Endpoints**
	[redacted] • [redacted] Only data from the Phase 1a will be taken into account. Data from subjects randomly assigned to the No-treatment control group after treatment received in the Phase 1b will not be pooled for the primary endpoint analysis. Superiority will be declared if: • the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and • the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and • the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and • the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12
Secondary effectiveness	
To assess the effectiveness of RHA[redacted] for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment	The secondary endpoints will consist of the following: • Proportion of subjects with both eyes with ≥1-grade improvement on the TIOHS as assessed: ○ By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/ initial treatment) = rate of responders at the given time point [redacted] ○ [redacted]

Objectives	Endpoints
	[redacted] • Proportion of subjects who were "improved" or "much improved" using the Global Aesthetic Improvement Scale (GAIS) as assessed: o By the BLE at each site visit starting from Visit 5 (12 weeks after randomization/ initial treatment) o [redacted] o By the subject at each site visit [redacted] • Proportion of subjects "satisfied" or "very satisfied" with the effect of the study treatment, using the Subject satisfaction scale as assessed by the subject at each site visit [redacted] • FACE-Q assessment by the subject through the Appraisal of lower eyelids (all questions) scale of the FACE-Q at each site visit starting from Baseline [redacted]
Safety	

Objectives	Endpoints
• To assess the safety of RHA[redacted] in subjects treated for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions up to 52 weeks after initial treatment and 12 weeks after retreatment [redacted]	The safety endpoints include: • Adverse events, with a focus on treatment related AEs based on the TI assessment, and AEs reported from the CTR diary, from randomization [redacted] • Post-injection CTR, including visual disturbances, through 30-day subject CTR diary [redacted]
[redacted]	
[redacted]	[redacted]

Abbreviations: AE = adverse event; [redacted] BLE = Blinded Live Evaluator; CTR = common treatment responses, GAIS = Global Aesthetic Improvement Scale; IPR = Independent Panel Review; OCR = optimal cosmetic result; PSAQ = Periorbital Subject Assessment Questionnaire; TI = Treating Investigator; TIOHS = Teoxane Infraorbital Hollows Scale; VAS = visual analog scale

6.3. Hypothesis

The RHA[redacted] group will be superior to the No-treatment control group for the correction of volume deficiencies in the infraorbital regions as determined by the Teoxane Infraorbital Hollows Scale (TIOHS – 5-point scale from grade 0 to 4) at 12 weeks after the initial treatment or randomization (for the No-treatment control group). [redacted]

Additionally, the following 2 conditions must be met:

- The responder rate for RHA[redacted] is ≥70%
- The difference between the responder rate for subjects treated with RHA[redacted] and the No-treatment control group is ≥50%

[redacted]

Additionally, the following 2 conditions must be met:

- The mean change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is ≥ 3
- The difference between the modified FACE-Q "Appraisal of lower eyelids" change from Baseline for subjects treated with RHA[redacted] and the No-treatment control group is ≥12

Superiority will be declared if:

- the lower bound of 2-sided 95% confidence interval for the responder rate for RHA[redacted] is at least 70%, and
- the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA[redacted] and the No-treatment control group is at least 50%, and
- the lower bound of 2-sided 95% confidence interval for the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA[redacted] is at least 3, and
- the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA[redacted] treated group and the No-treatment control group is at least 12

[redacted]

6.4. Risks and Anticipated Adverse Device Effects

The safety of the study devices has not been established during pregnancy or in breast feeding females.

The following risks have been associated with the use of HA dermal fillers in general, not just RHA[redacted]. There are various types of risks associated with the injection of a HA dermal filler in the infraorbital region:

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

6.4.1. Risks Associated With All Skin Injection Procedures

The following are risks associated with all skin injection procedures:

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

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

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

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

6.4.3. Risks That Are Typically Associated With RHA[redacted] and HA Dermal Fillers in General

The following risks are anticipated adverse device events when using a HA dermal filler:

- Common Treatment Responses (CTRs):
  - Redness (erythema)
  - Pain
  - Tenderness
  - Firmness (induration)

  - Swelling
  - Lumps/Bumps
  - Bruising
  - Itching
  - Discoloration (hyperpigmentation)
- Other common reactions such as inflammation or edema
- Other, less frequent risks have also been reported, such as paresthesia, rash, telangiectasia, dermatitis, scarring, scab, peeling/shedding, urticaria, abscess formation, papules, blister, product migration, nausea, headache, reactivation of herpes, malaise, hypersensitivity, lack of effect

[redacted]

- Skin necrosis

[redacted]

[redacted]

7. CLINICAL INVESTIGATION DESIGN

Enrollment

This is a multicenter, blinded evaluator, randomized, prospective, no-treatment control clinical study to identify whether RHA[redacted] is superior to no treatment for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions. The study [redacted] will include at least 20% of subjects with Fitzpatrick skin types IV-VI: including a minimum of 10% of subjects presenting with Fitzpatrick skin types V or VI, [redacted]

The TI and the BLE will evaluate the subject's infraorbital hollows independently of each other using the TIOHS at Screening (Visit 1) for eligibility. If the assessments of the TI and the BLE are the same or differ exactly by 1 point on the scale, the difference will be considered acceptable. The TI and the BLE must agree that the subject meets the inclusion criterion number 4 (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline of the primary endpoint. If the TI and the BLE do not agree on eligibility, or if their assessments differ by 2 points or more on the scale, the subject will not be eligible.

[redacted]

[redacted]

Phase 1a: Up to 12 weeks after the initial treatment for the RHA[redacted] group or after randomization for the No-treatment control group; primary endpoint

Subjects who will be randomly assigned to the RHA[redacted] group at Screening [redacted] will receive their injection at Visit 1. The TI or designee will call subjects 72 hours post-treatment (Visit 1 Call). Subjects will come to the site [redacted] 12 weeks (Visit 5, primary endpoint) after the initial treatment. Afterwards, subjects will proceed directly to Phase 2. Phase 1b is not applicable for subjects randomly assigned to the RHA[redacted] group.

Subjects randomly assigned to the No-treatment control group [redacted] at Screening will receive no treatment in Phase 1a of the study. They will come to the site [redacted] 12 weeks (Visit 5, primary endpoint) after randomization. After completing all assessments for Visit 5, subjects will immediately begin Phase 1b (Visit 1b is on the same day as Visit 5) and will receive their initial treatment with RHA[redacted]

[redacted]

Phase 1b: after the primary endpoint assessment up to 12 weeks after the initial treatment for the No-treatment control group

Phase 1b is only applicable to subjects initially randomly assigned to the No-treatment control group. Once all evaluations applicable for Visit 5 are completed, subjects will proceed directly to Visit 1b (on the same day). Evaluations completed at Visit 5 will be used for Visit 1b and will become the new Baseline for Phase 1b.

Subjects will receive their initial treatment with RHA[redacted] at Visit 1b.

Subjects will follow the same schedule as those initially randomly assigned to the RHA[redacted] group: RHA[redacted] will be administered on the same day (Visit 1b). The TI or designee will call the subject 72 hours post-treatment (Visit 1b Call). Subjects will come to the site [redacted] 12 weeks (Visit 5b) after their initial treatment. Afterwards, subjects will proceed to Phase 2.

Phase 2 and Exit Visit: 12 weeks after the initial treatment up to the end of the study for the RHA[redacted] group and the No-treatment control group

Phase 2 will occur 12 weeks after receiving initial treatment with RHA[redacted] for subjects in the RHA[redacted] group [redacted] and the No-treatment control group (after Phase 1b).

All these subjects will come to the site 24 weeks (Visit 6), [redacted] and 52 weeks (Visit 8) after their initial treatment. All subjects will be followed for 52 weeks after their initial treatment with RHA[redacted].

[redacted]

Subjects will be offered retreatment at Visit 8 (52 weeks after their initial treatment). Retreatment will be administered if the TI deems it to be appropriate and the subject agrees. If the subject does not receive retreatment, Visit 8 (52 weeks after initial treatment) will become the Exit Visit.

If the subject receives retreatment at Visit 8, the TI or designee will call him or her after 72 hours (Visit 8 Call). The subjects will come to the site [redacted] and 12 weeks (Visit 11) after retreatment for follow-up and safety assessments. Visit 11 will be the Exit Visit.

Assessments throughout the study: RHA[redacted] group [redacted] and No-treatment control group

The TI will conduct safety and effectiveness evaluations according to the schedule of events until the Exit Visit (Visit 8 or 11). Subjects with an ongoing adverse device effect (ADE) will be followed until the event(s) has resolved or resolved with sequelae, or deemed no longer necessary as per TI judgment, or if follow-up is no longer possible.

Subjects will report their Common Treatment Responses (CTRs) in a subject diary for 30 days after any injection (initial or retreatment).

The BLE will conduct assessments of effectiveness at all visits starting at Visit 5 (12 weeks after randomization). The primary endpoint assessment will be at Visit 5 (12 weeks after randomization) only. The primary endpoint will include data from subjects assigned to the RHA[redacted] and the No-treatment control group before receiving initial injection. Data from subjects randomly assigned to [redacted] the No-treatment control group after they receive treatment in Phase 1b will not be considered for the primary endpoint.

See Table 2-1, Table 2-2, Figure 7-1, Figure 7-2, and Figure 7-3.

[redacted]

[redacted]

[redacted]

7.1. Clinical Investigation Duration

[redacted]

Overall study duration: the original anticipated study length was approximately 22 months, including enrollment. [redacted]

However, this timing may also be extended depending on the public health emergency due to Coronavirus disease 2019 (COVID-19).

[redacted]

7.2. Clinical Investigation Enrollment

[redacted]

Subjects must have grade of 2 to 3 on the TIOHS (ranging from 0 to 4) and desire at least 1 point of correction. Overall, at least 20% of the subjects must be of Fitzpatrick skin types IV-VI (50 subjects): including a minimum of 10% of subjects presenting with Fitzpatrick skin types V or VI of which ≥3% of Fitzpatrick skin type V (at least 8 subjects) and ≥3% of Fitzpatrick skin type V (at least 8 subjects). [redacted] A 3:1 ratio between the RHA [redacted] group and the No-treatment control group is planned for the overall study enrollment [redacted]

[redacted]

[redacted]

The TI and the subject will not be blinded, while the BLE will be blinded to randomization to the RHA [redacted] group, [redacted] or the No-treatment control group. [redacted]

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

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

[redacted]

[redacted]

7.3. Clinical Investigation Sites

The clinical study is to be conducted at [redacted] up to 12 investigational sites in the US [redacted]

7.4. Selection of Clinical Investigation Subject Population

Subjects who seek correction of tissue volume deficiencies in the infraorbital area are possible candidates for the clinical investigation and will be screened for eligibility based on the following inclusion and exclusion criteria.

[redacted]

Vulnerable subjects:

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

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

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

7.4.1. Inclusion Criteria

A potential subject will be included in the study if he/she meets all of the following inclusion criteria:

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

   [redacted]
3. Subject is seeking treatment of volume deficiencies in the infraorbital regions (realistic and achievable as per TI opinion)
4. Has a grade of 2 to 3 (moderate to severe) on the TIOHS for both eyes

   Note: If the assessments of the TI and the BLE are the same or differ exactly by 1 point on the scale, the difference will be considered acceptable. The TI and the BLE need to agree that the subject meets the eligibility criterion (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline for the primary endpoint. If the TI and the BLE do not agree on eligibility, or if their assessments differ by 2 points or more on the scale, the subject will not be eligible
5. Able to follow study instructions and complete all required visits
6. Willing to sign the institutional review board-approved informed consent form, photographic release form, and the authorization for use and release of health and research study information (Health Insurance Portability and Accountability Act) form and, if applicable, the California Experimental Research Subject's Bill of Rights prior to any study-related procedures being performed

7.4.2. Exclusion Criteria

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

1. Known hypersensitivity or previous allergic reaction to any component of the study device, including local anesthetics of the amide type (e.g., mepivacaine, lidocaine), including known or suspected lidocaine hypersensitivity, or allergy to Gram-positive bacterial proteins
2. Known history of multiple severe allergies, or history of anaphylactic shock

[redacted]

4. Prior lower eyelid surgery, including orbital or midface surgery, or has a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments or plans to have it during the study
5. Is planning to undergo during the study or has undergone any type of facial, plastic, nonablative, or reconstructive surgery (e.g., blepharoplasty, face lift, or rhinoplasty) within 6 months before randomization. Subject is also excluded if residual swelling is present or complete healing has not occurred within at least 6 months of the treatment received

[redacted]

10. Known susceptibility to keloid formation, hypertrophic scars, hyperpigmentation, or compromised healing that would compromise the effectiveness outcome
11. Ongoing cutaneous infection at the site of injection at randomization

[redacted]

[redacted]

[redacted]

8. INVESTIGATION PROCEDURES

[redacted] Procedures by Visit [redacted]

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy. Separate informed consents will be used [redacted].

[redacted]

[redacted]

[redacted]

8.1.1. Phase 1a

Phase 1a is applicable for subjects in the RHA [redacted] group [redacted] and the No-treatment control group. [redacted]

8.1.1.1. Visit 1 (Screening/Randomization/Baseline/Initial Treatment)

Visit 1 is the first day of the study. Eligible subjects seeking treatment of volume deficiencies in the infraorbital regions will be screened for the study.

The **Screening procedures** will include the following assessments:

[redacted] Obtain written informed consent [redacted]

2. Collect demographic information
3. Record medical history, including ophthalmologic history
4. Collect prior and concomitant therapies (e.g., prescription and nonprescription medications) and previous surgeries
5. UPT for women of childbearing potential

[redacted]

7. Both the TI and the BLE perform the TIOHS assessment to assess eligibility and to establish the Baseline for future evaluations
8. Assess inclusion/exclusion criteria

If the subject is deemed eligible, the TI or designee will photograph the subject's eyes.

[redacted]

Subsequently, the subject will be randomly assigned to the RHA [redacted] /the No-treatment group [redacted].

The **Baseline procedures** (after randomization, before injection) will include the following assessments:

1. RHA [redacted] group
   [redacted]
   b. FACE-Q
2. No-treatment control group
   a. FACE-Q

[redacted] If the subject is randomly assigned to the No-treatment control group [redacted] the Visit 1 procedures will be considered completed after the Baseline procedures.

If the subject is randomly assigned to RHA [redacted] group, the TI will administer the filler according to the IB, Injection Guidelines, and Section 9.6. [redacted]

[redacted]

8.1.1.2. Visit 1 Call (+3 Days After the Initial Treatment)

Visit 1 Call is a telephone call 3 ± 2 days after the initial treatment and is applicable for subjects treated with RHA [redacted] at Visit 1. [redacted]

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

[redacted]

[redacted]

[redacted]

8.1.1.6. Visit 5 (Primary Endpoint; 12 Weeks After the Initial Treatment or Randomization)

Visit 5 is performed at the site 12 weeks ± 3 days after the randomization and is applicable for all subjects [redacted] Data from subjects in the RHA[redacted] group and the No-treatment control group from Visit 5 will be used for the primary endpoint assessment [redacted]

The following assessments will be performed at Visit 5:

[redacted]

2. BLE:
   a. GAIS
   b. TIOHS

[redacted]Subject [redacted]

   a. FACE-Q
   b. GAIS

[redacted]

   d. Subject satisfaction (RHA[redacted] group only)

After Visit 5, subjects initially assigned to the RHA[redacted] group [redacted] group will proceed directly to Phase 2. Subjects initially randomly assigned to the No-treatment control group will proceed to Phase 1b.

[redacted]

[redacted]**Phase 1b** [redacted]

[redacted]

8.1.2.1. Visit 1b (12 Weeks After the Randomization)

Visit 1b will occur on the same day as Visit 5. Results from these assessments at Visit 5 will be used as the new Baseline and used for pre-treatment assessments of Visit 1b [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.2.4. [redacted] Visit 5b (12 Weeks After the Initial Treatment at Visit 1b)

[redacted]

Visit 5b is performed at the site 12 weeks ± 3 days after the initial treatment at Visit 1b. Data from Visit 5 are not applicable for the primary endpoint assessment.

The following assessments will be performed at [redacted] Visit 5b:

[redacted]

2. BLE:
   a. GAIS (Visit 5b only)
   b. TIOHS (Visit 5b only)
3. Subject:
   a. FACE-Q
   b. GAIS
   [redacted]
   d. Subject satisfaction

After completing Visit 5b, subjects will proceed to Phase 2.

8.1.3. Phase 2

Phase 2 is applicable for all subjects randomly assigned to the RHA [redacted] and for subjects randomly assigned to the No-treatment control group after completing Phase 1b (Visit 5b). [redacted]

[redacted]

8.1.3.2. Visit 8 (52 Weeks After the Initial Treatment; Exit Visit for Subjects Without Retreatment)

Visit 8 is performed at the site 52 weeks ± 7 days after the subject's initial treatment and is applicable for subjects in the RHA[redacted] and in the No-treatment control group.

The following assessments will be performed at Visit 8:

[redacted]

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

After the assessments are completed, retreatment with RHA[redacted] will be offered to all subjects, if the TI deems it to be appropriate and the subject agrees[redacted]

For subjects who do not receive retreatment, Visit 8 will be the Exit visit. [redacted]

If the subject and TI agree that the subject will receive retreatment, prior to administration of the filler, the subject will undergo [redacted] a UPT, if she is a woman of childbearing potential

Afterwards, the TI will administer retreatment with RHA[redacted]

[redacted]

[redacted]

[redacted]

8.1.3.6. Visit 11 (12 Weeks After the Retreatment; Exit Visit for Subjects Who Received Retreatment)

Visit 11 is applicable only for subjects who received retreatment at Visit 8 and will take place 12 weeks after retreatment. The allowed visit window is ±7 days.

The following assessments will then be performed at Visit 11:

[redacted]

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

Visit 11 will be the Exit Visit for subjects who received retreatment. [redacted]

8.2. Assessments

8.2.1. Urine Pregnancy Test

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

[redacted]

[redacted]

8.2.2. Safety Assessments

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

8.2.2.1. Common Treatment Response

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

[redacted]

[redacted]

[redacted]

8.2.2.5. Adverse Events

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

[redacted]

[redacted]

8.2.3. Effectiveness Assessments

Effectiveness will be assessed by the [redacted] BLE, and subject [redacted]

8.2.3.1. Teoxane Infraorbital Hollow Scale

Infraorbital hollows will be assessed by [redacted] the BLE at time points in the schedule of events [redacted] using the live-validated 5-point TIOHS provided in Appendix B.

For eligibility purposes only: If the assessments of the TI and the BLE are the same or differ exactly by 1 point on the scale, the difference will be considered acceptable. The TI and the BLE need to agree that the subject meets the eligibility criterion (TIOHS grade 2 or 3). Bilateral symmetry is not required. If the subject is eligible, the BLE's assessment will be used for the Baseline for the primary endpoint. If the TI and the BLE do not agree on eligibility, or if their assessments differ by 2 points or more on the scale, the subject will not be eligible.

8.2.3.2. Subject Satisfaction

Subject satisfaction will be measured by using a 5-point balanced subjective scale [redacted] The subject will be instructed to "Rate your level of satisfaction with the effect of study treatment in the treated area by using the following scale" using the scale in Table 8-1.

Table 8-1 Subject Satisfaction Scale

Grade	Description
1	Very satisfied
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
5	Very dissatisfied

8.2.3.3. Global Aesthetic Improvement

Global aesthetic improvement assessment will be performed by the [redacted] BLE, and the subjects at time points in the schedule of events (Section 2.2) using a 5-grade GAIS (Table 8-2). [redacted]

Table 8-2 Global Aesthetic Improvement Scale

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

8.2.3.4. FACE-Q

The validated subject-reported outcome measure FACE-Q scale[13] will be assessed as in the schedule of events (Section 2.2). Only one selected scale from the FACE-Q will be used for the purpose of this study – Appraisal of Lower Eyelids. This scale measures the appearance of the area under the eyes with items that ask about the bags and wrinkled skin located in this area, as well as how tired or old these features make someone look. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. CLINICAL INVESTIGATION TREATMENT AND FOLLOW-UP

9.1. Subject Informed Consent

All suitable candidates being considered for enrollment in the clinical investigation will meet with the TI or designee and have the investigation explained in detail. This will include, but will not be limited to, the potential risks and benefits of participation. [redacted] Each subject will be provided with a written copy of the informed consent in a language he/she can comprehend and will be given ample opportunity to read and pose questions he/she may have about the investigation. If, after review, the subject agrees to participate, he/she will sign the ICF. If the subject subsequently fails to meet eligibility criteria, he/she will be considered a screen failure and will not receive treatment with the study device under the clinical investigation. The TI should, with the subject's consent, inform the subject's primary physician about his/her participation in the clinical study.

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

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

9.2. Randomization

[redacted]

[redacted]

9.3. Blinding/Unblinding Clinical Investigation Plan

9.3.1. General Blinding

The TI, unblinded to allocation to groups, will be asked to minimize the number of people who will have the allocation information or who will have any form of access to such information. [redacted]

The BLE and study personnel not involved with the site (e.g., data management, medical monitor) will be blinded to assignment to groups and, if possible, to subgroups. [redacted]

Subjects will not be blinded.

9.3.2. Blinded Procedures

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

Furthermore, to ensure that the BLE remains blinded and unbiased when making his/her assessments during the study, the BLE, the TI, and the subject will not be allowed to discuss each other's study assessments.

All subjects will be instructed to not discuss their study treatment, AEs, or CTRs with the BLE.

[redacted]

9.3.3. Unblinding Procedures

Unblinding in case of medical emergency is not applicable since the TI, who is in charge of safety follow-up of subjects, will be aware of the treatment administered.

Overall unblinding will take place at the end of the study only after database lock has occurred.

[redacted]

9.4. Pre-treatment Procedures and Tests

The procedures and tests to be performed prior to randomization are described for Visit 1 (Section 8.1.1.1).

[redacted]

9.5. Baseline Evaluations and Data Collection

All of the data collected at Visit 1 prior to randomization will be defined as Baseline for the purpose of the primary endpoint. Visit 5/Visit 1b data will become a new Baseline for subjects initially randomly assigned to the No-treatment control group for analyses that pool data from Visits 1b – 5b.

[redacted]

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

[redacted]

[redacted]

9.7. Clinical Investigational Product Treatment

The TI will inject RHA[redacted] either at Visit 1 [redacted] or at Visit 1b (subjects initially randomly assigned to No-treatment control group [redacted]).

[redacted]

9.7.1. Study Device

The study device is RHA[redacted]. Please see Section 5.4 and the IB[5] for further information.

9.7.2. Control Device

Not applicable. The control group will receive no treatment at Visit 1.

[redacted]

9.7.3. Injection of RHA[redacted]

Method of administration will be either with a 30G ½″ needle (included with the product) or a 25G ½″ cannula [redacted] Method of administration will be based on the site.

Injection area and depth: RHA[redacted] is injected from the sub-dermis to the periosteum in the infraorbital hollow.

Amount of filler to be administered: Up to 1.0 mL per eye at each treatment (max: 2.0 mL per treatment).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. ADVERSE EVENTS

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

All events will be reported and documented on the appropriate eCRF; AE information will be recorded in the eCRF Adverse Event Form.

[redacted]

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

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

[redacted]

10.1. Definitions

10.1.1. Adverse Events

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

10.1.2. Adverse Device Effects

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

[redacted]

[redacted]

10.1.6. Device Malfunction

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

[redacted]

10.2. Evaluation and Assessment

For the purposes of this investigation, any untoward medical occurrence, unintended disease, or injury, or any untoward clinical signs that occurs in a subject after randomization is considered an AE, regardless of the investigation group to which the subject is assigned.

Any medical conditions, problems, signs, symptoms, and findings that occur prior to randomization are to be reported as pre-existing conditions. Such conditions should be documented

[redacted]

and reported on the medical history eCRF as a pre-existing condition. If a pre-existing condition worsens after randomization (frequency increases and/or severity grade increases), it should be documented as an AE.

[redacted]

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

10.2.1. Relationship to Device

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

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

[redacted]

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

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

[redacted]Another possible etiology [redacted]

[redacted]

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

[redacted]

10.3. Safety Reporting

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

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

[redacted]

[redacted]

[redacted]

10.3.4. Device Malfunctions Reporting

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

[redacted]

10.4. Pregnancy

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

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

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

[redacted]

[redacted]

[redacted]

10.5. Data Monitoring Committee

Not applicable

10.6. Clinical Events Committee

Not applicable

11. STATISTICAL METHODS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that will describe the details of the analyses to be conducted and all statistical assumptions will be written and approved prior to database lock.

[redacted]

11.1. Analysis Populations

The following 4 analysis populations are planned for this investigation:

- Screening population: All subjects who provide informed consent and demographic and/or Baseline Screening assessment results, regardless of their randomization and treatment status in the investigation. The untreated control group will only be included in the Screening population as they will not receive RHA[redacted] treatment throughout the clinical study.
- Safety population (SAFT): All subjects who are assigned to either the RHA[redacted] group or the No-treatment control group and complete Visit 1 [redacted]
- Intent-to-Treat population (ITT): All subjects who are randomly assigned to either the RHA[redacted] [redacted] or the No-treatment control group and complete Visit 1. Subjects will be analyzed according to their initial arm assignment regardless of whether or not they received RHA[redacted].
- Per-Protocol population (PP): All subjects in the ITT population who completed up to Visit 5 (primary endpoint visit at 12 weeks) with no major CIP deviations that could affect effectiveness assessments. The sponsor will identify major CIP deviations prior to the database lock.

[redacted]

11.2. Sample Size Determination

[redacted]

[redacted]

11.3. Subjects and Demographics

[redacted]

11.3.2. Clinical Investigation Plan Deviations

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

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

11.3.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for SAFT, ITT, and PP analysis populations.

Demographic variables will include age, sex, [redacted]

11.4. Effectiveness Analyses

Effectiveness analyses will be performed primarily on ITT analysis set. [redacted]

[redacted]

[redacted]

One primary analysis will be performed:

- The RHA[redacted] group vs. the No-treatment control group

Primary effectiveness analysis: The rate of responders 12 weeks after randomization in RHA[redacted] will be compared with the rate of responders in the No-treatment control group using an independent testing based on a 2-group, 1-sided, Fisher's exact statistic test. [redacted]

The co-primary endpoint, change from Baseline in the modified FACE-Q Appearance of lower eyelids score (converted to a 0-100 scale using Rasch conversion) at 12 weeks will be evaluated.

[redacted]

The modified FACE-Q Appearance of lower eyelids change from Baseline score for subjects treated with RHA[redacted] will be compared with FACE-Q Appearance of lower eyelids for subjects of the No-treatment control group at 12 weeks (Visit 5) after randomization using t test or non-parametric equivalent like Wilcoxon rank-sum test.

[redacted]

Secondary effectiveness analysis:

No imputation will be performed for secondary (or pooled secondary) effectiveness endpoints, or safety outcomes; all analyses will utilize available data as observed.

For each treatment group, descriptive summary statistics (mean, minimum, maximum, SD, and 95% CI of the mean) and change from Baseline (absolute and relative) will be presented by study visit. Baseline is defined as the measurement preceding the initial treatment. For the No-treatment

control group, Baseline is defined as the last measurement at Visit 5 (12 weeks after randomization) before continuing to Phase 1b.

For endpoints with qualitative results, frequencies and percentages will be calculated and presented for each visit by treatment group.

The secondary endpoints will be analyzed at each applicable visit [redacted]

- Analysis from Visit 1/Visit 1b to Visit 11 with all subjects pooled together

For the FACE-Q, the answers to all questions of the scale will be pooled and data will be transformed and adapted to a scale of 100 units (i.e., worst/lowest score = 0; best/highest score = 100) as per FACE-Q user manual. The highest score will reflect positive outcome.

For the GAIS (all evaluators), proportions of "improved" and "much improved" will be presented, along with the number of subjects and 95% CI of the proportion at each applicable study visit.

For subject satisfaction, proportions of "satisfied" and "very satisfied" will be presented, along with the number of subjects and 95% CI of the proportion at each applicable study visit.

11.5. Safety Analyses

[redacted]

All safety endpoints [redacted] will be analyzed at each applicable visit [redacted]

[redacted]

- Analysis from Visit 1/Visit 1b to Visit 11 with all subjects pooled together

[redacted]

The TI, through questioning and observations, will report all AEs, their severity, and relationship to the study device.

All AEs will be coded using MedDRA. All AEs reported during the study will be described by system organ class and preferred term. The number and percentage of subjects experiencing at least 1 AE that are treatment related (ADE) will be presented.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

12.1. Investigator Responsibilities

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

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

[redacted]

12.1.1. Deviations From Clinical Investigation Plan

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

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

[redacted]

12.1.2. Maintaining Records

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

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

[redacted]

[redacted]

12.1.4. Prohibition of Promotion

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

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

[redacted]

12.2. Sponsor Responsibilities

12.2.1. General Duties

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

[redacted]

[redacted]

[redacted]

12.2.4. Changes in the Clinical Investigation Plan

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

[redacted]

[redacted]

13.1. Data Management

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

[redacted]

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

13.2. Confidentiality of Data

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

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

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

[redacted]

[redacted]

13.4. Electronic Case Report Forms

This investigation will use an eCRF as the primary data collection instrument and will record data by electronic capture. All data requested on the eCRF must be entered. All missing data must be explained. If an entry on the eCRF is left blank because the procedure was not done or the question was not asked, a query will be generated for the site data entry staff. If any entry error has been made, correct and enter the correct data in the eCRF. All such changes are recorded in the audit and queries report. All electronic data capture systems must be 21 CFR Part 11 and/or ISO 14155-compliant.

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

[redacted]

13.5. Record Retention

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

13.6. Clinical Data Monitoring Procedures

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

[redacted]

14. REVIEW OF THE TI SITE FILE ETHICS AND REGULATORY COMPLIANCE

14.1. Conduct of the Clinical Investigation

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

14.2. Conflict of Interest

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

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

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

14.3. Institutional Review Board/Competent Authority Approval

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

14.4. Clinical Investigation Informed Consent Approval

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

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

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

14.5. Subject Identification and Confidentiality

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

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

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

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

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

[redacted]

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

[redacted]

[redacted]

14.8. Insurance

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

14.9. Site Audit Plan

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

14.9.1. Internal Audits by Sponsor or Sponsor's Designee

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

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

14.9.2. External Audits

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

14.10. Investigational Product Traceability

Investigational product will be stored at each site according to the IB and records will be kept to document product storage and management; sponsor-provided unique identification number and labeling identifying it as IDE product will be clearly visible. All sites will maintain a device accountability log that will match subjects to a particular study device by a unique manufacturer number. At the conclusion of the investigation, all study devices will be returned to the sponsor.

Further information may be found in the Investigational Product Guidelines that will be provided to the participating sites.

14.11. Public Domain Access to the Clinical Investigation

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

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

17. ATTACHMENTS

17.1. Investigator's Agreement

CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
CLINICAL INVESTIGATION PLAN TITLE:	A Randomized, Blinded Evaluator, No-treatment Control, Multicenter, Prospective Clinical Study of RHA[redacted] for the Treatment of Moderate to Severe Tissue Volume Deficiencies in the Infraorbital Regions
FINAL CLINICAL INVESTIGATION PLAN:	[redacted] 24-Apr-2024

I have read this clinical investigation plan and agree to conduct this clinical investigation as outlined herein. I will ensure that all subinvestigators and other investigation staff members have read and understand all aspects of this clinical investigation plan. I agree to cooperate fully with TEOXANE SA and Premier Research during the investigation. I will adhere to all FDA, ICH, ISO 14155, GCP, Declaration of Helsinki, and other applicable regulations and guidelines regarding clinical investigations during and after investigation completion.

Treating Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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