1. TITLE PAGE

A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation

Clinical Investigation Plan

INVESTIGATIONAL PRODUCT:	RHA® 3
CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
INVESTIGATIONAL DEVICE EXEMPTION NUMBER:	G200102
DEVELOPMENT PHASE:	Pivotal
INDICATION:	Lip Augmentation
METHODOLOGY:	Controlled, randomized, double-blinded, multicenter, prospective
PROTOCOL VERSION:	[redacted]
PROTOCOL DATE:	Original Protocol Version 1.0, 13-Mar-2020
AMENDMENT 5 DATE:	Amended Protocol Version [redacted], 22-Mar-2021
PROTOCOL WRITTEN BY:	[redacted]
SPONSOR:	TEOXANE 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 Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation

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]
Clinical Program Manager
[redacted]

[redacted]
Clinical Development and Medical Affairs Director
[redacted]

[redacted]

SIGNATURE **DATE**

[redacted]

[redacted]

AMENDED PROTOCOL

Revision history:

TITLE:	A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation
CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
PROTOCOL VERSION:	[redacted]
ORIGINAL PROTOCOL DATE:	Original Protocol Version 1.0, 13-Mar-2020
AMENDMENT 1 DATE:	[redacted]
AMENDMENT 2 DATE:	[redacted]
AMENDMENT 3 DATE:	[redacted]
AMENDMENT 4 DATE:	[redacted]
AMENDMENT 5 DATE:	Amended Protocol Version [redacted], 22-Mar-2021

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

2. CLINICAL INVESTIGATION PLAN SUMMARY

2.1. Summary

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
CONTROL DEVICE NAME	[redacted]
INDICATION FOR USE	RHA® 3 injectable gel is intended to be used for injection in the vermillion body, vermillion border, and oral commissures to achieve lip augmentation and lip fullness in subjects aged 22 or older
DEVELOPMENT PHASE:	Pivotal
TITLE OF INVESTIGATION	A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation
MANUFACTURER/ SPONSOR	TEOXANE SA, Rue de Lyon 105, CH – 1203 Geneva, Switzerland
CLINICAL INVESTIGATION PURPOSE	The purpose of the clinical investigation is to evaluate the safety and effectiveness of RHA® 3 when compared to [redacted] to add volume and fullness to the lips 12 weeks after the last treatment (initial or touch-up)
OBJECTIVES	• Primary Effectiveness Objective: o To assess the effectiveness (non-inferiority) of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation, 12 weeks after the last treatment (initial or touch-up) • Secondary Effectiveness Objective: o To assess the effectiveness of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation up to 52 weeks o To assess the responder rate of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks o To assess the subject satisfaction and patient-reported outcome of the aesthetic procedure (FACE-Q) with RHA® 3 versus [redacted] after lip augmentation up to 52 weeks o To assess the Global Aesthetic Improvement Scale (GAIS) of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] • Safety Objective: o To assess the safety of RHA® 3 in subjects after lip augmentation
INVESTIGATION DESIGN	This is a multicenter, double-blinded, randomized, prospective, controlled clinical study to identify whether RHA® 3 is non-inferior to [redacted] for lip augmentation at Week 12 after the last treatment (initial or touch-up). The treating investigator (TI) will evaluate the subject's lip fullness using the live validated 5-grade Teoxane Lip Fullness Scale (TLFS grade 1 to 5) at Screening (Visit 1, 0 Week) for eligibility of the subject for the study. The blinded live evaluator (BLE) will evaluate the subject's lip fullness using the TLFS at Screening (Visit 1, 0 Week) to confirm eligibility and to establish a pretreatment score for assessment of effectiveness. This will be done independently of the TI. [redacted] [redacted] Enrolled subjects will be randomly assigned in a 3:1 ratio to either the RHA® 3 or the [redacted] treatment group. Subjects will be blinded to the study treatment. The TI will administer the fillers, and if necessary, subjects will receive a touch-up treatment 4 weeks after the initial treatment to optimize the results. If the touch-up treatment is administered, the subject will be asked to come to the site for an additional visit [redacted] 4 weeks after the touch-up injection. Subjects will be followed for 52 weeks after their last treatment (initial treatment or touch-up), at which point, they will be offered retreatment with RHA® 3, regardless of their original treatment, provided that the TI deems the treatment to be appropriate and the subject agrees. Reasons for not administering the retreatment will be documented. The subject will then be followed for an additional 4 weeks before exiting the study. If the subject or the TI declines retreatment, this visit ([redacted] 52 weeks after the last treatment) will be considered the study Exit visit. For subjects with retreatment, the Exit visit will be at [redacted] 4 weeks after the retreatment.

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	The TI will conduct safety and effectiveness evaluations at each study visit, which will occur at 4 weeks after the initial and touch-up treatment ([redacted] 36 weeks [redacted], and 52 weeks [redacted] after the last treatment, and 4 weeks [redacted] after retreatment or until all treatment-related ongoing adverse events (AEs) have resolved or resolved with sequelae as per TI judgment or if follow-up is no longer possible. A follow-up telephone call for safety will be performed 3 days after each treatment [redacted] initial, touch-up, and retreatment, respectively). Subjects will report their common treatment responses (CTRs) in a subject diary for [redacted] days after each injection. The diary will also include a list of selected AEs potentially associated with injection of dermal fillers for subjects to report if applicable. [redacted] Subjects who had entered the study under earlier versions of the CIP (version [redacted] and earlier) and who do not agree with the extension of their participation in the study as per CIP version 5.0, to 52 weeks after last injection, will be allowed to continue with the visits as originally planned. They will exit the study at [redacted] 36 weeks after last injection) or, if they receive retreatment [redacted] they will have a follow-up telephone call [redacted] and will exit the study [redacted] 4 weeks after retreatment. Further details are described in the CIP. A BLE will conduct assessments of effectiveness during the study, including assessment of the primary endpoint [redacted] 12 weeks after the last treatment). The BLE will conduct effectiveness evaluations at [redacted] 36 weeks after the last treatment), [redacted] 52 weeks after the last treatment), and [redacted] 4 weeks after the retreatment, if applicable).
PRIMARY EFFECTIVENESS ENDPOINT	The effectiveness of RHA® 3 will be demonstrated if the change from Baseline for subjects treated with RHA® 3 is statistically non-inferior to the change from Baseline for subjects treated with [redacted] at 12 weeks after the last treatment as assessed by the BLE using the TLFS. The difference in the TLFS change from Baseline to 12 weeks will be used to establish non-inferiority. A change in the TLFS ≥1 grade compared to pretreatment will be considered clinically meaningful. [redacted]
SECONDARY EFFECTIVENESS ENDPOINTS	• TLFS change from Baseline assessed: o By the BLE at Visit 4 and each visit at the study site afterwards [redacted] • Responder rate calculated using TLFS assessed: o By the BLE at Visit 4 and each visit at the study site afterwards [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	A responder will be defined as a subject who has a ≥1 grade improvement on the TLFS. • Subject satisfaction using the Subject Satisfaction Scale at each visit at the study site starting at Visit 2 • FACE-Q scores for each module (satisfaction with lips and satisfaction with outcome) assessed by the subject at each visit at the study site [redacted] • GAIS as assessed: o By the BLE starting at Visit 4 and each visit at the study site afterwards [redacted]
[redacted]	[redacted]
SAFETY ENDPOINT	• Adverse Events • Post-injection CTR from the subject's [redacted] day diary [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
SAMPLE SIZE	The primary endpoint of the study is the difference in the TLFS change from Baseline to 12 weeks after the last day of treatment between subjects treated with RHA® 3 and those treated with [redacted] [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
[redacted]	[redacted]
STUDY CENTERS AND LOCATION	[redacted]
ELIGIBILITY CRITERIA	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 seeking lip augmentation (realistic and achievable as per TI opinion).

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted]

6. Able to follow study instructions and complete all required visits.
7. 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.

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 or the control device.
2. Known sensitivity to local anesthetics of the amide type, including known or suspected lidocaine hypersensitivity, history of multiple severe allergies, or history of anaphylactic shock.
3. An outbreak of herpes labialis within 4 weeks of randomization or 4 or more outbreaks in the 12 months prior to randomization.
4. History of severe chronic systemic diseases, including but not limited to, poorly controlled diabetes mellitus (all types), congestive heart failure, severe liver disease, severe kidney disease, and others as judged by the TI.

[redacted]

6. Has an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound on the lips, in the area of the mouth, or the area around the mouth.

[redacted]

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] 8. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to randomization. [redacted]

[redacted]

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	18. Medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or compliance of the subject and, in the judgment of the TI, would make the subject unsuitable for entry into this study). [redacted] 21. Clinically significant alcohol or drug abuse or history of poor cooperation or unreliability. [redacted] 23. [redacted]
STUDY DURATION	Individual study participation: The minimum and maximum anticipated duration of subject participation are 52 [redacted]. The anticipated duration for subjects who were enrolled under CIP version [redacted] or earlier and who do not agree to the extension of their participation in the study as per CIP version 5.0 will be a minimum of 36 weeks [redacted]. [redacted]
HYPOTHESIS	The TLFS change from Baseline of subjects treated with RHA® 3 will be statistically non-inferior to the change from Baseline of subjects treated with [redacted] for the assessment of lip augmentation and fullness as determined by the BLE using the TLFS at Week 12 after the last treatment. [redacted] [redacted]

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]

EFFECTIVENESS EVALUATION	• TLFS – a live validated 5-point scale for assessing lip fullness
	• Global Aesthetic Improvement Scale (GAIS) – a subjective, balanced, 5-point scale assessing aesthetic improvement
	• FACE-Q scales – validated subject-reported outcome measure, assessed at each study visit by the subject. The following modules will be used in the study:
	  ○ Satisfaction with lips: This scale measures the appearance of the upper and lower lips with items that ask about size, shape, and fullness, as well as how the lips suit the face and how nice the lips look when smiling
	  ○ Satisfaction with outcome: This scale measures a subject's satisfaction with the result of their most recent procedure
	• Subject Satisfaction Scale – a subjective, balanced, 5-point scale assessing subject satisfaction with study treatment
	[redacted]

SAFETY EVALUATIONS	• Adverse Events • Post-injection CTR [redacted] [redacted]

[redacted]

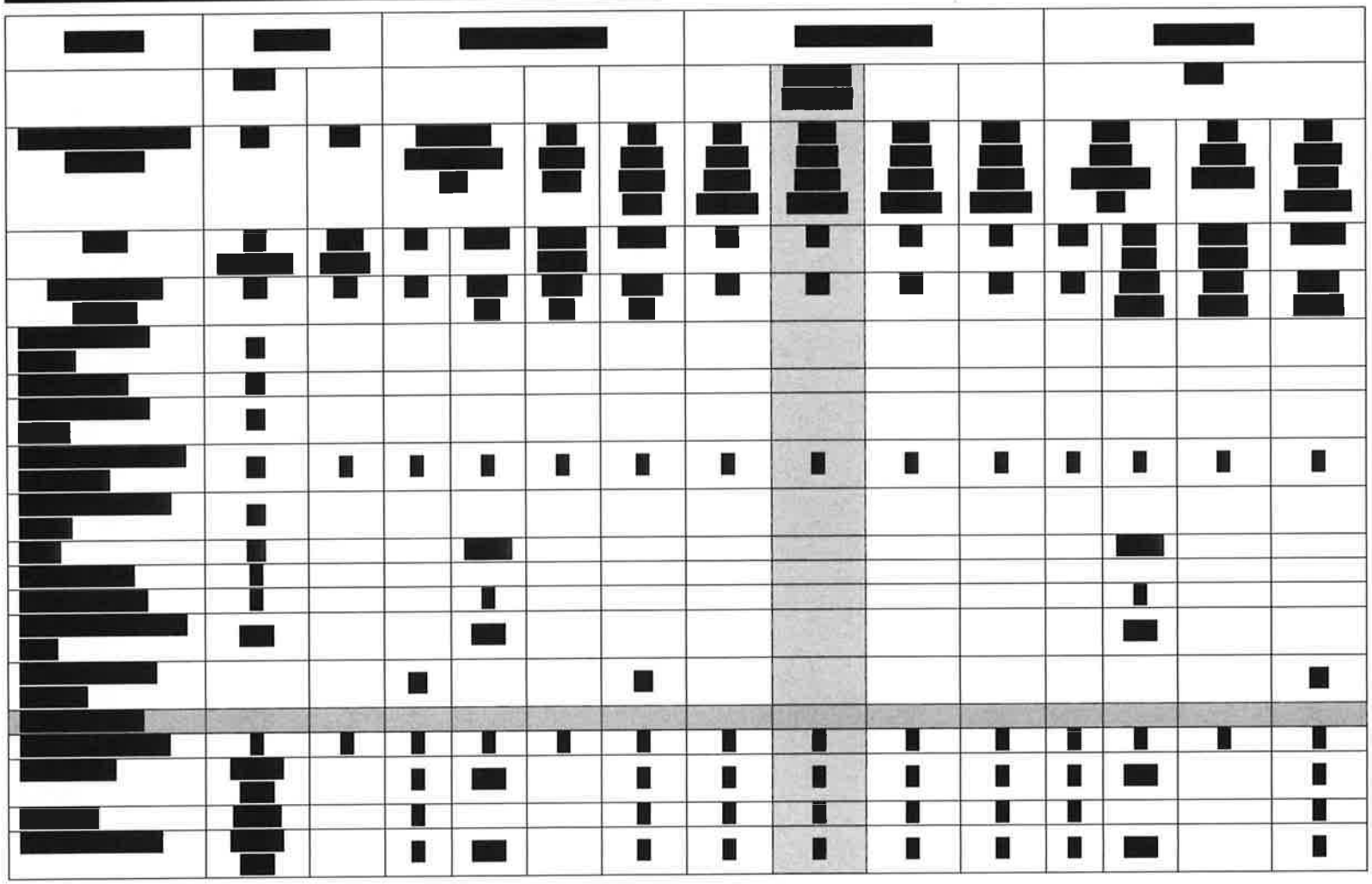
INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	• [redacted]
STATISTICAL METHODS AND ANALYSIS SUMMARY	All data will be recorded in an electronic case report form (eCRF). Quantitative data will be described by their mean, SD, and median, and extreme values. The 95% CI will also be produced when relevant. Qualitative data will be described by their number and percentage. The following analysis populations will be used: • Screening: All subjects who provide informed consent and demographic and/or Baseline screening assessment results, regardless of the subject's randomization and treatment status in the investigation. • Safety: All subjects who receive at least 1 treatment with RHA® 3 or [redacted]. • Modified intent-to-treat (mITT) analysis set will be used for the efficacy analysis. The mITT set is based on the conventional ITT: [redacted] [redacted]Per-protocol (PP): All subjects in the mITT population who receive treatment and do not have any major clinical investigation plan (CIP) deviations. [redacted] [redacted] Primary Effectiveness Analysis: *Non-inferiority analysis (main analysis):* To demonstrate non-inferiority of RHA® 3 compared to [redacted] at 12 weeks after the last treatment, the difference in the TLFS grade change between Baseline and 12 weeks will then be tested between groups ([redacted]). [redacted] [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] For each product, summary statistics (mean, minimum, maximum, SD, and 95% CI of the mean) for the above-mentioned parameters will be provided/presented for each study visit. For endpoints with qualitative results, frequencies and percentages will be calculated and presented for each study visit. [redacted]

INVESTIGATIONAL PRODUCT NAME	RHA® 3
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	[redacted] Safety Analysis: [redacted] The TI, through questioning and observations, will report all AEs, their severity and relationship to the study device.

INVESTIGATIONAL PRODUCT NAME	**RHA® 3**
CLINICAL INVESTIGATION PLAN (CIP) NUMBER	[redacted]
	All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. 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 device related (ADEs: adverse device effects) will be presented. [redacted]
DEVICE TREATMENT	[redacted] Injection area: The TI will inject each device into the vermillion body, vermillion border, and oral commissures as needed to achieve optimal aesthetic outcome. Amount of filler to be administered: Up to 1.5 mL per lip (upper and lower) at each treatment (initial, touch-up, and retreatment). [redacted]
TREATMENT GROUPS	Subjects will be randomly assigned (3:1 ratio) to 1 of the following groups: • RHA® 3 • [redacted]
BLINDING	The BLE and subjects will be blinded to treatment allocation. Furthermore, to ensure that they remain masked 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.

[redacted]



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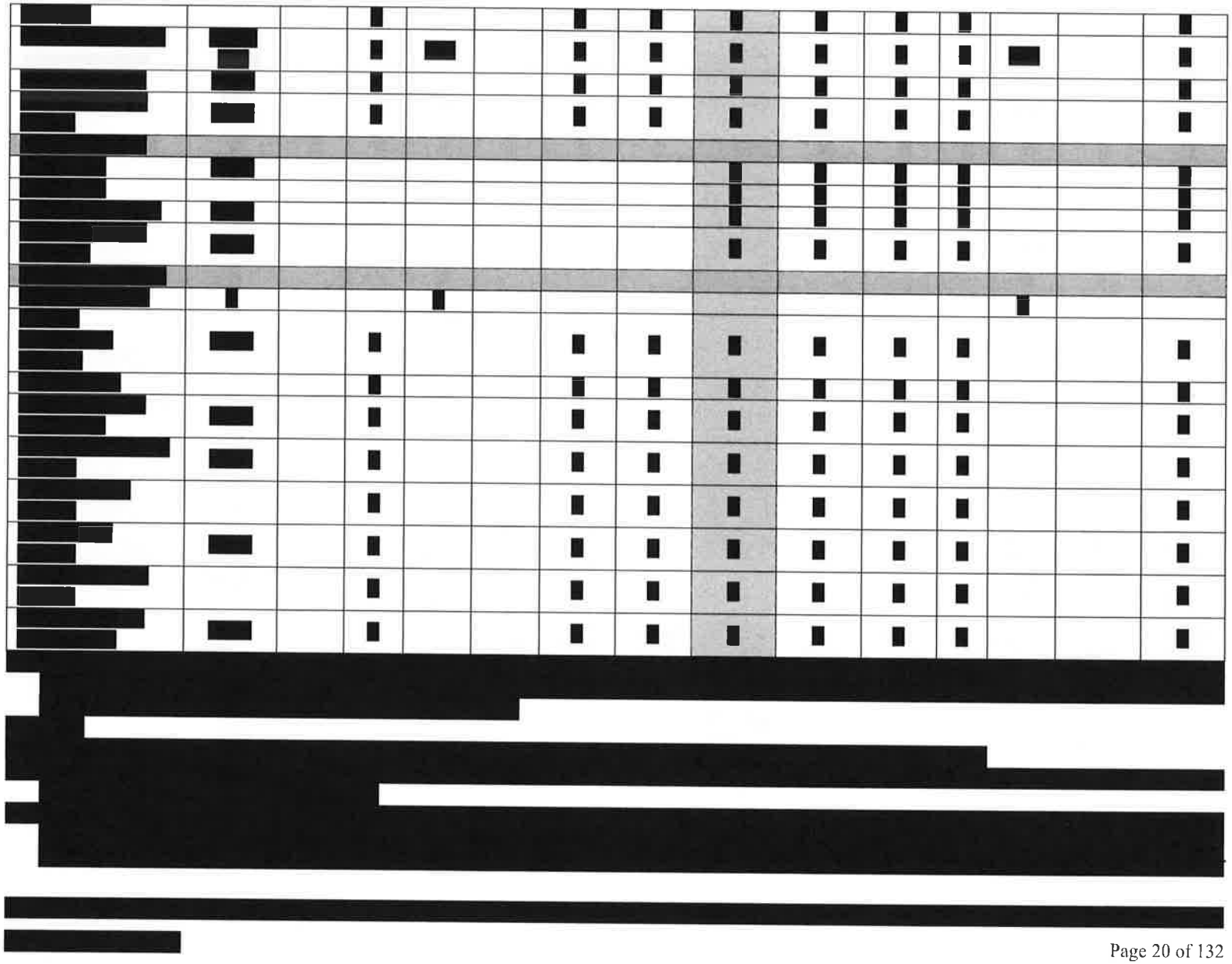

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Table 2-2 [redacted]

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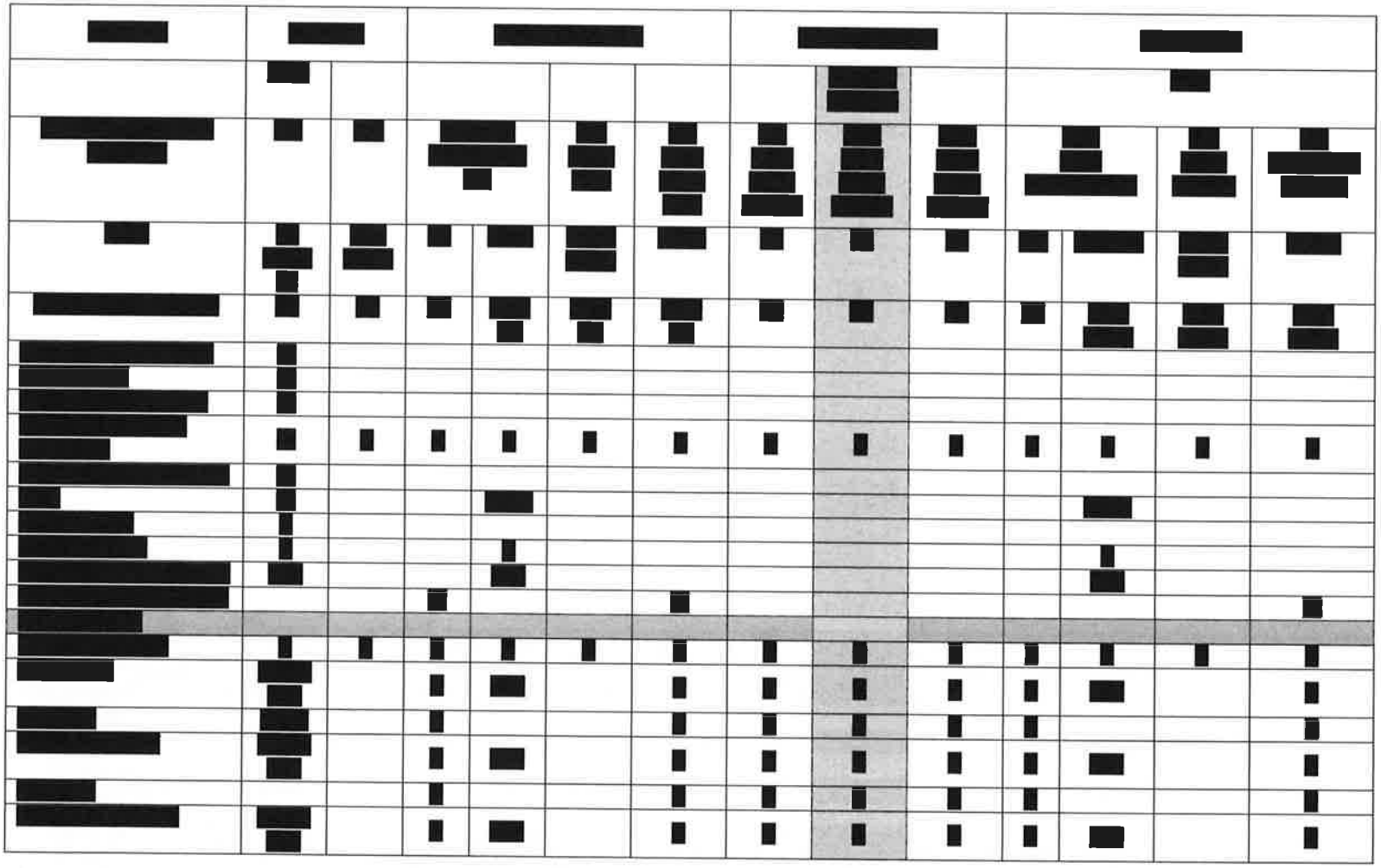

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3. TABLE OF CONTENTS

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5. INTRODUCTION TO THE CLINICAL INVESTIGATION

5.1. Background

Lips belong to the key features of the face, which together with eyes, nose, and cheek bones, are associated with youth and attractiveness. The shape and fullness of lips are influenced by many factors, including skeletal structure and subcutaneous fat distributions that can dramatically change their appearance over time.[1] In recent decades, a greater cultural value on youth and health, together with improved techniques, have resulted in an increase in cosmetic procedures.

Surgical and cosmetic techniques can change the appearance of the lips in several ways, whether to enlarge, reduce, or reconstruct after trauma or surgical resection. Lip augmentation procedure is one of the most sought-after procedures because it aims to return the youthful appearance and it is also able to improve the shape and fullness of the lips to make them more attractive based on the current fashion trends. Lip augmentation procedures usually include the implantation of additional material, either biologic or synthetic, into the lips, which can be injected, introduced by a threading technique, or by an open surgical approach.[2]

According to the statistics of the American Society of Plastic Surgeons for 2018,[3] the number of lip augmentation (other than injectable materials) procedures increased since 2000 by 66% to a total of 30,859 procedures in 2018. Even more significant is the use of soft tissue fillers in general, which were the second most frequent cosmetic minimally invasive procedure in 2018, with more than 2.6 million procedures performed during the year. Only botulinum toxin type A injection, with more than 7.4 million applications in 2018, was more frequent.[3]

Many fillers are used in cosmetic surgery, and they are generally registered as medical devices. A specific place can be reserved for autologous fat injections that may or may not use treatment kits intended for this purpose. Such kits are considered medical devices that need United States (US) Food and Drug Administration (FDA) clearance before commercialization. The duration of the fat injection effects varies greatly based on the graft survival. Harvested and prepared adipose grafts need to be injected with substantial overcorrection due to expected resorption, which can vary between 30 to 50% and is generally unpredictable.[4]

The effect of external fillers can be temporary, semipermanent, or permanent. The US FDA had only approved one permanent filler as of the end of year 2019 – polymethylmethacrylate beads suspended in bovine collagen with the addition of lidocaine.[5] It is sold under the brand name BellaFill® (Suneva Medical; previously known as ArteFill®); however, it is contraindicated for use in lip augmentation.[6]

Semipermanent fillers approved by the FDA include calcium hydroxylapatite sold as Radiesse® (Merz Aesthetics), which is expected to last approximately 18 months, and poly-L-lactic acid sold as Sculptra® Aesthetic (Galderma), which is expected to last about 2 years. Neither of these products have been approved by the FDA for injection into the lips nor are they recommended for injection into the lips as per their respective instructions for use (IFU).[7,8]

Temporary fillers include collagen and hyaluronic acid (HA) products. Several collagen fillers were approved by the FDA,[5] namely Evolence® Collagen Filler (Colbar Lifescience), CosmoDerm™ (Inamed), CosmoPlast™ (Inamed), Fibrel® (Serono), Zyplast® (Collagen Corp), and Zyderm® (Allergan); however, all these products have been discontinued by their manufacturers in the US market.[9]

Currently, the only fillers approved by the FDA for lip augmentation are those made with HA. These include Restylane® (Galderma), Restylane® Silk (Galderma), Restylane-L® (Galderma), Juvederm Volbella® XC (Allergan) and Juvederm® Ultra XC (Allergan).

Hyaluronic Acid (HA), also known as hyaluronan, is a long-chain, repeated dimer, of N-acetyl glucosamine and D-glucuronic acid polymer and it is the most abundant glycosaminoglycan found in the human dermis. It is a ubiquitous component of all mammalian connective tissues and is responsible for giving skin its volume while also binding collagen and elastin fibers into a supportive matrix that gives skin its structure. Due to this extended compatibility, HA can be used in humans without unacceptable adverse effects. The HA molecule (or hyaluronan) is a major component of the extracellular matrix. Due to its natural viscoelastic and hydrogel properties, hyaluronan is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction. Used as a dermal filler, HA has a long track record of safety data.

The persistence of HA in the tissues and its resistance to degradation can be obtained by chemical crosslinking. This does not affect the 2 specific functions of the molecule (carboxylic and N-acetyl functions) and allows modification of the rheological and physical properties of the HA, while maintaining the biocompatibility of the basic polymer.[10]

5.2. Study Device Name

RHA® 3.

5.3. Current Indication Statement

The study device under clinical investigation has been FDA approved for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs), in adults aged 22 years or older.[5] This study is investigating another indication.

5.4. Intended Purpose Statement

RHA® 3 injectable gel is intended to be used for injection in the vermillion body, vermillion border, and oral commissures to achieve lip augmentation and lip fullness in subjects 22 years or older.

5.5. Investigational Product Description

The device under clinical investigation is RHA® 3 manufactured by TEOXANE SA.[10,11]

[redacted]

[redacted]

5.5.1. Delivery System and Implantation

RHA® 3 is supplied in individual blisters containing a 1 mL treatment syringe with two 27 G x ½" needles. The content of the syringe is sterile and nonpyrogenic. It should not be resterilized or used if the package is opened or damaged.

[redacted]

5.5.2. Nonclinical Testing

RHA® 3 has been already approved by the FDA for another indication, it is considered biocompatible and details on nonclinical testing are provided in the IB,[10] IFU,[11] and the Summary of Safety and Effectiveness Data[12] for RHA® 3. [redacted]

5.5.3. Previous Clinical Experience

Details on previous clinical experiences are provided in the IB for RHA® 3.[10,11]

5.5.3.1. RHA® 3 EU Pilot Study

This study was a quantitative and comparative safety and effectiveness analysis of RHA® 2, RHA® 3, and RHA® 4 injectable dermal fillers in moderate and severe nasolabial folds treatment versus Conformité Européenne (CE)-marked comparators. It included 90 subjects with 2 visible

[redacted]

moderate or severe bilateral symmetrical nasolabial folds. Of these, 30 subjects were included in a group receiving either RHA® 3 or Juvederm® Ultra 4 (Allergan). The products were injected in nasolabial folds, one different product in each fold, in a split-face design. No significant difference was observed between the effects of tested medical devices and comparators, at any time point except after 18 months, where there was better improvement with RHA® 2, RHA® 3, and RHA® 4. The safety of RHA® 2, RHA® 3, and RHA® 4 was shown to be as good and equivalent to the comparators.[10,11]

5.5.3.2. RHA® 3 US Pivotal Study (IDE ref G140028)

This was a controlled, randomized, double-blinded, within-subject, multicenter, prospective clinical study of TEOSYAL® RHA 2 and TEOSYAL® RHA 3 versus Juvederm® Ultra XC in the treatment of moderate to severe nasolabial folds. TEOSYAL® RHA 2 and TEOSYAL® RHA 3 are the respective names of RHA®2, RHA®3, on the European Union market. A total of 174 subjects with moderate to severe bilaterally symmetrical aging defects in the nasolabial folds were randomized. The study was a split-face design with 1 nasolabial fold treated with the investigational product and the other nasolabial fold with the control device; 74 subjects were allocated to each treatment cohort, 26 subjects were untreated controls. Results showed non-inferiority of RHA® 2 and RHA® 3 compared to Juvederm®. Common Treatment Responses (CTR) and adverse events (AEs) were recorded and analyzed. For each category of CTR recorded in the diary (e.g., bruising, firmness, etc.), the proportion of subjects experiencing at least 1 CTR of each category was similar between treatment groups of each treatment cohort. Additionally, for the majority of CTRs experienced, the maximal severity experienced was "Mild" or "Moderate." For some CTRs, such as lumps/bumps and firmness, while the overall proportion of subjects with events recorded in their diary was similar, the proportion of subjects with events recorded on the last day of the diary was greater in the RHA® treatment groups compared to the Juvederm® treatment groups. By default, this led to comparatively higher rates of AEs associated with these CTRs in the TEOSYAL® RHA treatment groups. Importantly, virtually all treatment-related AEs were based on subjects' CTR diary entries, indicating that virtually all treatment-related AEs were typical (and expected) signs and symptoms observed after injection of a HA dermal filler.

A total of 27 subjects (36.0%; 95% confidence interval [CI] [30.5, 41.5]) in the RHA® 3 group and 26 subjects (34.7%; 95% CI [29.2, 40.2]) in the Juvederm® treatment group reported at least 1 treatment-related AE, respectively. No serious AEs (SAEs) or unanticipated adverse device effects (UADEs) were reported in the TEOSYAL® RHA 3/Juvederm® cohort. The proportion of subjects experiencing at least 1 treatment-related AE was lower in subjects with Fitzpatrick skin type IV-VI. In subjects with Fitzpatrick skin type I-III, treatment-related AEs were noted in 21 (47.7%) and 19 (43.2%) subjects in the TEOSYAL® RHA 3 and Juvederm® treatment groups, respectively. In subjects of Fitzpatrick skin type IV-VI, treatment-related AEs were noted in 6 (19.4%) and 7 (22.6%) subjects in the TEOSYAL® RHA 3 and Juvederm® treatment groups, respectively.[10,11]

5.5.3.3. RHA® Postmarketing Data

The following adverse events were reported as part of postmarketing surveillance on the use of RHA® 3 outside the US. These adverse events are listed in order of prevalence: lumps and bumps, firmness, unsatisfactory results, granuloma, implant migration papule, scarring, and anaphylactic reaction.

[redacted]

5.6. Control Device

The control device is [redacted]

[redacted] is a gel of HA generated by *Streptococcus* species of bacteria, chemically crosslinked with 1,4-butanediol diglycidyl ether (BDDE), stabilized and suspended in phosphate buffered saline at pH = 7 and concentration of 20 mg/mL with 0.3% lidocaine.

[redacted] is indicated for mid-to-deep dermal implantation for the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds. [redacted] is also indicated for submucosal implantation for lip augmentation in subjects over the age of 21 years.

[redacted] should be used according to its IFU.[13]

[redacted] Injection of RHA® 3 or [redacted]

[redacted]

Injection area: The TI will inject each device into the vermillion body, vermillion border, and oral commissures, as needed to achieve optimal aesthetic outcome.

Amount of filler to be administered: Up to 1.5 mL per lip (upper and lower) at each treatment (initial, touch-up, and retreatment).

The information about the injection technique, area of injection, and the amount of filler will be collected in the eCRF.

5.8. Justification for the Clinical Investigation

In the US, RHA® 3 is FDA approved for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as NLFs, in adults 22 years or older. Assuming a similar volumizing effect, the purpose of this study is to inject RHA® 3 into the lips to achieve lip augmentation and demonstrate that it is non-inferior to [redacted] for this indication in subjects aged 22 years or older. The goal is to show that treatment with RHA® 3 will result in added volume and fullness to the lips 12 weeks after the last treatment.

Expected risks include those associated with all skin injection procedures, such as injection pinpoint bleeding, pain, lightheadedness or fainting, nausea, and/or feeling flushed. Further risks are associated with the use of anesthetic agents, namely allergic reactions. Risks associated with the use of the RHA® 3 are expected to be similar to those associated with other HA dermal fillers.

In summary, the expected potential risks and benefits are generally similar to those observed with other HA dermal fillers.

5.8.1. Justification for the Clinical Investigation Design

The study is designed to evaluate RHA® 3 in lip augmentation procedures prospectively and to compare its safety and effectiveness to that of [redacted] The study design was selected to minimize bias by randomization and blinding of subjects and of the Blinded Live Evaluator (BLE), whose assessment will be used for the primary endpoint analysis. The comparison of the safety and effectiveness of the RHA® 3 and [redacted] fillers will be done between subjects and will include subjects from multiple sites [redacted].

6. CLINICAL INVESTIGATION PURPOSE, OBJECTIVES, AND ENDPOINTS

6.1. Clinical Investigation Purpose

The purpose of this clinical investigation is to evaluate the safety and effectiveness of RHA® 3 when compared to [redacted] to add volume and fullness to the lips 12 weeks after the last treatment (initial or touch-up).

6.2. Objectives

Objectives are summarized and mapped to the endpoints in Table 6-1.

6.2.1. Primary Effectiveness Objective

To assess the effectiveness (non-inferiority) of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation, 12 weeks after the last treatment (initial or touch-up).

6.2.2. Secondary Effectiveness Objective

- To assess the effectiveness of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation up to 52 weeks
- To assess the responder rate of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks
- To assess the subject satisfaction and patient-reported outcome of the aesthetic procedure (FACE-Q) with RHA® 3 versus [redacted] after lip augmentation up to 52 weeks
- To assess the Global Aesthetic Improvement Scale (GAIS) of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks

[redacted]

6.2.4. Safety Objective

- To assess the safety of RHA® 3 in subjects after lip augmentation

[redacted]

Table 6-1 Objectives Mapped to Endpoints

Objectives	Endpoints
Primary effectiveness	
• To assess the effectiveness (non-inferiority) of RHA® 3 versus [redacted] on adding volume and fullness to the lips in subjects seeking lip augmentation, 12 weeks after the last treatment (initial or touch-up)	• The effectiveness of RHA® 3 will be demonstrated if the change from Baseline for subjects treated with RHA® 3 is statistically non-inferior to the change from Baseline for subjects treated with [redacted] at 12 weeks after the last treatment as assessed by the BLE using the TLFS. The difference in the TLFS change from Baseline to 12 weeks will be used to establish non-inferiority [redacted] • [redacted]
Secondary effectiveness	
• To assess the effectiveness of RHA® 3 versus [redacted]® on adding volume and fullness to the lips in subjects seeking lip augmentation up to 52 weeks	• TLFS change from Baseline assessed: ○ By the BLE at Visit 4 and each visit at the study site afterwards ○ [redacted]
• To assess the responder rate of RHA® 3 versus [redacted]® after lip augmentation up to 52 weeks	• Responder rate calculated using TLFS assessed: ○ By the BLE at Visit 4 and each visit at the study site afterwards [redacted] A responder will be defined as a subject who has a ≥1-grade improvement on the TLFS
• To assess the subject satisfaction and patient-reported outcome of the aesthetic procedure (FACE-Q) with RHA® 3 versus [redacted] after lip augmentation up to 52 weeks	• Subject satisfaction using the Subject Satisfaction Scale at each visit at the study site starting at Visit 2 • FACE-Q scores for each module (satisfaction with lips and satisfaction with outcome) assessed by the subject at each visit at the study site [redacted]
• To assess the GAIS of RHA® 3 versus [redacted] after lip augmentation up to 52 weeks	• GAIS as assessed: ○ By the BLE starting at Visit 4 and each visit at the study site afterwards ○ [redacted]
[redacted]	[redacted]

[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
Safety	
• To assess the safety of RHA® 3 in subjects after lip augmentation	• Adverse events • Post-injection CTR [redacted] • [redacted]

[redacted]

6.3. Hypothesis

The TLFS change from Baseline of subjects treated with RHA® 3 will be statistically non-inferior to the change from Baseline of subjects treated with [redacted] for the assessment of lip augmentation and fullness as determined by the BLE using the TLFS at Week 12 after the last treatment (initial or touch-up). [redacted]

[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® 3. There are various types of risks associated with the injection of a HA dermal filler on the face or into the lips:

- Risks associated with all skin injection procedures
- Risks associated with the anesthetic agent (lidocaine) or other allergens
- Risks that are typically associated with RHA® 3, [redacted] and HA dermal fillers in general
- Other risks that are not typical but have been reported in the literature

6.4.1. Risks Associated With All Skin Injection Procedures

The following are risks associated with all skin injection procedures:

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

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

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

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

6.4.3. Risks That Are Typically Associated With RHA® 3, [redacted] and HA Dermal Fillers in General

The following have been associated with the use of HA dermal fillers. Although RHA® 3 has shown some differences compared to some of the HA dermal fillers currently available, they are expected to share a similar safety profile. The following risks are anticipated adverse device events when using a HA dermal filler:

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

[redacted]

[redacted]

For further and most recent information about RHA® 3, refer to the most recent version of the IB and the IFU.

7. CLINICAL INVESTIGATION DESIGN

This is a multicenter, double-blinded, randomized, prospective, controlled clinical study to identify whether RHA® 3 is non-inferior to [redacted] for lip augmentation at Week 12 after the last treatment (initial or touch-up).

The TI will evaluate the subject's lip fullness using the live validated 5-grade Teoxane Lip Fullness Scale (TLFS grade 1 to 5) at Screening (Visit 1, 0 Week) for eligibility of the subject for the study.

The BLE will evaluate the subject's lip fullness using the TLFS at Screening (Visit 1, 0 Week) to confirm eligibility and to establish a pretreatment score for assessment of effectiveness. This will be done independently of the TI. If the assessments of the TI and the BLE are the same or differ exactly by 1 point of the scale, the difference will be considered acceptable. The TI and the BLE need to agree on eligibility criteria of the subject (lip fullness grade 1 to 3). If the subject is eligible, the BLE's assessment will be used 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 of the scale, the subject will not be eligible.

[redacted]

Enrolled subjects will be randomly assigned in a 3:1 ratio to either the RHA® 3 or the [redacted] treatment group. Subjects will be blinded to the study treatment. The TI will administer the fillers, and if necessary, subjects will receive a touch-up treatment 4 weeks after the initial treatment to optimize the results. If the touch-up treatment is administered, the subject will be asked to come to the site for an additional visit [redacted] 4 weeks after the touch-up injection.

Subjects will be followed for 52 weeks after their last treatment (initial treatment or touch-up), at which point they will be offered retreatment with RHA® 3, regardless of their original treatment, provided that the TI deems the treatment to be appropriate and the subject agrees. Reasons for not administering the retreatment will be documented. The subject will then be followed for an additional 4 weeks before exiting the study. If the subject or the TI declines retreatment, this visit ([redacted] 52 weeks after the last treatment) will be considered the study Exit visit. For subjects with retreatment, the Exit visit will be [redacted] 4 weeks after the retreatment.

The TI will conduct safety and effectiveness evaluations at each study visit, which will occur at 4 weeks after the initial and touch-up treatment ([redacted] for subjects with touch-up), [redacted] 12 weeks [redacted] 36 weeks [redacted] and 52 weeks [redacted] after the last treatment, and 4 weeks ([redacted] after retreatment or until all treatment-related ongoing AEs have resolved or resolved with sequelae as per TI judgment or if follow-up is no longer possible.

A follow-up telephone call for safety will be performed at 3 days after each treatment ([redacted] initial, touch-up, and retreatment, respectively). Subjects will report their CTRs in a subject diary for [redacted] days after each injection. The diary will also include a list of selected AEs potentially associated with injection of dermal fillers for subjects to report if applicable. [redacted]

[redacted]

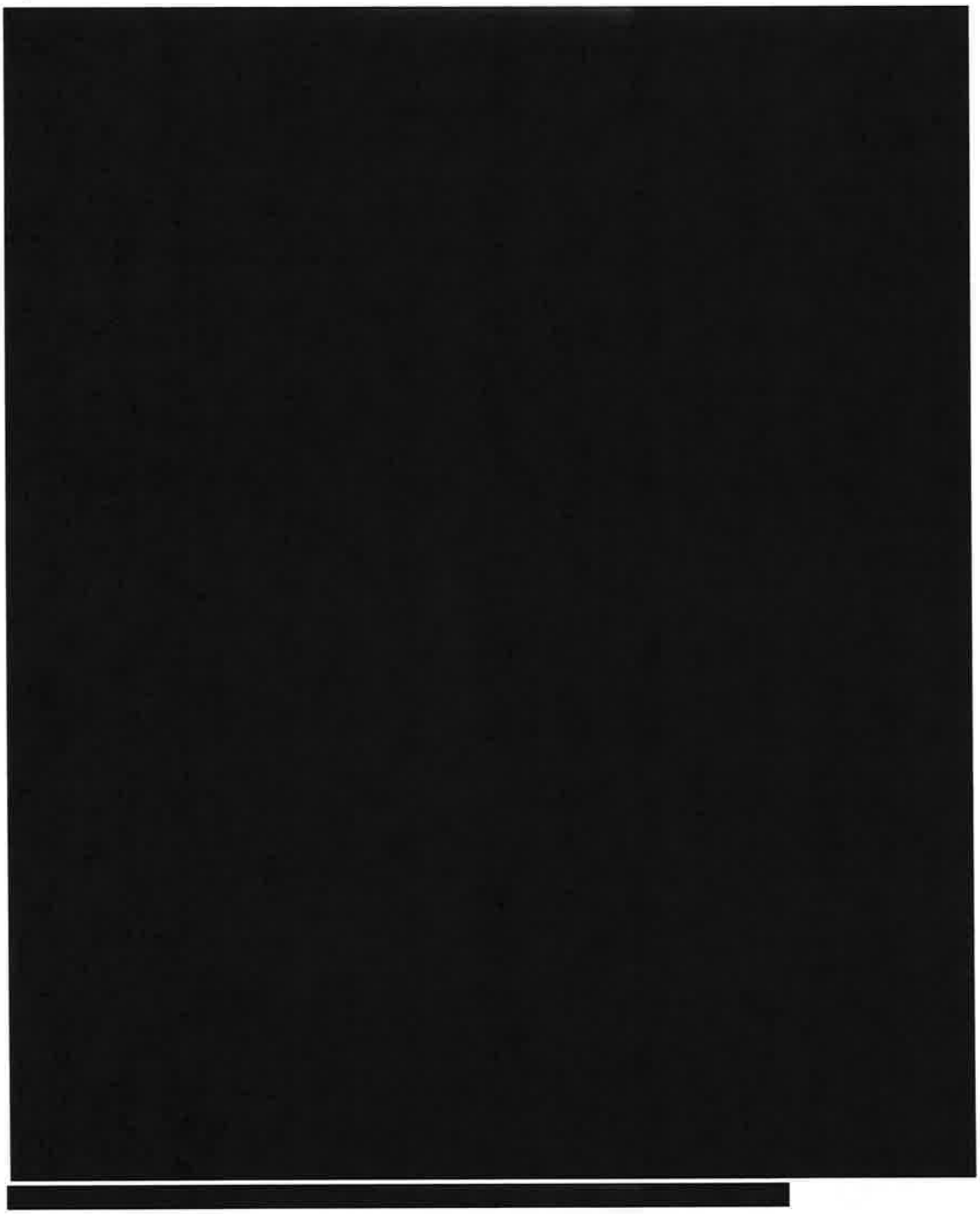
[redacted]

Subjects who had entered the study under earlier versions of the CIP (version [redacted] and earlier) and who do not agree with the extension of their participation in the study, to 52 weeks after last treatment, will be allowed to continue with the visits as originally planned (see Table 2-2). They will exit the study [redacted] 36 weeks after last treatment) or, if they receive retreatment [redacted] they will have a follow-up telephone call [redacted] and will exit the study [redacted] 4 weeks after retreatment.

A BLE will conduct assessments of effectiveness during the study, including assessment of the primary endpoint at Visit 4 (12 weeks after the last treatment). The BLE will conduct effectiveness evaluations [redacted]

[redacted]

Figure 7-1 Investigation Design



[redacted]

7.2. Clinical Investigation Enrollment

This study will enroll at least 200 subjects and a maximum of 202 subjects. Subjects must have lip fullness of grade 1 to 3 on the TLFS (ranging from 1 to 5) and desire at least 1 point of correction.

[redacted]

Eligible subjects will be randomly assigned in a 3:1 ratio to either the RHA® 3 or [redacted] group.

The TI will not be blinded, while the BLE and subjects will be blinded to treatment allocation.

[redacted]

All evaluations performed by the BLE will be performed completely separately from the TI;

[redacted]

Furthermore, to ensure that they remain masked 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.

[redacted]

[redacted]

7.3. Clinical Investigation Sites

The clinical study is to be conducted at 7 to 10 investigational sites in the US. [redacted]

7.4. Selection of Clinical Investigation Subject Population

Subjects who seek lip augmentation are possible candidates for the clinical investigation and will be screened for eligibility based on the inclusion and exclusion criteria below.

[redacted]

Vulnerable Subjects:

Part 21 CFR/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 seeking lip augmentation (realistic and achievable as per TI opinion).
4. [redacted]
6. Able to follow study instructions and complete all required visits.
7. 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 or the control device.
2. Known sensitivity to local anesthetics of the amide type including known or suspected lidocaine hypersensitivity, history of multiple severe allergies, or history of anaphylactic shock.
3. An outbreak of herpes labialis within 4 weeks of randomization or 4 or more outbreaks in the 12 months prior to randomization.
4. History of severe chronic systemic diseases, including but not limited to, poorly controlled diabetes mellitus (all types), congestive heart failure, severe liver disease, severe kidney disease, and others as judged by the TI.

[redacted]

6. Has an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound on the lips, in the area of the mouth, or the area around the mouth.

[redacted]

8. Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to randomization.

[redacted]

[redacted]

18. Medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or compliance of the subject and, in the judgment of the TI, would make the subject unsuitable for entry into this study).

[redacted]

21. Clinically significant alcohol or drug abuse or history of poor cooperation or unreliability.

[redacted]

[redacted]

[redacted]

8. INVESTIGATION PROCEDURES

8.1. Procedures by Visit

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

[redacted]

8.1.1. Visit 1 (0 Week)

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

Eligible subjects seeking lip augmentation will be screened for the study.

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

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

[redacted]

7. Both the TI and the BLE perform the TLFS assessment to assess eligibility
8. Assess inclusion/exclusion criteria

Signature of the written informed consent, collection of demographics, medical/surgical history, and prior/concomitant medication and washout of prohibited medications (see Section 9.4) may be performed up to 7 days before Visit 1. In any case, signature of the written informed consent must precede all study-related procedures.

[redacted]

[redacted]

Subsequently, the subject will be randomly assigned to RHA® 3 or [redacted] group; for details see Section 9.2.

The TI will **administer the allocated filler** maintaining the blinding described in Section 9.3 and according to the IB and Section 9.6.

[redacted]

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

Visit [redacted] is a telephone call 3 days after the initial treatment (3 days, 0 Week from the last treatment) for all subjects.

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

[redacted]

8.1.3. Visit [redacted] (4 Weeks After the Initial Treatment)

Visit [redacted] is performed at the site 4 weeks ± 3 days after the initial treatment.

[redacted]

If deemed necessary by the TI, an optional touch-up treatment can be administered at this visit. The touch-up treatment will be performed either with RHA® 3 or [redacted] depending on the treatment allocation at Visit 1.

[redacted]

[redacted]

[redacted]

8.1.7. Visit [redacted] (Primary Endpoint, 12 Weeks After the Last Treatment)

Visit [redacted] is at the site and will be scheduled 12 weeks after the last treatment (initial or touch-up). The assessments performed at this visit will be used for the primary endpoint evaluation. [redacted]

[redacted] the following assessments will be performed at Visit [redacted]:

[redacted]

3. BLE:
    a. TLFS
    b. GAIS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Assessments

8.2.1. Safety Variables

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

8.2.1.1. Common Treatment Response

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

[redacted]

8.2.1.2. Urine Pregnancy Test

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

[redacted]

[redacted]

[redacted]

8.2.1.5. Adverse Events

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

[redacted]

8.2.2.1. Teoxane Lip Fullness Scale

Lip fullness will be assessed by the TI and the BLE at time points in the schedule of events (Section 2.2) using the 5-point TLFS provided in Appendix B.

For eligibility purposes only: if the TI and BLE assessment differ by exactly 1 point on the TLFS, this is considered acceptable. If their assessment differs by more than 1 point, the subject will not be eligible.

8.2.2.2. 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 on your lip fullness by using the following scale" using the scale in Table 8-1.

Table 8-1 Subject Satisfaction Scale

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

8.2.2.3. Global Aesthetic Improvement

Global aesthetic improvement assessment will be performed by the [redacted] BLE [redacted] 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

8.2.2.4. FACE-Q

The validated subject-reported outcome measure FACE-Q scale[17] will be assessed as in the schedule of events (Section 2.2). Selected modules from the scale will be used for the purpose of this study:

- Satisfaction with lips: This scale measures the appearance of the lips with items that ask about size, shape, and fullness, as well as how the lips suit the face and how nice the lips look when smiling.

[redacted]

- Satisfaction with outcome: This scale measures a subject's satisfaction with the result of his/her most recent procedure.

[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. 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 or the control 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.

[redacted]

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

9.2. Randomization

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

[redacted]

[redacted]

9.3. Blinding/Unblinding Clinical Investigation Plan

9.3.1. General Blinding

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

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

9.3.2. Blinded Procedures

Investigators and research staff will make concerted efforts to withhold all information regarding the assigned treatment from the subject (including family, friends, or caregivers). Subjects will be required to wear an eye mask while the TI or designee is preparing the filler and during the injection.

All evaluations performed by the BLE will be performed separately from the TI [redacted]

Furthermore, to ensure that they remain blinded and unbiased when making their assessments during the study, the BLE, TI, and the subject will not be allowed to discuss each other's study assessments.

[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. Pretreatment Procedures and Tests

The procedures and tests to be performed prior to randomization are described for Visit 1 (0 Week).

[redacted]

[redacted]

9.5. Baseline Evaluations and Data Collection

All of the data collected at Visit 1 (0 Week) prior to randomization will be defined as Baseline for the purpose of the study and further analysis.

[redacted]

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

9.6. Clinical Investigational Product Treatment

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

[redacted]

[redacted]

9.6.1. Study Device

The study device is RHA® 3 [redacted] Please see Section 5.5 and the IB[10] for further information.

9.6.2. Control Device

[redacted] will be used as the active treatment control for the initial treatment and touch-up treatment, if applicable, in subjects randomly assigned to [redacted] group. [redacted] is approved for use in lip augmentation in the US and will be used according to the IFU.[13]

9.6.3. Injection of RHA® 3 or [redacted]

[redacted]

Injection area: The TI will inject each device into the vermillion body, vermillion border, and oral commissures, as needed to achieve optimal aesthetic outcome.

Amount of filler to be administered: Up to 1.5 mL per lip (upper and lower) at each treatment (initial, touch-up, and retreatment).

Information about injection technique, area, and amount of filler will be collected in the eCRF.

[redacted]

[redacted]

[redacted]

10. ADVERSE EVENTS

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

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

[redacted]

All observations and clinical findings, including the nature, seriousness, severity, and relationship to the study or to the control device and/or the procedure, will be assessed by the TI 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 any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, whether or not related to the study device, the control device, or the study procedures.

10.1.2. Adverse Device Effects

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

[redacted]

[redacted]

10.1.6. Device Malfunction

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

[redacted]

10.2. Evaluation and Assessment

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

10.2.1. Relationship to Device

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

[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]

10.3.4. Device Malfunctions Reporting

Device malfunctions will be reported using the Device malfunction 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 or the control 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.

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

[redacted]

10.5. Data Monitoring Committee

Not applicable.

[redacted]

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 describes the details of the analyses to be conducted will be written prior to database lock. The SAP will be submitted to the FDA during the course of the study.

[redacted]

11.1. Analysis Populations

The following 4 analysis populations are planned for this investigation:

- Screening: All subjects who provide informed consent and demographic and/or Baseline screening assessment results, regardless of the subject's randomization and treatment status in the investigation.
- Safety: All subjects who receive at least 1 treatment with RHA® 3 or [redacted]
- Modified intent-to-treat (mITT) analysis set will be used for efficacy analysis. The mITT set is based on the conventional ITT:

  [redacted]

[redacted] Per-protocol (PP): All subjects in the mITT population who receive treatment and do not have any major CIP deviations. [redacted]

[redacted]

[redacted]

11.2. Sample Size Determination

The primary endpoint of the study is the difference in the TLFS change from Baseline to 12 weeks after the last day of treatment between subjects treated with RHA® 3 and those treated with [redacted]

[redacted]

11.3. Subjects and Demographics

[redacted]

11.3.2. Clinical Investigation Plan Deviations

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

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

[redacted]

Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected [redacted]

11.4. Effectiveness Analyses

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

The primary analysis will be performed as follows: to demonstrate non-inferiority of RHA® 3 compared to [redacted] at 12 weeks after the last treatment; the difference in the change will then be tested between groups (RHA® 3 minus [redacted]

Secondary Effectiveness Analysis:

Secondary analyses will be of descriptive nature. [redacted]

For the parameters hereafter:

- TLFS: [redacted] BLE
- Responder rate based on TLFS
- GAIS: [redacted] BLE, [redacted]
- FACE-Q scores for each module: Subject (after data standardization, as detailed in SAP)
- Subject satisfaction score: Subject (quantitative scores and categories as described in SAP)

[redacted]

For each product, summary statistics (mean, minimum, maximum, SD, and 95% CI of the mean) for the above-mentioned parameters will be provided/presented for each study visit.

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

[redacted]

[redacted]

11.5. Safety Analyses

[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 who experience at least 1 AE that are device related (ADEs) will be presented.

[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
- 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® 3 and [redacted] as per the CIP and their respective IFU 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.
- Records of each subject's case history and exposure to the study or control device, [redacted]

[redacted]

[redacted]

12.1.4. Prohibition of Promotion

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

[redacted]

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

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]

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]

13.3. Source Documents

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

[redacted]

13.4. Electronic Case Report Forms

This investigation will use an eCRF as the primary data collection instrument and will record data by electronic capture. All data requested on the eCRF must be entered. All missing data must be explained. If an entry on the eCRF is left blank because the procedure was not done or the question was not asked, a query will be generated for the site data entry staff. If any entry error has been made, correct and enter the correct data in the eCRF. All such changes are recorded in the audit and queries report. All electronic data capture systems must be 21 CFR Part 11 and/or 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] access to information and clinical supplies related to the investigation. CRAs will verify data entered into the eCRFs against hospital records or other source documents to ensure accuracy and completeness of the eCRFs for each subject. Treating investigators and their staff agree to assist the monitors in their activities. Requests may be made to review subject charts by the sponsor or sponsor's designee so that CIP adherence and source documentation can be verified.

[redacted]

14. ETHICS AND REGULATORY COMPLIANCE

14.1. Conduct of the Clinical Investigation

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

14.2. Conflict of Interest

The FDA reviews the financial interests of TIs (or subinvestigators and their spouses and/or dependent children) in an IDE investigation. If the FDA believes that the financial interests of any TI 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), their spouses, 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 CFRs Part 11, 50, 54, 56 and 812), ISO 14155, the Declaration of Helsinki, and the ICH guidelines.

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

[redacted]

Should photograph(s) of a subject's face be used for potential publication, promotions, or other purposes, it must only include parts of the face that are necessary to illustrate or document the effect of the dermal filler used as per this study. The subject will be asked whether 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's designee's SOPs, the sponsor or sponsor's designee may request access to all investigation records, including source documents, for inspection. The TI will ensure the capability for inspections of applicable investigation-related facilities (e.g., catheterization laboratory, surgery suite, diagnostic laboratory, 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 products will be stored at each site according to the respective IFU and IB and records will be kept to document product storage and management; sponsor-provided unique identification numbers and labeling identifying them as IDE products will be clearly visible. All sites will maintain a device accountability log that will match subjects to a particular study device by a unique manufacturer number. At the conclusion of the investigation, all study and control devices will be returned to the sponsor.

14.11. Public Domain Access to the Clinical Investigation

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

15. GENERAL CONSIDERATIONS

15.1. Discontinuation of the Investigation

Discontinuation of individual subjects is described in Section 9.7.

[redacted]

[redacted]

[redacted]

17. ATTACHMENTS

17.1. Investigator's Agreement

CLINICAL INVESTIGATION PLAN NUMBER:	[redacted]
CLINICAL INVESTIGATION PLAN TITLE:	A Controlled, Randomized, Double-blinded, Between-subject, Multicenter, Prospective Clinical Study to Evaluate Safety and Effectiveness of RHA® 3 versus [redacted] for Lip Augmentation
AMENDED CLINICAL INVESTIGATION PLAN:	22-Mar-2021

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

Treating Investigator:

Printed Name:

_____

Signature:

_____

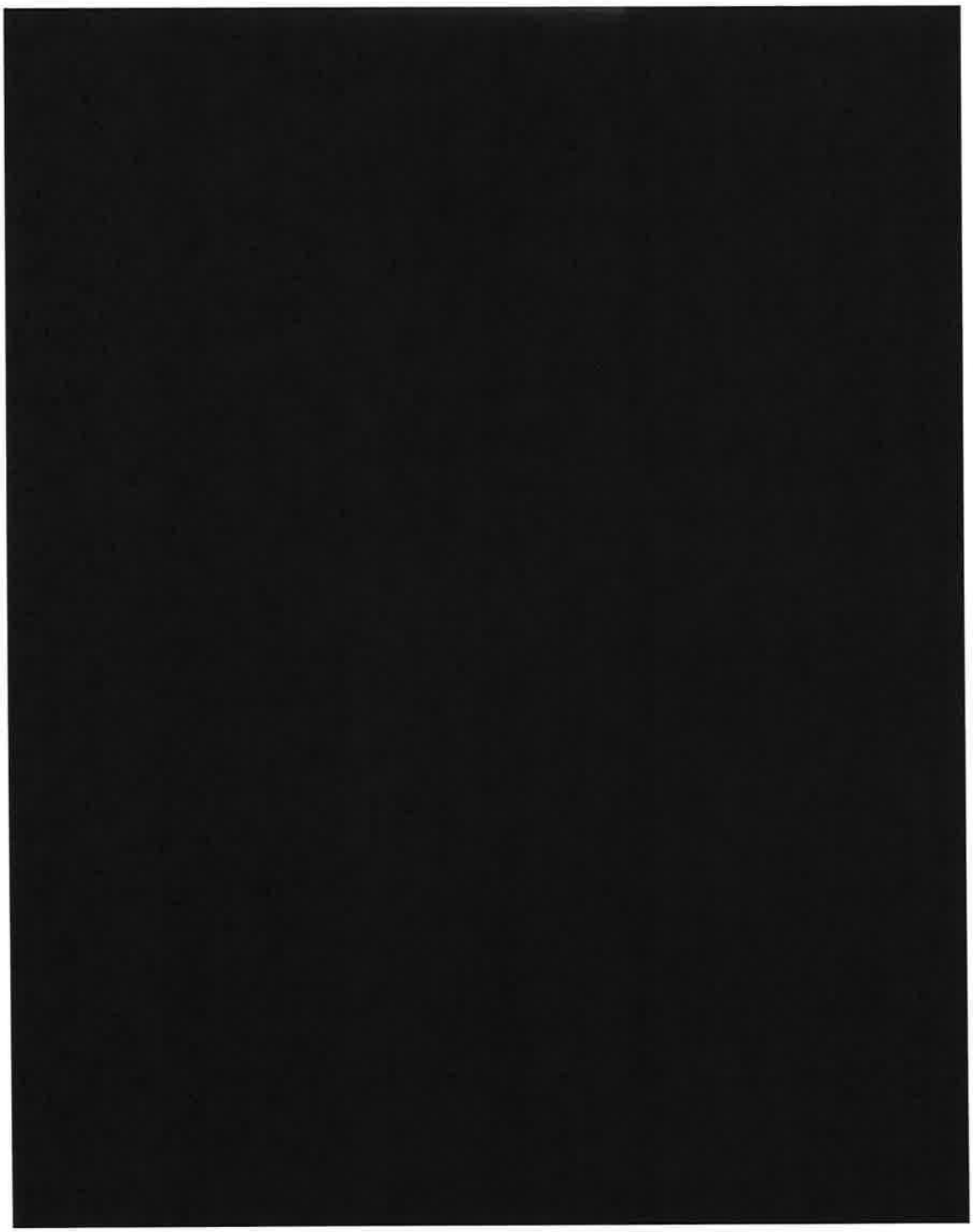
Date:

_____

[redacted]

[redacted]

[redacted]



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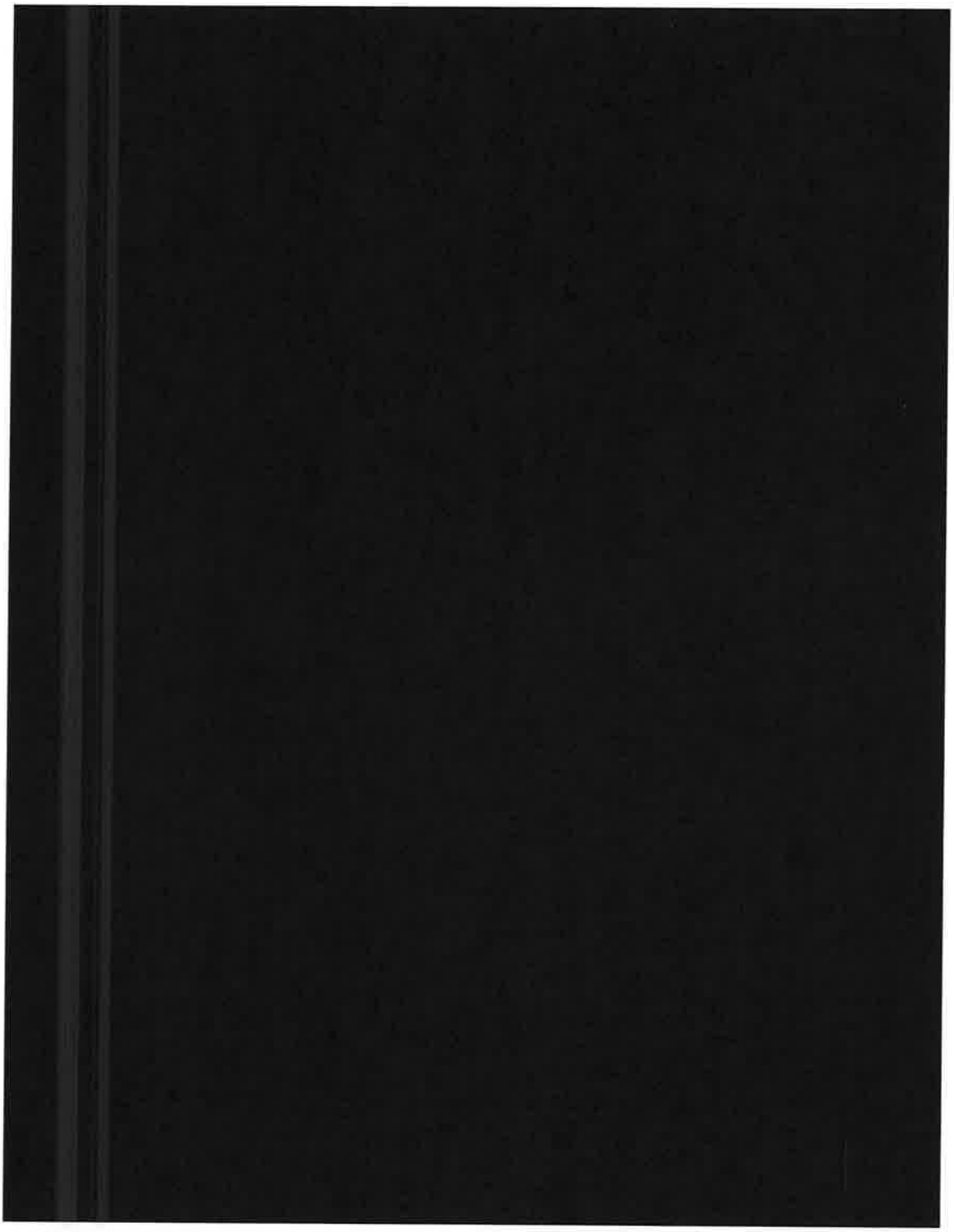
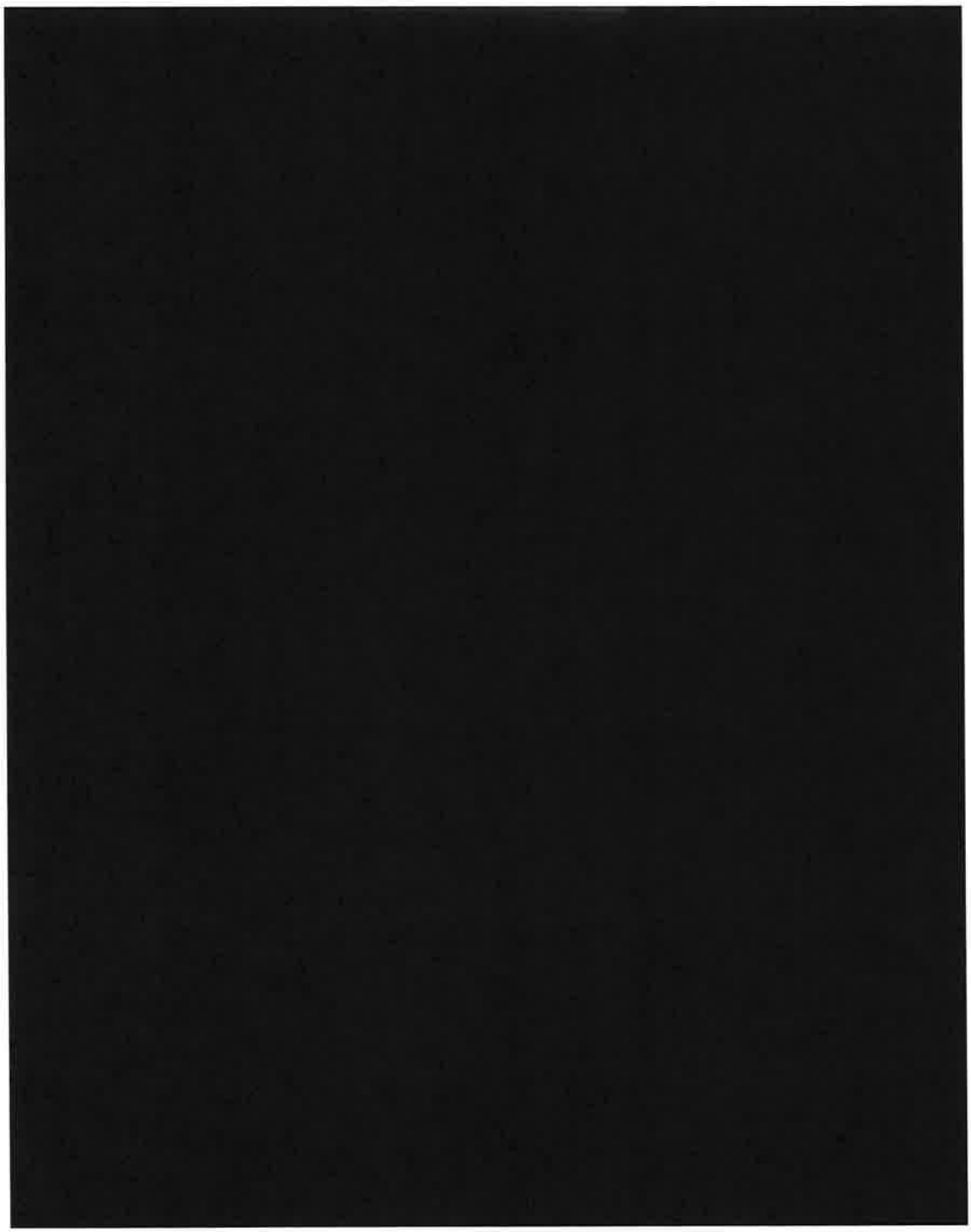
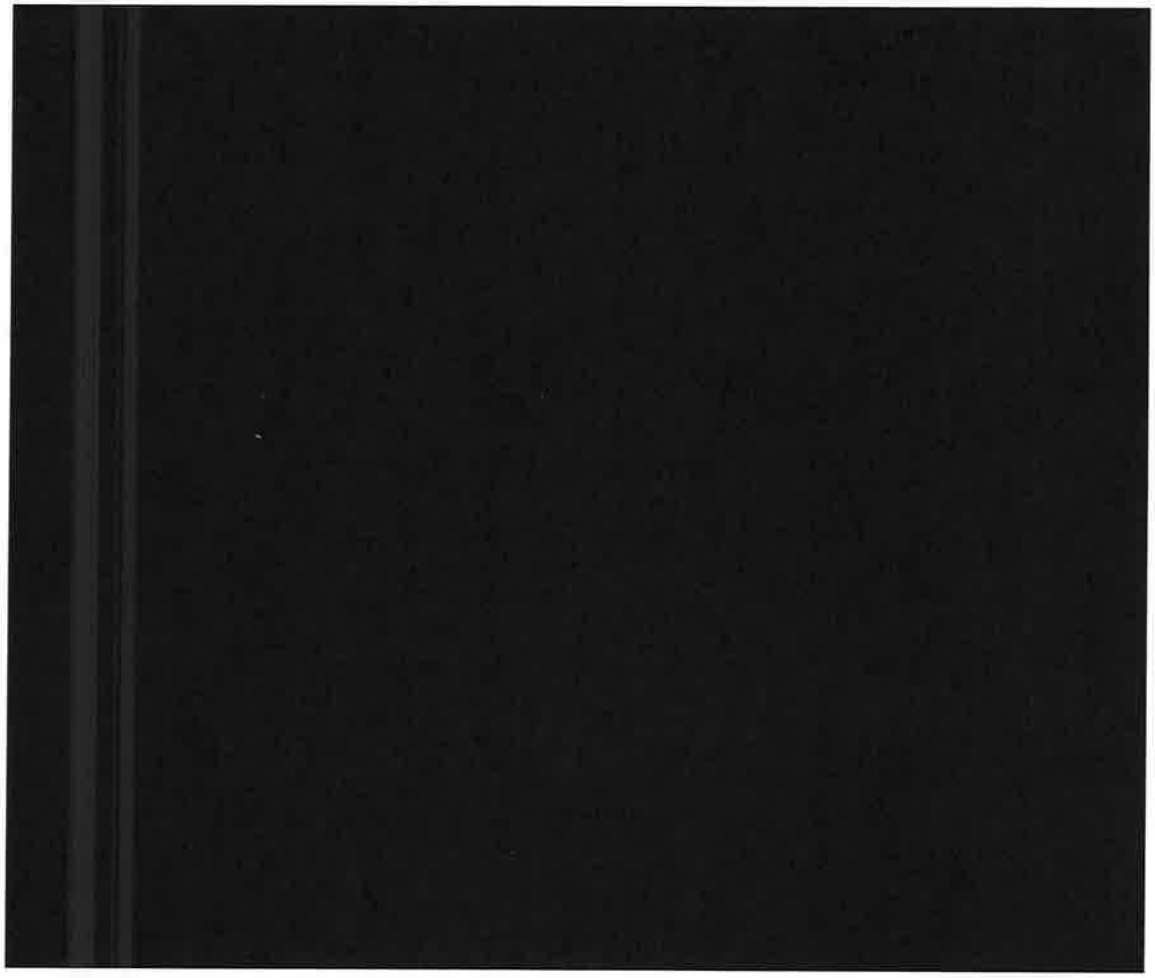
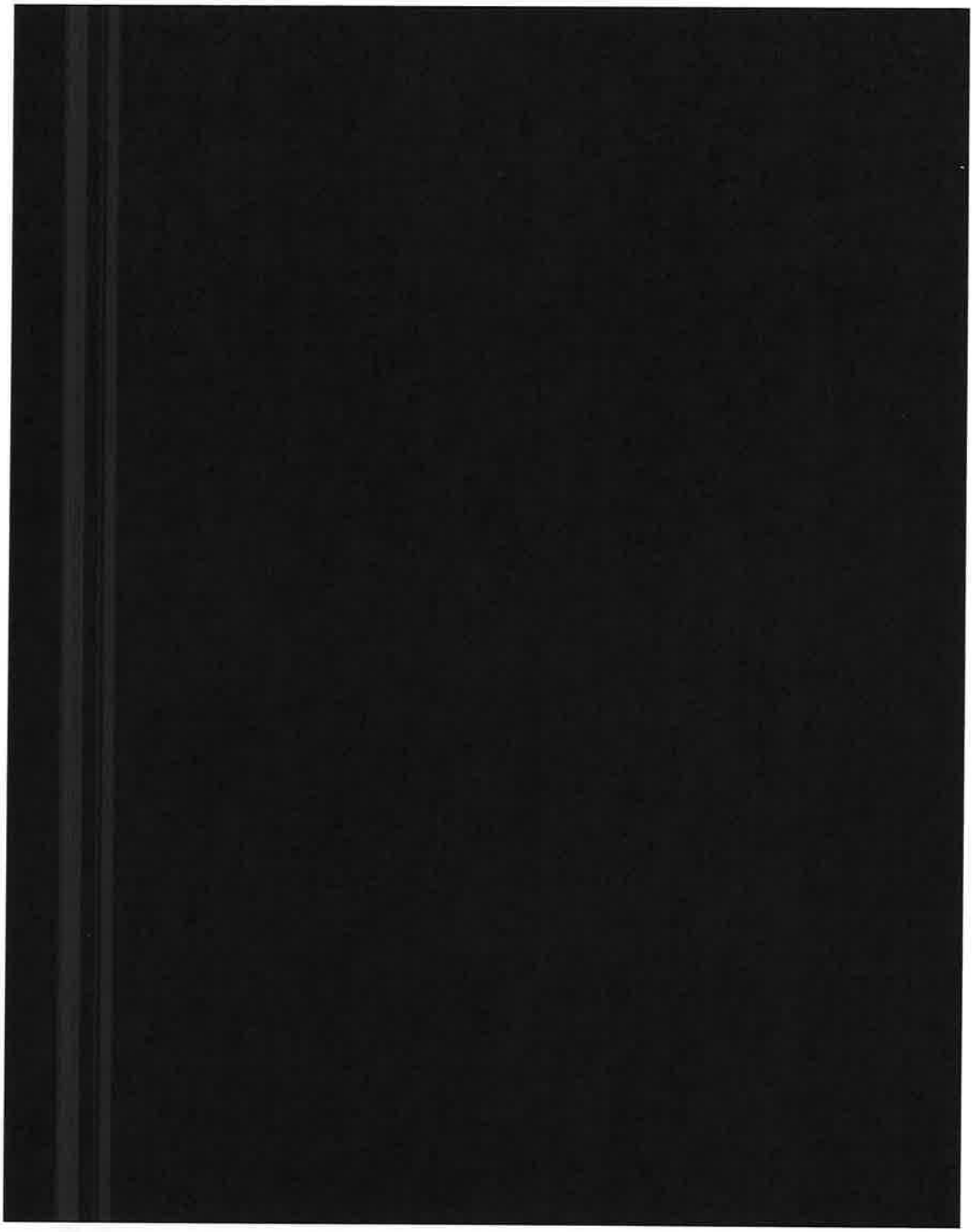




18.2. Appendix B



18.3. Appendix C



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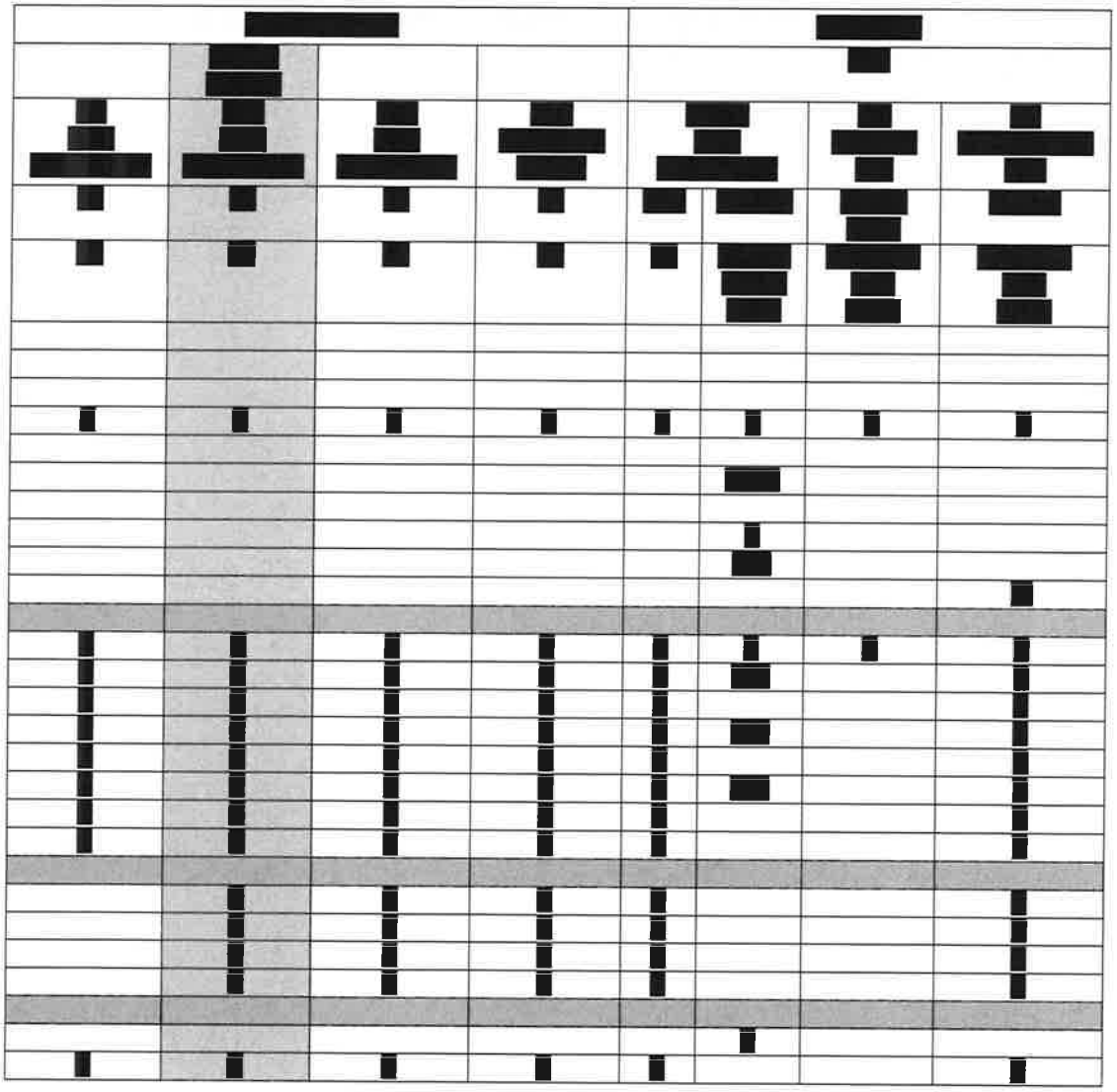

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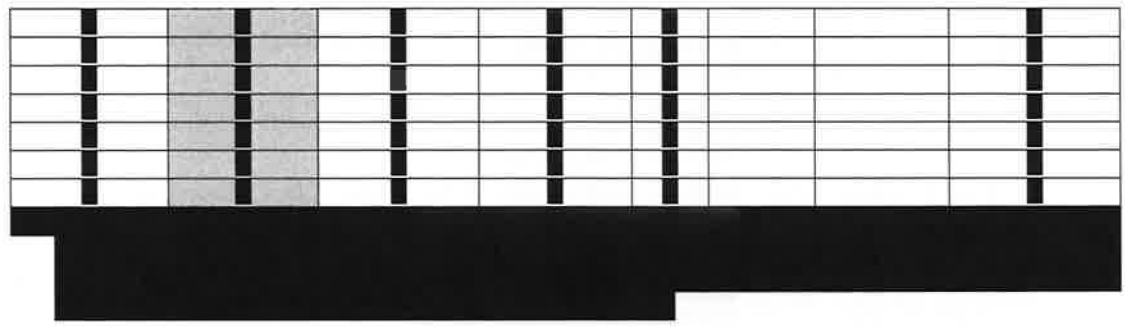

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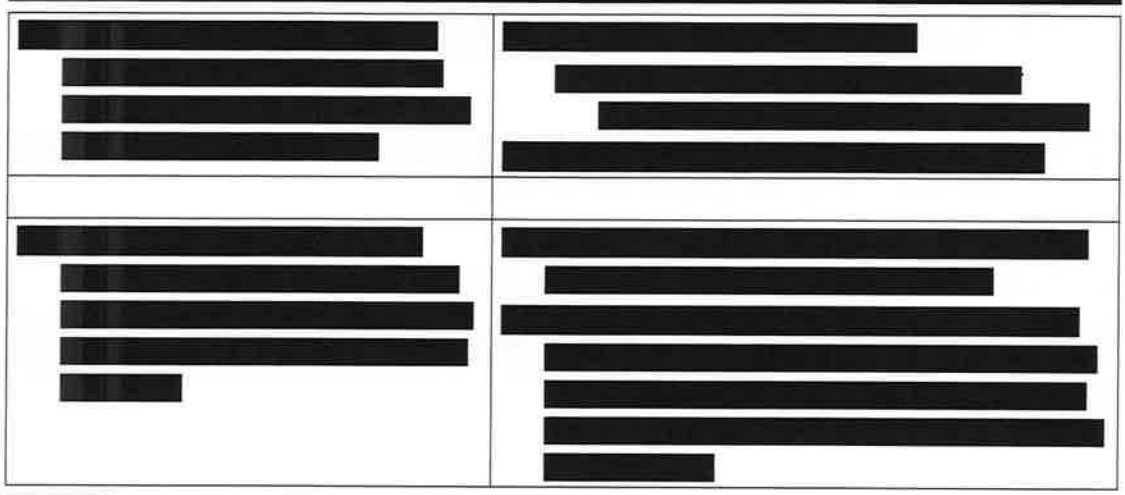

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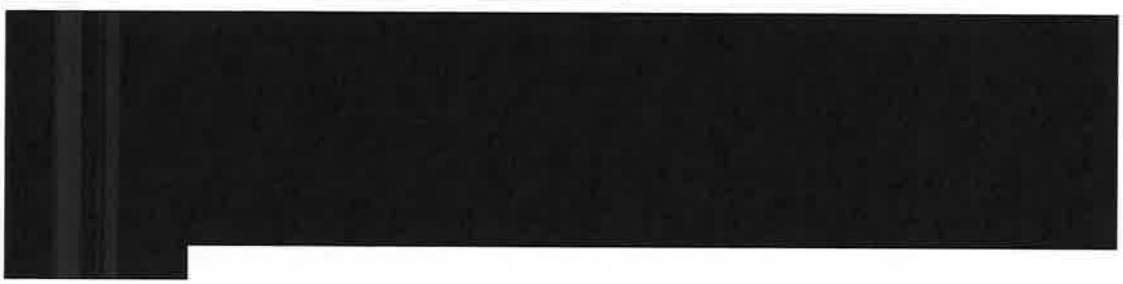

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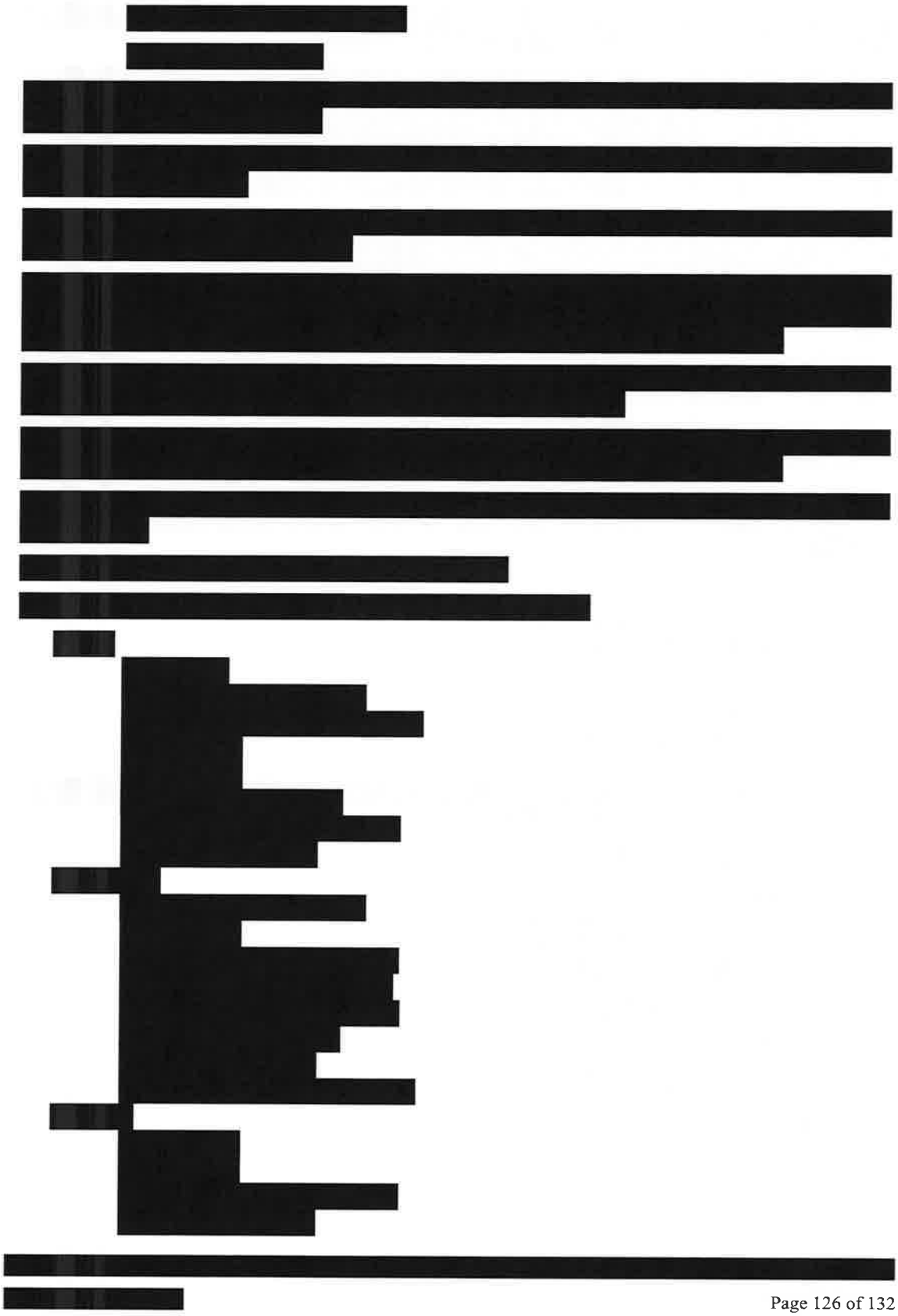

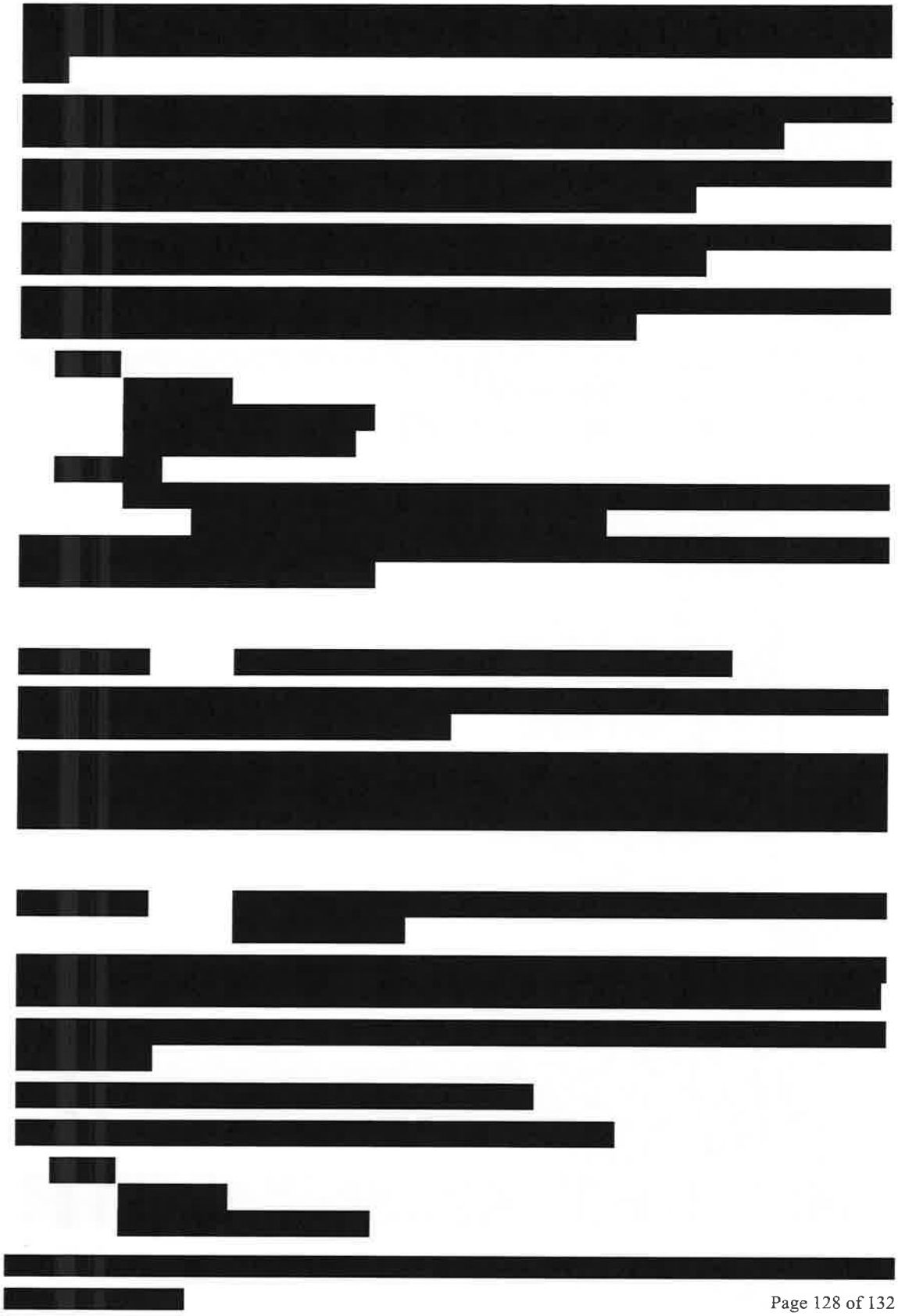

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