CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 05DF2209

This document contains confidential, proprietary information

TITLE PAGE

A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of *Restylane Lyft Lidocaine* for jawline definition.

Clinical Trial Number (CTN): 05DF2209

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Statements of compliance

The study should be conducted in compliance with the clinical trial agreement, the clinical study protocol, good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2020 should be followed. The International Conference on Harmonisation (ICH) guideline for GCP (E6 (R2)) should be followed as applicable for medical device. The study should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[1].

[1] (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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Contract Research Organization (CRO):	PPD

Details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Study Protocol (CSP) amendment.

SYNOPSIS

Clinical Study Title:	A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of *Restylane Lyft Lidocaine* for jawline definition.
Clinical Trial Number:	05DF2209
Country involved and Planned Number of Study Centers:	Canada No. of Study Centers: Approximately 10
Clinical Study Design:	• A prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter phase IV study to evaluate effectiveness and safety of *Restylane Lyft Lidocaine* for jawline definition. • Treatment in accordance with approved Instructions for Use in Canada. • Approximately 140 subjects will be included in the study. • Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. A follow-up telephone call should be made 72 hours after treatment. • Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. If optional touch-up is performed, a 72-hour follow-up telephone call and follow-up visit after 1 month should be scheduled. • Effectiveness and safety data will be collected for up to 12 months (48 weeks) after the last treatment including follow up visits at 1, 3, 6, 9 and 12 months. • Subjects in the No Treatment group will be offered optional treatment after 12 months from baseline (Day 1) followed by a safety assessment 2 weeks after the optional treatment. Subjects who decline treatment after 12 months will end their study participation. • Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments. Safety assessments will be performed by non-blinded personnel.
Indication:	*Restylane Lyft Lidocaine* is an injectable implant, intended to be used for jawline treatment within the approved indication (i.e., facial tissue augmentation) in adults.
Total Number of Subjects (Planned):	Approximately 140 subjects will be randomized (3:1) to Treatment or to No Treatment group.
Effectiveness Objectives and Endpoints:	The primary objective of the study is to assess the effectiveness of *Restylane Lyft Lidocaine* versus a no treatment control in jawline definition by comparing Galderma Jawline Scale (GJS) response rates. <u>Primary Endpoint:</u> Responder rate based on the Blinded Evaluators' live assessment of the GJS at 3 months after last treatment for the Treatment group or after baseline for the No Treatment group. A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently.

	The secondary objective is to assess the effectiveness of *Restylane Lyft Lidocaine* for jawline definition. Secondary Endpoints: 1. Responder rates based on the Blinded Evaluator's live assessment using the GJS at 6, 9 and 12 months after last treatment for the Treatment group or after baseline for the No Treatment group. *A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently, at each of the timepoints.* 2. Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS) on both jawlines concurrently, as assessed live by the Subject and Treating Investigator separately at 3, 6, 9 and 12 months after last treatment for the Treatment group and after baseline for the No Treatment group. C C I [redacted] One month is defined as 4 weeks in the study.
Safety Objectives and Endpoints:	To evaluate the safety of *Restylane Lyft Lidocaine* by assessments of adverse events (AEs) by the Treating Investigator throughout the study period. • Incidence, intensity, duration and onset of AEs collected during the study period. • Pre-defined, expected, post-treatment events reported for 28 days from treatment as recorded in the subject diary.
Subgroup Analyses:	Not applicable.
Clinical Study Duration:	First subject first visit (FSFV) to last subject last visit (LSLV): Approximately 18 months including 4 months recruitment period. • Treatment group: o Up to 21 days screening

	○ Treatment at baseline (Day 1) and TC at 72 hrs after initial treatment. ○ Optional touch-up at 1 month and TC at 72 hrs after touch-up. ○ Data collection and safety follow-up visits at 1, 3, 6, 9 and 12 months after last treatment. • No Treatment group: ○ Up to 21 days screening ○ Data collection and safety follow-up visits at 1, 3, 6, 9 and 12 months after baseline. ○ Optional treatment at 12 months after baseline followed by a safety assessment at 2 weeks after optional treatment. One month is defined as 4 weeks in the study.
Inclusion Criteria:	1. Male and female adults willing to comply with the requirements of the study and providing a signed written informed consent. 2. Consent the use of facial images for marketing purposes and educational material as described in the Informed Consent Form (ICF). 3. Subject with moderate to very severe (Grade 2 to 4) on the Galderma Jawline Scale (GJS) with no more than one grade difference between the left and right side at baseline as assessed by the Blinded Evaluator. 4. Subject is willing to abstain from any other facial, submental, and/or neck aesthetic procedure(s) or implant for the duration of the study. 5. Female of childbearing potential with a negative urine pregnancy test before treatment.
Exclusion Criteria:	1. Subjects presenting with known/previous allergy or hypersensitivity to hyaluronic acid (HA) filler, lidocaine or other amide-type local anesthetics. 2. Subjects presenting with known/previous allergy or hypersensitivity to streptococcal proteins. 3. Subject with bleeding disorders or subjects who are taking thrombolytics or anticoagulants. 4. Subject who is using substances that affect platelet function CCI [redacted] 5. Subjects using immunosuppressants. 6. Subjects with a previous implant other than HA in or near the intended treatment site. 7. History of other facial treatment/procedure in the previous 6 months HA in or near the intended treatment site that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g., Botulinum toxin injections or another HA filler. 8. Subject with a prior surgical procedure in the treatment area which, in the opinion of the Treating Investigator could interfere with the study.

	9. Presence of any disease or lesions near or on the area to be treated, CCI [redacted] 10. Presence of any condition which, in the opinion of the Treating Investigator, makes the subject unable to complete the study per protocol, CCI [redacted] 11. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 12. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company. 13. Participation in any other interventional clinical study within 30 days before treatment.
Investigational Product:	*Restylane Lyft Lidocaine* The sterilized gel contains 20 mg/mL crosslinked HA and 3 mg/mL lidocaine hydrochloride in a physiological buffer.
Comparator/Placebo Product:	No treatment control group.
Treatment area:	In the study, the treatment area extends from the mandibular angle, through the jawline and including the post- and pre-jowl area (from tip of ear to tip of chin) in order to create a smooth correction that blends well with the adjacent structures.
Treatment regimen:	Treatment group: Treatment will be administered at baseline (Day 1) and one optional touch-up treatment at 1 month after initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvement. Topical or local injection anesthetic may be used at the discretion of the Treating Investigator. No Treatment group: Optional treatment will be administered at 12 months. Use of anesthesia is left to the discretion of the Treating Investigator.

Mode of administration:	The injection technique is at the Treating Investigator´s discretion in the deep dermal and subcutaneous tissue. Deeper injections into the subcutaneous fatty tissue or supraperiosteal layer are appropriate for areas with adequate soft tissue support and soft tissue cover such as jawline. CCI [redacted] The correction site should be massaged to conform to the contour of the surrounding tissues. For each treatment site a maximum dosage of 2 mL per treatment session is recommended (i.e., 2 mL per side of the face per treatment session).
Statistical Method:	In general, all effectiveness, safety and baseline characteristics variables will be presented using descriptive statistics within each treatment group, and graphs as appropriate. Continuous endpoints will be summarized using descriptive statistics, e.g., mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level. For the primary effectiveness analysis, a responder will be defined as a subject with at least 1 point improvement from baseline based on the GJS. For a significant result, the two-tailed p-value of the comparison of responder rates between the treated and untreated subjects at 3 months using the Fisher's exact test needs to be smaller than 0.05. Secondary analyses will include analysis of responders at each visit. Robustness of the results of the primary endpoint and adverse events analysis will be investigated for the PP population. All formal statistical testing will be performed at a significance level of 5% (2-sided), primary objective. All other secondary effectiveness analyses will be done descriptively as appropriate.
Sample Size:	A total sample size of approximately 140 subjects will be included in this study. For the responder rate in GJS, a Fisher's exact test using a 5% two-sided significance level will have approximately 90% power to demonstrate difference between a responder rate of 70% in the *Restylane Lyft Lidocaine* group, and a responder rate of 35% in the No Treatment control group when the sample sizes are 105 and 35, respectively.

	Accounting for 10% dropouts, approximately 140 subjects need to be randomized in a 3:1 ratio.
Interim Analysis:	No formal interim analysis will be performed. However, analysis of data could take place at a time point after the last collection of primary endpoint data.
Effectiveness Assessments	• Blinded Evaluator GJS • Treating Investigator GJS (for assessing subject treatment needs only) • Treating Investigator GAIS • Subject reported GAIS [redacted]
Safety Assessments	• Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the subject or detected during each examination. • A subject diary will be dispensed to the Treatment group for daily completion over the first 28 days after each treatment to record the following pre-identified symptoms: bruising, redness, pain, tenderness, lumps/bumps, itching, swelling and other. Information from the diary will be presented separately from other AEs. • Device deficiencies will be assessed at treatment visits.

CLINICAL STUDY FLOW CHART

Figure 1 Study Flow Chart

All subjects should complete the visits stated in the flow-chart below. Subject receiving treatment should also complete Safety follow-up visits by Phone and additional follow-up visits as indicated. Subjects in the No Treatment group will be offered an optional treatment after 12 months from baseline (Day 1) followed by a safety assessment 2 weeks after the optional treatment.

[1]If no optional treatment, the visit will be the EOS visit: EOS = End of study; FUP = Follow-up; hrs = hours; TC = Telephone call; Tx = Treatment; TU = Touch-up

SCHEDULE OF EVENTS

Table 1 Schedule of events – Treatment group

Procedure	Visit 1	Visit 2	Visit 2a	Visit 3	Visit 3a[4]	Visit 3b[4]	Visit 4	Visit 5-6	Visit 7
	Day -21 to 1	Day 1	72 hrs after Tx (±24 hrs)	1 month after Tx (+7 days)	72 hrs after optional TU (±24 hrs)	1 month after optional TU (+7 days)	3 months after last treatment (±14 days)	6 and 9 months after last treatment (±14 days)	12 months after last treatment (±14 days)
	Screening	Baseline/ Tx	TC	Follow-up/ Optional TU	TC	Follow-up	Follow-up	Follow-up	Follow-up/ EOS
Informed Consent	X								
Med. Hx/prior therapies	X	X[1,2]							
Demographics	X								
Height/Weight[9]		X[1]							X
Inclusion/Exclusion Criteria	X	X[1,2]		X[1,5]					
Urine pregnancy test[3]	X	X[1,2]		X[1,5]					
Randomization		X[1]							
Treatment with study product		X		X[5]					
Evaluate device deficiencies		X		X[5]					
Dispense Subject Diary		X		X[5]					
Collect/Review Subject Diary			X[8]	X	X[8]	X			
Photography		X[1]		X[1]		X	X	X	X
Concomitant therapies	X	X[2]	X	X	X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X	X	X
Treating Investigator Assessments									
GAIS							X	X	X
Galderma Jawline Scale[6]	X	X[1,2]		X[1,5]					
CCI									
Blinded Evaluator Assessments									
Galderma Jawline Scale	X	X[1,2]					X	X	X
Subject Assessments									
GAIS							X	X	X
CCI									

[1]Prior to any planned treatment
[2]Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed
[3]For females of childbearing potential
[4]Visit is scheduled only if initial treatment or optional touch-up has been performed
[5]Omitted if optional touch-up is not performed
[6]For assessing subject treatment needs only
[7]Time for returning to social engagements asked to the Subject over the phone
[8]Review diary with Subject over phone
[9]Subject self-reported. Height only needs to be collected at baseline

AE = Adverse event
EOS = End of Study
GAIS = Global Aesthetic Improvement Scale
hrs = hours
TC= Telephone call
TU = Touch-up
Tx = Treatment

Table 2 Schedule of events – No Treatment group

Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4-6**	**Visit 7**	**Visit 7a[3]**
	Day -21 to Day 1	**Day 1**	**1 month after baseline** (+7 days)	**3, 6 and 9 months after baseline** (±14 days)	**12 months after baseline** (±14 days)	**2 weeks after optional Tx** (±7 days)
	Screening	**Baseline**	**Follow-up**	**Follow-up**	**Follow-up/ Optional Tx/ EOS**	**Follow-up/ EOS**
Informed Consent	X					
Med. Hx/prior therapies	X	X[1]				
Demographics	X					
Height/Weight[6]		X			X	
Inclusion/Exclusion Criteria	X	X[1]			X[4,5]	
Urine pregnancy test[2]	X	X[1]			X[4,5]	
Randomization		X				
Treatment with study product					X[4]	
Evaluate device deficiencies					X[4]	
Photography		X	X	X	X[5]	
Concomitant therapies	X	X[1]	X	X	X	X
Assessment of AEs		X	X	X	X	X
Treating Investigator Assessments						
GAIS				X	X	X
Galderma Jawline Scale[7]	X	X[1]			X[4,5]	
Blinded Evaluator Assessments						
Galderma Jawline Scale	X	X[1]		X	X[5]	
Subject Assessments						
GAIS				X	X[5]	X
CCI						

[1]Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed [2]For females of childbearing potential [3]Visit is scheduled only if optional treatment has been performed [4]Omitted if optional treatment is not performed [5]Prior to treatment [6]Subject self-reported. Height only needs to be collected at baseline [7]For assessing subject treatment needs only	AE = Adverse event EOS = End of Study GAIS = Global Aesthetic Improvement Scale Tx = Treatment

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
Blinded evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator should be a Health Care Professional and must not be involved in the treatment of the subject.
BOCF	Baseline observation carried forward
Childbearing Potential	A female (including pre-menopausal subjects) capable of becoming pregnant; this includes women on oral, injectable, or mechanical contraception or women whose male partners have been vasectomized or are utilizing mechanical contraceptive devices
COX-2	Cyclooxygenase-2
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CTN	Clinical Trial Number
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Curriculum vitae
DBL	Database lock
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data Management Plan
eCRF	Electronic case report form
EOS	End of study
EU	European Union
FSFV	First subject first visit
FUP	Follow-up
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
GDPR	General Data Protection Regulation, Regulation (EU) 2016/679
GJS	Galderma Jawline Scale
HA	Hyaluronic acid
HIV	Human Immunodeficiency Virus
hrs	Hours
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
Investigational product	Medical device being assessed for safety or performance in a study. “Investigational product” is the same as “study device”, “investigational device”, or “investigational medical device.”
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e., sub-Investigator, designated and supervised by the PI at a study center to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log. An Investigator should be a Physician.

Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
ISO	International Organization for Standardization
ITT	Intention-to-treat
LSLV	Last subject last visit (last subject who completed its last clinical study visit)
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Devices Regulation, Regulation (EU) 2017/745 on medical devices
mg	Milligram
mL	Milliliter
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
PI	Principal Investigator; qualified person responsible for conducting the study at a study center
PP	Per Protocol
PT	Preferred term
q.s.	Quantum satis
RA	Regulatory Authority
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
CCI	[redacted]
Study center	Institution or site where the study is carried out
Study files	The Investigator file and the Sponsor file
Study products	The investigational product under study
TC	Telephone call
Treating Investigator	Qualified physician to perform the study injections, should be aware of important neurovascular and anatomical structures near injection sites.
TU	Touch-up (Repeated injection to be performed after treatment, if necessary to achieve optimal correction)
Tx	Treatment
UPT	Urine pregnancy test
WHO	World Health Organization

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1. BACKGROUND INFORMATION

1.1 Medical background, indication and population description

From an aesthetic perspective, the jawline contributes significantly to facial proportional appearance and is a critical component in the perception of facial attractiveness in both men and women. An attractive jawline constitutes a well-defined, straight jawline. Aging across the mandibular border may be described by several mechanisms: Fat atrophy and volume loss; shifting of subcutaneous fat compartments; and mandibular septum dehiscence with submandibular fat hypertrophy.[1]

With aging, bone recession, combined with mid-face laxity, may produce sagging skin below the jawline as the supporting systems diminish. In the lower face, this age-associated volume loss leads to loss of definition of the jawline.[2]

Individuals are looking to create or enhance an attractive appearance by improving their natural definition of the jawline. In Europe, a consumer survey revealed that the jawline is a preferred feature to change for one-third of women aged 46-63 years.[3]

Further, enhancing to achieve a well-defined, "strong", masculine jawline is also desired by men.[4] Rejuvenation of the jawline is becoming part of routine aesthetic practice with injectable dermal fillers containing hyaluronic acid or calcium hydroxylapatite (NCT03712137, NCT03425253, NCT04645576 and NCT03583359 registered on www.clinicaltrials.gov).

Restylane Lyft Lidocaine is intended to be used for facial tissue augmentation and is used for shaping the contours of the face. In this study, *Restylane Lyft Lidocaine* will be used for Jawline treatment within the approved indication. It should be injected into the deep layer of the dermis and/or the surface layer of the subcutis. Deeper injections into the subcutaneous fatty tissue or supraperiosteal layer are appropriate for areas with adequate soft tissue support and soft tissue cover such as the midface and jawline (see the co-packed Instructions for Use (IFU)).

Lidocaine is added to the formulation of *Restylane Lyft Lidocaine* to diminish the pain resulting from the injection during the treatment.

The product is intended to be used only by authorized personnel, trained in the appropriate injection techniques, in accordance with local legislation. The study population consists of adult men and women meeting the inclusion/exclusion criteria.

1.2 Relevant previous data

1.2.1 Non-clinical documentation

Restylane Lyft Lidocaine is produced using the NASHA™ technology. The NASHA gels have been tested and meet all biocompatibility requirements specified in the International Organization for Standardization (ISO) 10993:1 Biological Evaluation of Medical Devices.

1.2.2 Clinical documentation

Restylane Lyft Lidocaine has been evaluated in clinical studies and is approved for use in Canada since 2010. Please refer to the co-packed IFU for detailed information. The IFU summarizes the adverse effects experienced with hyaluronic acid (HA) injections along with precautions that can minimize these potential complications.

1.3 Risks and benefits

The primary potential benefit of treatment is a perceived aesthetic improvement of jawline definition by facial tissue augmentation. Treatment with HA fillers are less invasive than surgical options and may offer less downtime from swelling and bruising. Adding volume in the jawline may improve subject satisfaction and restore youth by creating definition. HA fillers are becoming more popular for the treatment of jawline and have a good safety profile.

Injection site reactions (e.g., bruising, erythema, itching, swelling, pain or tenderness at the implant site) might occur. The resolution is spontaneous within a few days to a few weeks after injection into the skin.

The most common adverse events (AEs) reported in post-marketing surveillance data are swelling with immediate onset and onset up to several weeks after treatment.

Other AEs such as bruising/hematoma, discoloration/hyperpigmentation, erythema, papules/nodules, pain/tenderness and hypersensitivity/angioedema, inflammation, mass/induration, neurological symptoms and non-dermatological events have also been reported with short duration of effect.

Vascular compromise may occur due to an unintentional intravascular injection or as a result of vascular compression associated with implantation of any soft tissue filler in the face. This may manifest as blanching, discoloration such as a dusky or reticular appearance of the tissue, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected, or rarely as ischemic events in other organs due to embolization. Rare but serious cases of ischemic events associated with temporary or permanent vision impairment, blindness, cerebral ischemia or stroke have been reported following facial aesthetic treatments.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated, if necessary, since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended.

Post inflammatory pigmentation changes have been observed in clinical studies in people with dark skin (Fitzpatrick Type IV-VI).

Additional information about expected AEs and anticipated risks are included in the specific IFU.

To mitigate these risks, only study Investigators qualified by education and experience, who are skilled in the use of dermal fillers from their clinical practice and involvement in clinical research, and with knowledge of facial anatomy, understanding of the depth and plane of injection, as well as knowledge of the signs and symptoms and management of potential complications, will be chosen to participate in this study. This further ensures proper device implantation and management of study risk.

Given the anticipated low level of transient and acceptable AEs in connection with the injection, the protocol-required safety assessments, and the injection technique training provided, it was

determined the risk-benefit assessment for use of *Restylane Lyft Lidocaine* for jawline definition offer a clinical benefit at reasonable risk.

Exclusion criteria have been selected in alignment with contraindications, warnings and precautions in the co-packed IFU.

2. STUDY OBJECTIVES, ENDPOINTS

2.1 Study objectives

2.1.1 Primary objective and endpoint

The primary objective of the study is to assess the effectiveness of *Restylane Lyft Lidocaine* versus a no treatment control in Jawline definition by comparing Galderma Jawline Scale (GJS) response rates.

Primary Endpoint:

Responder rate based on the Blinded Evaluators' live assessment of the GJS at 3 months after last treatment for the Treatment group or after baseline for the No Treatment group.

A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently.

2.1.2 Secondary objective and endpoints

The secondary objective is to assess the effectiveness of *Restylane Lyft Lidocaine* for Jawline definition.

Secondary endpoints:

1. Responder rates based on the Blinded Evaluator's live assessment using the GJS at 6, 9 and 12 months after last treatment for the Treatment group or after baseline for the No Treatment group.

   A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently, at each of the timepoints.
2. Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS) on both jawlines concurrently, as assessed live by the Subject and Treating Investigator separately at 3, 6, 9 and 12 months after last treatment for the Treatment group and after baseline for the No Treatment group.

CCI [redacted]

CCI [redacted]

One month is defined as 4 weeks in the study.

2.1.3 Safety objectives and endpoints

To evaluate the safety of *Restylane Lyft Lidocaine* by assessments of adverse events (AEs) by the Treating Investigator throughout the study period.

- Incidence, intensity, duration and onset of AEs collected during the study period post treatment.
- Pre-defined, expected, post-treatment events reported for 28 days from treatment as recorded in the subject diary.

2.2 Appropriateness of measurements

The effectiveness of *Restylane Lyft Lidocaine* for jawline definition will be evaluated by demonstrating superiority in responder rates (defined as at least 1 grade improvement from baseline on both jawlines concurrently on the GJS) relative to No Treatment group.

The GJS is a 5-point scale for assessment of jawline (see Section 6.3). Each score in the GJS is exemplified by Photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject´s left and right jawline separately.

The GJS was developed as a quantitative assessment of the jawline area in clinical trials. For the GJS to be considered a reliable and valid tool for assessing aesthetic improvements, live subjects were rated by an independent panel at two sessions separated at least two weeks apart in order to assess the intra- and inter-rater reliability. Based on the validation results, the GJS was determined to be fit for use in clinical settings to detect changes to treatment by improving the jawline definition as a result of volume correction.

Primary effectiveness of *Restylane Lyft Lidocaine* for jawline definition will be evaluated by comparing the responder rate based on the Blinded Evaluators' live assessment of the GJS at 3 months after last treatment. Secondary effectiveness of *Restylane Lyft Lidocaine* by comparing the responder rates based on the Blinded Evaluator's live assessment using the GJS at 6, 9 and 12 months after last treatment for the Treatment group or after baseline for the No Treatment group.

Secondary effectiveness measurements include GAIS as a widely used and accepted measure within the aesthetic field. Other secondary effectiveness measurements are the validated CCI [redacted] and an additional CCI [redacted] as well as the CCI [redacted] that will be used to capture subjects' and treating investigators' assessment of the results.

Effectiveness evaluation in dermal filler clinical studies includes a combination of clinician-and subject-reported outcomes. As these are aesthetic devices and elective procedures, the incorporation of the subject perspective is critical to evaluate the study benefits associated with dermal fillers.

3. STUDY DESIGN

3.1 Overall design

This is a prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter phase IV study to evaluate effectiveness and safety of *Restylane Lyft Lidocaine* for jawline definition. Approximately 140 subjects will be included in the study, randomized (3:1) to *Restylane Lyft Lidocaine* or to No Treatment (control) group.

Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. A follow-up telephone call should be made 72 hours after treatment.

Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. If optional touch-up is performed, a 72-hour follow-up telephone call and a follow-up visit after 1 month should be scheduled.

Effectiveness and safety data will be collected for up to 12 months after the last treatment for the Treatment group and after baseline for the No Treatment group including follow up visits at 1, 3, 6, 9 and 12 months.

Subjects in the No Treatment group will be offered optional treatment after 12 months (48 weeks) from baseline (Day 1) followed by a safety assessment 2 weeks after the optional treatment. Subjects who decline treatment after 12 months will end their study participation.

The treatment will be performed in accordance with approved Instructions for Use in Canada.

Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments.

3.2 Study rationale and justification for design

The rationale of performing this study is to obtain further evidence of safety and effectiveness of *Restylane Lyft Lidocaine* for jawline definition in a randomized controlled trial. The intended use in this post-market study will be in accordance with the approved IFU. No treatment has been chosen as control as no treatment control is a commonly accepted comparator in aesthetic injectable filler trials.

A study of the safety and effectiveness of *Restylane Lyft Lidocaine* in the treatment of jawline will establish whether aesthetic jawline definition can be successfully achieved, with an acceptable safety profile.

By using a validated evaluation tool, the GJS assessed by the Blinded Evaluator and Investigator, the results of jawline definition reported can be confirmed by accurate measurements.

In addition, as established and used in other studies the GAIS and the validated CCI [redacted] will be used in this study and in addition a CCI [redacted] as well as an CCI [redacted]

3.3 Number of subjects and investigational centers

Approximately 140 subjects will be enrolled at approximately 10 study centers in Canada.

3.4 Study duration

The total duration of the study is estimated to approximately 18 months. This includes 4 months recruitment period.

- Treatment group:
  - Up to 21 days screening
  - Treatment at baseline (Day 1) and TC at 72 hrs after last treatment.
  - Optional touch-up at 1 month and TC at 72 hrs after last touch-up.
  - Data collection and safety follow-up visits at 1, 3, 6, 9 and 12 months after last treatment.
- No Treatment Control group:
  - Up to 21 days screening
  - Data collection and safety follow-up visits at 1, 3, 6, 9 and 12 months after baseline.
  - Optional treatment at 12 months after baseline followed by 2 weeks safety follow-up after optional treatment.

One month is defined as 4 weeks in the study.

3.5 Procedures/reasons for subject discontinuation

An investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed if such assessment is possible. The procedures designated for the closest upcoming study visit should be completed for a subject discontinuing the clinical study and the appropriate electronic Case Report Form (eCRF) should be completed.
All discontinuations and the reason for discontinuation are to be documented by the investigator on the Study Exit form.

For discontinuation due to an AE, the Adverse Event form is to be completed. The investigator should also ensure that the subject receives suitable therapy for the AE.

A subject who has been randomized cannot be replaced by another subject if he/she discontinues the clinical study for any reason.

Pregnancies occurring during the screening period are considered as screening failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, follow the procedures described in section 7.7.2. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

Potential reasons for discontinuation are defined below:

The withdrawal criteria are:

- **Medical Reasons** If the subject suffers from a medical condition and/or Adverse Events that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- **Withdrawal by Subject:** Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, confirm with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- **Other:** This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. Explain the reason for discontinuation.

If reason for discontinuation is “withdrawal by subject” or “other”, the subject will be questioned to rule out the possibility of an AE. If the AE led to discontinuation, then “Adverse Event” should be chosen as the reason for discontinuation, rather than “withdrawal by subject” or “other”.

If an AE which, according to the Investigator’s assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the Investigator shall follow-up the subject until the AE resolves, is assessed by the Investigator to be “chronic” or “stable” or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

3.6 Suspension or premature termination

The Sponsor will suspend or terminate the study when so instructed by the Research Ethics Board (REB) or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons. The Sponsor may also decide to close a single study center due to unsatisfactory subject enrollment or non-compliance with the CSP, Good Clinical Practice (GCP), or applicable regulatory requirements.
In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

4. STUDY POPULATION

Approximately 140 adult male and female subjects with Grade 2 to 4 (moderate to very severe) on the GJS with the intent to undergo bilateral jawline treatment will be included in this study.

4.1 Clinical study population characteristics

4.1.1 Inclusion criteria

1. Male and female adults willing to comply with the requirements of the study and providing a signed written informed consent.
2. Consent the use of facial images for marketing purposes and educational material as described in the Informed Consent Form (ICF).
3. Subject with moderate to very severe (Grade 2 to 4) on the Galderma Jawline Scale (GJS) with no more than one grade difference between the left and right side at baseline as assessed by the Blinded Evaluator.
4. Subject is willing to abstain from any other facial, submental, and/or neck aesthetic procedure(s) or implant for the duration of the study.
5. Female of childbearing potential with a negative urine pregnancy test before treatment.

4.1.2 Exclusion criteria

1. Subjects presenting with known/previous allergy or hypersensitivity to hyaluronic acid (HA) filler, lidocaine or amide type local.
2. Subjects presenting with known/previous allergy or hypersensitivity to streptococcal proteins.
3. Subject with bleeding disorders or subjects who are taking thrombolytics or anticoagulants.
4. Subject who is using substances that affect platelet function e.g., aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Cyclooxygenase-2 (COX-2) inhibitors are allowed.
5. Subjects using immunosuppressants.
6. Subjects with a previous implant other than HA in or near the intended treatment site.
7. History of other facial treatment/procedure in the previous 6 months HA in or near the intended treatment site that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g., Botulinum toxin injections or another HA filler.
8. Subject with a prior surgical procedure in the treatment area which, in the opinion of the Treating Investigator could interfere with the study.
9. Presence of any disease or lesions near or on the area to be treated, e.g.:
    - Inflammation, active or chronic infection (e.g., in mouth, dentals, head and neck region);
    - Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster;
    - Scars or deformities;
    - Cancer, or precancer such as actinic keratosis or actinic cheilitis.
10. Presence of any condition which, in the opinion of the Treating Investigator, makes the subject unable to complete the study per protocol, e.g.:
    - Subject is not likely to avoid other prohibited facial cosmetic treatments
    - Subject is not likely to complete the study because of other commitments

- Subject is anticipated to be unavailable for visits, incapable of understanding the investigational assessments, or has unrealistic expectations of treatment result
- Subject who has a concomitant condition (e.g., acute viral or bacterial infection with fever) that might interfere with study treatments or assessments
- Subject with unattainable expectations.

11. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
12. Study center personnel, close relatives of the study center personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
13. Participation in any other interventional clinical study within 30 days before treatment.

4.2 Medical history

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the eCRF using medical terminology.

4.3 Previous and concomitant therapies

4.3.1 Definition

Prior therapies are defined as therapies that have been used within 30 days preceding the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the Screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the Screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the study, or
- any new therapies received by the subject since the Screening visit.

4.3.2 Categories

The following two categories are to be considered for prior and concomitant therapies:

- Drugs/therapies including but not limited to prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to plastic surgery (surgery to either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.), facial tissue augmentation therapy or cosmetic procedures (e.g. lifting threads, tissue augmentation therapy, contouring or revitalization with permanent or non-permanent implants, silicone, fat, fillers, Botulinum toxin injections, deoxycholic acid injections, mesotherapy, laser, photo modulation, intense pulsed light (IPL), radio frequency, ultrasound, cryotherapy, dermabrasion, needling, chemical peeling, or other ablative/non-ablative procedures).

4.3.3 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (section 4.3.4), all therapies are authorized.

4.3.4 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the effectiveness and/or safety assessment of the study treatment.

- Anticoagulants or inhibitors of platelet aggregation (e.g., aspirin, NSAIDs), Omega-3 or Vitamin E should not be used within 2 weeks before any treatment to avoid increased bruising or bleeding at injection sites. Concomitant treatment with Omega-3 and Vitamin E is acceptable only as part of a standard multivitamin formulation and COX-2 inhibitors are allowed.
- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should however be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g., certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies, antiviral treatment for HIV or Hepatitis) is prohibited.
- Concomitant treatment with systemic corticosteroids or topical corticosteroids is prohibited (inhaled corticoids are allowed). Corticosteroids should be used with caution and should be adjudged as necessary by the Investigator.
- Planned aesthetic facial plastic surgery (e.g. surgery to the midface, facelift, rhinoplasty, facial liposuction etc.), facial tissue augmentation therapy or cosmetic procedures (e.g. lifting threads, tissue augmentation therapy, contouring or revitalization with permanent or non-permanent implants, silicone, fat, fillers, Botulinum toxin injections, deoxycholic acid injections, mesotherapy, laser, photo modulation, IPL, radio frequency, ultrasound, cryotherapy, dermabrasion, needling, chemical peeling, or other ablative/non-ablative procedures) are prohibited.
- Planned surgery including aesthetic facial surgical therapy, liposuction, sinus surgery or dental root surgery, piercing or tattoo in the area to be treated are prohibited.
- Participation in any other clinical study is prohibited.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Medical Monitor should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

4.3.5 Documentation and recording instructions

Prior and concomitant therapies are to be recorded on the appropriate form in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis or dose modification for a chronic condition.

4.4 Subject identification number

Prior to any study procedures being conducted, the subject must sign the informed consent form (ICF). Each subject who has signed the ICF will be assigned a subject number that will be allocated in ascending order within each center. A screen failure is a subject who signed the informed consent but never enrolled (i.e., was randomized and/or received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. A subject is considered enrolled when they have signed the ICF and are randomized and/or treated.

For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion. A subject identification log is required to be kept in the Investigator file.

5. STUDY INTERVENTION

5.1 Description of the investigational device

The term “investigational device” refers to *Restylane Lyft Lidocaine.*

5.1.1 Investigational device

Restylane Lyft Lidocaine is a sterile, transparent, biodegradable gel supplied in a glass syringe together with a 27G or 29G Thin wall (TW) needle(s). The product is for single use only. *Restylane Lyft Lidocaine* is a unique form of non-animal, stabilized hyaluronic acid (NASHA™). Hyaluronic acid is a natural polysaccharide which occurs as an important structural element in the skin and in subcutaneous and connective tissues as well as in the synovial tissue and fluid. Hyaluronic acid belongs to a group of very few substances which are identical in all living organisms.

Restylane Lyft Lidocaine co-packed with two sterilized needles 27G x ½" will be supplied to the study centers.

Composition

Hyaluronic acid, stabilized	20 mg/mL
Lidocaine hydrochloride	3 mg/mL
Phosphate buffered saline	q.s.

5.1.2 Reference product

Not applicable. The reference in this study is a No Treatment control.

5.2 Additional products and materials

The sponsor will provide pregnancy tests (urinary human chorionic gonadotropin [U-HCG]).

5.3 Packaging and labelling

Restylane Lyft Lidocaine is supplied in a blister packed, prefilled plastic syringe. The content of the syringe is sterilized using moist heat. For the purpose of this study, commercial products will be used. *Restylane Lyft Lidocaine* should be used according to approved labeling, as per Treating Investigator preference. The products are for single use only. In addition to the standard labelling of

the device, a study-specific label will be attached, containing study specific information in accordance with Canada labeling requirements for commercially available medical devices used in clinical trials. Detailed product information is provided in the IFUs (co-packed with product).

5.4 Instructions for use and administration

5.4.1 Treatment procedure

The investigational product is reserved for use by Treating Investigators who are experienced with deep dermal and subcutaneous injections in the facial area. Treating Investigators should be aware of important neurovascular and anatomical structures near injection sites, which include the facial artery and vein, mental nerve and artery, parotid gland, superficial temporal artery and vein, and marginal mandibular nerve. The treatment procedures for *Restylane Lyft Lidocaine* should follow the approved IFU in Canada (co-packed with product). Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the Subject Diary and potential risks involved with the treatment and when to contact the Treating Investigator in case of emerging symptoms.
Detailed information regarding the injection procedure, pre- and post-treatment care, and Subjects' instructions are provided in the IFU.

5.4.1 Pre-Treatment procedure

Before the treatment, the Subject's suitability for the treatment and the need for pain relief should be assessed. Normally, no anesthesia is necessary when shaping the contours of the face and correcting folds.

The Subject should be informed about the indications, expected result, contraindications, precautions, warnings and potential adverse events.

The treatment site should be cleaned with a suitable antiseptic solution.

5.4.2 Treatment regimen (dose and interval)

Subjects in the Treatment group will receive one *Restylane Lyft Lidocaine* treatment at baseline (initial treatment) and one optional touch-up treatment 1 month after initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvement. Subjects in the No Treatment control group will be offered treatment at the 12 months follow-up visit.

Subjects will be treated to obtain optimal jawline correction, which is defined as at least 1 GJS grade improvement from baseline and best correction that can be achieved as agreed upon by the Treating Investigator and the Subject.

Restylane Lyft Lidocaine will be administered by needle (27G x ½" or 29G (TW) x ½") or cannula (23-25G) injections. The Treatment procedures for *Restylane Lyft Lidocaine* should follow the approved IFU in Canada (co-packed with product).

The size and the length of the cannula will affect the force needed to extrude the gel. If a thinner cannula is used the resistance during injection may be too high resulting in an increased risk for leakage or separation of the cannula and syringe. The same considerations are applicable for needles.

The injection technique with regard to the depth of injection and the administered quantity may vary. Injection technique is at the Treating Investigator´s discretion in the deep dermal and subcutaneous tissue. Deeper injections into the subcutaneous fatty tissue or supraperiosteal layer are appropriate for areas with adequate soft tissue support and soft tissue cover such as jawline.

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For each treatment site a maximum dosage of 2 mL per treatment session is recommended (i.e., 2 mL per side of the face per treatment session). Care should be taken to avoid excess deposition of material into treatment area. The injection can bridge all the way from the mandibular angle, post-jowl and to the pre-jowl area (from tip of ear to tip of chin). The jawline should not be "overcorrected." If an overcorrection should occur, the area should be firmly massaged between fingers to obtain optimal results. Aspiration is recommended prior to each injection. Slow injection is recommended.

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5.4.3 Post-treatment care

When the injection is completed, the treatment area should be massaged to conform to the contour of the surrounding tissues.

If the treated area is swollen directly after the injection, melting ice or a cold pack can be applied on the site for a short period as per the Treating Investigator's normal procedure.

After the injection, some common injection-related reactions might occur. These reactions include bruising, erythema, itching, swelling, pain or tenderness at the implant site. Typically, resolution is spontaneous within a few days after injection into the skin.

Any medication or therapy used by the subject must be recorded in the eCRF.

The subject must avoid exposing the treated area to excessive sun or ultraviolet radiation or extreme cold until any signs of initial swelling and redness have disappeared.

5.5 Supplies management

5.5.1 Product accountability

The study products will be released to the PI or his/her authorized designee after study approvals have been received from the REB and the Clinical Trial Agreement (CTA) has been signed by all parties. The PI must ensure that the study products are kept in a secure location, with access limited to those authorized by the PI. The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the PI maintains accurate product

accountability records, i.e., documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, lot number, expiration date and amount received. In addition, dispensing logs shall be maintained including the product name, batch number, expiry date, dispense date, the number of syringes used, the subject receiving study product, and number of syringes left in stock at the site. When the study is completed, all unused or expired study product at each study center shall be returned to the Sponsor for destruction or destroyed locally at the center, if documented as agreed with the Sponsor. Any malfunctioning study products shall be reported as described in Section 8.3.3. Products deliberately or accidentally destroyed during shipment or at a study center shall be accounted for and documented. Used syringes, needles and cannula and any opened unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the center. Disposal of hazardous material i.e., syringes and needles, must conform to applicable laws and regulations. All study product(s) sent to the PI will be accounted for and no unauthorized use is permitted.

5.5.2 Storage of study product

The syringes should be stored in their original packaging at a temperature up to 25°C (77°F), protected from sunlight and freezing. Opened packages or partially used devices should not be reused. Detailed product information is provided in the IFU.

5.5.3 Dispensing and return

The treatment will be administered by the Treating Investigator at the study center and be documented in the accountability records.

When the study is completed, all unused or expired study products at each study center should be returned to the Sponsor representative for destruction, or to be destroyed locally at the study center if documented as agreed with Sponsor.

5.5.4 Treatment compliance

Not applicable; the treatment will be administered by the injector at the investigational center.

5.6 Randomization

Before starting the study, a computer-generated randomization list will be prepared using an Interactive Response System under the supervision of a designated statistician from the Sponsor. Approximately 140 subjects will be randomized in a 3:1 ratio to treatment with *Restylane Lyft Lidocaine* or no treatment. Randomization numbers will be allocated in ascending sequential order to each subject.

5.7 Blinding

The Treating Investigator will not be blinded to study treatments.

A Blinded Evaluator, to whom randomization and treatment are concealed, will conduct the blinded assessments. To the extent possible, the same Blinded Evaluator should assess an individual subject throughout the study.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products

and randomization assignment should be kept in a separate file not available to the Blinded Evaluator.

Safety assessments will be performed by non-blinded Investigator as treatment-related AEs are expected to occur during a few days after treatment, thereby revealing which subjects have received the study product.

5.7.1 Verification of blinding

Not applicable.

5.7.2 Emergency unblinding

Not applicable as the Treating Investigator is not blinded to treatment.

5.8 Post-trial provisions

In time, the implant will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result.

After the final study visit, the Sponsor will not supply any more treatments to the subjects in the Treatment group, even if the result does not persist.

6. EFFECTIVENESS ASSESSMENTS

6.1 Effectiveness Assessment Methods

The methods for collecting effectiveness data are described in the following sections. To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. For study evaluation purpose, the effectiveness assessments described below will be performed. Assessments should be performed according to the time points indicated in Table 1 and Table 2: Schedule of events and recorded in the eCRF.

6.2 Photography

Photographs will be taken prior to treatments with study product and at every follow-up visit in order to document treatment effect. Photographs may also be taken to document AEs at the Treating Investigator's discretion. Baseline photographs will be used as a reference in the GAIS assessment. Study site personnel will be thoroughly trained in the photographic equipment and techniques before study start.

Camera equipment will be provided by the Sponsor, or their designee and standardized photographs should be achieved. Further details regarding photography procedure will be specified in a separate user guide.

6.3 Galderma Jawline Scale (GJS)

The GJS is a validated 5-point scale for assessment of jawline (see Appendix 1). Each score in the GJS is exemplified by photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject's left and right jawline separately.

The Blinded Evaluator will perform GJS assessments as specified in the Schedule of Assessments (Table 1 and Table 2).

6.4 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to live assess the aesthetic improvement of the jawline, i.e., improvement from baseline appearance before the first treatment by the Treating Investigator and the Subject, independently of each other. The GAIS will be assessed by the Treating Investigator and the Subject as specified in the Schedule of Assessments (Table 1 and Table 2).

The baseline archival photographs (obtained prior to injection at baseline) will be used as a comparison for the GAIS evaluation. The Treating Investigator will assess the GAIS based on the definition in Table 3.

Table 3 Investigator Global Aesthetic Improvement Scale (GAIS)

Rating (Treating Investigator and Subject	**Definition (only for Treating Investigator)**
Very Much Improved	Optimal aesthetic result for the implant for this subject.
Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
Improved	The appearance is improved from the initial condition.
No Change	The appearance is essentially the same as baseline.
Worse	The appearance is worse than the initial condition.
Much Worse	Marked worsening in appearance from the initial condition.
Very Much Worse	Obvious worsening in appearance from the initial condition.

The Subject will respond to the question: *"How would you describe the aesthetic improvement of the treatment area today compared to the photograph taken before treatment?*" by using the categorical scale below.

Rating
Very Much Improved
Much Improved
Improved
No Change
Worse
Much Worse
Very Much Worse

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7. SAFETY ASSESSMENTS

7.1 General information

The safety assessment described below are included specifically for the study. For clinical practice the IFU supplied with the product will include information needed to handle the product safely. This includes information that the product has not been tested in pregnant or breastfeeding women or in children.

7.2 Subject Diary Data

The Subject from the Treatment group shall evaluate local tolerability in a 28 days diary, starting on the day of each treatment. The presence and maximum intensity of pre-defined, expected post-treatment events, i.e., bruising, redness, pain, tenderness, lumps/bumps, itching and swelling shall be assessed for the treated area.

The Investigator or study staff should review the diary for completion and clarify any events as needed. For events that are ongoing at the time of diary completion, the Investigator should follow them and record resolution in the subject's study file and eCRF. Diary data will be analyzed and displayed separately from AE data.

7.3 Laboratory assessment

For all women of childbearing potential, including those currently using contraception, a urine pregnancy test is required prior to receiving any study treatment (Day 1, optional touch-up or optional treatment). **The test result must be negative for the subject to receive any treatment with study product**. The test result will be documented in the subject's file and eCRF.

7.4 Adverse events

The definition of an Adverse Event (Medical Devices Regulation (MDR) article 2(57)): An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[I], in the context of a clinical investigation, whether or not related to the Investigational device.

This definition includes:

a) events related to the investigational product or the reference product

b) events related to the procedures involved

c) events that are anticipated as well as unanticipated

Adverse Event reporting on each subject shall start once a subject is enrolled (i.e., randomized and/or treated) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious, are to be reported as an AE in the eCRF. A request for additional information from the Sponsor/ Contract Research Organization (CRO) Medical Expert(s) for non-serious AEs, should be collected and answered using the Adverse Event Clarification Form.

7.4.1 Anticipated adverse events

Injection related AEs such as bruising, erythema, itching, swelling, pain and tenderness are anticipated. Information regarding anticipated AEs for *Restylane Lyft Lidocaine* is included in the IFU (co-packed with product).

7.4.2 Assessment of severity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable*)*

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

[I] For users or other persons, this definition is restricted to events related to the investigational product.

7.4.3 Assessment of causality

Each AE shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

In addition, each Serious Adverse Event (SAE) will be classified by both the Investigator and Sponsor separately, according to four different levels of causality:

1. **Not related** - Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to investigational device;
   - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/ exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

   In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
2. **Possible -** The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable** - The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. **Causal relationship** - the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/ exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
   - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;
   - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

   In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

7.4.4 Action taken

The action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn) for an AE should be recorded in the eCRF.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e. the Principal Investigator [PI]) or, where appropriate any other person entitled by national law to provide the relevant patient care.

7.4.5 Follow-up of adverse events

7.4.5.1 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end / or ongoing when subject early terminated study participation / or ongoing if study is temporarily halted, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up until resolved, assessed as chronic or stable, or subject is lost to follow up. Final outcome after the end of the study shall be reported on the AE Follow-up form. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

7.4.5.2 Follow-up of events occurring after subject termination of the study

All Adverse Events with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor by email to safety.q-med@galderma.com. The Investigator shall follow the subject until the event is resolved.

7.4.6 Documentation and recording instructions

Investigators, or other study site personnel, shall record all AEs in the eCRF, including:

a) Event term (recorded in standard medical terminology and avoiding abbreviations)

b) Affected area

c) Start date (first day with symptoms)

d) Stop date (last day with symptoms)

e) Intensity (mild, moderate, or severe according to definition in section 7.4.2)

f) Seriousness (serious or not serious, according to definition in section 7.5)

g) Relationship to study product or study product injection procedure (According to definition in Section 7.4.3)

h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)

i) Outcome of the AE (ongoing, resolved, resolved with sequelae, death) at the end of the study. The AE form/module in the eCRF must be signed and dated by the Investigator.

7.5 Serious Adverse Events

The Definition of a Serious Adverse Event (MDR article 2(58)):

A Serious Adverse Event (SAE) is any AE that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening[II] illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. hospitalization or prolonged hospitalization[III], or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
5. chronic disease

c) led to fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

[II] The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

[III] Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such.

When an AE is related to a device deficiency (refer to section 7.7.3), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.

7.6 Device deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[IV], or performance.

Note: Device deficiencies include malfunctions, user errors or inadequate information supplied by the manufacturer.

7.7 Safety report procedures and timelines

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at each study visit following the baseline visit. An event that occurs after the subject signs the ICF but before enrollment (i.e., randomized and/or treated) will be recorded in the subject's medical history. The question about AEs should be asked: "Since your last clinical visit have you had any health problems?" Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area or from a laboratory test, subject diaries, or spontaneous reports from the subjects or their relatives.

AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product.

7.7.1 Reporting of Serious Adverse Events

The Investigator shall report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report shall be submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Subject identification (age, gender, initials, subject number)
- Adverse event description
- Date when AE occurred
- Name of PI
- Name of study product

[IV] Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:

- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g., hospital notes, death certificate, autopsy reports etc.)

E-mail for SAE reporting: PPD

Fax number for SAE reporting: PPD

For non-urgent complementary information not possible to send by e-mail or fax, please use surface mail.

Surface mail for providing complementary information: PPD PPD

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor or designee. A copy of the fully completed SAE form shall be kept at the site.

In addition, the PI shall report SAEs to the responsible REB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her REB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

7.7.2 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to the Sponsor according to contact details

specified in Section 7.7.1. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure in utero report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

7.7.3 Device deficiencies

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to Section 7.4 and 7.7.1). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the clinical study complaint form the Sponsor will make the same assessment.

7.7.4 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor.

E-mail for device deficiencies reporting: PPD

Fax number for device deficiencies reporting: PPD

Phone number for device deficiencies reporting: PPD

Surface mail for device deficiencies reporting: PPD

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see Section 7.7.1).

If the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the REB.

The deficient study product shall be kept by the study center until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study center.

8. DESCRIPTION OF STUDY VISITS

8.1 Visit 1: Screening (Day-21-D1)

The following activities and screening assessments will be performed within 21 days prior to baseline/Day 1 visit:

- Obtain Informed Consent.
- Obtain demographic data: Date of birth, gender, ethnicity, race, and FST. For determination of the FST, see Table 4.
- Record the subject's medical history (including any prior dermatological procedures or implants) and prior or concomitant therapies.
- For all females of childbearing potential, perform urine pregnancy test (UPT) prior to treatment. Test result must be negative for the subject to be eligible for treatment.
- Assess GJS – Treating Investigator and Blinded Evaluator.
- Assess eligibility (inclusion and exclusion criteria).
- Schedule the baseline/Day 1 (initial treatment) visit or proceed to Day 1 activities if subject meets all eligibility criteria.

Table 4: Fitzpatrick Skin Type (FST)

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light[5].

8.2 Visit 2: Baseline (Day 1, Initial Treatment)

The screening visit and baseline visit (Day 1) may be performed on the same day if a subject is deemed eligible by the Treating Investigator.

If screening visit and baseline/Day 1 visit are not performed on the same day, the following procedures should be repeated at the baseline/Day 1 visit:

- Review for changes in medical history and concomitant therapies.
- Re-confirm eligibility criteria.
- Perform UPT for all females of childbearing potential Test result must be negative for the subject to be eligible for study treatment.
- Assess GJS – Treating Investigator and Blinded Evaluator (see Section 6.3).

Once the subject is deemed eligible for study participation by the Treating Investigator, the following procedures should be completed:

- Record the subject's self-reported height and weight.
- Obtain pre-treatment photographs of the jawline.
- Randomize the subject to treatment or to no treatment.
- Obtain pre-treatment/baseline responses to the CCI [redacted] with Lower Face and Jawline.

For subjects randomized to no treatment:

- Schedule Visit 3, 1 month (+7 days) after baseline visit),

For subjects randomized to treatment:

- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during, or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e., injection method and depth of injection).
- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in section 7.7.3.
- Evaluate post-injection AEs by Treating Investigator.
- Dispense Subject Diary and instruct subject on Diary completion. Remind the subject to bring the diary to next on-site study visit.
- Schedule the 72 hours (±24 hours) follow-up phone call (Visit 2a).
- Schedule Visit 3, 1 month (+7 days) after the baseline visit (Visit 2).

8.2.1 Visit 2a: Follow up 72-hour (±24 hours) telephone call after initial treatment

Visit conducted for subjects randomized to treatment only.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the return to social engagements, where the Subject will be asked on when (in hours after treatment) the subject feels comfortable returning to social engagements (public/social appearances) exemplified as returning to business office or other public workplace, having dinner in a public restaurant, attending a social event/gathering such as dinner party, etc.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.

- Remind subject of the next scheduled on-site visit.

8.3 Visit 3: Follow up visit 1 month (+ 7 days) after initial treatment / Optional touch-up or after baseline for the No Treatment group

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs (if treatment is given, ensure photos are taken prior to injection)

For subjects randomized to no treatment:

- Schedule Visit 4, 3 months (±7 days) after baseline visit).

For subjects randomized to treatment

- Collect and review Subject Diary:
    - Review diary entries for completeness and legibility.
    - If the subject handwrites entries on the diary pages, review these entries with the subject and clarify as needed. Record all clarifications on the subject's source documents and record the Diary data into the eCRF.
- Assess whether optimal aesthetic result has been achieved and determine whether optional touch-up is appropriate.
- Subject must meet eligibility criteria for touch-up to be provided.
    - Touch-up should <u>not</u> be provided if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a touch-up.
- Schedule Visit 4, 3 months (±7 days) after last treatment for subjects not receiving touch-up.

If touch-up is to be performed:

- Prior to any treatment, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the touch-up treatment.
- Prior to any treatment, assess GJS – Treating Investigator.
- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e. injection method and depth of injection).
- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 7.7.3.
- Evaluate post-injection AEs by Treating Investigator

- Dispense a new Subject Diary and instruct subject on Diary completion. Remind the subject to bring the diary to next on-site study visit.
- Schedule the 72 hours (± 24 hours) follow-up phone call (Visit 3a) and Visit 3b, 1 month (+ 7 days) after optional touch-up.

8.3.1 Visit 3a: Follow up 72-hour (±24 hours) telephone call after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 3.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the return to social engagements, where the Subject will be asked on when (in hours after treatment) the subject feels comfortable returning to social engagements (public/social appearances) exemplified as returning to business office or other public workplace, having dinner in a public restaurant, attending a social event/gathering such as dinner party, etc.
- Interview subject regarding Subject Diary completion and reported events since receiving treatment. Remind subject to complete the Subject Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

8.3.2 Visit 3b: Follow up visit 1 month (+ 7 days) after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 3.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Collect and review Subject Diary:
  - Review diary entries for completeness and legibility.
  - If the subject handwrites entries on the diary pages, review these entries with the subject and clarify as needed. Record all clarifications on the subject's source documents and record the Diary data into the eCRF.
- Obtain photographs.
- Schedule Visit 4, 3 months (±7 days) after last treatment

8.4 Visit 4 to 6: Follow-up visits 3, 6 and 9 months (± 14 days) after last treatment or after baseline for the No Treatment group

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.

- Obtain photographs.
- Assessments to be performed:
  - GJS – Blinded Evaluator
  - GAIS – Treating Investigator and Subject

CCI [redacted]

- Schedule Visit 5, 6 and 7, for 6, 9 and 12 months ± 7 days after the last treatment (Visit 2 or Visit 3) if any touch-up for the Treatment group or after baseline for the No Treatment group.

8.5 Visit 7: Follow-up visit 12 months (± 14 days) after last treatment / after baseline for the No Treatment group

- Interview the subject regarding concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Record subject's weight.
- Obtain photographs (if treatment is given, ensure photos are taken prior to injection)
- Assessments to be performed, prior to optional treatment:
  - GJS – Blinded Evaluator
  - GAIS – Treating Investigator and Subject

CCI [redacted]

For subjects in the No Treatment (control) group receiving optional treatment:

- Subject must meet eligibility criteria for treatment to be provided. Treatment should not be provided if the subject has a disease or condition described in the exclusion criteria or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

If treatment is to be performed:

- Prior to any treatment, assess GJS – Treating Investigator.
- Prior to any treatment, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the optional treatment.
- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e., injection method and depth of injection).

- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 7.7.3.
- Evaluate post-injection AEs by Treating Investigator
- Schedule the 14 days (± 7 days) follow-up visit (Visit 7a) after optional treatment.

For subjects in the Treatment group and No Treatment (control) group not receiving any optional treatment:

- Remind subjects to contact the study center if any new AE occurs after study exit. Subjects will be asked to return to the study center to be evaluated and receive treatment, if applicable.
- Complete the End of Study form in the eCRF

8.5.1 Visit 7a: Follow up visit 14 days (± 7 days) after optional treatment

This visit should only be conducted for subjects who received optional treatment at Visit 7.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Assessments to be performed:
  - GAIS – Treating Investigator and Subject
- Remind subjects to contact the study center if any new AE occurs after study exit. Subjects will be asked to return to the study center to be evaluated and receive treatment, if applicable.
- Complete Study Exit form in the eCRF.

9. STATISTICAL DESIGN AND ANALYSIS

9.1 General

A Statistical Analysis Plan (SAP) with a description of all statistical analyses will be developed.

All study data will be listed in subject data listings. All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals will be two-sided and constructed at a confidence level of 95%.

All endpoints will be summarized descriptively. Continuous endpoints will be summarized using mean, median, standard deviation (SD), minimum and maximum values, for the observed value as well as the change from baseline. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

9.2 Analysis populations

The following populations will be defined:

Safety population:

Includes all subjects who were treated with *Restylane Lyft Lidocaine*. Subjects are analyzed based on the as treated principle (i.e., according to the treatment actually received).

Intention-to-treat (ITT) population:

Includes all subjects who were randomized based on the as randomized principle (i.e. according to the treatment they were randomized to).

Per protocol (PP) population:

Includes all subjects in the ITT who complete the visit 4 after baseline without any deviations considered to have substantial impact on the primary effectiveness outcome.

The ITT is the primary population for all effectiveness analyses. The primary effectiveness analysis will be repeated using the PP analysis set if there is at least a 10% difference in the number of subjects between the PP and ITT sets. Safety analysis is performed based on the safety population. The disposition of subjects will be presented in tables and/or figures as appropriate.

9.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented by treatment group, based on the ITT analysis set using descriptive statistics, as appropriate.

9.4 Effectiveness analysis

Continuous endpoints will be summarized using descriptive statistics, e.g., mean, median, SD, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

Responder rate regarding GJS and GAIS will be presented together with a 95% confidence interval (based on the binomial distribution). The difference in responder rate regarding GJS and GAIS will be calculated between the two groups presented together with a 95% confidence interval.

For the primary effectiveness analysis, a responder will be defined as a subject with at least 1 point improvement from baseline based on the GJS. For a significant result, the two-tailed p-value of the comparison of responder rates between the treated and untreated subjects at 3 months using the Fisher's exact test needs to be smaller than 0.05.

No adjustment to the level of significance will be performed; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

Secondary analyses will include analysis of responders at each visit. Robustness of the results of the primary endpoint and adverse events analysis will be investigated across the PP population. All formal statistical testing will be performed at a significance level of 5% (2-sided).

9.5 Safety analysis

The number and percentage of subjects reporting each pre-defined, expected, post-treatment symptom, as collected in the 28-day diary, will be presented in total and by maximum intensity. Number of days with the event will be presented.

All AEs will be coded according to medical dictionary for regulatory activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT) and treatment. AEs related to the study device or injection procedure and unrelated AEs will be presented by maximum intensity, SOC and PT. For related AEs, the number of days to onset and the duration of the event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized by SOC and PT. Serious AEs will be listed.

In addition, a summary of all AEs will be provided, which will include (but is not limited to):

- number of subjects with at least one AE and number of events (in total as well as SAEs)
- number of subjects with at least one related AE and number of events (in total as well as SAEs)
- number of subjects with at least one un-related AE and number of events (in total as well as SAEs)
- number of subjects who did not have an AE

9.6 Handling of missing data

The number of missing values will be summarized and reported as appropriate. For the ITT analysis of the Treating Investigator GJS Responder rate at Month 3 after last treatment for Treatment group (primary endpoint), missing values will be assumed to be missing due to lack of effect. Therefore, the primary method of imputation will use the baseline observation carried forward (BOCF) method.

Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the observed cases, as well as worst-case and best-case imputation in the ITT set.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population

9.7 Interim analysis

No formal interim analysis will be performed. However, analysis of data could take place at a time point after the last collection of primary endpoint data. This will not affect the conduct of the study, and none involved in the study will have access to this data. The SAP will be final and signed before this data cut.

9.8 Independent data monitoring committee

Not applicable to this study.

9.9 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CSP deviations will be listed individually, including subject number, and observed deviation. Depending on the seriousness of the deviation, the subject may be excluded from the PP population, which shall be documented prior to database lock (DBL).

Deviations from the statistical plan will be documented in the Clinical Study Report (CSR). If the statistical plan needs to be changed before DBL, but after the finalization of the SAP, the SAP will be amended.

9.10 Sample size

A total sample size of approximately 140 subjects will be included in this study. For the responder rate in GJS, a Fisher's exact test using a 5% two-sided significance level will have approximately 90% power to demonstrate difference between a responder rate of 70% in the *Restylane Lyft Lidocaine* group, and a responder rate of 35% in the no treatment control group when the sample

sizes are 105 and 35, respectively. Accounting for 10% dropouts, approximately 140 subjects need to be randomized in a 3:1 ratio.

10. ETHICS AND GENERAL CLINICAL STUDY CONDUCT

10.1 Ethical considerations

10.1.1 Statement of ethical compliance

The study shall be conducted in compliance with the CTA, the Clinical Study Protocol (CSP), GCP, and applicable regional and national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study).

The study shall follow the international standard for clinical study of medical devices for human subjects, ISO 14155:2020.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e., the PI) or, where appropriate any other person entitled by national law to provide the relevant patient care.

10.1.2 Application to research ethics board and/or regulatory authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CSP/CSP amendment(s) from the REB The study shall not begin until the required favorable opinion from the REB has been obtained. The PI shall file all correspondence with the REB in the Investigator file and copies of REB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the REB or regulatory authorities (RA), shall be followed.

The study does not require application for approval from the RA as it is a post approval phase IV study. The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

10.2 Subject information and consent

The PI or his/her authorized designee must always use the REB-approved subject information and ICF and it must not be changed without prior discussion with the Sponsor and approval from the applicable REB.

It is the responsibility of the PI or his/her authorized designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g., explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the REB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any consequences to his/her future medical care, treatment, or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the ICF and to consider participation in the study. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.

All signed ICF shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study.

10.3 Personnel training

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

The product is reserved for use by the PI or his/her authorized designee in accordance with local legislation, trained in the appropriate aseptic injection techniques and expected to follow the recommendations in the study specific IFUs. Additional training for treatment with the study products in the midface will be provided by the Sponsor.

10.4 Data management and documentation

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens, and program will be designed in accordance with the CSP and the eCRF specification. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and MedDRA dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

10.4.1 Data entry and collection

An electronic data capture application, compliant with regulatory requirements for software validation will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screened subject (screening visit) and included subjects (subsequent visits). The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete,

or inaccurate. Study data should be entered directly from the source documents, which are to be defined at each study center before inclusion of the first subject.

Authorized study center personnel designated by the Investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation study center personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study center as part of the Investigator file.

Any delegation of collection of data should be specified in a signature and delegation log.

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e., the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

The monitor shall review the eCRFs and evaluate them for completeness and consistency. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study center personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study center personnel, time, and date is logged.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

10.4.2 Source documentation

Source documents are all documents used by the Investigator or study center that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion

criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These should be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed, or rendered illegible to preserve individual confidentiality.

10.4.3 Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation European Union (EU) 2016/679 (General Data Protection Regulation, GDPR) and the regulation EU 2017/745 (MDR) on the protection of individuals with regard to the processing of personal data and on the free movement of such data, the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada. All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The ICF shall contain information about what personal data to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all subjects to give their consent not only to the participation in the study, but also to the processing of personal data. Such information includes information regarding the purposes of the collecting, processing, data transfer to other countries. If a subject decides to terminate the study prematurely, data collected before withdrawal of consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor, CRO or a RA may visit the study center to perform audits/inspections, including source data verification (SDV), i.e., comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

10.4.4 Archiving / record keeping

The PI/Institution should permit study-related monitoring, audits, REB review, and RA inspections and should provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e., eCRF, medical records, original signed ICF and detailed records of study product accountability). The records should be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring SDV. In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record or other relevant source.

10.5 Protocol deviations

The PI is not allowed to deviate from the CSP and no up-front waivers from the CSP will be issued. Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken.

Under emergency circumstances, deviations from the CSP to protect the rights, safety and well-being of the subjects may proceed without prior approval of the Sponsor and the REB. Such deviations should be documented and reported to the REB as soon as possible. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations will be performed as described in the monitoring manual. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor (within 24 hours following detection) as well as the REB required.

10.6 Quality control / quality assurance

10.6.1 Clinical Monitoring

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CSP, subsequent amendment(s), GCP and the applicable regulatory requirements. Specific details about monitoring in the study will be outlined in a separate Monitoring Plan.

10.6.2 Audits / inspections

The study center may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

10.7 Protocol amendments

10.7.1 Amendments

The PI and other site personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the REB, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version-controlled written protocol amendment.

10.8 Financing, indemnification and insurance

This study is fully sponsored by Galderma LLC and Q-Med AB. The CTA between Sponsor (or the CRO) and Investigational sites outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

10.9 Publication policy

The PI's, Institution's, Galderma LLC and Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database www.ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[V]. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above-mentioned criteria, one author will be appointed by Galderma LLC and Q-Med AB to take primary responsibility for the overall work as primary author.

[V] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

11. REFERENCES

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3. Yutskovskaya YA, Sergeeva AD, AI K, Marina. L. Contouring of Lower Face and Chin in Consideration of Facial Morphotypes and Shapes- Is it a More Accurate Approach?: Madridge Journal of Dermatology & Research; 2017. p. 26-31.
4. Wat H, Wu DC, Goldman MP. Noninvasive Body Contouring: A Male Perspective. Dermatol Clin. 2018;36(1):49-55.
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12. Appendices

Appendix 1 Galderma Jawline Scale (GJS)

CCI

[redacted]

CCI

[redacted]

CCI

CCI

CCI

SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

CTN: 05DF2209

Title of the CSP: *A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of Restylane Lyft Lidocaine for jawline definition.*

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the instructions for use (IFU) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study center

SPONSOR SIGNATURES

The Clinical Study Protocol is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.

Senior Medical Expert:	PPD , MD, MPH
Head of Clinical Project Management:	PPD , MBA
Global Head of Clinical Scientists:	PPD PhD
Head of Medical Affairs Strategy Ax	PPD , MD
Senior Clinical Scientist:	PPD , MSc
Statistician:	PPD , MSc

SIGNATURES PAGE

Date	Signed by
2022-10-20 16:59	PPD
Justification	Compiled by
2022-10-20 18:46	PPD
Justification	Approved by Technical Expert
2022-10-21 09:30	PPD
Justification	Approved by Owner
2022-10-21 09:59	PPD
Justification	Approved by
2022-10-21 10:51	PPD
Justification	Approved by Medical Affairs
2022-10-21 11:05	PPD
Justification	Approved by Technical Expert