Protocol number: 43CH2305

Clinical Study Protocol

A Randomized, Split-Hand, Subject-Blinded Study Comparing Pain, Safety and Effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without Lidocaine for Improved Appearance of the Dorsal Hand in Chinese Subjects

Name of Investigational Medical Device: Crosslinked Sodium Hyaluronate Gel for Injection

Model & Specification： Restylane® Skinboosters™ Vital Lidocaine, 1mL/syringe

Whether it is the Class III medical device which needs clinical study approval from NMPA?
Yes☐ No☒

Leading Clinical Study Institution: Huashan Hospital, Fudan University

Coordinating Investigator: PPD

Sponsor：

Galderma SA
Zählerweg 10
6300 Zug
Switzerland
Telephone: +41 76 352 2430

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Abbreviations list

AE	Adverse Event
BOCF	Baseline observation carried forward
Co-ordinating Investigator	An Investigator assigned the responsibility for the coordination of Investigators at different centers participating in a multicenter study
CSP	Clinical Study Protocol
CTA	Clinical Trial Agreement
CTN	Clinical trial number
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
FAS	Full Analysis Set
FSFV	First Subject First Visit
G	Gauge
CCI	[redacted]
GCP	Good Clinical Practice
HA	Hyaluronic acid
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
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 clinical studies are conducted.
Investigator	The Principal Investigator or other qualified person, i.e. sub-Investigator, designated and supervised by the Principal Investigator at a study site to perform critical study-related procedures and/or make important study-related decisions as specified on the delegation log.

Investigator File	Essential documents relating to a clinical study as defined in GCP guidance document and maintained by the Investigator.
ISF	Investigator Site File, see above.
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
NSAIDs	non-steroid anti-inflammatory drugs
PI	Principal Investigator
PP	Per protocol
QA	Quality assurance
RA	Regulatory authority
PT	Preferred term
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.
TSE	Transmissible spongiform encephalopathy
TW	Thin Wall
U-HCG	Urinary human chorionic gonadotropin
VAS	Visual Analogue Scale
WHO	World Health Organization

Protocol Synopsis

Clinical Study Title:	A Randomized, Split-Hand, Subject-Blinded Study Comparing Pain, Safety and Effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without Lidocaine for Improved Appearance of the Dorsal Hand in Chinese Subjects.
Clinical Trial Number:	43CH2305
Indication:	The study products are intended for injection in the dorsal hand to improve its appearance by increasing the tissue volume in patients over the age of 18.
Study Population:	Subjects of Chinese origin, age ≥ 18 years, who are eligible for treatment to improve the appearance of the dorsal hand by increasing tissue volume.
Country(ies) Involved and Planned Number of Study Centers:	Country(ies): China No. of Study Centers: 3
Total Number of Subjects (Planned):	Approximately 90 subjects will be enrolled.
Clinical Study Design:	This is a randomized, multi-center, split-hand, subject-blinded study comparing pain, safety and effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without lidocaine for improving appearance of the dorsal hands in Chinese subjects. Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomization on Day 1. The Screening Visit and Baseline Visit can be performed on the same day. Each subject will receive treatment on Day 1 with Restylane Skinboosters Vital Lidocaine® in one hand and Restylane Vital in the opposite hand, as randomly assigned. Study treatment will be unblinded for the Treating Investigator. The first injection will always start in the right hand. No topical or local anesthetic or other pain-relieving medication should be used before all Visual Analogue Scale (VAS) assessments are completed. Ice for pain relief is allowed and should be applied equally on both hands before treatment. Ice may also be used after all VAS evaluations have been completed, and an approximately two-minute ice application time per hand is recommended. The second treatment, that is the injections in the left hand, will be performed after the treatment of the first (right) hand and the VAS assessment at T0 of the right hand is completed. The subject will assess pain experienced directly after treatment on a 100 mm VAS at the end of each treatment (before massaging the treatment area). The

	time should be recorded in the electronic Case Report Form (eCRF) and the pain will thereafter be assessed by the subject at 10±3, 20±3, and 30±3 minutes on the VAS after the treatment on the right and left hand, respectively. After the treatment of each hand is finished, and after the T0 pain assessment is complete, massage can be performed on the treated area of that hand. It is recommended not to exceed five minutes of massage to avoid affecting subsequent VAS assessments. It is not necessary to massage both hands simultaneously. A safety follow-up telephone call should be made 72 hours after treatment. CCI [redacted] CCI [redacted]
Primary Effectiveness Objective and Endpoint:	To demonstrate that Restylane Skinboosters Vital Lidocaine is associated with less pain than Restylane Vital when injected in the dorsal hand for improvement of appearance. *Endpoint:* The within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at end of injection (T0).

CCI [redacted]

	CCI [redacted]
Exploratory Objective and Endpoint:	Not applicable
CCI [redacted]	[redacted]
Clinical Study Duration:	From First Subject First Visit (FSFV) to LSLV (Last Subject Last Visit) throughout the study interval: approximately 16 weeks; including: • 12 weeks enrollment • 2 weeks screening • 2 weeks follow-up after treatment
Inclusion Criteria:	1. Signed and dated informed consent to participate in the study 2. Chinese origin 3. Age at least 18 years 4. The subject is willing and able to comply with the requirements of the study and agrees to adhere to the visit schedule and to be compliant to the study instructions 5. Subjects eligible for treatment to improve appearance of the dorsal hand by increasing tissue volume 6. Same grade of tissue degeneration and need for treatment in both

	hands

Exclusion Criteria:	1. Any previous non-permanent or permanent implant/filler in the hands, including autologous fat 2. Any mesotherapy or resurfacing procedure (laser, chemical peels or other ablative or non-ablative treatment) in the hands within 6 months prior to baseline 3. Any previous hand surgery including sclerotherapy 4. Any fibrosis or scarring or deformities on the hands 5. Advanced photoaged/ photodamaged skin (e.g. advanced skin elastosis, multiple lentigo solaris lesions) or skin condition with very crinkled or fragile skin on the dorsal hands 6. Subjects with active skin disease, inflammation or related conditions in the hand 7. Subjects with a history of precancerous (e.g. actinic keratosis) or cancerous lesions in the hands 8. Subjects with a history of Raynaud´s disease or phenomenon, or history of other disease that may affect peripheral circulation 9. History of neurological disease that may affect peripheral neurological function 10. Subjects with a history of autoimmune disease or joint disease or connective tissue disease (e.g. rheumatoid arthritis, lupus, scleroderma etc) 11. Subjects with known hypersensitivity to any ingredient of the study product or anesthesia used in the study or with a history of any significant Adverse Events caused by dermal fillers 12. Use of topical retinoids on the dorsal hands within 6 weeks prior to baseline or use of systemic retinoids within 6 months prior to baseline 13. History of chronic lymph edema or breast cancer /mastectomy with potential to cause edema 14. Concomitant thrombolytic or anticoagulant therapy and therapy with inhibitors of platelet aggregation, (e.g. non-steriod anti-inflammatory drugs, acetylsalicylic acid, Omega 3 and Vitamin E) within 2 weeks

	prior to treatment, or a history of bleeding disorders. Cyclooxygenase-2 (COX-2) inhibitors are allowed. 15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (dorsal hands) corticosteroids (inhaled corticoids are allowed) within three months before study treatment 16. History of untreated epilepsy or other significant medical conditions 17. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 18. Subjects participating in another interventional clinical study within 30 days of baseline 19. Subjects with unattainable expectation with regard to the aesthetic results of the treatment 20. Subjects who are involved in conducting the study (e.g. colleagues within the same department) or close relatives to any of the study staffs (e.g. parents, children, siblings or spouse) as well as subjects who are employed by the Sponsor company, or close relatives of employees at the Sponsor company 21. Subjects with any other condition which in the opinion of the Investigator, might compromise the subject's ability to tolerate the injection procedure or comply with requirements of the study
Investigational Product:	**Restylane Skinboosters Vital Lidocaine** Composition: • Crosslinked sodium hyaluronate 20 mg/mL • Lidocaine hydrochloride 3 mg/mL • Phosphate buffered saline q.s. ad 1 mL Restylane Skinboosters Vital Lidocaine is supplied in a glass syringe, packed in a blister and outer carton. The product has a built in dose-guide, SmartClick System, which when activated creates a clicking sound and haptic feedback to indicate each injected dose. The 1 mL syringe gives approximately 100 such doses of 10 µL each. Disposable sterile 29G x ½" TW (thin wall) needles are co-packed with the study product.

Comparator Product:	**Restylane Vital** Composition: • Crosslinked sodium hyaluronate[1] 20 mg/mL • Phosphate buffered saline pH 7 ad q.s. 1 mL [1]Produced from pharmaceutical grade sodium hyaluronate and crosslinking agent BDDE. Restylane Vital will be provided in a glass syringe containing 1 ml of gel. The study sites will be provided with disposable sterile 29G x ½" TW needles for use in the study.
Treatment area/ Treatment regimen/ Mode of administration:	The study product is intended for injection in the dorsal hand. Disposable 29G x ½" TW needles should be used for both study products. Study product should be injected in the dermal layer of the skin, preferably in the deeper part of dermis. Allowed injection techniques are; multipuncture or short linear. Inject slowly while pulling the needle backwards. No more than 20 µL should be injected per injection point when using the multipuncture technique. Slowly inject 20 µL droplets in the dermal layer of the skin, spacing droplets 0.5-1.0 cm apart to cover the entire treatment area. 20 µL equals to 2 clicks when injecting with the smart click function activated on the Restylane Skinboosters Vital Lidocaine syringe. The volume for each treatment should be adjusted depending on the subject's need and a volume of 0.5-1 mL for one hand per treatment session will be allowed. The same volume should be used for both hands. *Treatment Blinding* To ensure the subject is kept treatment-blind the following measures are to be employed at the study site when injecting: - The same injection techniques, volume per injection point and similar total volume should be used for both hands as described above. - At the discretion of the investigator, the subject can listen to white noise/music in headphones during the treatment to cancel out the click sounds from the syringe when injecting Restylane Vital Skinboosters Lidocaine. - The injection will be performed behind a screen to prevent the subject from seeing the type of syringe used in order to achieve subject blinding. *Post-treatment care* No topical or local anesthetic or other pain-relieving medication should be used

	before all VAS assessments are completed. Ice for pain relief is allowed after all VAS evaluation is completed. If any irregularities are noted after the use of ice pack, the treated area can be massaged again. A cream can be used during massage at the discretion of the investigator. The subjects will be asked to avoid intensive physical stress (training) or intensive manual activities involving the hand, extensive heat (sauna)/sun or extreme cold in the first 2 days after the treatment . The subjects will also be asked to avoid extensive exposure to potential skin irritants (e.g. cosmetics or laundry detergent) that could affect the skin in the treated area before the skin has healed completely in order to prevent infections.
Effectiveness Assessments:	• Pain assessment by Visual Analogue Scale (VAS) [redacted]
Safety Assessments:	• Adverse Events (AEs) [redacted]
Other Assessments:	• Pregnancy Test • Photography
Statistical Method:	In general, all effectiveness, safety and baseline characteristics variables will be presented using descriptive statistics and graphs as appropriate. Continuous data will be summarized by descriptive statistics n (number of observations), mean, standard deviation, median, minimum and maximum value, while categorical data will be presented by number of subjects and percentage. **Primary analysis** The primary endpoint in this study is defined as the within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at the end of injection. The null hypothesis (H_0) that the within-subject difference in VAS is greater than or equal to 0 mm will be tested against the alternative hypothesis (H_1) that the within-subject difference in VAS is less than 0 mm using a one-sample t-test. More formally, the following statistical hypotheses will be tested, with the within-subject difference denoted by Δ: $\begin{cases} H_0: \Delta \geq 0\ mm \\ H_1: \Delta < 0\ mm \end{cases}$ If the one-sided p-value of the test is <0.025, the pain at the end of injection will be considered statistically significantly lower after treatment with Restylane Skinboosters Vital Lidocaine than after treatment with Restylane

	Vital, and thus the primary objective will be considered met. Results will include mean VAS by treatment, mean within-subject difference in VAS, and the p-value along with standard descriptive statistics and two-sided 95% confidence interval around the difference. If the distribution of the within-subject differences indicates deviation from the normality assumption, non-parametric methods will be used. CCI [redacted]
Sample Size:	Several studies have been performed comparing the same hyaluronic acid (HA) filler product with and without the addition of lidocaine or other analgesics. In the study 43CH1504, comparing Restylane for treatment of nasolabial folds with and without Lidocaine in subjects with Chinese ethnicity, the observed within-subject difference in VAS during injection was 33.0 mm with a standard deviation of 24.4 mm. In another study, in subjects with Chinese ethnicity, 43TW1628, comparing Restylane Perlane with and without Lidocaine, the mean within-subject difference in VAS at injection was 32.0 mm with a standard deviation of 19.5 mm. However, due to the many injection points in the treatment of the hands, it is believed that the within-subject difference in VAS will be considerably less in this study than what was seen in the NLFs in the two previous studies referred to. Thus, assuming a true mean within-subject difference of -10 mm and a standard deviation of 25 mm, a significance level of 2.5% and using a one-sided one-sample t-test, inclusion of 68 subjects will give a power of 90% to reject the null hypothesis of ≥0 mm within-subject difference. To ensure sufficient power in the event of the need of a non-parametric test for the primary analysis, approximately 15% more subjects will be added to the 68 needed for the t-test. Hence, approximately 80 subjects will be needed for the primary analysis. In addition, a drop-out rate of approximately 10% is assumed. Thus, approximately 90 subjects will need to be randomized in order to have at least 80 evaluable subjects for the statistical analysis.

Interim Analysis:	Not applicable – no interim analysis is planned to be performed in this study.

1 Sponsor's Information

1.1 Sponsor's Name:

Galderma SA

1.2 Sponsor's Address

Zählerweg 10
6300 Zug
Switzerland

1.3 Sponsor's Contact Information

Sponsor's Contact Information:	PPD
Name, Address, Contact information and relevant certifications of Agent	PPD PPD

2 The Information of Clinical Study Institutions and Principal Investigators

The final list of sites participated in the study will be filed in the study files.

3 Background Information of Clinical Study

3.1 Background Information of Research and Development

Among the different materials used as raw materials in injectable fillers for aesthetic use, sodium hyaluronate, also denoted hyaluronic acid when found in vivo and hereinafter referred to as HA, is the most frequently used.[1] Hyaluronic acid is a naturally occurring polysaccharide found in all vertebrates and in some bacteria.[1,2] The chemical structure of HA is very simple with repeating disaccharide units of glucuronic acid and N-acetylglucosamine. As the chemical structure of HA is identical in all species and tissues, it is non-allergenic.

To eliminate the risk for transmitting diseases between closely related species (i.e. transmissible spongiform encephalopathy; TSE), the HA used in the manufacture of HA gels in Restylane Vital is of non-animal source, biosynthesised from Streptococcus species of bacteria.

During manufacturing, cross-links are introduced between the HA chains using the NASHA™ technology in order to obtain a gel network. As a result, the duration of the gel in the body is several months, as compared to only a few days for a solution of native HA.

Restylane Vital is injected in the skin to improve its appearance by increasing the tissue volume. The mode of action is based on the physical effects of the gel when integrated in the skin. The effects originate from the ability of crosslinked hyaluronic acid to bind water. Restylane Vital will degrade gradually in the body. With degradation the effect will disappear. The patients, who want to keep the effect can receive follow-up treatment when the effect becomes less visible or disappears. In a clinical study conducted in China, the effect remained at least 3 months after the initial injection in most patients. These subjects were injected with Restylane Vital in the dorsal hand three times 4 weeks apart.

Restylane Vital indicated for dorsal hands to improve its appearance by increasing the tissue volume in patients over the age of 18 has been approved in China since Dec 2019. This study is initiated to assess if Restylane Skinboosters Vital Lidocaine provides a pain-relieving effect comparing to Restylane Vital without lidocaine.

3.2 Clinical Rational for Addition of Lidocaine in Restylane Vital

From a historical point of view it's worth mentioning that incorporation of lidocaine in collagen based dermal fillers to improve treatment comfort was introduced already in the 1980s. As the collagen based dermal fillers position as industrial standard for dermal fillers was replaced by hyaluronic acid based dermal fillers in the mid 1990s, the interest of incorporating lidocaine into those products to enable an improved treatment comfort has been present.

Restylane Vital, similar to other dermal fillers, is injected into the dermis. Clinical study data has demonstrated that injections in the dermis and the subcutaneous fat with the addition of lidocaine provide a more comfortable treatment due to pain reduction.[3,4]

Pain experienced during treatment with dermal fillers can be attributed to pain generated during the initial space occupation of the gel and therefore the addition of lidocaine reduces pain from

skin penetration of needle or cannula. In addition, there are indications from the literature that lidocaine has an inhibitory effect on proinflammatory as well as pain-mediating substance.[5,6] During an initial expansion of the tissue, as is the case when injecting and depositing the gel, a tension pressure occurs until the surrounding tissue has adjusted to the gel deposit. A rapid expansion of the tissue as well as the insertion of the needle cause damage in the tissue with transient release of proinflammatory and pain-mediating substances, which contributes to anticipated injection related reactions such as tenderness, redness, pain (including burn) and swelling.

Added ancillary lidocaine in the injected gel has thus some capacity to counteract this effect and thereby a potential to give increased post treatment comfort, including decreased overall treatment associated pain and post treatment pain. The clinical finding of improved treatment comfort with the addition of lidocaine has led Galderma SA to evaluate the beneficial effect of adding lidocaine to Restylane Vital.

3.2.1 Mode of Action and Performance

Restylane Skinboosters Vital Lidocaine is injected in the skin to improve its appearance by increasing the tissue volume. The mode of action is based on the physical effects of the gel when integrated in the skin. The effects originate from the ability of crosslinked hyaluronic acid to bind water. Restylane Skinboosters Vital Lidocaine will degrade gradually in the body. With degradation the effect will disappear. The patients, who want to keep the effect can receive follow-up treatment when the effect becomes less visible or disappears.

3.3 Basic Information of Investigational Product

3.3.1 Description of the Device

Restylane Skinboosters Vital Lidocaine is an injectable, sterile, transparent, biodegradable gel of non-animal crosslinked sodium hyaluronate. Restylane Skinboosters Vital Lidocaine has the addition of lidocaine hydrochloride. They are supplied in a glass syringe. The products have a built in dose-guide, SmartClick System, which when activated creates a clicking sound and haptic feedback to indicate each injected dose. The 1 mL syringe gives approximately 100 such doses of 10 µL each. The contents of the syringe are sterilized using moist heat. The products are for single patient and single session use only. Disposable 29G needles sterilized using ethylene oxide are provided.

3.4 Previous Clinical Study

Restylane Vital was approved for marketing in Europe 2004. It has been in clinical use in Asian population for many years, e.g. in Hong Kong (marketing approval 2007), Taiwan (marketing approval 2008) and South Korea (marketing approval 2009). Restylane Vital was approved for marketing indicated for dorsal hands in China in Dec 2019 based on a pivotal study 43CH1406.[7]

Restylane® Skinboosters™ Vital Lidocaine is part of the Restylane family and is, similar to Restylane, manufactured using the NASHA Technology. The product obtained CE mark in 2004 (without lidocaine) and in 2011 (with lidocaine) with the intended use to restore skin hydrobalance, improve skin structure and the elasticity of the skin.[8]

As Restylane Skinboosters Vital Lidocaine is originally intended to rejuvenate the skin, it is believed to be suitable for the correction of wrinkles in areas with thin skin. The product is supplied in a glass syringe and has since 2014 a built-in dose-guide, the SmartClick™ injector system, which when activated permits controlled small injection volumes by creating a clicking sound to indicate each injected dose. The 1 mL syringe gives approximately 100 doses. Restylane Vital Lidocaine was the original brand names of the product and it was re-branded to Restylane Restylane Skinboosters Vital Lidocaine when introducing the integrated SmartClick injector system.

The pain-relieving effect of lidocaine added to other Restylane products produced with the NASHA® Technology have been studied in several clinical investigations. It has been shown that the addition of lidocaine does not affect the intended performance of the product. Although the pain-relieving effect has not been studied in clinical investigations of Restylane Skinboosters, it is reasonable to assume that the addition of lidocaine will provide a pain-relieving effect similar to that demonstrated for other Restylane products.

There were 3 clinical studies investigating the effectiveness and safety of Restylane Vital Lidocaine so far:

Study 05DF1206 is an open, non-comparative study on the efficacy and safety of treatment of acne scars with Restylane Vital Lidocaine. In this study, 12 subjects were enrolled for treatment of acne scars and surrounding skin with up to 4 mL of Restylane Vital Lidocaine in 3 treatment sessions spaced 4 weeks apart. The findings demonstrated improvements in the appearance of atrophic, depressed, facial acne scars and in the quality of the surrounding skin following three treatment sessions of Restylane Vital Lidocaine. For the investigator-reported GAIS, 92% of the subjects were assessed to be at least somewhat improved at week 4 and from week 8 to 28, 100% of the subjects were improved. At week 36, 75% of the subjects were satisfied with the structure of the skin compared to 8% at baseline before treatment. In all cases, the satisfaction was increased from week 12, when the treatment regimen was completed, until study end. In terms of safety, eight subjects reported at least one AE that was assessed by the investigator to be procedure-related, and the most common AEs were implant site nodule and implant site redness, each event reported by 5 subjects. All events resolved during the study. Subject diary data showed that the majority of subjects experienced injection-site reactions (such as bruising, redness, swelling, pain (including burn), tenderness, itching and bumps) after treatment. Frequency and severity of all symptoms decreased over time and the majority of the injection-site reactions were resolved within 14 days after each treatment session.[9]

Study 05DF1211 is an evaluator-blinded, within-group, multi-center study of the effectiveness and safety of combined treatment with Azzalure, Restylane/Emervel fillers, and Restylane Skinboosters Vital Lidocaine compared with single treatment with either Azzalure alone (Group A) or Restylane/Emervel filler alone (Group B) in face. There were 61 subjects randomized (1:1) to either Group A or Group B. The study result revealed that the majority of subjects in the study population (83%) as well as in Group A (74%) and Group B (93%) separately, showed a superior

global facial aesthetic appearance after the first combined treatment compared to the single treatment as assessed by the blinded evaluator. A majority of subjects reported GAIS score improvement one month after single and combined treatments. All subjects had improved GAIS at Month 7 and Month 13 as assessed by the investigator. For safety, 27 subjects reported 48 AEs, out of which 41 were considered related to study product or injection procedure. These 41 events included bruising, hematoma, implant site inflammation, edema, swelling, and muscular weakness. All treatment-related AEs were resolved at study end except for two cases of muscle weakness after Azzalure injection. One Serious Adverse Event (SAE) (angina pectoris), considered unrelated to study product was reported.[10]

Study 05DF1404, a randomized, multi-center, parallel-group, efficacy and safety study evaluating two and three initial treatment sessions of Restylane Skinboosters Vital Lidocaine (with the use of the SmartClick system) in the face in which 53 subjects were randomized in a 1:1 ratio to either 3 (Group A) or 2 (Group B) initial treatment sessions showed that a majority of subjects (Group A: 75%; Group B: 84%) were assessed as having superior facial aesthetic appearance at Month 3 after treatment compared to baseline by the blinded evaluator. Subject satisfaction questionnaires showed that subjects were more satisfied with the skin after treatment. Skin hydration was significantly increased compared to baseline at several time-points in both groups, while skin elasticity parameters showed some occasional (but not consistent) improvement after treatment. A total of 46 AEs in 17 subjects (65%) in Group A (3 initial treatment sessions) and 42 AEs in 14 subjects (52%) in Group B (2 initial treatment sessions) were reported. Eight AEs in 4 subjects (16%) in Group A and 16 AEs in 5 subjects (19%) in Group B were assessed as related to the product or injection procedure. The most common related AE was implant site swelling with 5 events in 2 Group A subjects (8%) and 6 events in 2 Group B subjects (7%); reported as mild in intensity. The reported related events were; bruising, swelling, discoloration, nodules, pain at injection site and abnormal skin texture. All events were resolved.[11]

Based on the clinical studies above, Restylane Vital Lidocaine (with a study including the use of the SmartClick system) used in face have shown to improve global aesthetic appearance as well as subject satisfaction, improvement in appearance of scars, skin hydration and elasticity. Overall, the completed clinical studies have shown that treatment of Restylane Vital Lidocaine in face is well-tolerated and safe. The majority of events reported after treatment with Restylane Vital Lidocaine in the face were injection-related, such as bruising, redness, swelling, pain (including burn) and hematoma. The reported events were mostly of mild to moderate character and resolved spontaneously without intervention.

3.5 Scope of Application and the Relevant Information

3.5.1 Intended Purpose

Restylane Skinboosters Vital Lidocaine is for aesthetic use to improve appearance of dorsal hands. The addition of lidocaine provides a pain-relieving effect during treatment.

3.5.2 Indication and Target Population

This product is intended for injection in the dorsal hand to improve its appearance by increasing

the tissue volume in subjects over the age of 18. It should be injected in the dermal layer of the skin, preferably in the deeper part of dermis. The addition of lidocaine is intended to increase overall treatment comfort.

The products shall not be used in patients under 18 years of age.

3.5.3 Intended Users

Injections of Restylane Skinboosters Vital Lidocaine must only be done by plastic surgeons, dermatologists and cosmetic doctors at hospitals and medical plastic surgery institutions officially approved by the administrative authorities. These institutions include clinics for medical cosmetic and plastic surgery, dermatology departments, medical cosmetic outpatient departments and plastic surgery departments in general hospitals and specialized hospitals for medical cosmetic and plastic surgery, which must have obtained a ”Medical Institution Business License”.

3.5.4 Contraindications

- Do not use in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Do not use in patients with a history of hypersensitivity to streptococcal proteins, as the product may contain trace amounts of such material.
- Do not use in patients with known hypersensitivity to lidocaine or to amide-type local anaesthetics.

3.5.5 Warnings and Precautions

3.5.5.1 Warnings

- Use at specific sites where there is active disease, such as inflammation (skin eruption such as cysts, pimples, rashes or hives), infection or tumours, in or near the intended treatment site should be avoided until the underlying process has been controlled.
- Restylane Skinboosters Vital Lidocaine is only intended for use as an intradermal implant. The product should not be used for breast site injections.
- This product must not be injected intramuscularly or intravascularly. Localized superficial ischemia and necrosis with potential scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area. Areas with limited collateral blood flow have an increased risk of ischemia.
- Unintentional intravascular injection may lead to embolization, thrombosis, occlusion of the vessels, ischemia, necrosis or infarction at the implant site or in the area supplied by the blood vessels affected. Stop the injection immediately if blanching occurs or if a patient complains of unusual pain or exhibits any symptoms suggestive of inadvertent intravascular injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate specialist doctor should an intravascular injection occur.
- Patients with bleeding disorders or patients using substances that affect platelet function, thrombolytics or anticoagulants may, as with any injection, experience increased bruising or bleeding at injection site.

- Special care should be taken to avoid injection into tendons in the hand as it may weaken tendons and cause tendon rupture.
- This product should not be mixed with other products prior to injection

3.5.5.2 Precautions

- Doctors are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- This product should only be used by doctors who have appropriate training, experience, and knowledge about the anatomy at and around the site of injection in order to minimize the risks of potential complications (perforation or compression of vessels, nerves and other vulnerable structures).
- Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be followed.
- Use with caution in patients with risk factors for developing hand skin irritation.
- Use in dorsal hand in patients with disease, injuries or disabilities of the hand has not been studied. Care should be used in treating patients with autoimmune disease affecting the hand, Dupuytren's contracture, history of hand tumour, vascular malformations, Raynaud's disease and patients at risk for tendon rupture.
- Avoid injecting into areas with, or in close proximity to, prior implants other than sodium hyaluronate, as this could aggravate latent adverse events or interfere with the aesthetic outcome of the treatment.
- Large bolus injection, injecting too superficially and injections in areas with limited soft tissue support or soft tissue cover, or thin skin, may result in contour irregularities and palpable lumps and/or bluish discolouration.
- Inflammatory pigmentation changes and scarring might occur following soft tissue injections. Patients with abnormal wound healing or dark skin (Fitzpatrick Type IV–VI) may be more prone to developing hypertrophic scarring and keloid formation.
- Injection procedures can lead to reactivation of latent or subclinical herpes viral infections.
- This product should be used with caution in patients with autoimmune disease or on immunosuppressive therapy.
- Patients with unattainable expectations are not suitable candidates for treatment.
- This product is packaged for single patient and single session use only and should be discarded immediately after use. Do not resterilize or reuse the product in order to avoid risks of infections.
- Do not use the product if package is opened or damaged, or if the expiry date or lot number is illegible.
- Patients should avoid excessive sun, UV lamp exposure and extreme temperatures at least until any initial swelling and redness have resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is performed after treatment with this product, there is a theoretical risk of eliciting an inflammatory reaction at the implant site. This also applies if the product is administered before the skin has healed completely after such a procedure.
- The safety for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

- The product contains lidocaine. If additional nerve block or topical lidocaine or other local anesthetics or agents structurally related to amide-type local anesthetics are used concurrently with the product the following considerations should be observed:
  - Use with caution in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.
  - High doses of lidocaine (more than 4.5 mg/kg of bodyweight) can cause acute toxic reactions manifesting as symptoms affecting the central nervous system and cardiac conduction.
  - Systemic toxic effects could be additive.

4 Study Objectives

4.1 Primary Effectiveness Objective

To demonstrate that Restylane Skinboosters Vital Lidocaine is associated with less pain than Restylane Vital when injected in the dorsal hand for improvement of appearance.

Endpoint:

- The within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at end of injection (T0).

CCI [redacted]

CCI [redacted]

4.4 Exploratory Objective

Not applicable

5 Study Design

5.1 Overall of Study Design and Rationale

5.1.1 Overall Study Design

This is a randomized, multi-center, split-hand, subject-blinded study comparing pain, safety and effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without lidocaine for improving appearance of the dorsal hands in Chinese subjects.

Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomization on Day 1. The Screening Visit and Baseline Visit can be performed on the same day.

Each subject will receive treatment on Day 1 with Restylane Skinboosters Vital Lidocaine® in one hand and Restylane Vital in the opposite hand, as randomly assigned. Study treatment will be unblinded for the Treating Investigator. The first injection will always start in the right hand. No topical or local anesthetic or other pain-relieving medication should be used before all Visual Analogue Scale (VAS) assessments are completed. Ice for pain relief is allowed and should be applied equally on both hands before treatment, and an approximately two-minute ice application time per hand is recommended. Ice may also be used after all VAS evaluations have been completed. The second treatment, that is the injections in the left hand, will be performed after the treatment of the first (right) hand and the VAS assessment at T0 of the right hand is completed.

The subject will assess pain experienced directly after treatment on a 100 mm VAS at the end of each treatment (before massaging the treatment area). The time should be recorded in the electronic Case Report

Form (eCRF) and the pain will thereafter be assessed by the subject at 10±3, 20±3, and 30±3 minutes on the VAS after the treatment on the right and left hand, respectively.

After the treatment of each hand is finished, and after the T0 pain assessment is complete, massage can be performed on the treated area of that hand. It is recommended not to exceed five minutes of massage to avoid affecting subsequent VAS assessments. It is not necessary to massage both hands simultaneously.

A safety follow-up telephone call should be made 72 hours after treatment.

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CCI [redacted]

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5.1.2 Study Rationale

Restylane Vital has been subject to a pivotal study confirming safety and efficacy of the product for the treatment of dorsal hands in Chinese populations.

The pain-relieving effect of lidocaine added to other Restylane products produced with the NASHA® Technology have been studied in several clinical investigations, where the addition of lidocaine does not affect the intended performance of the product[1-2]. Therefore, it is reasonable to assume that the addition of lidocaine to Restylane Vital will provide a pain-relieving effect similar to that demonstrated for other Restylane products.

The study aims to evaluate the pain-relieving effect of Restylane Skinboosters Vital Lidocaine on aged skin on the dorsal hand compared to Restylane Vital.

5.2 Selection of Subjects

5.2.1 Inclusion Criteria

1. Signed and dated informed consent to participate in the study
2. Chinese origin
3. Age at least 18 years
4. The subject is willing and able to comply with the requirements of the study and agrees to adhere to the visit schedule and to be compliant to the study instructions

5. Subjects eligible for treatment to improve appearance of the dorsal hand by increasing tissue volume
6. Same grade of tissue degeneration and need for treatment in both hands

5.2.2 Exclusion Criteria

1. Any previous non-permanent or permanent implant/filler in the hands, including autologous fat
2. Any mesotherapy or resurfacing procedure (laser, chemical peels or other ablative or non-ablative treatment) in the hands within 6 months prior to baseline
3. Any previous hand surgery including sclerotherapy
4. Any fibrosis or scarring or deformities on the hands
5. Advanced photoaged/ photodamaged skin (e.g. advanced skin elastosis, multiple lentigo solaris lesions) or skin condition with very crinkled or fragile skin on the dorsal hands
6. Subjects with active skin disease, inflammation or related conditions in the hand
7. Subjects with a history of precancerous (e.g. actinic keratosis) or cancerous lesions in the hands
8. Subjects with a history of Raynaud´s disease or phenomenon, or history of other disease that may affect peripheral circulation
9. History of neurological disease that may affect peripheral neurological function
10. Subjects with a history of autoimmune disease or joint disease or connective tissue disease (e.g. rheumatoid arthritis, lupus, scleroderma etc)
11. Subjects with known hypersensitivity to any ingredient of the study product or anesthesia used in the study or with a history of any significant Adverse Events caused by dermal fillers
12. Use of topical retinoids on the dorsal hands within 6 weeks prior to baseline or use of systemic retinoids within 6 months prior to baseline
13. History of chronic lymph edema or breast cancer /mastectomy with potential to cause edema
14. Concomitant thrombolytic or anticoagulant therapy and therapy with inhibitors of platelet aggregation, (e.g. non-steriod anti-inflammatory drugs, acetylsalicylic acid, Omega 3 and Vitamin E) within 2 weeks prior to treatment, or a history of bleeding disorders. Cyclooxygenase-2 (COX-2) inhibitors are allowed
15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (dorsal hands) corticosteroids (inhaled corticoids are allowed) within three months before study treatment
16. History of untreated epilepsy or other significant medical conditions

17. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
18. Subjects participating in another interventional clinical study within 30 days of baseline
19. Subjects with unattainable expectation with regard to the aesthetic results of the treatment
20. Subjects who are involved in conducting the study (e.g. colleagues within the same department) or close relatives to any of the study staffs (e.g. parents, children, siblings or spouse) as well as subjects who are employed by the Sponsor company, or close relatives of employees at the Sponsor company
21. Subjects with any other condition which in the opinion of the Investigator, might compromise the subject's ability to tolerate the injection procedure or comply with requirements of the study

5.2.3 Screening and Subject Numbers

Each screened subject will be assigned a screening number consisting of "S" and the site number followed by a consecutive number starting with 01 at each site, e.g. S101, S102.The screening number shall be listed on a subject screening and inclusion log.

A "screening failure" is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the eCRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log.

When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each enrolled subject will be assigned a subject number by the eCRF consisting of the site number followed by a consecutive number starting with 01 at each site, e.g. 101, 102.

The subject number, subject name, and other information sufficient to link the eCRF to the medical records (e.g. national identification number, chart number, etc.) shall be recorded on a subject identification list. The subject identification list shall only be available at the site, both throughout and after the study.

5.2.4 Withdrawal of Subjects

Each subject shall be advised in the Informed Consent Form that the subject has the right to withdraw from the study at any time, for any reason, without prejudice. Subjects may also be discontinued from this study if the Investigator determines that it is in the subject's best interest to do so, and may be withdrawn at the Investigator's discretion at any time.

The withdrawal criteria are:

- **Medical reasons**: If the subject suffers from a medical condition that in the judgement of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons shall document the specific condition for withdrawing the subject.
- **Withdrawal of informed consent:** 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 authorised 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, e.g. call three times at different hours and leave messages if applicable before declaring the subject lost to follow-up.
- **Other:** Examples of other reasons for withdrawal may be failure to comply with protocol requirements or to complete the protocol-specified evaluations.

The reason and date for withdrawal shall be documented in the eCRF. When possible, an explanatory comment shall be added in the study termination module/pages to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible together with the study termination eCRF module.

If withdrawal of a subject occurs between regular study visits the subject should when possible (irrespective of the reason for withdrawal) be scheduled for a termination visit. In these cases the eCRF for the early termination visit should be completed. The subject will need to follow the same requirements for the final visit.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses.

A withdrawn or discontinued subject must not be replaced or re-entered into the study.

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, such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or for at least three months.

5.2.5 Duration of Subject Participation

The study subjects will be treated at the baseline visit and thereafter followed for 2 weeks. The total duration of participation in this study for each subject will be approximately up to 4 weeks.

5.3 Effectiveness Assessments

5.3.1 Primary Efficacy Assessment:

5.3.1.1 Pain assessment by Visual Analogue Scale (VAS)

The VAS is a subjective scale to measure pain intensity (Appendix 1). The subject shall be instructed to put a vertical mark, approximating the pain experienced after the procedure, on a 100 mm horizontal line labelled "no pain" at the left end and "the worst pain you can imagine" at the

right end. The distance in mm from the left end (no pain) to the subject's VAS mark shall be measured with a standard ruler. Each hand will be evaluated independently.

Subjects will evaluate injection site pain for each hand at the time of injection completion (before massaging) and at 10, 20, and 30 minutes post-treatment by completing a VAS.

CCI

[redacted]

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

[redacted]

5.3.3 Basis of Efficacy Parameter Determination

VAS score has been widely used in many clinical studies of HA as efficacy endpoints to evaluate the pain-relieving effect of the lidocaine added to the product, including trials sponsored by Galderma SA and its group companies**Error! Reference source not found.**.

CCI [redacted]

5.4 Safety Assessments

Safety assessments will be conducted for all subjects at the screening visit (after informed consent is signed) and at subsequent visits (see Section 5.7.2.3, Schedule of events). Safety parameters include an evaluation of AEs and Post-treatment events collected in the subject diary.

5.4.1 Adverse Events (AEs)

AEs are to be monitored throughout the course of the clinical study from the time the Informed Consent Form (ICF) has been signed (see Section 5.7.2.3, Schedule of events). All AEs are to be reported on the AE form in the eCRF with complete information as required.

If AEs occur, the main concern shall be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical study site personnel for reporting AEs and medical emergencies.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example, “Have you noticed any change in your health since the last visit?” Additional questioning and examination will then be performed as appropriate.

CCI [redacted]

CCI

5.4.3 Basis of Safety Parameter Determination

Both AE and pre-defined expected post-treatment events evaluated in a subject diary have been widely adopted as safety parameters in many clinical studies of medical devices, including several trials sponsored by Galderma SA and its group companies and the pivotal study of Restylane Vital for the treatment of soral hands, 43CH1406**Error! Reference source not found.,Error! Reference source not found.**.

5.5 Photography

Photographs will be taken at baseline, prior to the first injection of the study product and at the follow-up visit at Day 15. The baseline photographs were used for the assessment CCI. The photographs could also be used to document AEs in the treatment area.

Camera equipment will be provided by the Sponsor and standardized photographs will be obtained according to detailed instructions in a separate photography user manual. Each hand will be photographed separately. Each Investigator and other study site personnel designated to take photographs, if applicable, shall be thoroughly trained in the equipment and techniques, and how to upload photographs to the secured web portal, if applicable, before study start. For further details, please see the instruction in photography user manual.

5.6 Study Medical Device and Control Medical Device

5.6.1 Study Medical Device (Investigational Product)

Restylane Skinboosters Vital Lidocaine

Restylane Skinboosters Vital Lidocaine is a sterile, transparent and biodegradable gel of crosslinked hyaluronic acid of non-animal origin with the addition of 0.3% lidocaine hydrochloride. It is supplied in a glass syringe with a luer-lock fitting. The product has a built in dose-guide, Smart Click™ System, which when activated creates a clicking sound and haptic feedback to indicate each injected dose. The 1 ml syringe gives approximately 100 doses of 10 µL each. The contents of the syringe are sterilized using moist heat. The exterior of the syringe, including finger grip and plunger rod are not sterile. The product is for single use only. Three disposable 29G TW (thin wall) needles, sterilized using ethylene oxide, are provided.

Composition:

- Crosslinked sodium hyaluronate 20 mg/mL
- Lidocaine hydrochloride 3 mg/mL
- Phosphate buffered saline pH 7 ad q.s. 1 mL

Needle

Three disposable sterile 29G TW (thin wall) x ½ “ needles are provided. The size, length or wall thickness of the needle can affect the force needed to extrude the gel. The longer the needle is, and

the smaller the inner diameter is, the higher the resistance during injection and the higher the risk of leakage or separation of the needle from the syringe.

5.6.2 Packaging, Labelling and Storage

Restylane Skinboosters Vital Lidocaine manufactured by Q-Med AB, Sweden who will supply the study products.

The syringe filled with Restylane Skinboosters Vital Lidocaine gel and the supplied needles are packed in a blister and put in a carton. The syringes are labelled with name of the product, name of the manufacturer (Q-Med AB). The carton will be labelled in local language, specifying the protocol number, lot number, expiry date and that the product is to be used for clinical studies exclusively.

Opened syringes should not be re-used. Accountability will be performed as specified in section 5.6.4.

Restylane Skinboosters Vital Lidocaine should be stored up to 25° C. Protect from freezing and sunlight.

5.6.3 Control Medical Device (Comparator Product)

Restylane Vital

Restylane Vital will be provided in a glass syringe containing 1 ml of product. The study sites will be provided with 29 G needles Disposable sterile 29G x ½" TW needles for use in the study.

Composition:

- Crosslinked sodium hyaluronate* 20 mg/mL
- Phosphate buffered saline pH 7 ad q.s. 1 mL

*Produced from pharmaceutical grade sodium hyaluronate and crosslinking agent BDDE.

In terms of packaging, labelling, and storage of Restylane Vital, please see co-packed Restylane Vital Instructions for Use (IFU).

5.6.4 Product Accountability

The study product will be released to the PI or his/her authorised designee after study approvals have been received from the IEC and the 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 authorised by the PI.

The study product must be traceable from the manufacturer to its use in subjects until

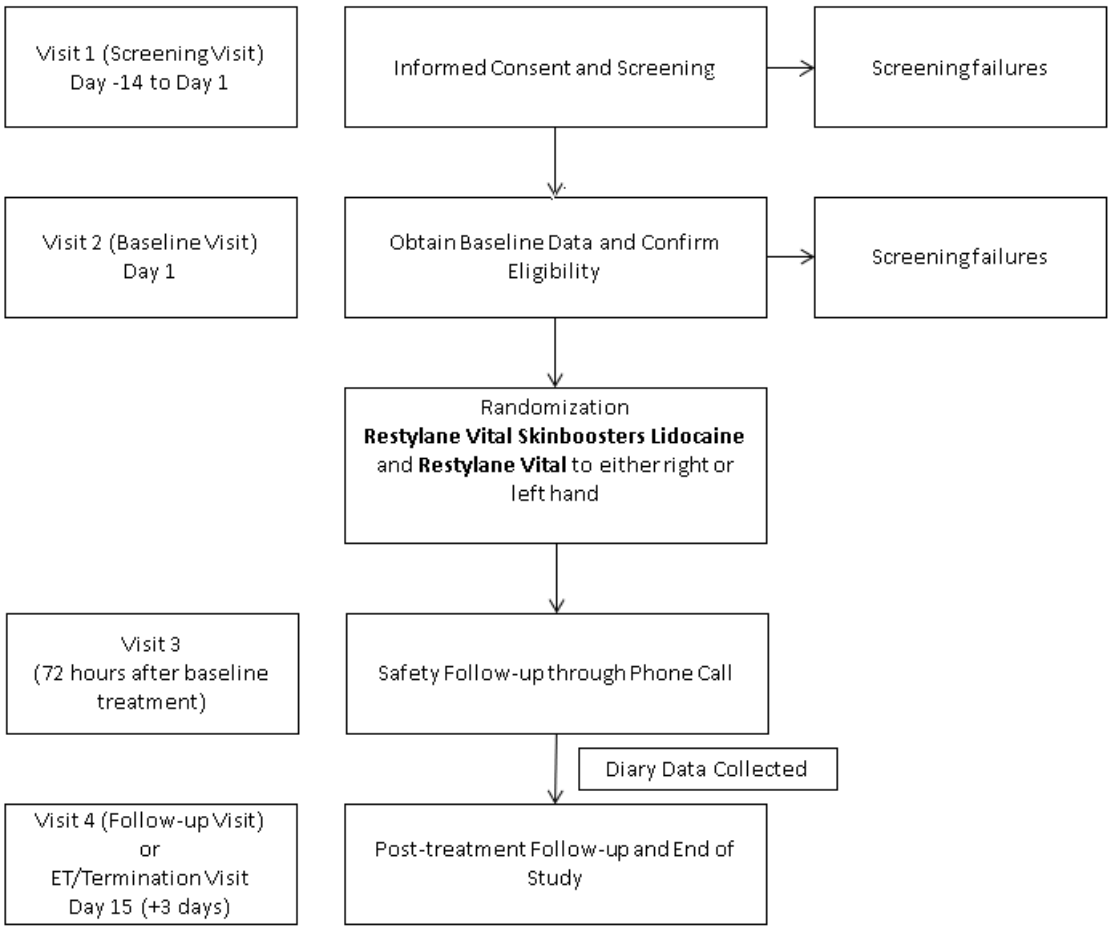
return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study product between the Sponsor or a third-party vendor and the PI, and documentation of administration of product to the subjects. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, batch number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, dispense date, the number of syringes used, the number of syringes left in stock, and the subject receiving study product. A log for accountability procedure is provided by the Sponsor.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor or a third-party vendor for destruction. Any malfunctioning study products shall be reported as described in the protocol.

Product deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, disposable needle, and any opened unused material must be discarded and must not be reused according to standard procedures at the site. Disposal of hazardous material, i.e. syringes and needles must conform to applicable laws and regulations. The study product must not be used outside the study.

5.7 Study Procedures

5.7.1 Study Flowchart



5.7.2 Study Execution

5.7.2.1 General Outline

This is a randomized, multi-center, split-hand, subject-blinded, study comparing pain, safety and efficacy of Restylane Skinboosters Vital Lidocaine and Restylane Vital without lidocaine for improving appearance of the dorsal hands in Chinese subjects.

5.7.2.2 Number of subjects

There will be approximately 90 subjects randomized to receive treatment with Restylane Vital on one hand and Restylane Skinboosters Vital Lidocaine on the other hand.

5.7.2.3 Schedule of events

Assessment/Event Visit windows are calculated from Visit 2.	**Visit 1** Screening[1] Day -14 to 1	**Visit 2** Baseline Treatment Day 1	**Visit 3** 72 hours after Baseline (Phone Call) (±24 hours)	**Visit 4** End of Study/Early Termination Day 15 (+3 days)
Informed Consent	X			
Demographic Data[2] including, medical history & concurrent diseases, previous hand treatments/procedures	X	X		
Demographic Data of Height and Weight		X		
Eligibility criteria	X	X		
Urine Pregnancy Test[3]		X		
Photography		X[4]		X
Randomization		X		
Treatment		X[5]		
VAS pain assessment		X[6]		
CCI				
Device deficiencies		X		
CCI				
Concomitant Meds/Procedures	X	X	X	X
Adverse Events		X	X	X
CCI				

1. Screening and baseline/treatment may be performed on the same day.
2. Includes date of birth, gender, and ethnicity.
3. Only for women with childbearing potential. Should be done before randomization and must be negative for subject to be enrolled. U-HCG should be analyzed at the local hospital laboratory
4. Should be done before injection and after injection, also be done once AE occurs after injection
5. Right and left hand will be assigned treatment with either Restylane Vital Skinboosters Lidocaine or Restylane Vital. The right hand should be treated first, and the injections in the left hand will be performed after the treatment of the first (right) hand and the VAS assessment at T0 of the right hand is completed.
6. Subjects will evaluate injection site pain for each hand using the VAS at the end of treatment and 10±3, 20±3, and 30±3 minutes post-treatment.

[redacted]

5.7.2.4 Visit Description

Visit 1: Screening (Day -14 to 1)

- The subject must be informed about the study both orally and in writing, and the Informed Consent Form must be signed before any study-related activity is performed.
- The Investigator shall verify the inclusion and exclusion criteria for each subject (Section 5.2).
- All demographic and baseline assessments according to Section 5.7.2.5 shall be performed by the Investigator.
- Record concomitant medications/procedures
- The subjects shall be informed that they should try their best to use their usual hand skincare and cleaning procedures of the hands during the study.
- For subjects who fail any of the inclusion or exclusion criteria, applicable parts of the screening visit eCRF should be completed, and the subject should be recorded as a screening failure in the Screening and Enrolment Log (Section 5.2.3) and in the eCRF.

Visit 2: Baseline Treatment (Day 1)

- All demographic and baseline assessments according to Section 5.7.2.5 shall be performed by the Investigator.
- The Investigator shall verify the inclusion and exclusion criteria for each subject (Section 5.2.1 and 5.2.2).
- The Investigator shall ask for any health problems since the last visit and any changes in hand skin care, concomitant medications or procedures performed.
- A pregnancy test (urinary human chorionic gonadotropin; U-HCG) shall be performed in subjects of childbearing potential.
- If the subject is still eligible for the study, the subject shall be randomized in accordance with the randomization procedure (Section 5.8.1).
- For eligible subjects both hands will be treated with study products. The first injection will always start in the right hand. No topical or local anesthetic or other pain-relieving medication should be used before all VAS assessments are completed. Ice for pain relief are allowed and should be applied equally on both hands if used.

- Subjects will evaluate injection site pain for each hand using the VAS at the end of treatmentof each hand and at 10±3, 20±3, and 30±3 minutes post-treatment of each hand.
- Photographs should be taken after the subject has washed their hands. Photographs of the hands shall be obtained according to Section 5.5.
- The injection technique and volume used should be verified and any changes to the procedure described in Section 3.5 must be recorded in the eCRF.
- Any technical problems (device deficiencies) or AEs shall be recorded in the eCRF.
- Record concomitant medications/procedures
- CCI [redacted]

- *Visit 3: 72 hours after Baseline Treatment (Telephone Call)*
  - The Investigator shall ask for any health problems since the last visit and any changes in concomitant medications or procedures performed.
  - CCI [redacted]
  - Any AEs shall be recorded in the eCRF.

Visit 4: End of Study/ Early Termination (Day 15)

- The Investigator shall ask for any health problems since the last visit and any changes in concomitant medications or procedures performed.
- Photographs should be taken after the subject has washed their hands. Photographs of the hands shall be obtained according to Section 5.5.
- The investigator and subject shall, independently of each other, CCI [redacted] (Section 5.3.2.1).
- CCI [redacted]

- Any AEs shall be recorded in the eCRF.
- CCI [redacted]

5.7.2.5 Demographics and baseline assessments

Demographics and baseline assessments include:

- Informed consent date
- Date of birth
- Gender
- Initials
- Ethnic origin
- Inclusion and exclusion criteria
- Relevant medical history/concurrent diseases
- Previous surgery, tissue augmenting therapy or revitalization treatments performed in the hands and products used if applicable.
- Concomitant medications and treatments
- Pregnancy test (for women of childbearing potential)

5.7.3 Instruction of Device Use

Restylane Vital and Restylane Skinboosters Vital Lidocaine are injectable, sterile, transparent, biodegradable gels of non-animal crosslinked sodium hyaluronate. Restylane Skinboosters Vital Lidocaine has the addition of lidocaine hydrochloride. They are supplied in a glass syringe. Restylane Skinboosters Vital Lidocaine has a built in dose-guide, Smart Click System, which when activated creates a clicking sound and haptic feedback to indicate each injected dose. The 1 mL syringe gives approximately 100 such doses of 10 µL each. The contents of the syringe are sterilized using moist heat. The products are for single patient and single session use only. Disposable 29G needles sterilized using ethylene oxide are provided.

In terms of the Instruction of use for Restylane Vital, please see co-packed Restylane Vital IFU.

5.7.3.1 Assembly of needle to syringe for Restylane Skinboosters Vital Lidocaine

Improper assembly may result in separation of the needle and syringe during injection. A strict

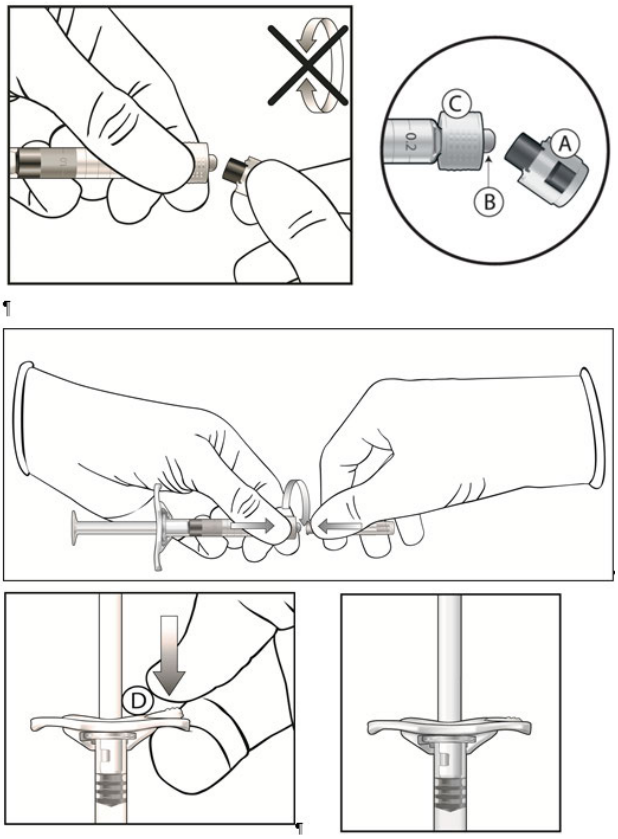
aseptic technique must be followed during the assembly procedure described below.

1) Put on medical gloves.
2) Use your thumb and forefinger to hold firmly around both the syringe-barrel and the luer-lock adapter part (C) of the closure system, see Picture below.
3) With your other hand, take hold of the tip cap (A) at the end of the closure system and bend (do not rotate) until the cap disconnects and can be pulled off (tamper proof seal will be broken), see Picture below.
4) Do not touch the syringe tip (B) to keep it sterile, see Picture below.
5) Open the needle and grasp the needle shield.
6) Assure to hold both the syringe barrel and the luer-lock adapter (C), see Picture below.
7) To facilitate proper assembly, both push and rotate the needle firmly clockwise.
8) Make sure the needle is screwed on all the way so that the needle shield touches the luer lock adapter (C), see Picture below.
9) To remove the needle shield, hold the syringe and the luer lock adapter. With your other hand hold the needle shield and pull straight out. Do not rotate.

5.7.3.2 Treatment Procedure for Restylane Skinboosters Vital Lidocaine

1) Prior to treatment, a medical history should be obtained for proper patient selection. The patient shall be informed about the indications, precautions, treatment responses, potential adverse events, and advised to contact a healthcare professional if they experience anything unusual at the treatment area.
2) Clean the treatment site thoroughly with a suitable antiseptic solution.
3) To avoid breakage of the needle, do not attempt to bend it before or during treatment. If the needle gets bent, discard it and complete the procedure with a replacement needle.
4) This product should be injected in the dermal layer of the skin, preferably in the deeper part of dermis. The injection technique and the administered quantity may vary. The multi puncture technique or short linear technique can be used.
5) Before injecting, remove the air by pressing the rod carefully until a small droplet is visible at the tip of the needle.
6) If desired, the Smart Click System is activated by pressing down the button located on the finger grip (D) until it locks into place, see Picture.
7) When the Smart Click System is switched on, again press the plunger rod carefully until the first click is heard to prime the system before use and to avoid a slightly larger volume of the first dose injected when the system is initially activated. The Smart Click System can be deactivated at any time by pushing the button in the finger grip upwards. It should be noted that it is not possible to perform an aspiration manoeuvre when the Smart Click system is activated.
8) When using the multi puncture technique it is recommended to inject approximately 20 µL (i.e. 2 clicks if the Smart Click System activated) per injection, 0.5 - 1 cm apart.

9) The gel should be evenly distributed in the areas where treatment is needed.
10) Do not apply excessive pressure to the syringe at any time. Presence of scar tissue may impede advancement of the needle. If resistance is encountered the needle should be partially withdrawn and repositioned or fully withdrawn and checked for function.
11) If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal colour. Blanching may represent a vessel occlusion. If normal skin colouring does not return, do not continue with the injection.
12) It is recommended to change needle for each new treatment site or following multiple punctures to avoid use of blunt needles and minimize the risk of infections.
13) A too large volume or a too superficial injection may give bumps on the treatment site.
14) Treated areas can be gently massaged after the injection if any irregularities are noted.



5.7.3.3 Treatment Area and Treatment Regimen for Restylane Skinboosters Vital Lidocaine

The study product is intended for injection in the dorsal hand. Disposable 29G x ½" TW needles should be used for both study products. Study product should be injected in the dermal layer of the skin, preferably in the deeper part of dermis. Allowed injection techniques are; multipuncture or short linear. Inject slowly while pulling the needle backwards.

No more than 20 µL should be injected per injection point when using the multipuncture

technique. Slowly inject 20 µL droplets in the dermal layer of the skin, spacing droplets 0.5-1.0 cm apart to cover the entire treatment area. 20 µL equals to 2 clicks when injecting with the smart click function activated on the Restylane Skinboosters Vital Lidocaine syringe.

The volume for each treatment should be adjusted depending on the subject's need and a volume of 0.5-1 mL for one hand per treatment session will be allowed. The same volume should be used for both hands.

5.7.3.4 Post-treatment care

No topical or local anesthetic or other pain-relieving medication should be used before all VAS assessments are completed.

Ice for pain relief is allowed after all VAS evaluation is completed.

If any irregularities are noted after the use of ice pack, the treated area can be massaged again. A cream can be used during massage at the discretion of the investigator.

The subjects will be asked to avoid intensive physical stress (training) or intensive manual activities involving the hand, extensive heat (sauna)/sun or extreme cold in the first 2 days after the treatment .

The subjects will also be asked to avoid extensive exposure to potential skin irritants (e.g. cosmetics or laundry detergent) that could affect the skin in the treated area before the skin has healed completely in order to prevent infections.

5.7.4 Instruction of Concomitant Treatment

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the PI or his/her authorized designee considers it medically necessary.

Information regarding any use of concomitant medications, including over-the-counter medications administered during the study is to be recorded in the eCRF. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the eCRF.

The following medications, treatments, and procedures are restricted or prohibited during the study:

- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (*e.g.,* monoclonal antibodies) is prohibited.
- Long term concomitant treatment with systemic or topical (on dorsal hands) corticosteroids are prohibited (inhaled corticoids are allowed). Corticosteroids should be used with caution and should be adjudged as necessary by the Investigator.
- Use of systemic or topical (on the dorsal hands) retinoic acid is prohibited.
- Planned hand surgery including sclerotherapy is prohibited.

- Participation in any other clinical study within 30 days of baseline and during the study conduct is prohibited.

If a subject has used any of the above prohibited medications or performed any of the above prohibited procedures, a protocol deviation will be documented. The subject should continue in the study for the scheduled follow-up visits.

5.8 Bias Control Measures

5.8.1 Randomization and Blinding

5.8.1.1 Randomization

Approximately 90 subjects will be randomized to determine which hand to receive treatment with Restylane Skinboosters Vital Lidocaine, and Restylane Vital to the other hand. Before starting the study, a computer-generated randomization list will be prepared under the supervision of a designated statistician.

Each subject will be assigned a subject number as they arrive for the treatment visit. Randomization will be assigned via the eCRF system. The treatment information will be kept by the Treating Investigator during the study not to be disclosed to the subjects.

5.8.1.2 Treatment Blinding

Only the subject will be blinded. Treating Investigator will not be blinded to the treatment assignment.

The Treating Investigator is not allowed to discuss treatment assignment per hand with the subjects. All documents with information on study products shall be kept in a separate binder not available to the subjects.

To ensure the subject is kept treatment-blind the following measures are to be employed at the study site when injecting:

The same injection techniques, volume per injection point and similar total volume should be used for both hands as described above.

At the discretion of the investigator, the subject can listen to white noise/music in headphones during the treatment to cancel out the click sounds from the syringe when injecting Restylane Vital Skinboosters Lidocaine.

The injection will be performed behind a screen to prevent the subject from seeing the type of syringe used in order to achieve subject blinding.

5.8.1.3 Emergency Unblinding

Not applicable as the Treating Investigator is unblinded.

6 Statistical Consideration

6.1 Sample Size Estimation

6.1.1 Calculation Formula, parameter value and its basis of determination, calculation results.
Several studies have been performed comparing the same HA-filler product with and without the addition of lidocaine or other analgesics. In the study 43CH1504[1], comparing Restylane for treatment of nasolabial folds with and without Lidocaine in subjects with Chinese ethnicity, the observed within-subject difference in VAS during injection was 33.0 mm with a standard deviation of 24.4 mm. In another study, in subjects with Chinese ethnicity, 43TW1628[2], comparing Restylane Perlane with and without Lidocaine, the mean within-subject difference in VAS at injection was 32.0 mm with a standard deviation of 19.5 mm.

However, due to the many injection points in the treatment of the hands, it is believed that the within-subject difference in VAS will be considerably less in this study than what was seen in the NLFs in the previous two studies referred to. Thus, assuming a true mean within-subject difference of -10 mm and a standard deviation of 25 mm, a significance level of 2.5% and using a one-sided one-sample t-test, inclusion of 68 subjects will give a power of 90% to reject the null hypothesis of >0 mm within-subject difference. To ensure sufficient power in the event of the need of a non-parametric test for the primary analysis, approximately 15% more subjects will be added to the 68 needed for the t-test. Hence, approximately 80 subjects will be needed for the primary analysis. In addition, a drop-out rate of 10% is assumed. Thus, approximately 90 subjects will need to be randomized in order to have at least 80 evaluable subjects for the statistical analysis.

6.1.2 Sample Size of Each Disease in the Study, and its Rationale (if applicable)

Not applicable

6.2 Analyzed Data Set

The following populations will be defined:

- Safety — Includes all subjects who were injected in at least one hand. Subjects are analyzed based on the as treated principle.
- Full Analysis Set (FAS) — Includes all subjects who were treated with Restylane Skinboosters Vital Lidocaine in one hand and Restylane Vital in the other hand. Subjects are analyzed according to the randomization assignment.
- Per Protocol (PP) — Includes all subjects in FAS that comply to the protocol procedures with no deviations considered to have a substantial impact on the evaluation of the primary variable.

The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population.

6.3 Criteria of Subjects Excluded

For this study, the following protocol deviations that will exclude subjects from PP are identified (but not limited to):

- VAS assessment at end of injection missing for at least one side
- Study products not administered according to randomization
- Any topical or local anesthetic or other pain-relieving medication used before all VAS assessments are completed
- Significantly different injection volumes in left and right hand

6.4 Statistical Methods

6.4.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be written and finalized prior to database lock (DBL). All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.4 or higher).

Continuous variables will be summarized using standard statistical measures, such as mean, median, standard deviation, minimum and maximum values. Categorical variables will be presented in frequency tables with number and percent of observations for each level.

All confidence intervals will be two-sided and use the 95% confidence level. All statistical testing will be one-sided and performed at a significance level of 2.5% unless otherwise specified.

6.4.2 Demographics, baseline assessments, and subject characteristics

Demographic, baseline, and subject characteristics endpoints will be presented in total (or by study product where applicable) using descriptive statistics.

6.4.3 Effectiveness Analysis

6.4.3.1 Primary Analysis

The primary endpoint in this study is defined as the within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at the end of injection. The null hypothesis that the within-subject difference in VAS is greater than or equal to 0 mm will be tested against the alternative hypothesis that the within-subject difference in VAS is less than 0 mm using a one-sample t-test. More formally, the following statistical hypotheses will be tested, with the within-subject difference denoted by Δ:

$$\begin{cases} H_0: \Delta \geq 0\ mm \\ H_1: \Delta < 0\ mm \end{cases}$$

If the one-sided p-value of the test is <0.025 the pain at the end of injection will be considered statistically significantly lower after treatment with Restylane Skinboosters Vital Lidocaine than after treatment with Restylane Vital, and thus the primary objective will be considered met. Results will include mean VAS by treatment, mean within-subject difference in VAS, and the p-value along with standard descriptive statistics and two-sided 95% confidence interval around the difference.

If the distribution of the within-subject differences indicates deviation from the normality assumption, non-parametric methods will be used.

CCI [redacted]

CCI [redacted]

6.4.4 Safety Analysis

CCI [redacted]

All AEs will be coded according to MedDRA.

Related AEs will be summarized by System Organ Class (SOC), PT and intensity and by treatment (or in total as applicable). In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT and treatment (or in total where applicable) using mean, SD, min, max and median.

Serious AEs will be listed.

Non-related AEs will be summarized by SOC, PT, and intensity and by treatment (where applicable).

6.5 Handling of Missing data and Abnormal Value

Number of missing values will be summarized and reported as appropriate.

As the design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both hands in most of the cases. A majority of the deviations to the protocol can be expected to affect both hands and evaluations of the same subject the same way.

FAS analysis of VAS at the time of injection will impute a difference (Restylane Vital - Restylane Skinboosters Vital Lidocaine) of 0 mm as the primary method of imputation. This corresponds to assuming no pain relief using Restylane Skinboosters Vital Lidocaine compared to Restylane Vital and is considered as a worst case approach.

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

To obtain an estimate of the true, clinical treatment effect, the primary effectiveness analysis will be performed using the PP.

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

6.6 Interim Analysis

No interim analysis is planned.

6.7 Data Monitoring Committee

Not applicable for this study.

6.8 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 Clinical Study Protocol (CSP) deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to DBL.

7 Monitoring Plan

A thorough and consistent monitoring plan will be implemented throughout this clinical trial in China to ensure data accuracy, participant safety, and adherence to the study protocol and regulatory requirements set by the National Medical Products Administration.

7.1 Site Selection Visit

Before the initiation of the trial, a site selection visit will be conducted. The purpose of this visit is to assess the site's readiness, review the study protocol with the site's staff, and confirm the site's capabilities to perform the study in accordance with Good Clinical Practice (GCP) guidelines.

7.2 Site Initiation Visit

Once the site is selected, an initiation visit will be performed to review the protocol, the Case Report Forms (CRFs), and other relevant documents, and to train the study team on trial-specific

procedures.

7.3 Routine Monitoring Visits

The frequency of monitoring visits will be determined based on the complexity of the study, the rate of participant enrollment, and the site's performance. During these visits, the monitor will review the informed consent process, verify source data against CRFs, assess protocol compliance, check the adequacy of the site's investigational product storage and handling, and monitor adverse event reporting.

7.4 Close-Out Visit

Upon completion of the study, a close-out visit will be performed to ensure all study activities have been completed, all data queries have been resolved, and the investigational product and study materials have been returned or appropriately disposed of.

7.5 Remote Monitoring

Depending on the circumstances, remote monitoring may also be performed to complement on-site visits.

7.6 Reporting

Monitors will generate a detailed report after each visit, which will document their findings, actions, and recommendations. These reports will be reviewed by the clinical trial management team to ensure continuous oversight and quality control.

7.7 Adverse Event Monitoring

The clinical trial monitors will ensure that all adverse events are reported promptly, recorded accurately, and followed up appropriately in accordance with NMPA requirements.

7.8 Audits and Inspections

The study may be subject to audits performed by the Sponsor and inspections performed by the NMPA. These audits and inspections will review the study's compliance with the protocol, the GCP guidelines, and the regulatory requirements.

8 Data Management

8.1 Data Management

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 handling eCRFs, 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. 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 medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAEs and pregnancies) 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.

8.2 Electronic Case Report Forms

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 will be transcribed directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorized study site 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 shall not be made available in any form to third parties 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 site as part of the Investigator file.

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

9 Analysis of Risks and Benefits

The primary potential benefit of Restylane Skinboosters Vital Lidocaine or Restylane Vital is an improvement in the skin quality and an increased subject satisfaction. Restylane Vital was approved for use in Europe 2004 with the indication to restore skin hydrobalance, improve skin structure and the elasticity of the skin. Restylane Vital indicated for dorsal hands to improve its appearance by increasing the tissue volume in patients over the age of 18 has been approved in China since Dec 2019, and is now regulatory cleared in more than 70 countries worldwide. The product is considered safe and effective for its intended use when injected in the dermal layer of the skin.

In the pivotal study done in China, 43CH1406, Restylane Vital significantly improved skin quality conditions of the dorsal hand as assessed by a blinded evaluator. In addition, the treated hand had significantly better skin hydration and skin elasticity compared to the untreated control hand. The skin hydration and aesthetic appearance showed improvement throughout the whole 60-week study period.

Restylane Vital and Restylane Skinboosters Vital Lidocaine and all other injectable medical devices have the potential to cause complications. Most events are related to injected volume and injection technique, though some could be associated with properties or constituents of the substance itself.

In the pivotal study 43CH1406, the majority of the subjects reported anticipated injection-related reactions after the treatments. The most commonly reported injection-related reactions after the treatments were redness, bruising and, swelling. The majority of symptoms were mild in severity and most symptoms had onset within 1-2 days after injection. Median duration of symptoms was 2-4 days. There was no increase in frequency, severity, or duration of injection-related reactions after repeated treatments in the same hand or treatment of the contralateral hand.

The majority of related adverse events (AEs) were mild or moderate in intensity and occurred after the third treatment. A few of the subjects reported AEs with delayed onset (>21 days after last treatment) including symptoms of injection/ implant site pruritus, injection site swelling, injection site pain, injection site discoloration, implant site redness, rash, folliculitis, and injection site nodule. All AEs with delayed onset were resolved at study completion for the respective subject. It was assessed that the reported AEs with delayed onset might be perceived as inflammatory reactions. Several of these subjects had occupational risk factors for developing hand skin irritation which might have contributed to the reactions. There were no serious or unexpected events reported related to the study product or injection procedure.

However, given the anticipated low level of transient and acceptable AEs in connection with the injection, the risk-benefit assessment of the use of these products for the correction of the signs of aging appears to offer a clinical benefit at reasonable risk. Only Investigators qualified by education and experience and who are skilled in the use of dermal injections will be chosen to ensure proper device administration and management of study risk.

Additional information about reported AEs and anticipated risks are included in the Investigators Brochure.

9.1 Potential Complications and Side Effects

9.1.1 Anticipated Injection-related Reactions

Injection-related reactions (including bruising, redness, itching, swelling, pain (including burn) or tenderness at the implant site) might occur after treatment. Typically resolution is spontaneous within a few days after injection into the skin.

9.1.2 Post-marketing Adverse Event Reporting

The following post-marketing adverse events have been reported voluntarily from worldwide sources (non-exhaustive list) after treatment with Restylane Vital/Restylane Skinboosters Vital with or without Lidocaine (including hand and other treatment areas). The frequency of reporting is based on the number of estimated treatments performed with the products.

1/1 000 – 1/10 000	Swelling/edema with immediate onset and onset up to several weeks after treatment.
1/10 000 – 1/100 000	Papules/nodules, Mass/induration, Redness, Pain (including burn)/tenderness, Inflammation, Infection/abscess including purulent discharge and pustules, Bruising/bleeding, Ischemia/necrosis including pallor, livedo reticularis and vascular occlusion, Other injection site reactions and skin reactions including burning sensation, discomfort, irritation and warmth, Discoloration, Pruritus, Hypersensitivity/angioedema.
<1/100 000	Device ineffective, Scar/scab/skin atrophy, Granuloma/foreign body reaction, Asymmetry/deformity, Neurological symptoms including paresthesia and hyperesthesia, Urticaria, Blisters/vesicles, Rash, Eye disorders including ocular discomfort, increased lacrimation, eyelid ptosis and visual impairment, Acne, Dermatitis, Device dislocation, Capillary disorder such as telangiectasia, Encapsulation, Discharge, Reactivation of herpes infection, Muscle disorders such as muscle spasm, Non-dermatological events including pyrexia, headache discomfort and fatigue, Other dermatological events including dry skin, skin tightness and skin disorder.

When required, treatments for these events may include ice, massage, warm compress, nitroglycerine paste, corticosteroids, antibiotics, antihistamines, analgesics, antiviral agents, diuretic agents, aspiration/incision drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Reports of serious adverse events are rare. The most commonly reported serious adverse events were ischemia/necrosis, infection/abscess, mass/induration and hypersensitivity. Other concurrent serious events included scarring and swelling.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or in rare cases, 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. Treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, hyperbaric oxygen and surgery.

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. The prolonged use of any medication, e.g., corticosteroids or antibiotics in treatment of adverse events should be carefully assessed, since this may carry a risk for the patient. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using a short course of corticosteroids, in order to palpate any remaining product more easily.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

10 Quality Control in Clinical Study

10.1 Quality Control

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.
Any CSP deviation shall be reported in the study, which shall be verified, discussed, and collected, by the monitor and appropriate corrective and preventive actions shall be taken. 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 as well as the Independent Ethics Committee (IEC) if required by national regulations. Deviations shall be reviewed to determine the need to amend the CSP or to terminate the study.

10.2 Quality Assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate regulatory authority (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.

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.

11 Ethics and Informed Consent in Clinical Study

11.1 Ethical Considerations

11.1.1 Statement of Ethical Compliance

The study shall be conducted in compliance with the Clinical Trial Agreement (CTA), the Clinical Study Protocol (CSP), applicable Good Clinical Practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on Harmonisation (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

11.1.2 Application to Independent Ethics Committee and/or Regulatory Authorities

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

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.

11.2 Informed Consent Process

11.2.1 Subject information and informed consent

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

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 IEC. 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 effect on 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 Informed Consent Form and to consider participation in the study. Before any study-related activities are performed, the Informed Consent Form shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and transferred to countries outside China. The data will not contain any information that can be used to identify any subject.

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

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

12 Requirements on Adverse Events and Device Deficiency Reporting

12.1 Definition of Adverse Events and Reporting Requirements

12.1.1 Definitions of Adverse Events (AEs)

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*, whether or not related to the study product.

This definition includes:

- Events related to the investigational product or the reference product
- Events related to the procedures involved

**For users or other persons, this definition is restricted to events related to the investigational product*

12.1.2 Recording Instructions

AE will begin to be collected after ICF signed. Each subject will be questioned about AEs at each clinical visit following the screening visit. The question asked will be "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 or from a laboratory test, observations by the study personnel, subject diaries or spontaneous reports from the subjects.

When an AE is related to a device deficiency (refer to section 12.2), including technical device malfunction, the AE shall be recorded on the AE module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.

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

- Event term (recorded in standard medical terminology and avoiding abbreviations),
- Description of event and affected area (if applicable),
- Start date (First day with symptoms)

- Stop date (Last day with symptoms)
- Intensity (mild, moderate or severe according to definition in section 12.1.3)
- Seriousness (serious or not serious, according to definition in section 12.3)
- Causal relationship to study product and study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment or other procedures/ tests, subject withdrawn)
- Outcome of the AE (ongoing, resolved, resolved with sequelae, death)

The AE module in the eCRF must be signed and dated by the Investigator.

12.1.3 Intensity

For each reported AE, the intensity will be recorded. The following definitions of intensity are to be used:

Mild: A mild AE means awareness of symptoms or signs, but easily tolerated (acceptable).

Moderate: A moderate AE means enough discomfort to interfere with usual activity (disturbing).

Severe: A severe AE means incapacity to work or to do usual activity (unacceptable).

If the intensity changes over time the maximum intensity of the AE should be recorded.

12.1.4 Causal Relationship and Seriousness

Each AE, serious as well as non-serious, will 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) will be used for 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.

12.1.5 Reporting of Adverse Events

AE reporting on each subject will start after the ICF has been signed. The reporting will 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.

12.1.6 Follow-up of Unresolved Events after Study Termination and New Events after Study Termination

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure with onset after subject participation in the study has ended shall be collected and reported to Sponsor on a paper AE form or in the post marketing AE form or SAE paper form if applicable. The events shall thereafter be followed up until resolved or considered chronic or stable, or for at least three months. Final outcome shall be reported on the AE follow up form.

12.1.7 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must continue to be followed within the study and the outcome of pregnancy must be reported even if the expected date of 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 1.3. 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 will not be reported as AEs.

12.1.8 Anticipated Adverse Events

After the injection some common injection-related reactions might occur with both products. These reactions include bruising, redness, itching, swelling, pain (including burn) or tenderness at the implant site. Typically these reactions start on the day of treatment and resolve spontaneous within a few days after injection into the skin, as observed in the Chinese clinical study for Restylane Vital and in consistent with international results for the product.

12.2 Device Deficiency

12.2.1 Definition of Device Deficiency

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

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

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

12.2.2 Recording Instructions

When a device deficiency is discovered the Clinical Study Complaint Form in the eCRF will 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 module or a SAE Form should be completed following instructions in section 12.4. 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

The Sponsor will also make the same assessment in the Clinical Study Complaint Form.

12.2.3 Reporting Device Deficiency

The Investigator will complete the Clinical Study Complaint Form to the Sponsor using the contact details specified in section 1.3. A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to section 12.4.

In order to fulfil regulatory reporting requirements, all deficiencies with the study product must be assessed by both the Investigator and the Sponsor to determine if it could have led to a SAE.

If an SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to an SAE the event will be reported in accordance with Regulatory requirements, as applicable.

The deficient study product shall be kept, if applicable, by the study site until the QA complaints group has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

12.3 Definition of Serious Adverse Events

A SAE is an AE that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
    1. a life-threatening** illness or injury, or
    2. a permanent impairment of a body structure or body function, or
    3. in-patient or prolonged hospitalisation***, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

- led to foetal distress, foetal death, or a congenital abnormality or birth defect

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.

***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).*

**** Planned hospitalisation 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).*

12.4 Reporting Process, Contact Person Information

After aware of any SAE, the Investigator shall report it to his/her administrative department of medical device clinical trials under the clinical trial institution, which in turn shall notify the Sponsor Representative in writing. This initial report can be made via fax or e-mail.

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:

- CTN
- Subject identification (age, gender, subject number)
- AE description
- date when AE occurred
- date when AE became serious
- Name of PI and original reporter (if other than Investigator)
- Name of study product
- Treatment specification

The Investigator will assure completeness of the SAE information and the supporting documentation.

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor via Sponsor's representative 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 Medication Form/list
- Concomitant Procedure/Treatment Form/list

- AE Form/list
- Medical History Form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

Fax number for SAE reporting: +46 (0)18 474 91 75

E-mail for SAE reporting: safety.q-med@galderma.com

Surface mail for providing complementary information: safety.q-med@galderma.com

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

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 (contact details refer to 24-hour contact person list in the Investigator Site File [ISF]). A copy of the fully completed SAE form shall be kept at the site.

In addition, according to national regulations, the investigator will report a SAE Form to the administrative department of medical device clinical trials in his/her hospital, and they should, within 24 hours, deliver a written report to the corresponding Ethics Committee. In case of a death incident, the clinical trial institutions and investigators should furnish the Ethics Committee and the Sponsor Representative with all required materials.

The Sponsor shall report to other medical device clinical trial institutions, ethics committees and principal investigators participating in the clinical trial, report to the drug regulatory authorities of the provinces, autonomous regions and municipalities directly under the central government where the Sponsor is located, report to the drug regulatory authority and health administrative authority of the province, autonomous region or municipality directly under the central government where the medical device clinical trial institution is located, and take risk control measures within 7 days after being informed of death or life-threatening serious adverse events related to the clinical trial medical device, and within 15 days after being informed of non-death or non-life-threatening serious adverse events related to the clinical trial medical device and other serious safety risk information.

13 Requirements on Protocol Deviation and Protocol Amendments

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

administrative changes are to be documented in the Sponsor file without requiring a protocol amendment.

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

Deviations from the statistical plan will be documented.

14 Access to Source Data and Source Documents

14.1 Source Documents

The eCRF is essentially considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital 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 photographs, memoranda, material dispensing records, subject files, etc.

The PI is responsible for maintaining source documents. These shall 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 photographs, should be clearly identified with the subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

14.2 Record Keeping and Access to Source Data

The PI/institution shall permit study-related monitoring, audits and IEC review and shall 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 Informed Consent Forms 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 shall be documented and the Sponsor should be informed in writing.

The Sponsor shall 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 shall be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; 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.

The source data location log specifies what data that should be available in the medical record. The source data location log should also specify the data for which the eCRF serves as the source. Such data only need to be recorded in the eCRF and are typically associated with study-specific procedures and not with normal clinical care practice. For this type of study data the Investigator

would not be expected to duplicate the information into the medical record.

14.3 Document and Data Retention

All records pertaining to the conduct of the study, including signed eCRFs, Informed Consent Forms, study product accountability records, source documents, and other study documentation must be retained after study completion according to national legislation and the CTA. Sponsor will inform the sites as to when these documents no longer needs to be retained. Measures should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorised access, preferably by storage in a fire-proof cabinet). Refer to the CTA.

After study completion and database lock, a security sealed CD with electronic study data shall be provided by the eCRF vendor for archiving.

It is the PI's responsibility to inform Galderma SA in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

15 The Contents of Clinical Study Report

The Clinical Study Report (CSR) for this clinical trial will be developed in accordance with the regulatory standards set by the National Medical Products Administration (NMPA). The report will provide an exhaustive and detailed account of the clinical trial's implementation, outcomes, and inferences. Overall, the CSR will encompass but not limited to the following elements:

- Title Page
- Synopsis
- Basic Information on Clinical Trials
- Implementation Status
- Statistical Analysis Method
- Trial Results
- Adverse Events
- Report on Device Defects and Their Handling
- Discussion and Analysis of Trial Results
- Conclusion of Clinical Trials
- Ethical Situation Explanation

- Existing Issues and Improvement Suggestions

16 Confidentiality

For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the PI are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and the PI are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

The Informed Consent Form 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 countries outside China, and the length of time during which personal data will be stored. The subject shall have the right of access to stored personal data, and the right to correction of incorrect information. If a subject decides to terminate the study prematurely, data collected before withdraw of consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor or a RA may visit the study site to perform audits/inspections, including source data verification, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

17 Responsibilities of Each Party

A contractual agreement, the CTA, outlines the Site's responsibilities, compensation and payment terms of the study and must be signed between the CRO/Sponsor and each investigator/institution before the first subject is screened in the study. This document will contain supplementary information, including financial terms, confidentiality, the clinical study schedule, third party responsibility, and publication rights. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

18 Any Other Information to be Specified

18.1 Financing, Indemnification, and Insurance

The CTA 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. Galderma SA's obligations in this clinical study are covered by the Galderma group'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.

18.2 Publication Policy

The PI's, institutions, and Galderma SA'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 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 multicentre 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*. 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 should be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Galderma SA to take primary responsibility for the overall work as primary author.

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

18.3 Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IEC or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the CSP, GCP, or applicable regulatory requirements.

In the event of premature termination, Galderma SA will provide information on the handling of currently enrolled subjects who have not completed the study.

Statement of Principal Investigator

I acknowledge:

(1) Strictly follow Declaration of Helsinki, the current regulations in China and the requirements of study protocol to conduct this study

(2) Record all required study data into case report form (CRF) accurately, and contribute to clinical study report

(3) Study medical device is only used in this study. The shipment and use of study medical device in this study should be documented completely and accurately, and kept in a proper manner

(4) Allow the monitor and auditor authorized or assigned by Sponsor, and the regulatory authority to monitor, audit and inspect this study

(5) **Strictly follow clinical study contract/agreed terms by all parties**

I have already read and understood the study protocol, including above mentioned statements, and I agree all contents above.

Principal Investigator

Signature:

yyyy-mm-dd

Clinical Study Institution

Stamp

yyyy-mm-dd

Sponsor

Stamp

yyyy-mm-dd

References list

1. Monheit GD, Coleman KM. Hyaluronic acid fillers. Dermatol 2006 May.
2. Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. J Cosmet Dermatol 2009 Dec;8(4):301-7.
3. 43CH1504 Clinical Study Report, Internal Doc. No. MA-33230 ver 2.0.
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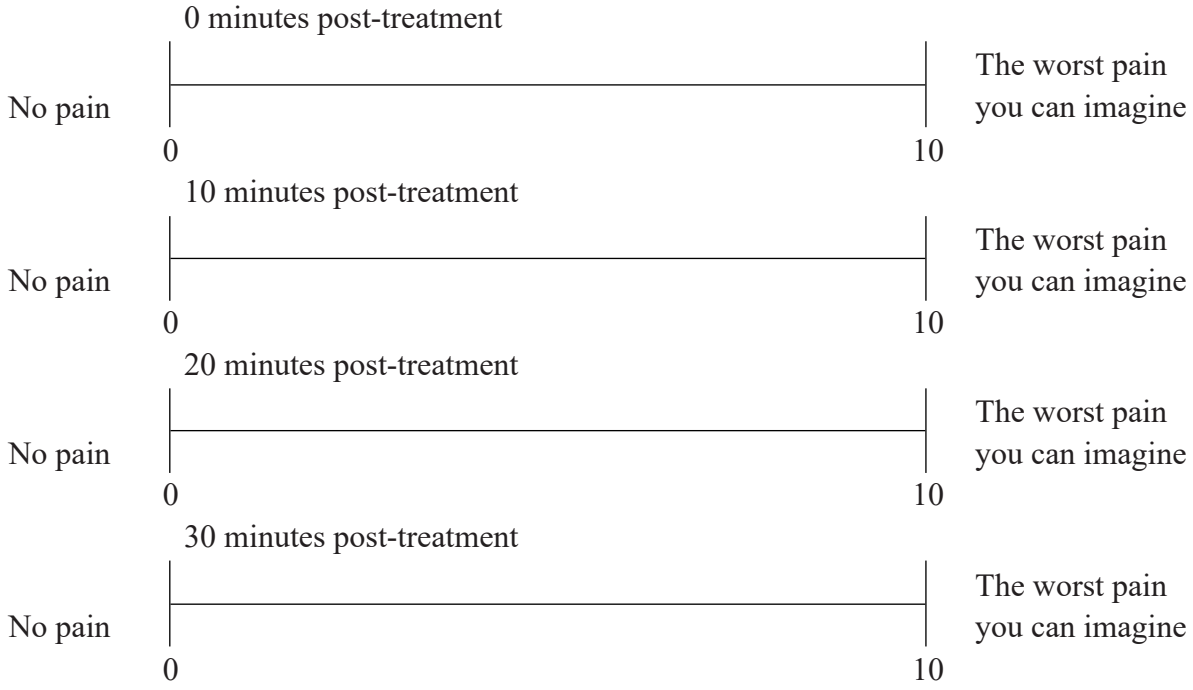
5. Caracas HC et al. The use of lidocaine as an anti-inflammatory substance: a systematic review. Dent. 2009 Feb;37(2):93-7.
6. Dias MP et al. The inhibitory effects of local anaesthetics on the vascular flare responses to bradykinin and substance P in human skin. Anaesthesia 2008:63(2):151-5.
7. 43CH1406 Clinical Study Report, Internal Doc. No. MA-35796 ver 1.0.
8. Galderma protocol QMS-7483. Instructions for use Restylane Vital Lidocaine.
9. Clinical Study Report CTN 05DF1206 Acne scars. Dierickx C, Larsson MK, Blomster S. Effectiveness and Safety of Acne Scar Treatment With Nonanimal Stabilized Hyaluronic Acid Gel. Dermatol Surg. 2018 Nov;44 Suppl 1:S10-S18.
10. Clinical Study Report 05DF1211. Hedén P, Hexsel D, Cartier H, Bergentz P, Delmar H, Camozzato F, Siega C, Skoglund C, Edwartz C, Norberg M, Kestemont P. Effective and Safe Repeated Full-Face Treatments With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin Boosting Hyaluronic Acid. J Drugs Dermatol. 2019 Jul 1;18(7):682-689. .
11. 05DF1404 Clinical Study Report, Internal Doc. No. MA-36906. .

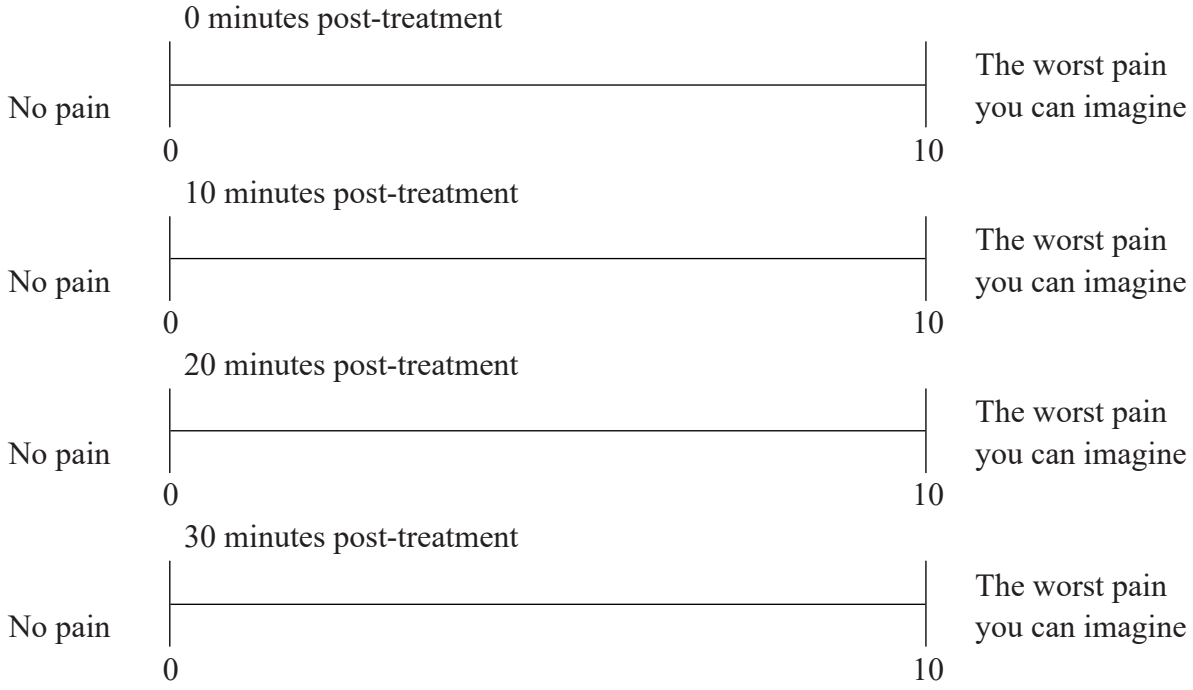
Appendix 1 Visual Analogue Scale (VAS)

Please mark, with a vertical line, how much pain you feel at the different timepoints.

VAS pain assessment **RIGHT** hand:

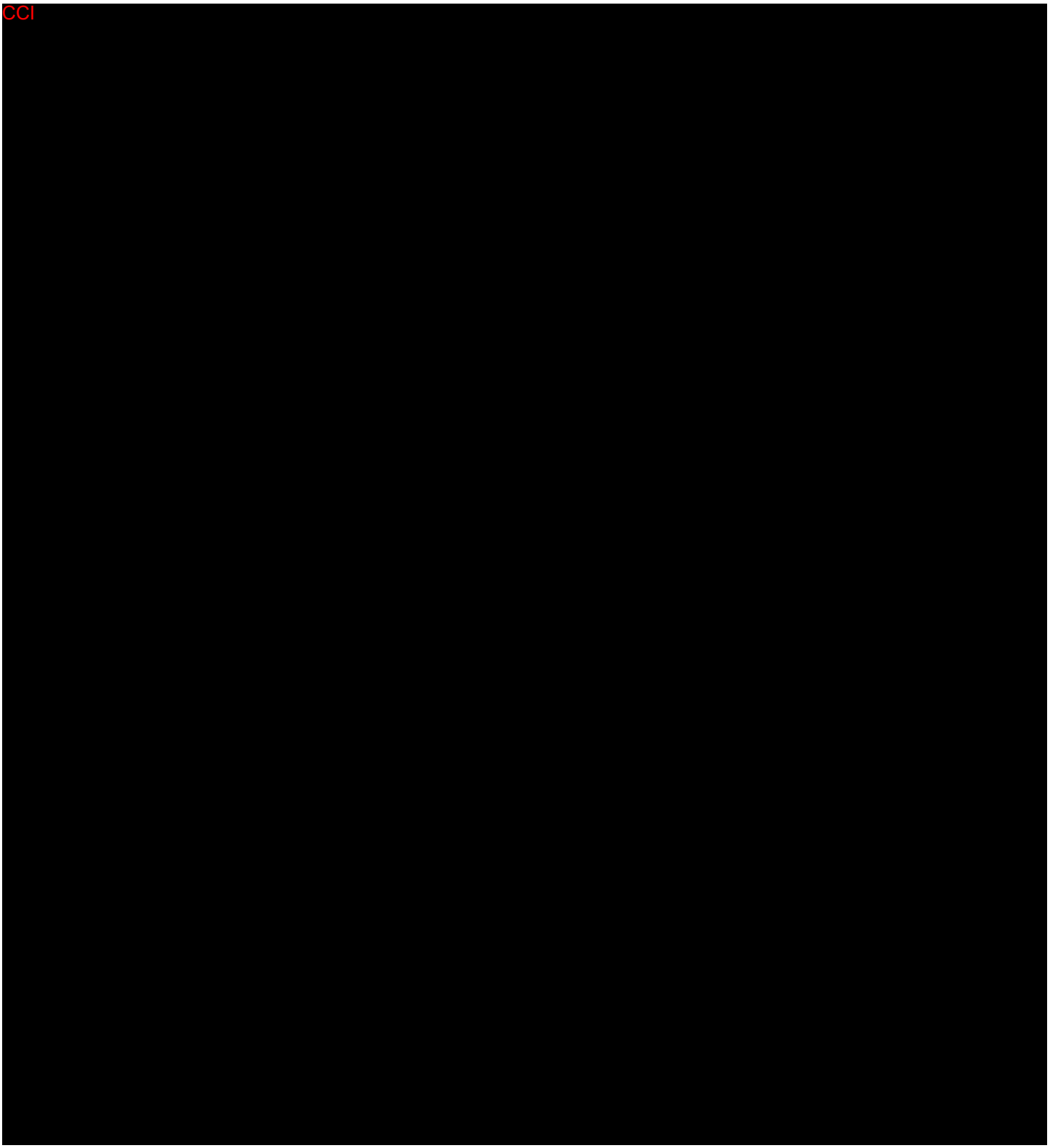


VAS pain assessment **LEFT** hand



GALDERMA EST. 1981	Title **43CH2305 CSP Vital-Lido-Hand-2w**	Doc id **MA-57336**

CCI



GALDERMA EST. 1981	Title **43CH2305 CSP Vital-Lido-Hand-2w**	Doc id **MA-57336**

CCI

GALDERMA EST. 1981	Title **43CH2305 CSP Vital-Lido-Hand-2w**	Doc id **MA-57336**

GALDERMA EST. 1981	Title **43CH2305 CSP Vital-Lido-Hand-2w**	Doc id **MA-57336**

SIGNATURES PAGE

Date	Signed by
2024-03-12 19:39	PPD
Justification	Approved by Technical Expert

2024-03-13 01:47	PPD
Justification	Approved by Trainer

2024-03-13 08:22	PPD
Justification	Approved by Technical Expert

2024-03-13 11:45	PPD
Justification	Approved by Owner