1.5 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

ANSM registration #:	**2022-A01183-40**
Clinical investigation plan #:	**22E0978**
Title of the clinical investigation:	**SAFETY AND EFFECTIVENESS CLINICAL EVALUATION OF THE RANGE OF INJECTABLE MEDICAL DEVICES FILLGEL IN FACIAL AESTHETIC TREATMENT**
Sponsor:	**KYLANE LABORATOIRES SA** Chemin du Pré-Fleuri 1-3 CH-1228 Plan-les-Ouates SWITZERLAND
Development phase	Exploratory study
Objectives:	The primary objective is to evaluate the effectiveness of the FILLGEL range used on different treated zones one month (M1) after treatment using clinical evaluation of the global aesthetic improvement (GAIS) rated by the independent investigator. The secondary objectives of the study are to collect data for the FILLGEL range on: - the effectiveness of the range used on different treated zones six months (M6) and twelve months (M12) after treatment using clinical evaluation of the global aesthetic improvement (GAIS) rated by the independent investigator . - the safety using clinical evaluation of the Injection Site Reactions (ISR) rated by the subject and the investigator, and by collection of adverse events (AEs) at M1, M6 and M12. - subject's satisfaction and subject's opinion on aesthetic improvement on the different treated zones using clinical evaluation of the GAIS at M1, M6 and M12. - the injector's satisfaction on the injection quality using subjective evaluation questionnaire, Another objective will be to illustrate the device effectiveness by realization of face macrophotographs.
Design:	♦ Open study, ♦ intra-individual, ♦ single dose, ♦ single centre.
Planned Sample Size:	68 subjects in total divided in 4 subgroups of 17 subjects, according to the kind of filler injected: Group 1: 17 subjects treated in peri-oral lines by FILLGEL 0 Group 2: 17 subjects treated in nasolabial folds and/or in lips by FILLGEL 1 (with at least 10 in nasolabial folds and 7 in lips, both indications possible on the same subjects). Group 3: 17 subjects treated in cheek/cheekbones by FILLGEL 2. Group 4: 17 subjects treated in cheek/cheekbones and/or chin by FILLGEL 3 (with at least 10 in cheeks/cheekbones and 7 in chin, both indications possible on the same subjects).
Number of investigational study sites:	1 (Eurofins Dermscan Pharmascan)

Inclusion criteria:	1. Healthy Subject. 2. Sex: male or female. 3. Age: between 18 and 65 years. 4. Subject seeking an improvement of her/his face aspect with HA filler. *<u>For group 1</u>: Subject with moderate to severe peri-oral lines (score 3 to 5 on Bazin Upper lip scale) ; *<u>For group 2</u>: Subject with moderate to severe nasolabial folds (score 3 to 4 on WSRS scale) and/or subject with thin lips (score 1 or 2 for superior and/or inferior lip on the Rossi scale) and seeking an improvement of lip volume; *<u>For group 3</u>: Subject with moderate to severe cheeks/cheekbones volume deficit (score 3 to 4 on Ascher lipoatrophy scale); *<u>For group 4:</u> Subject with moderate to severe cheeks/cheekbones volume deficit (score 3 to 4 on Ascher lipoatrophy scale) and/or subject seeking improvement of chin enhancement. 5. Subject whose weight did not fluctuate in the last 6 months and who agrees to keep a stable weight during the study. 6. Subject having given their free, express, and informed consent. 7. Subject psychologically able to understand the information related to the study, and to give their written informed consent. 8. Subject registered with a social security scheme. 9. Women of childbearing potential should use a contraceptive method considered effective since at least 4 weeks and throughout the study.
Exclusion criteria:	<u>In terms of population</u> 1. Pregnant or nursing woman or planning a pregnancy during the study. 2. Subject who had been deprived of their freedom by administrative or legal decision or who is under guardianship. 3. Subject in a social or sanitary establishment. 4. Subject suspected to be non-compliant according to the investigator's judgment. 5. Subject having received a total of 4.500 euros as compensations for their participation in research involving human beings in the last 12 months, including their participation in the present study. 6. Subject enrolled in another study or whose non-enrollment period is not over. 7. Subject with scar(s), mole(s), hair or any other lesion on the studied zones which might interfere with the evaluation (tattoo, permanent make-up…). <u>In terms of associated pathology</u> 8. Subject suffering from a severe or progressive disease or any other pathology that may interfere with the evaluation of the study results and/or subject safety. 9. Subject with known history of or suffering from autoimmune disease and/or immune deficiency. 10. Subject suffering from active disease such as inflammation, infection, tumours, inflammatory and/or infectious cutaneous disorders (herpes, acne, rosacea, porphyria …) in the 6 months before screening visit. 11. Subject with a history of streptococcal disease or an active streptococcus infection. 12. Subject prone to develop inflammatory skin conditions or having tendency to bleeding disorders.

	13. Subject predisposed to keloids or hypertrophic scarring or having healing disorders. 14. Subject having history of severe allergy or anaphylactic shock including known hypersensitivity to one of the ingredients of the investigational device (i.e. HA), to antiseptic solution (Diaseptyl®) or to amide-type anaesthetics (EMLA®), related to previous or current treatments. 15. Subject with previous hypersensitivity reactions to hyaluronic acid injections after a COVID-19 vaccination. <u>Relating to previous or ongoing treatment</u> 16. Any medication which may interfere, at the interpretation of the investigator, with the study objectives. 17. Subject having received treatment with a laser, ultrasound or radiofrequency treatment, a dermabrasion, a surgery, a chemical peeling or any other procedure based on active dermal response on the face within the past 6 months or who plans to undergo any of these procedures during the study. 18. Subject having received within the past 18 months or planning to receive during the study any injections outside of those in the study protocol including non-permanent fillers (e.g., HA, Calcium Hydroxyapatite), autologous fat, mesotherapy or botulinum neurotoxin on or near the treated zone. 19. Subject having received at any time or planning to receive a permanent filler on the face (e.g., polylactic acid, Polymethylmethacrylate, silicone) during the study. 20. Subject with subcutaneous retaining structure on the face (meshing, threads, gold strand). 21. Subject using medication such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, thrombolytics or anticoagulants within one week prior to injection visit or being a chronic user. 22. Subject undergoing a topical treatment on the test area or a systemic treatment: - anti-inflammatory medication and/or antihistamines within the past 2 weeks and during the study, - corticosteroids within the past 2 weeks and during the study, - retinoids and/or immunosuppressors within the past 3 months and during the study. <u>In terms of lifestyle</u> 23. Intensive exposure to sunlight or UV-rays within the previous month and/or planning to do so during the study. 24. Subject planning to change her/his life habits during the study. 25. Subject with an excessive consumption of alcohol (more than 2 glasses of wine per day) and/or tobacco (more than 10 cigarettes per day).
Investigational device: **Name / code** **Galenic form** **Indication**	**FILLGEL range: Injectable sterile gels in syringe** **1. FILLGEL 0:** Indication: Peri-oral lines **2. FILLGEL 1:** Indication: Nasolabial folds / lip volume **3. FILLGEL 2:** Indication: Cheeks, cheekbones

	4. FILLGEL 3: Indication: Cheeks, cheekbones / chin
Endpoints:	Primary endpoint: Proportion of subjects having an improvement of the zone treated with the overall FILLGEL range of devices as assessed by the independent investigator, one month after treatment, using the GAIS. An improvement is defined as a subject with “very much improved”, “much improved” or “improved” score on the GAIS. Secondary endpoints: - The safety of the FILGEL range and of each FILLGEL device independently will be assessed by: • collection of immediate and early Injection Site Reactions (ISRs) by the subjects on a daily-log every day up to one month after treatment. • collection of immediate and early ISRs by the independent investigator immediately and one (M1), six (M6) and twelve months (M12) after treatment. • collection of AEs throughout the study. - Proportion of subjects having an improvement of the zone treated with the overall FILLGEL range of devices as assessed by the independent investigator, six and twelve months after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with each FILLGEL device for the four indications independently as assessed by the independent investigator, one, six and twelve months after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with the FILLGEL range of devices overall as assessed by the subjects, one, six and twelve months after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with each FILLGEL device for the four indications independently as assessed by the subjects, one, six, and twelve months after treatment, using the GAIS. - Evaluation of the effectiveness on wrinkles/lines filling of the device FILLGEL 0 used in the peri-oral lines as assessed by the independent investigator one, six and twelve months after treatment, using the Bazin Upper lip wrinkles scale. - Evaluation of the effectiveness on folds filling of the device FILLGEL 1 used in the nasolabial folds as assessed by the independent investigator one, six and twelve months after treatment, using the WSRS scale. - Evaluation of the effectiveness on lip volume increase of the device FILLGEL 1 used in lips as assessed by the independent investigator one, six and twelve months after treatment, using the Rossi scale. - Evaluation of the effectiveness on volume restauration of the device FILLGEL 2 used in the cheeks/cheekbones as assessed by the independent investigator, one, six and twelve months after treatment, using the Ascher lipoatrophy scale.

	- Evaluation of the effectiveness on volume restauration of the device FILLGEL 3 used in the cheeks/cheekbones as assessed by the independent investigator, one, six and twelve months after treatment, using the Ascher lipoatrophy scale. - Injector's satisfaction on the injection quality using a questionnaire completed immediately after injection on D0. - Illustration of the treatment effect one, six and twelve months after treatment compared to baseline by photographs taking.
Study Procedures:	Screening, D0, D7 (phone call for safety), M1, M6, M12
Statistical methods:	The statistical analysis will be performed by the CRO biostatistician. The analysis of the primary performance parameter will be performed on the ITT and PP population. The analysis of the secondary effectiveness parameters will be performed on the ITT and PP population. In case the ITT and PP population differ by less than 10%, only the PP population will be analyzed. The analysis of the safety/tolerance parameters will be performed on the "safety" population. A descriptive analysis of the population will be performed, including subject's characteristics, subject's disposition, deviations to the protocol, injections characteristics. **For the primary evaluation criteria:** For the parameter GAIS investigator with the **5 level scores** (at D0 after injection, M1, M6 and M12), the frequencies and percentages will be presented for the **overall face score** and for the scores **by product**. Two derived parameters will be defined based on the parameters GAIS subject and investigator as a scores of 2 levels (1=Improvement (Very much improved, Much improved and Improved) and 2=No change or worsening). At each time point, these parameters will be described in frequencies, percentages and Confidence Interval (CI) 95%. **Inferential analysis for the primary evaluation criteria** For the new derived parameters at M1 (1 month after injection) for the GAIS Investigator, a binomial exact test (bilateral approach) vs 50% will be applied at each time point for the **overall face score**. This test will compare the proportion of improvement to 50%. **For the secondary evaluation criteria:** All the variables will be described using adapted statistics according to their type (quantitative data or qualitative data). Statistical tests will be performed, to assess the change from baseline (Wilcoxon signed rank test). The bilateral approach will be used with a significance level of 0.05.

Estimated dates of the study:	Clinical investigation beginning: Q4 2022 Clinical investigation end: Q4 2023/Q1 2024 Expected recruitment period duration: 3 months Clinical investigation overall duration: 12 months + recruitment period Duration by subject: 12 months + screening period

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Procedure	Visit 1 Screening	Visit 2 Day 0	Phone call Day 7	Visit 3 M1	Visit 4 M6	Visit 5 M12
Days	D-x	D0	D7 ± 1	D30±7	D180±14	D365±14
Informed consent form signature	●					
Medical examination	●					
Medical history and previous and concomitant treatments collection	●					
Verification of the inclusion and exclusion criteria	●					
Urinary pregnancy test (for women with childbearing potential)		●[b]				
Confirmation of eligibility		●[b]				
Photographs (full face + 2 profiles)		●[b]		●	●	●
Scoring of effectiveness using specific scales		●[b]		●	●	●
Injection		●				
Injector satisfaction questionnaire		●[a]				
GAIS live assessment by the independent investigator		●[a]		●	●	●
GAIS assessment by the subjects				●	●	●
Distribution of a subject daily-log	●	●		●	●	●
ISR collection by subject		● Each day during one month after injection, on the daily-log				
ISR investigator		●[a]		●	●	●
AE and concomitant treatments and procedures collection	●	●	●	●	●	●

a : after injection, b : before injection
AE: Adverse Event - GAIS: Global Aesthetic Improvement Scale- ISR: Injection Site Reaction