1.5 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

ANSM registration #:	**2023-A01479-36**
Clinical investigation plan #:	**23E1077**
Title of the clinical investigation:	**SAFETY AND EFFECTIVENESS CLINICAL EVALUATION OF THE RANGE OF INJECTABLE MEDICAL DEVICES VISCOL IN 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 VISCOL range used on different treated zones (facial and body areas) one month (M1) after treatment using clinical evaluation of the global aesthetic improvement (GAIS) rated by an independent investigator. The secondary objectives of the study are to collect data for the VISCOL range on: - the effectiveness of the range used on different treated zones four months (M4) after treatment using clinical evaluation of the global aesthetic improvement (GAIS) rated by an independent investigator. - the effectiveness on the improvement of facial skin quality by objective measurements of skin biomechanical parameters using Cutometer® and skin hydration using Moisturemeter® one (M1) and four (M4) months after treatment. - subject's satisfaction and subject's opinion on aesthetic improvement on the different treated zones using clinical evaluation of the GAIS at M1 and M4. - the injector's satisfaction on the injection quality using subjective evaluation questionnaire after injection on D0. - 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 Day 0 (D0) one month (M1),four months (M4) and six months (M6). Another objective will be to illustrate the device effectiveness by realization of face and body macrophotographs.
Design:	♦ Open study, ♦ intra-individual, ♦ single dose, ♦ single centre.
Planned Sample Size:	86 subjects in total divided in 2 groups, according to the kind of treated zone: Group 1 (VISCOL Face): 64 subjects treated by VISCOL (one injection on D0) on both sides of the face in the following areas: malar and sub-malar areas (obligatory areas) and optional areas mandibular and/or chin. Group 2 (VISCOL Body): 22 subjects treated by VISCOL (one injection on D0) on both sides in the following areas: decolletage and neck areas (obligatory areas) and one optional area abdomen or internal face of the arm.

Number of investigational study sites:	1 (Eurofins Dermscan Pharmascan in France)
Inclusion criteria:	1. Healthy Subject. 2. Sex: male or female. 3. Age: between 35 and 70 years. 4. Subject seeking an improvement of her/his face (at least malar and sub-malar areas and optionally mandibular and/or chin areas) or body (at least decolletage/neck areas and optionally abdomen or internal face of the arm areas) aspect with HA skin quality improvement product. 5. For Group 1 (Face): Subjects with dry skin (skin hydration rate on cheekbones < 60UA confirmed using Corneometer® measurement). 6. For Group 2 (Body): If applicable: subject with mild to moderate laxity of the tissues of the internal face of the arms (from 1 to 3 on Bazin Texture of the arm scale) or the abdomen (from 2 to 5 on Bazin Abdomen texture scale) 7. For Group 2 (Body): Subject with BMI <30. 8. Subject whose weight did not fluctuate in the last 6 months and who agrees to keep a stable weight during the study. 9. Subject having given his/her free, express, and informed consent. 10. Subject psychologically able to understand the information related to the study, and to give their written informed consent. 11. Subject registered with a social security scheme. 12. Women of childbearing potential should use a contraceptive method considered effective since at least 12 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 6.000 euros as compensations for their participation in clinical research 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 risk of hypersensitivity to one of the components of the composition of the investigational device , to antiseptic solution (Diaseptyl®) or to amide-type anaesthetics (EMLA®), related to previous or current treatments. 15. Subject with symptoms consistent with COVID-19 or are suffering from previous COVID-19 infection. 16. Subject with previous hypersensitivity reactions to hyaluronic acid injections after a COVID-19 vaccination. <u>Related to previous or ongoing treatment</u> 17. Subject having received a dose of COVID-19 vaccine within the 3 weeks prior to injection visit or planning to receive a dose in the 2 weeks following injection. 18. Any medication which may interfere, at the interpretation of the investigator, with the study objectives. 19. 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 treated areas within the past 6 months or who plans to undergo any of these procedures during the study. 20. 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) or autologous fat on or near the treated areas. 21. Subject having received within the past 9 months or planning to receive during the study any injections outside of those in the study protocol including mesotherapy or botulinum neurotoxin on or near the treated areas. 22. Subject having received at any time or planning to receive a permanent filler on treated areas (e.g., polylactic acid, Polymethylmethacrylate, silicone) during the study. 23. Subject with subcutaneous retaining structure on treated areas (meshing, threads, gold strand). 24. 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. 25. 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> 26. Intensive exposure to sunlight or UV-rays within the previous month and/or planning to do so during the study. 27. Subject planning to change her/his life habits during the study. 28. 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**	**VISCOL range: Injectable sterile gels in syringe**

Indication	**1. VISCOL Face:** Indication: malar, sub-malar, mandibular and chin areas **2. VISCOL Body:** Indication: decolletage, neck, abdomen and internal face of the arms areas
Endpoints:	<u>Primary endpoint:</u> Proportion of subjects having an improvement of the zone treated with the overall VISCOL range of devices as assessed by an independent investigator, one month (M1) after treatment, using the GAIS. An improvement is defined as a subject with “very much improved”, “much improved” or “improved” score on the GAIS. <u>Secondary endpoints:</u> - Proportion of subjects having an improvement of the zone treated with the overall VISCOL range of devices as assessed by an independent investigator four months (M4) after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with each VISCOL device for the 2 groups independently as assessed by the independent investigator one month (M1) and four months (M4) after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with the VISCOL range of devices overall as assessed by the subjects, one month (M1) and four months (M4) after treatment, using the GAIS. - Proportion of subjects having an improvement of the zone treated with each VISCOL device for the 2 groups independently as assessed by the subjects, one month (M1) and four months (M4) after treatment, using the GAIS. - Change from baseline of facial skin hydration measured with Moisturmeter® one month (M1) and four months (M4) after treatment. - Change from baseline of facial skin biomechanical parameters measured with Cutometer® one month (M1) and four months (M4) after treatment. - Patient’s satisfaction on the treatment outcomes using a subjective evaluation questionnaire completed at one month (M1) and four months (M4) after treatment. - Injector’s satisfaction on the injection quality using a subjective evaluation questionnaire completed immediately after injection on D0. - The safety of the VISCOL range and of each VISCOL 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 Injection Site Reactions (ISRs) by the injector immediately after treatment. • collection of ISRs by the independent investigator one month (M1) and four months (M4) after treatment. • collection of AEs throughout the study. Illustration of the treatment effect one month (M1) and four months (M4) after treatment compared to baseline by photographs taking.

Study Procedures:	Screening, D0, D7 (phone call for safety), M1, M4, M6 (phone call for safety)
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 as sensitivity analysis. The conclusion of the primary performance parameter will be performed on the ITT 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. **<u>For the primary evaluation criteria:</u>** **<u>Descriptive statistics:</u>** For the parameter GAIS investigator with the **<u>5 level scores</u>** (at M1 and M4), the frequencies and percentages will be presented for the **overall face and body score** and for the scores **by product** (separated by the 4 zones: "face", "decolletage and neck", "area abdomen" and "arm"). A two derived parameter will be defined based on the parameters GAIS subject and investigator as a score 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 IC95% for the **overall face and body score** and for the scores **by product** (separated by the 4 zones: "face", "decolletage and neck", "area abdomen" and "arm"). • For group 1 : if **GAIS value** on face is "Very much improved", "Much improved" or "Improved" then the subject is **responder** (Responder='Yes') Else the subject is not **responder** (Responder='No') • For group 2 : if **GAIS value** on "decolletage and neck" is "Very much improved", "Much improved" or "Improved" then the subject is **responder** (Responder='Yes') Else the subject is not **responder** (Responder='No') **<u>Inferential analysis for the primary evaluation criterion</u>** For the derived outcome **responder rate** at M1 (1 month after injection) for the GAIS Investigator, a binomial exact test (bilateral approach) vs 60% will be applied for the overall score. This test will compare the proportion of improvement to 60%.

	In addition, a sensitivity analysis will be performed on a global binary variable based on both GAIS scores, assessed by the investigator and by the subject. If the subject is considered as improved by both scores, then the outcome will be "Improved" else the outcome will be "Not improved". This composite parameter will be summarized in frequency and percentage and presented associated with its 95% CI, by time-point for the overall face and body scores and by product (separated by the 4 zones: "face", "decolletage and neck", "area abdomen" and "arm"). **For the secondary evaluation criteria:** **GAIS subject :** For the parameter GAIS subject with the **5 level scores** (at M1 and M4), the frequencies and percentages will be presented for the **overall face and body scores** and for the scores **by product** (separated by the 4 zones: "face", "decolletage and neck", "area abdomen" and "arm"). **Biometrological parameters:** All the parameters measured with Cutometer® and Moisturemeter® will be summarized using the descriptive statistics for quantitative data for each time point (D0, M1, M4). For each parameter, a two-tailed paired t-test will be carried out to assess whether each time point after injection (M1, M4) differ significantly from the baseline value (D0). **Subjective questionnaire statistical analysis:** The distribution of each item of the injector and subject questionnaires will be described in frequencies and percentages. For each item of the subject questionnaire, the percentage of subject satisfied, (percentages of answers "totally agree", "agree") will be computed and described in frequencies and percentages. For each item of the injector questionnaire, the percentage of answers "satisfied" or "very satisfied" will be computed and described in frequencies and percentages. **Safety analysis:** - The injection site reactions parameters assessed by the investigator and the subject will be described. - The individual listing of AE will be provided. AE/ADE will be summarized by product. AE/ADE will be further tabulated by seriousness, severity and relationship to the investigational device and procedure.
Estimated dates of the study:	Clinical investigation beginning: Q4 2023 Clinical investigation end: Q3 2024 Expected recruitment period duration: 4 months. Clinical investigation overall duration: 6 months + recruitment period Duration by subject: 6 months + screening period

FLOW-CHART

Procedure	**Visit 1 Screening**	**Visit 2 Day 0**	**Phone call 1 Day 7**	**Visit 3 M1**	**Visit 4 M4**	**Phone call 2 M6**
Days	D-x	D0	D7 ± 1	D30±4	D120±7	D180±7
Informed consent	●					
Medical examination to check inclusion and exclusion criteria	●					
Medical history and previous/ ongoing treatment(s)	●					
Confirmation of eligibility	●	●				
Urinary pregnancy test for women of childbearing potential		●[b]				
Injection by injector		●				
ISR by the injector		●[a]				
Subjective evaluation questionnaire by the injector		●[a]				
Subjective evaluation questionnaire by the patient				●	●	
GAIS by an independent investigator				●	●	
GAIS by the subjects				●	●	
ISR by an independent investigator				●	●	
ISR by the subjects		● Each day during 1 month after injection, on the daily-log				
Group 1: Macrophotographs (full face + 2 profiles)		●[b]		●	●	
Group 1: Cutometer® + Moisturemeter®		●[b]		●	●	
Group 2: Macrophotographs of the treated zone(s)		●[b]		●	●	
Adherence control, record of AE, concomitant treatments	●	●	●	●	●	●
End of study form						●

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