CLINICAL STUDY PROTOCOL

A multi-center, prospective and observational study to evaluate long-term safety and biodegradability of YVOIRE volume s injected into the nasolabial folds

Study Medical Device: **YVOIRE volume s**

Study No.: **LG-HAOS005**

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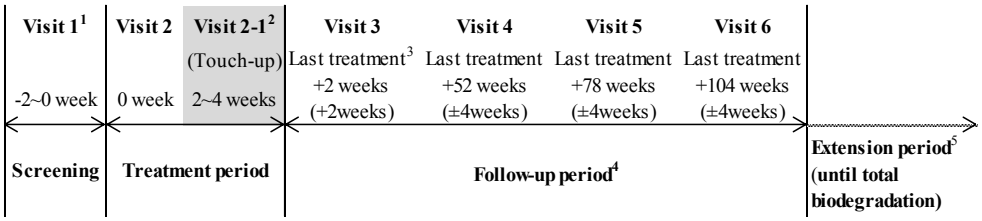
LG Life Sciences

CLINICAL STUDY SYNOPSIS

Title	A multi-center, prospective and observational study to evaluate long-term safety and biodegradability of YVOIRE volume s injected into the nasolabial folds
Study phase	Phase IV
Study period	Subjects will participate in the study until they reach the total biodegradation status or lost to follow-up.
Study objective	To evaluate long-term safety of YVOIRE volume s by incidence of adverse events including injection site local reactions and biodegradability assessed by changes in Wrinkle Severity Rating Score (WSRS). Subjects will be followed up until they reach the total biodegradation status defined as WSRS change score from pre-treatment ≥0 (i.e., same or worse compared to the pre-treatment wrinkle status).
Sample size	Total 500 subjects Sample size calculation is based on 0.7% incidence rate of the least reported adverse events (hyperpigmentation) in hyaluronic acid fillers. Assuming a Poisson distribution of the incidence rate, 428 subjects are calculated for the 95% confidence interval. With an assumption of approximately 20% of potential drop-out rate, a total of 500 subjects are needed.
Study medical device and application	YVOIRE volume s is a gel type product in a prefilled syringe filled with 1.0 mL of colorless clear and viscous liquid. YVOIRE volume s is injected into the deep dermis layer and/or subcutaneous layer of the human facial skin. The injection procedure should strictly be in compliance with the basic rules of aseptic surgical technique in order to prevent contamination during the administration procedure.
Indication	Correction of nasolabial folds
Eligibility criteria	Subjects will be enrolled in the study in the order of available subjects meeting the following eligibility criteria: **Inclusion criteria** 1) Subjects whose age is over 18 years old and under 65 years old 2) Subjects whose WSRS grade is equal or greater than 2 3) Subjects must be willing and able to provide written informed consent form 4) Subjects who are scheduled to be treated with YVOIRE volume s for facial tissue augmentation to correct the nasolabial folds **Exclusion criteria** 1) Subjects who are sensitive to hyaluronic acid or any excipients of YVOIRE volume s 2) Subjects who have received permanent implantation (silicone, PAAG, PMMA, CaHA

	etc) on the nasolabial folds 3) Subjects who have received nonpermanent aesthetic treatments, such as botulinum toxin injection or filler on the nasolabial folds within 9 months before screening 4) Subjects who have received face lifting or plastic surgery on face within 9 months before screening 5) Subjects who have received laser therapy on the nasolabial folds, chemical peeling or peeling on face within 3 months before the screening 6) Subjects who have any skin diseases (including inflammation and skin cancer) or infectious diseases on the injection sites 7) Subjects who tend to have hypertrophic scars 8) Subjects with a history of streptococcal disease, severe allergy or anaphylaxis or bleeding disorders. 9) Women in pregnancy or lactation
Study design and method	Study design Multi-center, prospective and observational study  [1] Visit 1 and 2 can be on a same day if a subject satisfies all eligibility criteria. [2] Visit 2-1 is only applicable to subjects who receive touch-up treatment. [3] All follow-up visit schedules are counted in weeks from the day of the last treatment (Visit 2 or 2-1) given to a subject as specified in the study protocol. [4] For each subject, the study completes when he/she reaches 'total biodegradation' (defined as the WSRS score change from pre-treatment is ≥0, i.e., same or worse compared to the pre-treatment wrinkle status). [5] If total biodegradation of a subject is not achieved by 104 weeks from the last treatment, the subject will be followed up at every 26 weeks interval until showing total biodegradation or lost to follow-up. In the study, total biodegradation is defined as the WSRS score change from pre-treatment is ≥0 (i.e, same or worse compared to the pre-treatment wrinkle status). On the day of visit 1, a subject will be screened for eligibility for the study. A treating investigator should carefully review and record subject's medical history including aesthetic treatments on face. If a subject meets all eligibility criteria, agrees to participate in the study and signs the informed consent form, then, WSRS will be assessed by the treating investigator. And the grade will be used as the pre-treatment baseline rating. On visit 2, YVOIRE volume s will be injected on the nasolabial folds. Visits 1 and 2 can be on a same day if a subject qualifies for study participation. Volume of injection on each side of nasolabial folds is at the investigator's discretion, but it is recommended to avoid

	using more than 1.5mL for each side. The injection procedure should strictly be in compliance with the basic rules of aseptic surgical technique. And the amount injected should be recorded. After the treatment, a 30-minute rest will be recommended. While a subject taking a rest, he/she will be observed for any occurrence of adverse events including injection site local reaction – pain, tenderness, swelling, redness, bruising, itching, papule, and pigmentation. A take-home subject diary will be distributed to subjects for observation and record of adverse events up to visit 3. Visit 3 will be made after 2 weeks (+ 2 weeks) from the initial injection. An investigator will check status of treating sites. For optimal correction, touch-up treatment can be given if 1) improvement of wrinkles is less than one grade or 2) augmentation of each fold is unbalanced. A treating investigator will decide whether to give touch-up treatment or not. If touch-up treatment is given, the visit becomes visit 2-1. Subject will receive necessary touch-up treatment. Investigator will record volume of injection and assess subject status including safety. A subject diary distributed at visit 2 will be collected, and new subject diary will be distributed for observation of adverse events about touch-up treatment. Visit 3 will be made after 2 weeks (+2 weeks) from the treatment. At visit 3, a subject diary distributed at visit 2 or 2-1 will be collected. Investigator will assess adverse events including injection site local reactions and ask whether he/she has received any aesthetic treatments on the face during the period. The investigator evaluates WSRS score in a same manner performed during visit 1. After all assessments are completed, next visit will be scheduled. After 2 (+2weeks), 52, 78, and 104 (±4weeks) weeks from the last treatment given (visit 2 or 2-1), Visit 3, 4, 5, and 6, respectively, will be made. Investigator will assess safety of subject including subject's status on the day of visit and any episodes of adverse events between visits. And each subject will be asked to fill out the subject satisfaction survey as well, which asks the overall improvement in each nasolabial fold by comparing their appearance at each time point against before treatment of YVOIRE volume s. WSRS evaluation will be performed. History of aesthetic treatment will be asked. If subjects have received other aesthetic treatment on the face including the nasolabial folds, the types, product, date, and location of treatments will be recorded. If a subject shows total biodegradation at any visit, that visit will be the last visit of the subject in the study, and the subject will be considered as completing the study. In the follow-up period, lost to follow-up is defined as subjects who do not make at least one visit after visit 3 even three follow-up attempts are made over a month for each

	scheduled visits. For subjects who do not reach total biodegradation by week 104 visit (visit 6), their follow-up visits will be scheduled at every 26-week interval until showing total biodegradation or lost to follow-up. When a subject does not show up for a scheduled visit in extension period, three follow-up attempts over a month will be made. If subjects do not make a follow-up visit even after the 3 attempts over a month, they will be regarded as lost to follow-up.
Study variables	***Safety*** - Incidence of adverse events including injection site local reactions ***Biodegradability*** Total biodegradation is defined as the WSRS score change from pre-treatment is ≥0 (i.e., same or worse compared to the pre-treatment wrinkle status). *Primary variable* - Percentage of subjects whose WSRS change is ≥0 at any time during or after 104 weeks (visit 6) from pre-treatment (visit 1) (i.e., post minus pre) *Secondary variables* - Percentage of nasolabial folds whose WSRS change is ≥0 at any time during or after +104 weeks (visit 6) from pre-treatment (visit 1) (i.e., post minus pre) - Percentage of subjects whose WSRS change from pre-treatment at week 52 (Visit 4) and 78 (Visit 5) is ≥0 (i.e., post minus pre) - Percentage of nasolabial folds whose WSRS change from pre-treatment at week 52 (Visit 4) and 78 (Visit 5) is ≥0 (i.e., post minus pre) - Mean WSRS change score at week 2 (Visit 3), 52 (Visit 4), 78 (Visit 5), and 104 (Visit 6) from pre-treatment (Visit 1) - Mean WSRS change score at week 52 (Visit 4), 78 (Visit 5), and 104 (Visit 6) from week 2 (Visit 3) *Subject Satisfaction* - Percentage of subjects whose GAIS change is ≥ 1 at any time during or after 104 weeks (Visit 6) - Mean GAIS grade evaluated by subjects at week 2 (Visit 3), 52 (Visit 4), 78 (Visit 5), and 104 (Visit 6)
Statistical analysis	***Safety*** **Local reactions on the injection sites** : the number and percentage of subjects who experienced each local reaction at least once (i.e., pain, tenderness, swelling, redness, bruising, itching, papule and pigmentation) for overall and by duration, seriousness and severity **Adverse events**

	All adverse events will be presented as followings : frequency and percentage of adverse events : frequency and percentage of subjects who experienced an adverse event at least once : frequency and percentage of adverse events related to YVOIRE volume s : frequency and percentage of subjects who experienced an adverse event at least once by seriousness, severity, relatedness, duration, outcomes, onset time interval (e.g., <12, 12 ~ 18, 18 – 24, >24 months), and status of biodegradation at various study period ***<u>Biodegradability</u>*** The WSRS change at each post-treatment visit from pre-treatment (visit 1) will be used for all analyses to assess biodegradation. Post-treatment visit weeks are counted from the day of the last treatment, including touch-up if available.. : The primary biodegradability variable, percentage of subjects whose WSRS change during or after week 104 visit (visit 6) after the last treatment compared to pre-treatment (i.e., post minus pre) is ≥0, will be summarized using descriptive statistics (N, %) and the 95% confidence interval (CI). : For the secondary variables and subject satisfaction, (1) continuous variables will be summarized at each time point using descriptive statistics (mean, standard deviation, median, min, and max); and (2) categorical variables will be summarized using the frequency(N) and percentage(%) along with its 95% CI.
Interim & Final analysis	Full data will be analyzed twice, (1) one interim analysis as defined below; and, (2) the final analysis when all subjects have reached the scheduled week 104 visit day (visit 6) either by meeting the total biodegradation criteria prior to week 104, by still being followed up without meeting the total biodegradation criteria, or by lost to follow-up. The data from the subjects who are still being followed up at the time of database closure for the final analysis will be summarized separately when all subjects complete the study either by reaching the total biodegradation status or by having lost to follow up; and, the summary will be included in the final study report as an addendum For the license renewal of YVOIRE volume s in China by October 2017, interim data collected by April 2017 will be analyzed to describe biodegrading characteristics of the product. In the interim analysis, all available data from all enrolled subjects will be included. At the time of interim analysis 500 subjects are expected to be enrolled, and all 500 subjects would have passed their scheduled week 52 visit date, and approximately 160 subjects are expected to have passed their scheduled week 104 visit date. All the data available in the database will be included in the interim analysis. Biodegradability will be

	assessed using the WSRS change score from pre-treatment at weeks 52 and 104 visits. Adverse events data summary and GAIS grades evaluated by subjects will be also included.
Withdrawal	1) Subjects who receive any aesthetic treatments which would have potential impact on the WSRS evaluation, per investigator's judgment will be withdrawn from the study. 2) Subjects who withdraw the consent 3) Subjects who are unable or inappropriate to continue the study for any other reasons per investigator's judgment