STATISTICAL ANALYSIS PLAN

A randomized, double-masked, active controlled, within-subject equivalency clinical trial to compare effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvederm Ultra 4® (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe nasolabial folds

NCT Number: NCT06509477

Date: 2021 August 14

STATISTICAL ANALYSIS PLAN

A randomized, double-masked, active controlled, within-subject equivalency clinical trial to compare effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe nasolabial folds

Name of Test Drug:	Lunaphil Ultra
Phase:	IV
Methodology:	Randomized, double-masked, active controlled, within-Subject equivalency clinical trial
Sponsor:	Espad Pharmed Company Office: Espad Pharmed, Third floor, No. 56, Azimi St., Nafisi St., Ekbatan, Tehran Phone: 021-44631124
Sponsor Representatives:	Zist Orchid Pharmed Co.
Statistical Analysis Plan Date:	2021 August
Statistical Analysis Plan Version:	Version 1.0

Contents

Synopsis

Title	A phase IV, randomized, double-masked, active controlled, within-Subject equivalency clinical trial to compare effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe nasolabial folds (NLFs)
Aim of Study (Primary endpoint)	The Primary objective of this study is to verify the effectiveness of Lunaphil Ultra (produced by Espad Pharmed Co.) compared with Juvéderm® Ultra 4 by mean level of improvement from baseline in NLF severity score
Secondary objectives	The secondary objectives of this study are to verify the effectiveness and safety of Lunaphil Ultra (produced by Espad Pharmed Co.) compared with Juvéderm® Ultra 4
Study Design	The study is designed as phase IV, randomized, double-masked, active controlled, within-Subject equivalency clinical trial with primary endpoint of mean level of improvement from baseline in NLF severity score
Sponsor	Espad Pharmed Company
Investigational Drug	Lunaphil Ultra (produced by Espad Pharmed Co.)
Comparator	Juvéderm® Ultra 4 (the reference drug, produced by Allergan Co.)
Sample size	In an equivalence test of means using two one-sided tests on data from a paired design, a sample size of 97 achieves 80% power at a 2.5% significance level when the true difference between the means is 0, the standard deviation of the paired differences is 0.510, and the equivalence limits are -0.17 and 0.17. Considering a 10% drop-out rate, total sample size required is 108.
Eligibility criteria	**Inclusion Criteria:** • Subjects ≥ 30 years of age • Visible bilateral NLFs that were approximately symmetrical both and of equal severity with a rating of moderate or severe (assessed at the deepest part) • Able to follow study instructions and likely to complete all required visits • Signed informed consent **Exclusion criteria:** • History of bleeding disorders or patients receiving or recently exposed (≤3 weeks) to continuous treatment with thrombolytics, anticoagulants,

	platelet inhibitors, or NSAIDs • Acute herpetic eruption • Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders • Known sensitivity to local anesthetics of the amide type (such as lidocaine), history of hypersensitivity to gram-positive bacterial proteins, history of multiple severe allergies, history of anaphylactic shock • Known hypersensitivity to any component of the study drugs or excipients (like hyaluronic acid) • History of receiving immune therapy or a history of autoimmune disease • History of active chronic debilitating systemic disease • History of connective tissue disease, history of malignancy (excl. non-melanoma skin cancer) within past 5 years • Clinically significant active dermatologic disorders within 6 months • Use in the 4 weeks before study randomization (or intent to use during the study) of oral retinoids, OTC or prescription antiwrinkle treatments, microdermabrasion, or chemical peels in the NLF area • Any prior cosmetic procedure or tissue augmentation at the NLF injection site in 1 year before study entry (or intent to undergo such a procedure during the study) • Pregnancy or breastfeeding
Randomization	The subjects will be randomized into two possible treatment groups. The first treatment group will receive Lunaphil Ultra on the right side and Juvéderm® Ultra 4 on the left side of their face. The second treatment group will receive Juvéderm® Ultra 4 on the right side and Lunaphil Ultra on the left side of their face. The randomization plan of the subjects will be carried out centrally using an R-CRAN software version 4.0.3. Blocks (with the size of 2) will be made using permuted block randomization for a total of 108 subjects (1:1 allocation ratio).
Blinding	To prevent the influence of any bias caused by knowing the intervention face-side, the study will be double-blinded. Hence, patients and those who assess the study outcomes will remain unaware of allocation to test- or reference-Hyaluronic acid.
Intervention	Subjects will be treated with Juvéderm® Ultra 4 in one NLF and Lunaphil Ultra in the opposite NLF.

	Two treatments will be allowed over a 2-week period (initial treatment plus one touch-up) to achieve optimal correction of the NLFs. The level of correction will be assessed by the evaluating investigator at week 2 after the initial treatment and, if less than optimal, the treating investigator will be directed to retreat the undercorrected NLF(s).
Outcomes	**Efficacy and safety outcomes** *Primary outcome:* Mean level of improvement from baseline in NLF severity score by WSRS (wrinkle severity rating scale) at 24 weeks *Secondary outcomes:* • Number of subjects with improvement score for the 5-point Physician Global Aesthetic Improvement Scale (PGAIS) at 24 weeks • Proportion of NLFs maintaining a clinically significant improvement in NLF severity score (≥1-point reduction from baseline) at 24 weeks • Volume to Obtain Optimal Cosmetic Result (Initial Treatment + Touch-up) • Number of NLFs receiving touch-up treatment • Incidence of adverse events (Injection Site Reactions) and incidence of adverse events (Injection Site Reactions) based on severity
Statistical Plan	Processes of cleaning, inspecting, and transforming will be done in the procedure of data analysis. Also, the descriptive analysis will be performed using frequency and percentage, average and standard deviation regarding the type of the variables. **Primary Endpoint:** The mean level of improvement from baseline in NLFs severity score based on assessments by evaluating investigators will be analyzed using a paired t-test or a signed-rank test. **Secondary Endpoint:** The number of patients with improvement score for the PGAIS will be

	analyzed using a McNemar test. The proportion of NLFs with clinically significant improvement will be analyzed using a McNemar test. Injection volume to obtain optimal result will be analyzed with a paired t-test or a signed-rank test. The number of NLFs receiving touch-up treatment will be analyzed using a McNemar test. **Safety:** The safety data will be analyzed primarily using summary statistics. The incidence, frequency, and severity of adverse events (Injection Site Reactions) will be reported.
Withdrawal Criteria	• Withdrawal of consent by the patient • Noncompliance, including refusal of study medical requirements, refusal of procedures as stated in the study protocol, or use of prohibited medications • The occurrence of an undesirable event that causes the investigator to consider the patient's exclusion from the study • Not possible to follow the patient's condition (Loss to follow-up) • Change in patient's conditions which needs change of treatment due to investigator decision or administration of prohibited medications in protocol

Study Timeline

	Study period					
	Screening	**Intervention**				
Time point	**Screening visit**	**Visit 1**	**Visit 2 (Touch-up)** *	**Visit 2'** **	**Visit 3**	**Visit 4**
Time	*-7 to -1 days*	*Day 1*	*2 weeks ± 3days*	*4 weeks ± 3days*	*12 weeks ± 3days*	*24 weeks ± 3days*
Informed consent	×					
Eligibility Criteria	×					
Randomization and allocation		×				
Medical History	×					
Face photography	×	×	×	×	×	×
Intervention		×	×			
NLF severity score assessment	×		×	×	×	×
PGAIS assessment		×***	×	×	×	×
Concomitant Medications	×	×	×	×	×	×
Adverse Events reporting	×	×	×	×	×	×

***** Two treatments will be allowed over a 2-week period (initial treatment plus one touch-up) to achieve optimal correction of the NLFs. The level of correction will be assessed by the evaluating investigator at week 2 after the initial treatment and, if less than optimal, the treating investigator will be directed to retreat the under corrected NLF(s).

** This visit is only conducted in patients with touch-up injection.

*** PGAIS in visit 1 is assessed after the intervention.

List of Abbreviations and Definition of Terms

Abbreviation	Description
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practice
HA	Hyaluronic Acid
ICH	International Council for Harmonization of Technical Requirements for
MedDRA	Medical Dictionary for Regulatory Activities
NLF	Nasolabial Fold
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PGAIS	Physician Global Aesthetic Improvement Scale
PMS	Postmarketing Surveillance
PT	Preferred Term
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO	World Health Organization
WSRS	Wrinkle Severity Rating Scale

Section 1: Administrative information

Title and Trial registration

A phase IV, randomized, double-masked, active controlled, within-subject equivalency clinical trial to compare effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe nasolabial folds (NLFs)

Ethics Approval Number

IR.TUMS.MEDICINE.REC.1400.1011

SAP Version (SAP version number with dates)

Version: 1.0, Date: 2021 August 14

Section 2: Introduction

Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the planned statistical analyses for the Phase IV randomized, double-blind, parallel-group, active-controlled clinical trial designed to assess the therapeutic equivalence in efficacy and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) in managing moderate or severe NLFs.

The objective of this SAP is to outline the statistical methodologies and analysis principles that will be applied to evaluate the primary and secondary endpoints of the study, as well as the handling of missing data, analysis sets, and subgroup analyses. This SAP is intended to ensure transparency and reproducibility of the planned analyses, and it has been finalized prior to database lock and unblinding of the study data.

Rationale and Background

Skin aging is a complex and multifactorial process resulting in various functional and aesthetic changes in the skin (1). It is an inevitable process that can be described clinically as features of wrinkles, sun

spots, uneven skin color, and sagging skin (2). Additional clinical findings include tear trough, a drop of the angle of the mouth, loss of definition in the mandibular border, platysmal bands, evident veins, and NLFs as one of the typical clinical manifestations of facial aging (3).

The perception of health and age is a critical aspect in the common judgment of attractiveness and people are judged to be less attractive as they age (4). Attractiveness influences both self-perception and social behavior and is related to traits such as self-confidence and social acceptance. Therefore, aesthetic interventions can improve psychological well-being and quality of life (5).

Dermal fillers are widely used for the correction of deep wrinkles, including NLFs. Treatments with dermal fillers provide favorable aesthetic outcomes with minimal invasiveness and no downtime following surgical procedures (6). Hyaluronic acid (HA) fillers, the most popular dermal fillers (7), demonstrate desirable effects on the fibroblast phenotype, including higher cell proliferation and type I collagen synthesis (8). HA fillers have predictable efficacy, a good safety profile, quick recovery, and simplicity in administration (9, 10).

Different factors, including HA concentration, polymer chain length, and crosslinking degree or technology, influence filler properties such as the requisite needle size, particle size, duration, extrusion force, and elastic Modulus (G'). All of these factors will critically influence product selection and indication (11). Among these factors, crosslinking is essential to slowing down the enzymatic degradation rate of the HA by endogenous hyaluronidase and prolonging the product's half-life. The extent of crosslinking strongly impacts the biophysical and biological properties of a filler, including tissue integration, water uptake, resistance to degradation, and filler biocompatibility and consequently might have clinical implications (12).

Lunaphil Ultra intradermal filler is a cross-linked HA soft tissue filler manufactured by Espad Pharmed Company. It contains 24 mg/ml of HA and 0.3% lidocaine as a supplemental anesthetic. Since pain is the most commonly reported complaint with dermal fillers, a local anesthetic like lidocaine is included in their formulation to reduce procedural pain and bypass the need for additional anesthesia (13).

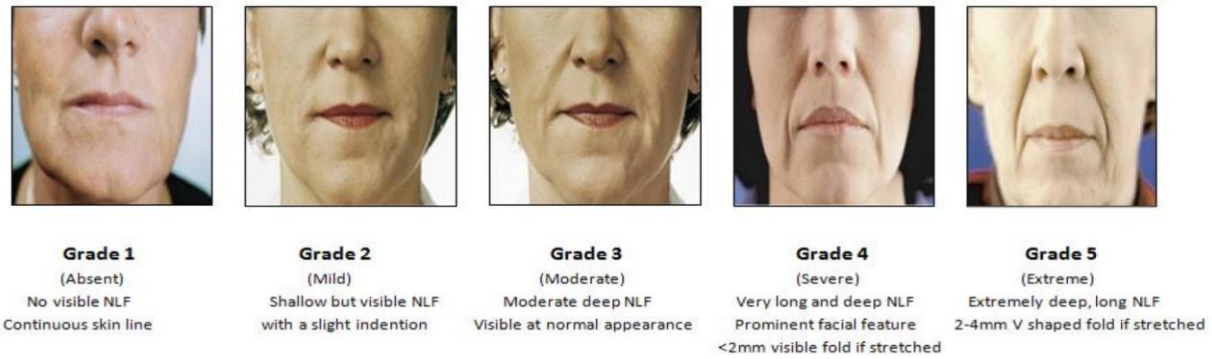
The aim of this study is to compare the effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) in managing moderate or severe NLFs.

Objectives

This study aims to assess the safety and effectiveness of Lunaphil Ultra for the management of moderate or severe nasolabial folds (NLFs).

Primary objective(s)

Mean level of improvement from baseline in NLF severity score by WSRS at week 24



Secondary objective(s)

1. Number of subjects with an improvement score based on PGAIS at week 24
2. Proportion of NLFs maintaining a clinically significant improvement in NLF severity score (≥1-point reduction from baseline) at week 24
3. The injected volume to obtain optimal aesthetic result (initial treatment + touch-up)
4. The number of NLFs receiving touch-up treatment
5. The incidence, severity and causal relationship of adverse events

Section 3: Research Methods

Study Design

This is a randomized, double-masked, active controlled, within-subject, and equivalency study to compare the effectiveness and safety of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) versus Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe NLFs.

Intervention

Subjects will be treated with Juvéderm® Ultra 4 in one NLF and Lunaphil Ultra in the opposite NLF. Two treatments will be allowed over a 2-week period (initial treatment plus one touch-up) to achieve optimal correction of the NLFs. The level of correction will be assessed by the evaluating investigator at week 2 after the initial treatment and, if less than optimal, the treating investigator will be directed to retreat the undercorrected NLF(s).

Randomization

The subjects will be randomized into two possible treatment groups. The first treatment group will receive Lunaphil Ultra on the right side and Juvéderm® Ultra 4 on the left side of their face. The second treatment group will receive Juvéderm® Ultra 4 on the right side and Lunaphil Ultra on the left side of their face. The randomization plan of the subjects will be carried out centrally using an R-CRAN software version 4.0.3. Blocks (with the size of 2) will be made using permuted block randomization for a total of 108 subjects (1:1 allocation ratio).

Blinding

To prevent any bias arising from awareness of face-side allocation, this study will be performed in a double-blind manner. For each participant, one side of the face will receive the investigational hyaluronic acid product and the other side will receive the reference Hyaluronic acid product, according to the pre-specified randomization plan. Both the participants and all investigators responsible for administering injections and assessing outcomes will remain blinded to the allocation throughout the study.

Sample size

In an equivalence test of means using two one-sided tests on data from a paired design, a sample size of 97 achieved 80% power at a 2.5% significance level. When the true difference between the means was 0.000, the standard deviation of the paired differences was 0.510, and the equivalence limits were -0.170 and 0.170. Considering a drop-out rate of 10%, total sample size required is 108.

Study Population Criteria

Inclusion Criteria

1. Subjects ≥ 30 years of age

2. Visible bilateral NLFs that are approximately symmetrical and have an equal severity ranging from moderate to severe (assessed at the deepest part)
3. Able to follow study instructions and likely to complete all required visits
4. Signed informed consent

Exclusion Criteria

1. History of bleeding disorders or participants receiving or recently exposed (≤ 3 weeks) to continuous treatment with thrombolytics, anticoagulants, platelet inhibitors, or NSAIDs
2. Acute herpetic eruption
3. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders
4. Known sensitivity to local anesthetics of the amide type (such as lidocaine), history of hypersensitivity to gram-positive bacterial proteins, history of multiple severe allergies, history of anaphylactic shock
5. Known hypersensitivity to any component of the study products or excipients (like hyaluronic acid)
6. History of receiving immune therapy or a history of autoimmune disease
7. History of active chronic debilitating systemic disease
8. History of connective tissue disease, history of malignancy (except for non-melanoma skin cancer) within the last 5 years
9. Clinically significant active dermatologic disorders within the last 6 months
10. Use of oral retinoids, OTC or prescription antiwrinkle treatments, microdermabrasion, or chemical peels in the NLF area within the last 4 weeks or intention to use them during the study
11. Any prior cosmetic procedure or tissue augmentation at the NLF injection site within 1 year before study entry (or intent to undergo such a procedure during the study)
12. Pregnancy or breastfeeding

Withdrawal Criteria

1. Withdrawal of consent by the participant
2. Noncompliance, including refusal of study medical requirements, refusal of procedures as stated in the study protocol, or use of prohibited medications
3. The occurrence of an undesirable event that causes the investigator to consider the participant's exclusion from the study
4. Not possible to follow the participant's condition (Loss to follow-up)

5. Change in participant's conditions, which needs change of treatment due to investigator decision or administration of prohibited medications in the protocol

Data sources and measurement

All data will be collected by specialists and recorded in a booklet comprising five visits. Baseline information (demographics, past medical history, history of filler injection, patients' medications), intervention information (e.g., dosage at visit 1 and touch up), WSRS, and PGAIS will be recorded.

All adverse events (AEs) will be documented and categorized according to their frequency, severity (graded using the Common Terminology Criteria for Adverse Events version 5.0) (14), and their assessed causality, following the World Health Organization guidelines (15). The AEs will be reported using the Medical Dictionary for Regulatory Activities (MedDRA) under both the preferred term (PT) and system organ class (SOC) (16). Serious adverse events (SAEs) will be documented in compliance with the E2B(R2) guideline (17) and will be defined as any AE that "results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or other medically important condition."

Section 4: General issues for statistical analysis

Analysis populations

Primary efficacy will be analyzed on a per-protocol population. Also, the primary outcome and secondary key variables of the study will be examined on the intention-to-treat population, and sensitivity analysis will be used to compare the primary outcome in the two populations. All analyzes of complications will be performed based on the safety population.

1. Per-protocol population: all patients who were randomly treated with the study drug and did not have a major deviation from the protocol.

2. Intention-to-treat population: all patients randomly assigned to one of the treatment groups. Patients are analyzed according to the treatment they received randomly.

3. Safety population: All patients who randomly received at least one dose of the study drug. Patients are analyzed according to the treatment they actually received.

Protocol violations and deviations

A protocol deviation refers to any change, non-compliance, or departure from the approved protocol such as enrolling a participant who did not meet all the inclusion/exclusion criteria, visit non-compliance, incorrect execution of the consent form, participant declines to complete scheduled research activities, use of unapproved recruitment procedures, use of an unapproved version of the Participant Information and Consent Form, dispensing or dosing error for study medication/drug, and any change, divergence, or departure from the study design or procedures defined in the protocol. The per-protocol (PP) population is a subset of the Intention-To-Treat (ITT) population, which includes participants who completed the study without any major violations of the protocol. Description of which protocol deviations will be summarized. No participants will be excluded from the ITT analyses due to protocol deviations.

Statistical Software

The analysis will be carried out using Stata (StataCorp LP, USA) and R statistical software.

Missing Data

The missing WSRS scores at week 24 for participants with available week 12 data will be imputed based on their WSRS scores at week 12. For participants with missing WSRS scores at week 12, no imputation will be performed. In the ITT population, imputation for this outcome will be conducted as described above.

Outlier data

Outliers are identified by examining standard charts, and those that are visually "distinct" are evaluated to check the impact on the results by comparing the results of the analysis with and without outliers.

Data Transformations

No transformations of raw data are planned prior to statistical analysis. All variables will be analyzed using their original measurement scales, unless transformation is deemed necessary during model diagnostics. In such cases, justification and details will be documented in the statistical outputs and Clinical Study Report (CSR).

Multiple comparisons and multiplicity

No formal procedures for multiplicity adjustment are planned for this study, as the study was not designed to perform multiple statistical comparisons for primary or key secondary endpoints. Therefore, the overall Type I error rate will not be adjusted.

Covariate Adjustment

No covariate adjustment will be done.

Planned subgroup analysis

No subgroup analysis will be done.

Section 5: Outcome Variables

Primary Outcomes

The main outcome of this study is the evaluation of the equivalency of the efficacy of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) compared to Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.), which is measured by evaluate the mean level of improvement from baseline in NLF severity score by WSRS at week 24.

Secondary Outcomes

Evaluating the effectiveness of Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) compared to Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.) in the following criteria:

- The number of participants with improved score in Physician Global Aesthetic Improvement Scale (PGAIS) at week 24 compared to baseline which was assessed by two evaluators

- The proportion of NLFs that sustained a clinically meaningful reduction in severity score (≥1-point reduction from baseline) at week 24

- The injected volume to obtain optimal aesthetic result (initial treatment + touch-up)

- The number of NLFs receiving touch-up treatment

Safety outcome

The incidence, severity and causal relationship of adverse events will be reported. The intensity of AEs will be graded according to the CTCAE v5.0, and terminology for AEs will be chosen according to the MedDRA system organ class and preferred term (MedDRA Desktop Browser 4.0 Beta). Seriousness will be also recorded for all AEs.

Section 6: Descriptive statistics

Participant flow

The flow of participants throughout the study is planned to be summarized. A participant flow diagram will illustrate the number of subjects at each stage of the study, including:

- Number of subjects randomized to each treatment group

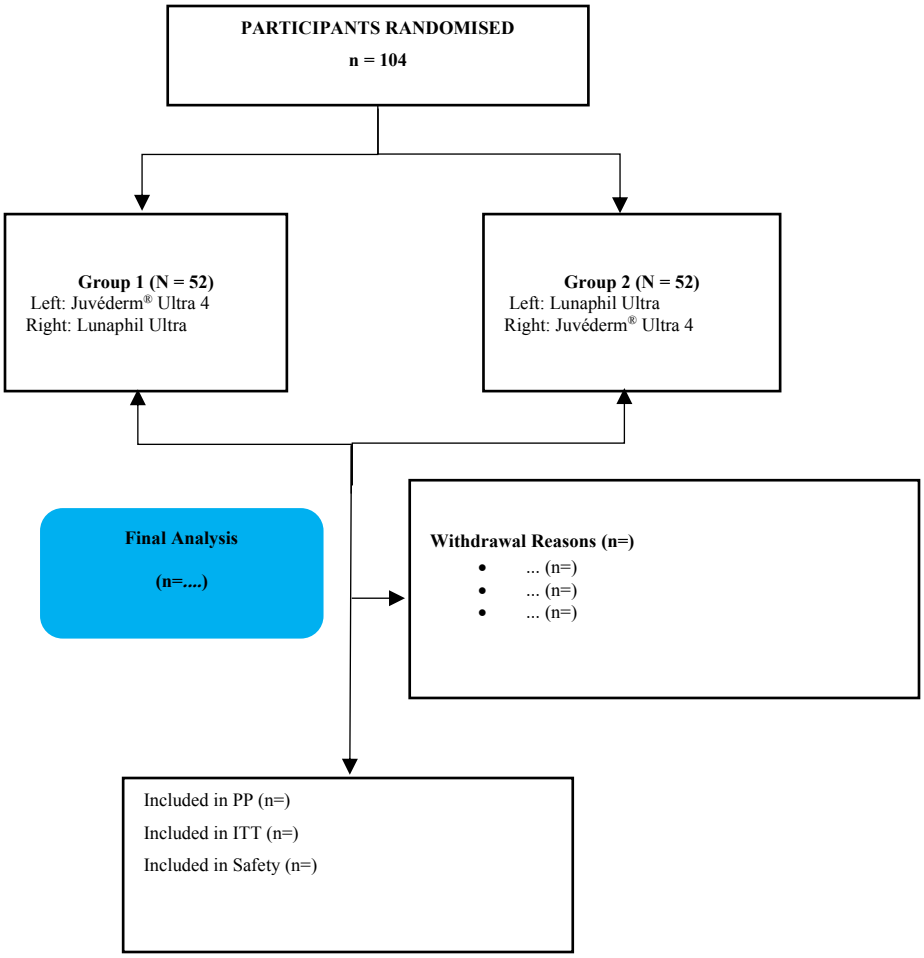
- Number of subjects who received at least one dose of study treatment

- Number of subjects who completed the study and those who discontinued (with reasons)

- Number of subjects included in each analysis set (PP, ITT, Safety)

Tabulations of participant disposition will also be provided, including counts and percentages by treatment arm. The reasons for exclusion from each analysis set will be documented in the subject listings and summarized in the Clinical Study Report (CSR).

All flow and disposition data will be based on the data recorded in the clinical database up to the date of database lock.



Baseline characteristics

Baseline characteristics	**Categories**
Age	-
Sex	Male/Female
History of filler injection in NLF	Yes/No
WSRS	1 to 5

Descriptive statistics for baseline characteristics will be presented as mean and standard deviation for continuous variables, and as frequency and percentage for categorical variables.

Section 7: Statistical Analysis

This section describes the planned statistical analyses for efficacy and safety outcomes. Results will be summarized using appropriate descriptive statistics and analyzed using suitable statistical models depending on the data type. Treatment effects will be presented with 95% confidence intervals and two-sided p-values, using a significance level of 0.05.

Primary Endpoint Analysis

For the statistical analysis of the primary outcome (equivalence assessment of the mean level of improvement from baseline in NLFs severity score), both categories of Per-Protocol and Intention-to-Treat statistical population will be examined. Although the main approach is the results of the statistical analysis of the Per-Protocol population, eventually a sensitivity analysis will be performed between the results of the said analysis and the results of the statistical analysis of the Intention-to-Treat population.

Paired t-test or a signed-rank test will be used to compare the mean level of improvement from baseline in NLFs severity score based on assessments by evaluating investigators between Lunaphil Ultra (Hyaluronic acid, produced by Espad Pharmed Co.) compared to Juvéderm® Ultra 4 (Hyaluronic acid, produced by Allergan Co.). The 95% confidence interval (CI) for the mean difference between the two treatments will be calculated. Equivalence will be concluded if the entire 95% CI falls within the pre-specified equivalence margin of ±0.17.

Secondary Endpoints Analysis

- The number of patients with improvement score for the PGAIS will be analyzed using a McNemar test.
- The proportion of NLFs maintaining a clinically significant improvement will be analyzed using a McNemar test.
- Injection volume to obtain optimal result will be analyzed with a paired t-test or a signed-rank test.

The number of NLFs receiving touch-up treatment will be analyzed using a McNemar test.

Safety Analysis

All adverse events (AEs) data will be descriptively analyzed. Also, AEs in two groups are compared

using Pearson chi-square test.

The incidence and percentage of treatment-emergent adverse events will be reported, categorized by system organ class (SOC) and preferred term (PT). Adverse events' severity, seriousness, and causality assessment will be reported.

Methods used for assumptions to be checked for statistical methods

For t-test, normality of distributions will be assessed using the Shapiro-Wilk test.

References

1. Voropai D, Dayan S, Botero LF, Botti C, Miller L, Pirayesh A. Aging of Skin, Soft Tissue, and Bone. Aesthetic Facial Anatomy Essentials for Injections: CRC Press; 2020. p. 13-6.
2. Vashi NA, de Castro Maymone MB, Kundu RV. Aging Differences in Ethnic Skin. J Clin Aesthet Dermatol. 2016;9(1):31-8.
3. Grablowitz D, Sulovsky M, Höller S, Ivezic-Schoenfeld Z, Chang-Rodriguez S, Prinz M. Safety And Efficacy Of Princess(®) FILLER Lidocaine In The Correction Of Nasolabial Folds. Clin Cosmet Investig Dermatol. 2019;12:857-64.
4. He D, Workman CI, Kenett YN, He X, Chatterjee A. The effect of aging on facial attractiveness: An empirical and computational investigation. Acta Psychologica. 2021;219:103385.
5. Waldman A, Maisel A, Weil A, Iyengar S, Sacotte K, Lazaroff JM, et al. Patients believe that cosmetic procedures affect their quality of life: an interview study of patient-reported motivations. Journal of the American Academy of Dermatology. 2019;80(6):1671-81.
6. Fallacara A, Manfredini S, Durini E, Vertuani S. Hyaluronic acid fillers in soft tissue regeneration. Facial Plastic Surgery. 2017;33(01):087-96.
7. Stojanovič L, Majdič N. Effectiveness and safety of hyaluronic acid fillers used to enhance overall lip fullness: a systematic review of clinical studies. Journal of Cosmetic Dermatology. 2019;18(2):436-43.
8. Cabral LRB, Teixeira LN, Gimenez RP, Demasi APD, de Brito Junior RB, de Araújo VC, et al. Effect of Hyaluronic Acid and Poly-L-Lactic Acid Dermal Fillers on Collagen Synthesis: An in vitro and in vivo Study. Clin Cosmet Investig Dermatol. 2020;13:701-10.
9. Campiglio G, Srdanović N. Comparison Between Fat and Fillers. Plastic and Aesthetic Regenerative Surgery and Fat Grafting: Springer; 2022. p. 69-88.
10. Urdiales-Gálvez F, Barres-Caballer J, Carrasco-Sánchez S. Ultrasound assessment of tissue integration of the crosslinked hyaluronic acid filler VYC-25L in facial lower-third aesthetic treatment: A prospective multicenter study. Journal of Cosmetic Dermatology. 2021;20(5):1439-49.
11. Patrick Micheels M, Didier Sarazin M, Christian Tran M. Effect of different crosslinking technologies on hyaluronic acid behavior: a visual and microscopic study of seven hyaluronic acid gels. Journal of Drugs in Dermatology. 2016;15(5):600-6.
12. Guarise C, Barbera C, Pavan M, Panfilo S, Beninatto R, Galesso D. HA-based dermal filler: Downstream process comparison, impurity quantitation by validated HPLC-MS analysis, and in vivo residence time study. Journal of Applied Biomaterials & Functional Materials. 2019;17(3):2280800019867075.
13. Smith L, Cockerham K. Hyaluronic acid dermal fillers: can adjunctive lidocaine improve patient satisfaction without decreasing efficacy or duration? Patient preference and adherence. 2011:133-9.
14. Services USDOHAH. Common Terminology Criteria for Adverse Events (CTCAE) Accessed August 13, 2024, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
15. Centre UM. The use of the WHO-UMC system for standardised case causality assessment Accessed August 13, 2024, https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf
16. Medical Dictionary for Regulatory Activities (MedDRA). https://www.meddra.org/about-meddra/evolving-meddra. Accessed August 13, 2024, https://www.meddra.org/about-meddra/evolving-meddra

17. Use ICoHoTRfRoPfH. maintenance of the ICH guideline on clinical safety data management: Data elements for transmission of individual case safety reports E2B(R2). Accessed August 13, 2024, https://admin.ich.org/sites/default/files/inline-files/E2B_R2_Guideline.pdf