A Post-Authorization Safety (and Effectiveness) Study Protocol

Title	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
Date	14/08/2021
IRCT register number	Not Applicable
Active substance	Hyaluronic acid (M09AX01)
Medicinal product	Hyaluronic acid (Lunaphil Ultra®)
Product reference	Juvederm Ultra 4®
Procedure number	Not Applicable
Joint PASS	No
Research question and objectives	This study aims to assess the safety and effectiveness of Lunaphil Ultra for the management of moderate or severe nasolabial folds (NLFs)
Country(-ies) of study	Iran
Author	Dr. Kamran Balighi Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Table of Contents

1 List of Abbreviations

Table 1-1. List of abbreviations

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 Pharmaceuticals
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

2 Responsible Parties

2.1 Principal Investigator

Roles and Responsibilities:

- Conducting the study according to the agreed protocol, International Council for Harmonization and good clinical practice (GCP) guidelines
- Selecting study team and ensuring adequate training and familiarity with the roles
- Organizing training sessions for existing and newly recruited team members whenever necessary
- Supervising and approval of suitable places for participant visit
- Cooperation with monitors during the conduction of the study

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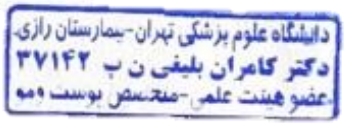

Names:

Names of investigators are presented in Table 2-1**Error! Reference source not found.**.

Table 2-1. Names of investigators

Investigators
Dr. Kamran Balighi
Dr. Kamran Jazayeri
Dr. Omid Zargari

3 Other responsible parties

3.1 Sponsor

Roles and Responsibilities:

- Study protocol preparation
- Preparing CRFs
- Obtaining necessary approvals from external organizations for conducting the study
- Providing SOP for the investigators in study centers
- Funding provision for site staffs collaborating in data collection via signing contracts with the chief and principal investigators
- Providing necessary training for the staff
- Recruiting necessary workforce to conduct monitoring of the trial and the data management
- Planning and conducting statistical analyses.

- Preparing required study reports.

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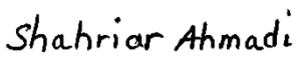
Signature**:** 

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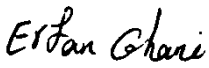
Signature: 

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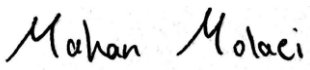
Signature: 

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4 Abstract

Title

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 (NLFs)

Dr. Kamran Balighi

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Keywords

Lunaphil Ultra, Hyaluronic Acid, Nasolabial Folds

Rationale and Background

Skin aging is a complex process that results in various changes in the skin, including wrinkles, sun spots, and sagging skin. The NLF is a natural change that becomes more prominent with aging and significantly affects the beauty of the

facial skin. Dermal fillers, particularly HA fillers, are commonly used to correct these signs of aging. This study aims to compare the effectiveness and safety of Lunaphil Ultra with Juvederm Ultra 4® for treating NLFs.

Research Question and Objectives

Primary objective:

Effectiveness assessment of Lunaphil Ultra

Secondary objectives:

Effectiveness and safety assessment of Lunaphil Ultra

Study Design

This is a randomized, double-masked, active controlled, within-subject, and equivalency clinical trial.

Setting

Subjects will be treated with Lunaphil Ultra in one NLF and Juvederm Ultra 4® in the opposite NLF.

A total of 108 participants will be enrolled in the study. For each participant, the products will be injected in the first visit and if needed an additional injection will be done (touch-up) at visit 2 (week 2). The duration of the study is 24 weeks for each participant.

Subjects and study size, including drop-outs

A population of 108 participants will be enrolled in the study, and during 24 weeks, study-related data will be collected.

Variables and Data Sources

Lunaphil Ultra will be administered over a 2-week period (initial treatment plus one touch-up) to achieve optimal correction of the NLFs.

The primary objective of this study is effectiveness assessment, including the mean level of improvement from baseline in NLF severity score by Wrinkle Severity Rating Scale (WSRS) at week 24.

Variables in this study includes patient demographic information (age, sex), history of filler injection, baseline WSRS and subsequent scores at other visits, patient's medical history, patient's medications, injection volume, receipt of touch-up treatment, Physician Global Aesthetic Improvement Scale (PGAIS) at each visit, and adverse events (AE) reporting.

Name and affiliation of principal investigator

Dr. Kamran Balighi

Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Data Analysis

The primary endpoint will be assessed by measuring the mean level of improvement from baseline in NLFs severity score using either a paired t-test or a signed-rank test.

The number of patients with an improved score for the PGAIS, proportion of NLFs with clinically significant improvement and the number of NLFs receiving touch-up treatment 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 safety data will be analyzed primarily using incidence and frequency. AEs' severity, seriousness, and causality assessment will be reported.

5 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 Juvederm Ultra 4® (Hyaluronic acid, produced by Allergan Co.) in managing moderate or severe NLFs.

6 Research Question and Objectives

Primary objective:

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

Secondary objective:

- Number of subjects with an improvement score based on PGAIS at week 24
- Proportion of NLFs maintaining a clinically significant improvement in NLF 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
- The incidence, severity and causal relationship of adverse events

7 Amendments and Updates

There are no amendments and updates throughout the study.

8 Research Methods

8.1 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 Juvederm Ultra 4® (Hyaluronic acid, produced by Allergan Co.) for the management of moderate or severe NLFs.

8.2 Setting

8.2.1 Subjects

A total of 108 participants with moderate to severe NLFs will be enrolled in the study.

Inclusion Criteria

- Subjects ≥ 30 years of age
- Visible bilateral NLFs that are approximately symmetrical and have an equal severity ranging from moderate to 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 participants 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 products 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 (except for non-melanoma skin cancer) within the last 5 years
- Clinically significant active dermatologic disorders within the last 6 months
- 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
- 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)
- Pregnancy or breastfeeding

Withdrawal Criteria

- Withdrawal of consent by the participant
- 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 participant's exclusion from the study
- Not possible to follow the participant's condition (Loss to follow-up)
- Change in participant’s conditions, which needs change of treatment due to investigator decision or administration of prohibited medications in the protocol

8.3 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.

8.4 Variables

The primary objective of this study is effectiveness assessment, including the mean level of improvement from baseline in NLF severity score by WSRS at week 24. The secondary outcomes of this study are to evaluate other effectiveness and safety parameters, including the number of subjects with improvement score in PGAIS at week 24 compared to baseline, the proportion of NLFs maintaining a clinically significant improvement in NLF severity score (≥1-point reduction from baseline) at week 24, the volume required for optimal cosmetic result (initial treatment + touch-up), the number of NLFs receiving touch-up treatment, and the incidence of adverse events (injection site reactions) based on their severity.

Variables in this study include patient demographic information (age, sex), history of filler injection, WSRS at each visit, patient's medical history, patient's medications, injection volume, receiving touch up treatment, PGAIS at each visit.

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.

8.5 Data Sources and Measurement

All data will be collected by specialists and recorded in a booklet comprising five visits. The baseline information (demographics, past medical history, history of filler injection, patients' medications), intervention information (e.g., dosage at visit1 and touch up), WSRS, and PGAIS will be recorded. All AEs will be reported based on the Medical Dictionary for Regulatory Activities (MedDRA) terms as the preferred term (PT) and system organ class (SOC) (14). All reported AEs will be graded according to the common terminology criteria for adverse events v5.0 (CTCAE v5.0) (15). Moreover, the seriousness of AEs will be specified using ICH-E2B guidelines (16). The causality relation will be assessed based on the World Health Organization (WHO) criteria (17).

8.6 Study 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.

8.7 Statistical Methods

8.7.1 Main Summary Measures

The descriptive analysis will be performed using frequency and percentage for categorical variables and mean and standard deviation for continuous variables.

8.7.2 Main Statistical Methods

The mean level of improvement from baseline in NLFs severity score based on assessments by evaluating investigators and the injection volume to obtain optimal result will be analyzed using either a paired t-test or a signed-rank test. The number of patients with an improved score for the PGAIS, proportion of NLFs with clinically significant improvement and the number of NLFs receiving touch-up treatment will be analyzed using a McNemar test.

The safety data will be analyzed primarily using summary statistics. Summary statistics are included the number of subjects (number and percentages) and then classified according to system organ class and preferred term for AEs and SAEs. The incidence of the preferred term for grades 3 and 4 of AEs will be reported. Moreover, causality will be assessed and its results will be reported by frequency and percentage.

8.8 Quality Control

Espad Pharmed Co. conducts this study according to procedures that incorporate the ethical principles of GCP. The investigators participating in this study are among the most professional dermatologists in Iran.
Before initiating the study, the PMS booklet will be checked and confirmed by the principal investigator regarding conformity with the study protocol. An instruction manual will be provided to train the personnel involved in filling the booklets. Participants' recorded data in PMS booklets will be regularly monitored in terms of verification and validity. The recorded data in the booklets will be regularly exported and checked by a certified statistician for outlier determination to verify if data entry errors have occurred, and they will be rechecked if needed.

8.9 Limitations of the Research Methods

The decision for a touch-up injection can be participant-driven rather than based on a real need to achieve optimal aesthetic results.

9 Protection of Human Subjects

This study will be conducted in full conformance with the principles of the Declaration of Helsinki and GCP, along with local ethical approval requirements. Ethical approval is obtained from the local ethics committee of the affiliated university of the principal investigator. An informed consent form will be signed by the candidates who voluntarily accept to participate in the study. All personal data will be confidentially recorded and archived during the study and thereafter.

10 Management and Reporting of Adverse Events/Adverse Reactions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

All AEs will be classified based on their severity and in accordance with the approved guidelines in the CTCAE v.5, published on November 27, 2017. According to these guidelines, Grade refers to the severity of the AE. Accordingly, Grades 1 to 5 with unique clinical descriptions of the severity of each AE are specified as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)[1].

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

The causality relation will be assessed based on the WHO criteria. To determine the relationship between an AE or ADR and the treatment used in the study, the following definitions are considered:

Unrelated

An adverse event for which no relationship can be inferred between it and the drug under consideration.

Related

Certain: Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary

Probable / Likely: Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required

Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

Unlikely: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Conditional / Unclassified: Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination

[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Unassessable / Unclassifiable: Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Recording Adverse Events

All AEs that occur following drug administration will be meticulously documented in the patient's medical records.

Seriousness of AEs will be assessed based on ICH-E2B guidelines

seriousness criteria:

− Results in death

− Is life-threatening

− Requires inpatient hospitalization or prolongation of existing hospitalization

− Results in persistent or significant disability/incapacity (as per reporter's opinion)

− Is a congenital anomaly/birth defect

− Other medically important condition

11 Plans for Disseminating and Communicating Study Results

Study report will be prepared and submitted according to the ICH guidelines, and a journal article will be written to submit in peer-reviewed journals.

12 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. Medical Dictionary for Regulatory Activities (MedDRA). https://www.meddra.org/about-meddra/evolving-meddra 2005 [Available from: https://www.meddra.org/about-meddra/evolving-meddra.
15. Services USDOHAH. Common Terminology Criteria for Adverse Events (CTCAE) 2017 [updated Published: 27 November 2017. Version 5.0 [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
16. Use ICoHoTRfRoPfH. maintenance of the ICH guideline on clinical safety data management: Data elements for transmission of individual case safety reports E2B(R2) 2001 [updated 5 February 2001 [Available from: https://admin.ich.org/sites/default/files/inline-files/E2B_R2_Guideline.pdf
17. Centre UM. The use of the WHO-UMC system for standardised case causality assessment 2018 [updated 4 June 2018] [Available from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf.

13 Appendices

Not applicable.