

Research Article

Safety and Efficacy Assessment of a Cross-linked Hyaluronic Acid Dermal Filler for Correction of Moderate-to-Severe Nasolabial Folds in Skin Types III and IV

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Introduction. Hyaluronic acid fillers are widely used to correct nasolabial folds. This treatment provides favorable aesthetic outcomes. The aim of this study was the safety and efficacy evaluation of Lunaphil Ultra intradermal filler for correcting nasolabial folds in the Iranian population with Fitzpatrick skin types III and IV. **Methods.** In this before and after clinical study, Lunaphil Ultra dermal filler was injected in nasolabial folds of 24 female and 6 male volunteers (mean age: 43.36 and SD: 11.55). Two independent physicians assessed the severity of nasolabial folds before injection and 2, 12, and 24 weeks later, according to the Allergan scale. The volume, depth, and area of both nasolabial folds and the thickness and density of the dermis in the right nasolabial fold were also measured. Adverse events and subject satisfaction were also recorded. **Results.** One grade or more improvement was detected in 81%, 57%, and 65% of participants at weeks 2, 12, and 24, respectively. The median score for the Allergan scale decreased significantly in all follow-up visits. The median value of the area of nasolabial folds significantly reduced in all follow-up visits. Two weeks after injection, dermis density showed a significant increase. The mean score for pain level during the injection was 1.96 out of 10. Adverse events were mild and transient. The median satisfaction scores were 9–10 out of 10 at different visits. **Conclusion.** The findings showed that cross-linked hyaluronic acid dermal filler containing lidocaine could be applied in clinical practice for correction of nasolabial folds in skin types III and IV, with high safety and efficacy. More comprehensive future research could approve these results. This trial is registered with IRCT20150101020514N11.

1. Introduction

Skin aging is a multifactorial process resulting in several esthetic changes in the skin [1]. It is an unavoidable process which is described as specifications of sagging skin, sun spots, uneven skin color, and wrinkles [2]. Among these, nasolabial folds (NLFs) are one of the most common clinical manifestations of facial aging [3].

Since beauty and attractiveness affect self-perception and are associated with self-confidence and social acceptance, aesthetic interventions can improve psychological wellbeing [4]. The age of a person, as a special outstanding

feature of the face, affects the perception of beauty and attractiveness [5].

Treating aging signs with dermal fillers creates favorable aesthetic outcomes with the least invasiveness and without the downtime following surgical procedures [6]. So, dermal fillers are widely used to correct deep wrinkles, including NLFs. Hyaluronic acid (HA) fillers are the most favorite dermal fillers [7] and provide desirable effects on the fibroblast phenotype, including higher cell proliferation and type I collagen synthesis [8]. HA fillers have appropriate efficacy, good safety profile, and fast recovery time, and they are simple to administer [9, 10].

Many filler properties, such as elastic Modulus (G'), requisite needle size, particle size, and extrusion force are influenced by HA concentration, polymer chain length, and crosslinking degree or technology of gel [11]. Among these factors, crosslinking is necessary to slow down the enzymatic degradation rate of the HA by endogenous hyaluronidase and to prolong the half-life of the product. The extent of crosslinking strongly impacts the biophysical and biological properties of a filler, including water uptake, tissue integration, resistance to degradation, and filler biocompatibility, and consequently may have clinical implications [10, 12].

Lunaphil Ultra intradermal filler is a cross-linked HA soft tissue filler manufactured by Espad Pharmed Daru Company containing HA (24 mg/ml) and lidocaine 0.3% as a supplemental anesthetic. Since pain is the most prevalent complaint reported by patients, a local anesthetic like lidocaine is included in the formulation to decrease the pain of the procedure and eliminate the need for other types of anesthesia [13]. On the other hand, there is controversy about the lidocaine effect on the effectiveness and safety of HA fillers, while its use increases patient satisfaction. However, investigation in the case of safety and efficacy of lidocaine-containing cross-linked HA fillers is relatively limited and there is even more limitation in the case of Fitzpatrick skin types III and IV.

The aim of this study was the tolerability, safety, and efficacy evaluation of Lunaphil Ultra intradermal injectable filler for correcting moderate-to-severe NLFs in the Iranian population with Fitzpatrick skin types III and IV, which has not been studied before. Moreover, our assessments included precise objective devices alongside subjective ones.

2. Method

2.1. Study Design and Participants. In this single group, before and after clinical study, 30 male and female cases of moderate to severe NLFs based on the validated 5-point photonic Allergan NLF Severity Scale, with Fitzpatrick skin types III and IV and age of 18 to 65 years old were enrolled in the study from April 2021 to September 2022. The sample size was considered according to the "Food and Drug Administration of Iran" guidelines, and it reached enough statistical power to show the differences in the functional outcome of the study. The setting of the study was Pharmaceutical, Cosmeceutical, and Hygienic Products Clinical Evaluation Lab (DermaLab), Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran.

The exclusion criteria included pregnant or lactating women, treatment with HA-based dermal fillers within the last 12 months, cosmetic facial procedures, including chemical peel, laser, radio frequency, dermabrasion, ablative or nonablative procedures, and botulinum toxin in the lower two thirds of the face within the last three months, planning to undergo any of above procedures at any time during the study, allergy or sensitivity to lidocaine or HA products, active inflammation, infection, cancerous or precancerous lesion or unhealed wound in the NLF region, current

treatment with anticoagulation therapy or using non-steroidal anti-inflammatory drugs or other substances known to increase coagulation time within 7 days before enrolment, uncontrolled seizure disorders, heart failure, porphyria, or recurrent streptococcal infections, people prone to hypertrophic scar formation, history of autoimmune or immune-deficiency diseases or using any immune-suppressive drug, and history of anaphylaxis. If a volunteer missed more than two consecutively scheduled visits, he/she was dismissed from the study.

2.2. Product. The product was a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, and homogeneous gel implant in the form of prefilled syringes with a volume of 1 ml and contained HA gel, 24 mg; lidocaine hydrochloride, 3 mg; and phosphate buffer (pH 7.2).

Mechanical properties, biocompatibility, and biodegradability of HA can be different according to the method of modifying the chemical and physical structure. Sodium hyaluronate has carboxylic, hydroxy, and acetamido functional groups. Based on these functional groups, various methods, and polymerization techniques are proposed to form cross-linked HA. The following can be mentioned: Schiff-base reaction, thiol-modified HA, Diels-Alder click, enzyme, thermo responsive, ionic, and photo crosslinking. One of the common methods to modify HA is to activate the hydroxy group on the backbone. In this case, it is possible to carry out the following four reaction types: ether, ester, hemiacetal, and oxidation formation.

Temperature, pH, and ionic conditions can be mentioned among the factors that play an essential role in creating cross-links by the physical method. With changes in each of these factors, physical and chemical interactions such as hydrophobic interactions, breaking or creating hydrogen bonds, and changes in electrostatic charge will change.

In this study, injectable filler "Lunaphil Ultra" cross-linked HA was prepared using a chemical modification method.

The molecular weight of HA cross-linked with BDDE (1,4-butanediol diglycidyl ether) is 0.2 to 2.5×10^6 Da and it makes swellable polymer networks that help to attract and bind to water molecules to help maintain volume resulting in skin hydration.

2.3. Technique

2.3.1. Intervention. One treatment session with 1-2 ml of Lunaphil Ultra injectable filler in both NLFs was performed. The injection was performed using a needle (gauge 27) or cannula (gauge 23), selected by the physician, and by retrograde linear threading.

The injection area was anesthetized with lidocaine 2%-prilocaine 2% cream (Xyla-P® cream, Tehran Chemie Pharmaceutical Company, Iran) under an occlusive dressing for 30 minutes. Before injection, the treatment site was completely disinfected with povidone-iodine.

The volume of injection was determined according to the subject's needs and by the physician. The injection volume in

the two nasolabial folds was 2 ml for 25 participants, 1.6 ml for two participants, 1.4 ml for two participants, and 1 ml for one participant. After injection, the treated area was massaged. Then, an ice pack was applied for a few minutes. After two weeks, clients who needed a corrective injection according to the physician's opinion and received an additional injection with a maximum of 1 ml of Lunaphil Ultra intradermal injectable gel. All injections were performed in the dermis.

2.3.2. Assessments. The primary outcome was the assessment of the efficacy of Lunaphil Ultra dermal filler using the Allergan Nasolabial severity scale. The Allergan scale is a 5-point photometric grading scale, and its improvement has been shown up to one year after injection in some studies [14, 15]. The severity of NLFs according to the Allergan scale, 2, 12, and 24 weeks after the baseline evaluation have been shown in Figure 1. Figure 2 shows the amount of improvement of the Allergan nasolabial fold severity scale after 2, 12, and 24 weeks in one of the volunteers, and written informed consent for publication of this identifying image was obtained.

Secondary endpoints included the volume, depth, and area of NLFs measured by Visio Face® 1000 D and Complete Skin Investigation (CSI) software, thickness, and density of the dermis measured by 22 MHz ultrasound probe of DUB skin scanner device, subject satisfaction, pain assessment using a 10-point visual analogue scale, and safety profile.

Allergan nasolabial severity scale was assessed before treatment, after 2, 12, and 24 weeks of treatment by two independent physicians.

Full face photography by Visio Face® 1000 D was performed before treatment, immediately after injection, and after 2, 12, and 24 weeks of treatment. Measurement of volume, depth, and area of nasolabial folds was performed using this device and Complete Skin Investigation (CSI) software.

High-frequency skin ultrasound was performed before, after 2, and 24 weeks of treatment on right NLF. The thickness and density of the dermis were measured by a 22 MHz ultrasound probe of this device. Its penetration depth is up to 8 mm and its maximum axial resolution is 72 μ m. The scan width is 12.8 mm linear (app. 33 μ m step width). Water was a coupling medium between the transducer and the skin surface. The ultrasound probe was held perpendicular to the skin to avoid compressing the skin. It was placed in the middle of the nasolabial fold and transversal to the fold. The mean dermal thickness and density of the whole skin segment assessed by the probe were calculated automatically by the device.

Moreover, an evaluation of safety indicators and adverse events including swelling, headache, pain, redness, dryness, bruising, and lump formation during the intervention and subsequent visits was performed.

2.4. Statistical Analysis. A standard statistical analysis was performed using Excel and SPSS version 24 statistical software. Data are expressed as the mean and standard deviation (SD), median and range, and percentages as appropriate [16].

The efficacy of treatment was assessed by comparing the mean/median value of each parameter among four visits using the repeated measure ANOVA or the Friedman test. The statistical significance level was defined as $p < 0.05$.

2.5. Ethical Considerations. The study protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences in March 2021 (code: IR.TUMS.MEDICINE.REC.1399.1271). This study was performed according to the Helsinki Declaration and Good Clinical Practice guidelines. Written informed consent was obtained before enrolment, and participants were fully informed about the study's risks and benefits. The protocol was registered at the Iranian Registry of Clinical Trial Registry (IRCT) with the registration code IRCT20150101020514N11.

3. Results

Thirty subjects including 24 females and six males aging between 26 and 65 years, with a mean $\pm$ SD of 43.36 ± 11.55 years were participated in the study. Table 1 shows the baseline characteristics of volunteers. The total injection volume in the two NLFs was 2 ml for 25 participants, 1.6 ml for two participants, 1.4 ml for two participants, and 1 ml for one subject.

As the primary outcome, a significant improvement was detected in the severity of NLFs according to the Allergan scale, 2 weeks (median, range: 1, 2; p value < 0.01), 12 weeks (median, range: 2, 3; p value < 0.01), and 24 weeks (median, range: 1.5, 3; p value: 0.013) after baseline evaluation (median, range: 2, 1) (Figure 1). One grade or more improvement was detected in 81%, 57%, and 65% of the participants after 2 weeks, 12 weeks, and 24 weeks, respectively. Figure 2 shows two grade improvements in the Allergan nasolabial fold severity scale in one of the volunteers.

The mean (right and left) of depth, area, and volume of nasal folds, calculated based on images obtained from the Visio Face camera and CSI software, are shown in Table 2 as the median and range for each visit. 2 weeks, 12 weeks, and 24 weeks after injection, the area of NLFs significantly decreased compared to the baseline (p values: 0.010, 0.022, and < 0.01 , respectively). The decrease in the volume of the folds was significant only at week 2 (p value < 0.01).

Table 3 shows the dermis thickness and density, assessed by ultrasound at the baseline, 2 and 24 weeks later. There was a significant increase in dermal density two weeks after the intervention compared to the baseline (p value: 0.039).

The median subject satisfaction scores with the treatment, which were recorded based on the visual analogue scale (0–10) were 10 (range: 6), 9.5 (range: 9), and 9 (range: 10) at week 2, 12, and 24, respectively. The mean score of pain severity recorded during injection was estimated to be 1.96 out of 10 (maximum 5).

Safety indicators and adverse events during the intervention and subsequent visits are shown in Table 4. A 37-year-old female who received 2 ml of filler using a cannula reported pain and swelling at injection sites up to 48 hours

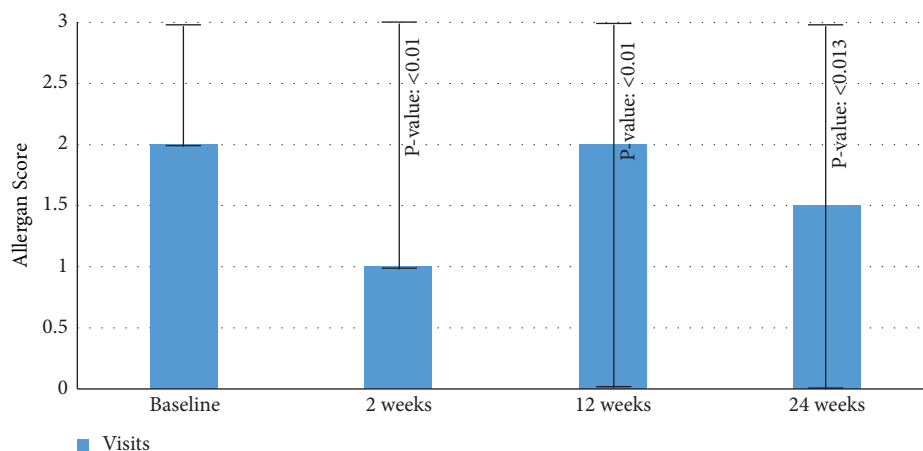


FIGURE 1: Severity of nasolabial folds according to the Allergan nasolabial fold severity scale (median and range). *p* values are related to comparison of each follow-up visit with the baseline.

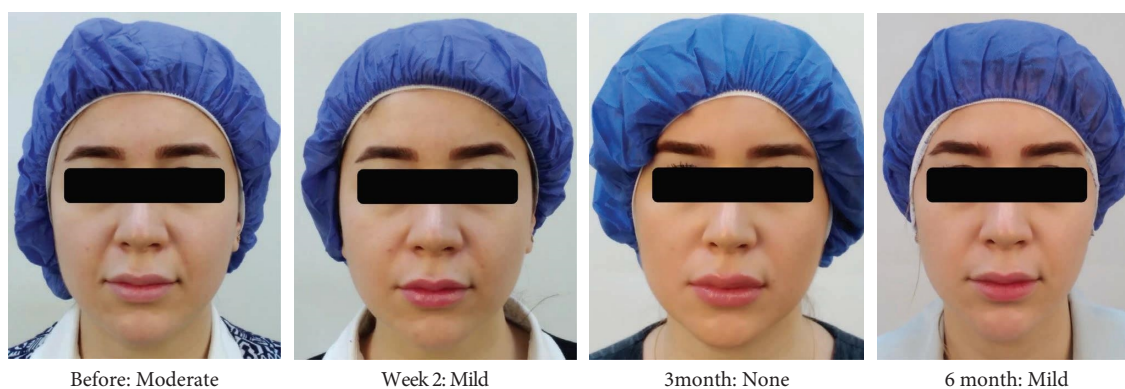


FIGURE 2: Two grades improvement in the Allergan nasolabial fold severity scale in one of the volunteers.

TABLE 1: Baseline characteristics table.

Variable	Characteristics	<i>n</i> (%)
Age	Mean	43.36
	SD	11.55
Sex	Female	24 (80%)
	Male	6 (20%)
Allergan score	Moderate	18 (60%)
	Severe	12 (40%)

SD: standard deviation, *n*: number.

after injection, which was a definite complication of treatment. The subject was treated with oral amoxicillin 500 mg and metronidazole, and the symptoms were resolved within 48 hours. The subject also complained of nodule formation at the injection site, which was treated with massage after two weeks. A 51-year-old female who received 2 ml of filler using a cannula reported asymmetric swelling of the face. The subject had a history of collagen injection in this area several years ago. She was treated with a long-acting betamethasone injection, cephalexin 500 mg capsules, and cetirizine tablets for three days. The symptoms were completely disappeared after 72 hours. A 39-year-old man presented with recurrent and unilateral swelling on one side of the face six weeks after injecting

2 ml of filler using a needle. He was treated with hyaluronidase and was withdrawn from the study in the third month.

Other adverse events included redness in five subjects (16.6%), bruising in three subjects (10%), pain in five subjects (16.6%), and headache in one subject (3%), all of which were mild and lasted less than 48 hours. Skin dryness in one subject (3%) and a lump in three subjects (10%) were mild but lasted more than 48 hours. Mild swelling occurring in 21 subjects (70%) lasted less than 48 hours and in two others (6%) lasted more than 48 hours. Three subjects (10%) showed moderate to severe swelling, which lasted more than 48 hours.

4. Discussion

The investigation of aesthetic and anesthetic efficacy and safety profile of Lunaphil Ultra intradermal filler injection to treat moderate to severe NLF was performed. The primary objective was achieved, and this cross-linked HA filler containing lidocaine was shown to be efficient in skin types III and IV, regarding treatment of NLFs and reducing injection site pain in the respective indication. The addition of lidocaine did not affect the effectiveness and safety of HA filler. Choi's research has also revealed this finding [17].

TABLE 2: Comparison of mean depth, area, and volume of nasolabial folds calculated by CSI software, Visio Face device before the intervention, 2, 12, and 24 weeks after injection.

Variable	Baseline	2 weeks Median (range)	12 weeks	24 weeks	<i>p</i> value ¹	<i>p</i> value ²	<i>p</i> value ³
Visio Face depth (px)	10 (8–12)	10 (7.5–12)	10.5 (8–13)	9.75 (7.5–13.5)	0.749	0.06	0.715
Visio Face area (px ²)	4.90 (1.28–17.54)	2.07 (0.69–14.84)	3.34 (1.19–16)	3.25 (0.49–17.19)	<0.01*	0.022*	0.010*
Visio Face volume (px ³)	50.81 (12.36–202.22)	20.56 (5.96–168.40)	37.91 (14–186.32)	34.14 (3.97–201.56)	<0.01*	0.70	0.26

^{1–3}*p* values are related to the comparison of baseline with weeks 2, 12, and 24, respectively. px: pixels. *: significant *p* value.

TABLE 3: Comparison of dermis thickness and density before the intervention 2 and 24 weeks after injection.

Variable	Baseline	2 weeks Mean (SD)	24 weeks	<i>p</i> value ¹	<i>p</i> value ²
Thickness of dermis (μm)	1617.16 (279.75)	1529.11 (350.72)	1585 (347.57)	0.184	0.59
Density of dermis	25.80 (7.54)	29.03 (8.32)	28.24 (9.7)	0.039*	0.185

^{1,2}*p* values are related to the comparison of baseline with weeks 2 and 24, respectively. *: significant *p* value.

TABLE 4: Safety indicators and adverse events during the intervention and subsequent visits.

Adverse events	Number (percentage)	
	Less than 48 hours	More than 48 hours
Swelling	21 (70%) mild	2 (6%) mild 3 (10%) moderate to severe
Headache	1 (3%) mild	0 (0%)
Pain	5 (16.6%) mild	0 (0%)
Redness	5 (16.6%) mild	0 (0%)
Dryness	0 (0%)	1 (3%) mild
Bruising	3 (10%) mild	0 (0%)
Lump	0 (0%)	3 (10%) mild

HA as a natural ingredient of human skin is naturally absorbed with a lifetime of 6 months. Lidocaine hydrochloride is quickly released after injection and rapidly removed from the body because of a short half-life of about one and a half hours [3].

Management of discomfort and pain during filler injection is one of the main concerns of subjects and practitioners. Although various anesthetic methods are applied to subjects to reduce pain before injection, enough anesthesia is not always attained. Therefore, the idea of adding lidocaine to fillers was suggested [18]. Injections in this study were well-tolerated with average pain levels relatively lower than those reported in the scientific texts.

HA-based fillers are the most prevalent treatment for improvement the severe facial wrinkles and folds, restoring the natural contour of the face [19, 20]. The filler used in the current study, with this technology, was safe, well tolerated, and effective for reducing the severity of NLFs. It caused at least one grade improvement in 80% of the subjects after 2 weeks. In general, the treatment response to HA fillers has been reported as 45%–81% [15]. Also, in a study conducted on two HA fillers in China in 2019, 68.70% and 52.17% of the participants showed one grade or more improvement in the severity of NLF six months after injection [21]. This was quite similar to the results obtained in the present study.

Specific safety profiles of injectable fillers vary by material and injection site. Common adverse events include

infection and swelling, and serious events include traumatic injury leading to necrosis and blindness [22]. Side effects in the current study were mild and transient, which shows a good safety profile of this filler. They included redness, bruising, and mild swelling at the injection site, and the type and prevalence of adverse effects were alike to similar products studies [23, 24]. Knowledge of the rheological characteristics of HA fillers would help place the appropriate filler in the right layer to achieve more accurate and predictable results with minimal side effects [25].

It is demonstrated that resilient HA fillers made of lightly cross-linked long chains, are effective for the correction of NLF in subjects of diverse skin phototypes. Patient satisfaction and aesthetic improvement were high and durable, treatments were well tolerated and safe [26, 27]. The current study showed this efficacy too and emphasized in skin phototypes III and IV. The median subject satisfaction scores in our study were 10, 9.5, and 9 out of 10 at different visits, which means “appropriate satisfaction” with the treatment process.

To hydrodynamic volume displacement of the intercellular matrix, the intradermal use of HA filler in different cross-linking densities and chain lengths is applied regularly. It has been shown that the metabolic and proliferative tasks of skin fibroblasts would be enhanced by native noncross-linked HA [28]. Investigation on whether these effects can be proved for cross-linked HA is in progress. Comparison of cross-linked and noncross-linked HA about efficacy of the proliferative activity of skin keratinocytes and fibroblasts in vitro showed that HA directly affects cells depending on density and type of the cross-linkage and the practical relationship in terms of a metabolic filler efficacy requires rechecked in future clinical studies [28].

Safety and efficacy investigation of a new Poly-L-lactic acid filler compared with a widely used biostimulatory filler in 2023 showed that Poly-L-lactic acid filler was noninferior, concerning the correction of NLFs and even had higher investigator satisfaction [29].

Ultrasound evaluation of tissue integration made by the cross-linked HA fillers in facial aesthetic treatment has been

done in a prospective multicenter study and showed that these fillers could create an important improvement in restoration and volumization of the lower face. But the limitation of the study was that it did not perform objective measurements, such as dermis thickness and density, which could provide valuable information [10]. One of the strong points of the current study is objective measurements of dermis characteristics, which showed that there was a significant increase in dermal density two weeks after the intervention. This increase in the dermis density is probably due to the presence of filler in the injection area. In the third month due to the absorption of gel in the skin tissue, the density returned to the baseline value [30]. Ultra-high-frequency ultrasound is proposed for the follow-up of patients undergoing HA filler injections due to the high precision in detecting the deposition of the product and the low invasiveness [31].

To the best of the authors' knowledge, the Lunaphil Ultra intradermal filler is the first locally manufactured HA filler, and this paper is one of the few publications which report the safety and efficacy of a cross-linked HA dermal filler containing lidocaine for correction of moderate-to-severe NLFs in Iranian people with skin types III and IV. The absence of a control group, small sample size, and short follow-up duration could be the limitations of the current study. Conducting future comparative and randomized control studies with more levels of evidence, a greater sample size of people with these specific skin types and a longer period of evaluation are recommended.

5. Conclusion

Treatment with Lunaphil Ultra intradermal injectable filler is a safe, well-tolerated, and effective method to reduce the severity of NLFs. More than 80% of the subjects showed an improvement in their NLF severity of at least one grade after two weeks compared to their baseline status, and this improvement was maintained in 65% of the participants for 24 weeks. The median satisfaction scores were 9-10 out of 10 at different visits, which means "appropriate satisfaction." Adverse events were limited to mild and transient symptoms at the injection area.

Data Availability

At present, our data are not available in an easily portable format, and we have not developed a Web interface to explore them.

Conflicts of Interest

One of the authors Mr. Hamidreza Kafi is the medical manager of Orchid Pharmed company, which is in collaboration with Espad Pharmed Daru company (sponsor) with respect to conducting clinical trials. Other authors declare that they have no conflicts of interest in this article's content.

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