Safety and efficacy assessment of deoxycholic acid (Embella®) injectable solution for the reduction of unwanted submental fat

Location of study:
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

Date: 20 November 2022

Contents

Sponsor:

- Espad Pharmed Darou Co.

Roles and Responsibilities:

- Providing quality-controlled products for using in the study and transferring them to the study site
- All associated costs are the responsibility of the sponsor
- Providing compensation for patients who experience adverse events
- Offering financial support for all activities outlined in the study protocol through a contractual agreement with the principal investigator

Sponsor Representative:

- Zist Orchid Pharmed Co.

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

Researchers:

- **Principal Investigator (PI)**:

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Roles and Responsibilities:

- Preparation of clinical study protocol and other required forms
- Conducting the study according to the approved protocol
- Creating a working team to carry out the study
- Conducting practice sessions for new and current team members whenever needed
- Preparing suitable places for patient enrollment
- Arranging an appropriate storage location for the investigational drugs at the site.

- No part of this study may be published without prior approval from the sponsoring company.

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Roles and Responsibilities:

- Conducting the study in accordance with the protocol approved by the principal investigator, ethics committees, and the Food and Drug Administration (FDA).
- Establishing a dedicated team for this purpose at the study site.
- Organizing training sessions for both new and existing team members as needed.
- Arranging appropriate facilities for patient intake.
- Providing suitable storage for the medications used in the study.
- Collaborating with monitors during the course of the study.
- All medical documents related to the study must be sent to Espad Pharmed Darou Co. at the conclusion of the study. A copy of these documents may be retained by the investigator.
- All medical documents related to the study must be kept by the investigator for the duration of the study and for five years following its completion.
- Confidentiality of the protocol and study data must be maintained, with no disclosure without written permission from Espad Pharmed Darou Co. and the principal investigator, except as necessary for obtaining informed consent from individuals to whom the product will be administered.

Introduction:

Submental fat (SMF) is considered aesthetically unappealing and can have a negative psychological impact on patients (1). Concerning the increasing demands of people for aesthetic prospects like decreasing the unwanted submental fat, evidence supports the effectiveness of noninvasive alternative procedures for liposuction and plastic surgery (2).

Amongst them, injection of deoxycholic acid (DCA) is a minimally invasive procedure. In 2015, the U.S. Food and Drug Administration (FDA) approved DCA, for treating fat beneath the chin (3). The mechanism of action of the drug is through the lysis of fat cell membranes and the physical destruction of cells (4)

The efficacy and safety of DCA in reducing the SMF have been demonstrated in multiple phase I to III clinical studies. (5). Phase I studies demonstrated that DCA administration did not significantly impact on liver function, kidney function, heart rate, or levels of cholesterol, triglycerides, free fatty acids, or proinflammatory cytokines (6,7). Phase II studies examined treatment regimens and dosages, revealing that the optimal dose for DCA was $2mg/cm^2$ administered via 0.2 ml injections spaced 1 cm apart in the submental area. The recommended injection interval was 28 days (8, 9). Phase III studies have shown the efficacy and safety of DCA in SMF reduction. Accordingly, in a 12-week double-blind, placebo-controlled study including physician examinations, patient satisfaction, and MRI fat mass measurements, the clinical evaluation revealed that 70% of the individuals who received the medicine showed one grade of improvement in SMF score. Additionally, 13.4% of the subjects demonstrated two grades improvement, while no improvement was observed in the placebo group. These findings underscore the safety and effectiveness of the drug in treating moderate to severe submental fat. In the MRI evaluation, the proportion of responders was significantly higher in the intervention group compared to placebo group (46.3% vs. 5.3%; $p < 0.001$). Researchers concluded that DCA is an effective and safe injectable drug in reducing SMF (10).

The drug is administered to individuals aged 18 to 65. Common adverse events included pain, swelling, hematoma, and bruising at the injection site. There were some rare case reports, of damage to the mandibular nerve resulting in an asymmetric smile that generally resolves without any intervention (11). Another potential side effect is dysphagia, and the drug is contraindicated for individuals with a history of dysphagia (12).

The purpose of this study is the safety and efficacy assessment of Embella® injectable solution containing deoxycholic acid (manufactured by Espad Darou Pharmed Company) for the reduction of unwanted submental fat.

Objectives

Primary objective:

- Safety and efficacy assessment of Embella® injectable solution in reducing the unwanted submental fat.

Secondary objectives:

- Assessment of the efficacy of Embella® injectable solution, in improving the standard grading of submental fat (SMF)
- Assessment of the efficacy of Embella® injectable solution in reducing the diameter of submental fat
- Patient's satisfaction with the treatment process
- Pain assessment during the injection using a 11-point visual analogue scale
- Safety assessment of Embella® injectable solution

Study Method

It was a single group, before and after the clinical study. The study protocol as well as other essential documents (such as CRF, ICF, etc.) were approved by the Undersecretary of Research, Tehran University of Medical Sciences .

Also, all mentioned documents were approved by the ethics committee of Tehran University of Medical Sciences on 17 January 2023 (code: IR.TUMS.TIPS.REC.1401.102). The protocol was registered in the Iranian Registry of Clinical Trial Registry (IRCT) with registration number IRCT20190210042676N29.

Inclusion Criteria

- Age between 18 and 65 years old
- Individuals with any severity of unwanted submental fat
- Voluntarily signed the informed consent form and consented to the 3-month follow-up
- Willing to actively participate in the study and the scheduled visits

Exclusion Criteria

- Any previous interventions to treat SMF
- Anatomical features or previous trauma in the injection site which is liable to interfere with SMF evaluation or result in an aesthetically unacceptable outcome after treatment
- Evidence of any cause of submental enlargement other than SMF
- Patients with a body mass index (BMI) > 30 kg m^2
- Those undergoing or considering a weight-reduction program
- Patients with a history of sensitivity to any components of the study medication or topical or local anesthetics
- Patients with a history of dysphagia
- Any inflammation, active infection, unhealed wound, or tissue scar at injection site
- Those using anticoagulants or NSAID or other medications that increase the risk of coagulation disorders within 7 days before injection
- Unrealistic expectations
- Pregnant or lactating women
- Those undergoing low sodium diets like hypertensive patients

Intervention

- Minimum 1 and maximum 3 treatment sessions (with at least 4 weeks intervals) with 2 ml of Embella® injectable solution, which contains 20 mg of DCA.
- 4 weeks after the first and second injections, the patient will be evaluated by the physician and research team. If necessary, they will receive additional injections; otherwise, they will proceed with post-injection follow-up.
- The product is a 2 ml sterile, transparent, and colorless vial containing 20 mg of DCA. Additional ingredients include hyaluronic acid, water for injection, sodium chloride, sodium hydroxide, hydrochloric acid, and disodium phosphate anhydrous.
- Use of ice/cold packs, topical and/or injectable local anesthesia (e.g., lidocaine) may enhance patient comfort.

Method of administration

The product is indicated for subcutaneous administration only.

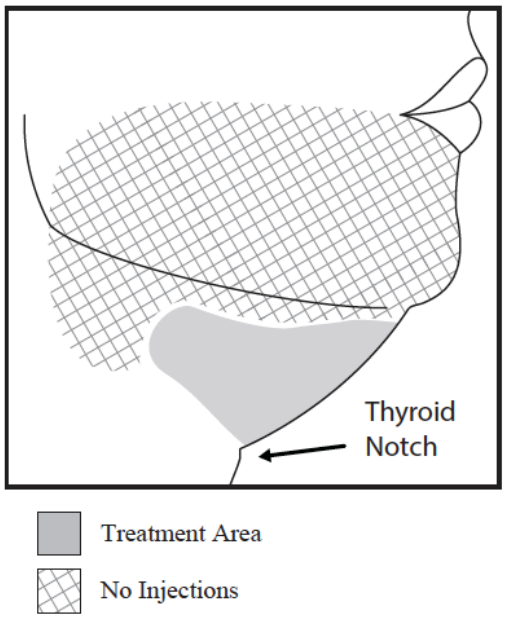
EMBELLA® is supplied in ready-to-use, single-use vials. Gently invert the vial several times before use. Do not dilute.

EMBELLA® shall be prepared for injections in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap is damaged, do not use it.
2. Attach a large bore sterile needle to a sterile single-use 1 ml syringe.
3. Introduce the large bore sterile needle into the stopper of the vial and draw 1ml of EMBELLA® into the 1ml syringe.
4. Replace the large bore needle with a 30 gauge (or smaller)-0.5-inch needle. Expel any air bubbles in the syringe barrel before injecting the product into the subcutaneous fat.
5. To withdraw the remaining contents of the vial, repeat steps 3 and 4.

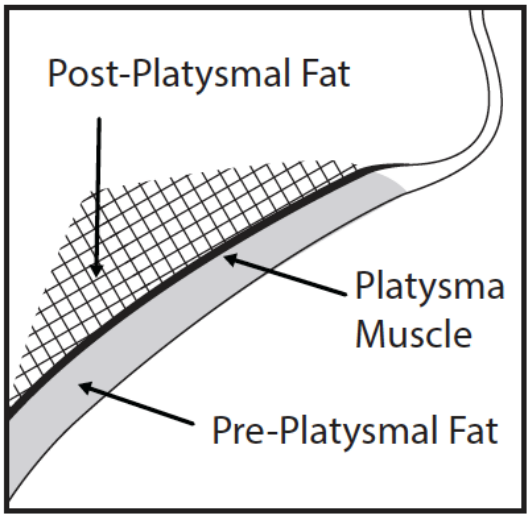
For injection, the needle is inserted perpendicular to the skin, and injection should be avoided in the area defined by a line 1 to 1.5 cm from the angle of the mandible to the mentum (Figure 1).

Figure 1. Avoid the Marginal Mandibular Nerve Area



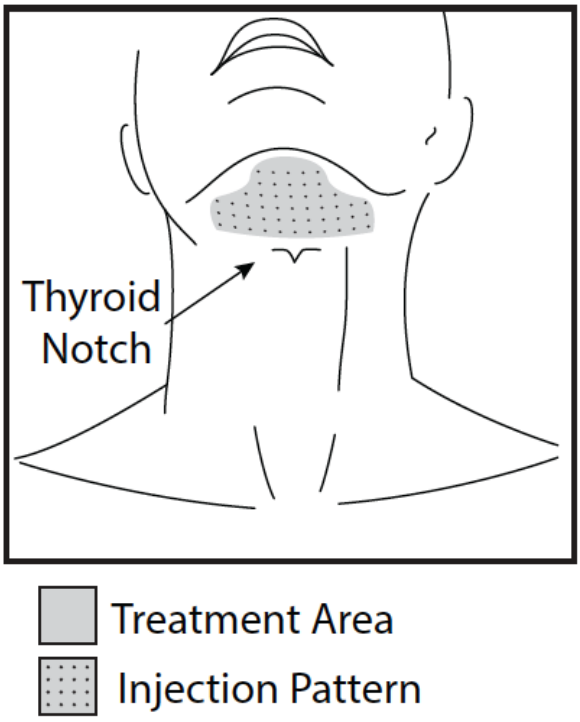
Avoid injection into the platysma. Prior to each treatment session, palpate the submental area to ensure sufficient submental fat and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) within the target treatment area (Figure 2).

Figure 2. Sagittal View of Platysma Area



Outline the planned treatment area with a surgical pen and apply a 1 cm^2 injection grid to mark the injection sites (Figures 3).

Figure 3. Injection Pattern



WARNINGS AND PRECAUTIONS

- Embella® should only be injected within the defined parameters. Each vial is intended for use in one patient and should be discarded after use.
- Store the product between 15°C and 30°C.
- Use of ice/cold packs, topical and/or injectable local anesthesia, and NSAIDs may enhance patient comfort.

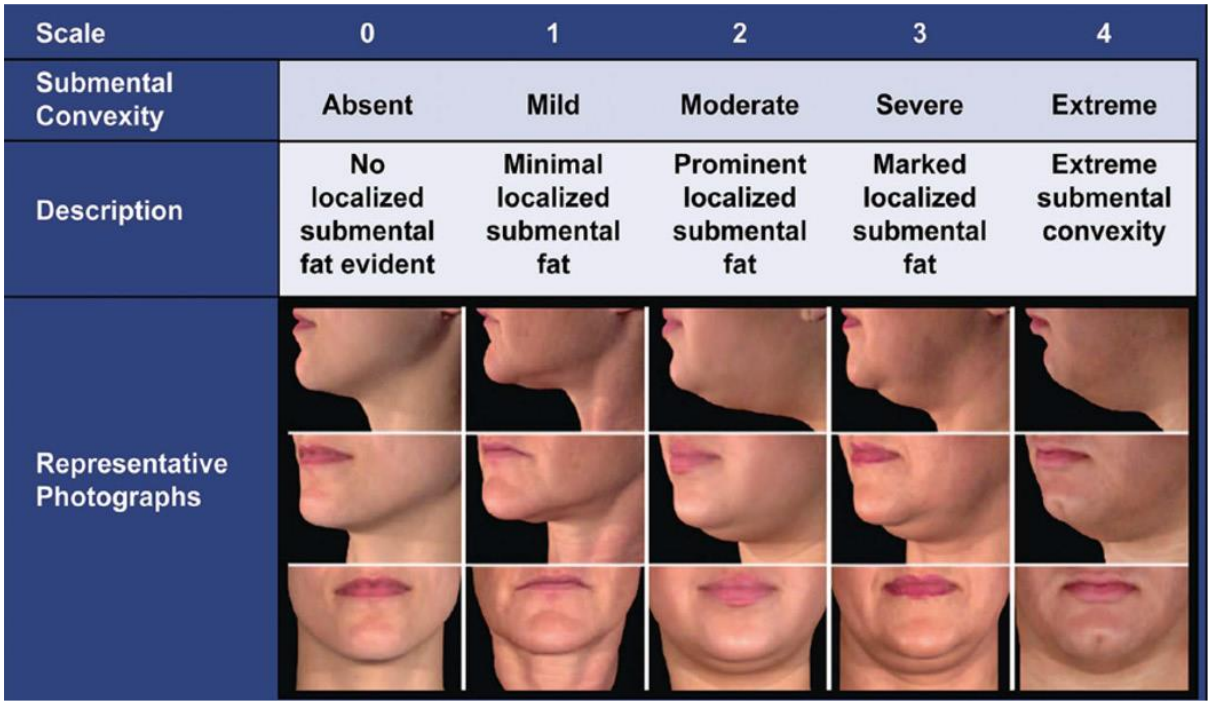
Endpoints

Primary and secondary endpoints are evaluated before injection and 4 and 12 weeks after the last injection.

Primary Endpoint

At least one-grade improvement in standard grading of submental fat (SMF) evaluated at 4 and 12 weeks after the last injection (Figure 4)

Figure 4: Standard grading of submental fat (SMF)



Secondary Endpoints

- Submental fat diameter will be measured with the calliper at 4 and 12 weeks after the last injection
- Intensity of procedural pain will be assessed using the Visual Analogue Scale (VAS), ranges from 0 (complete painlessness) to 10 (maximum pain).
- Patient satisfaction will be assessed using the Visual Analogue Scale (VAS), ranges from 0 (not satisfied at all) to 10 (maximum satisfaction).
- Any observed or reported adverse events will be recorded after the injections and at 4 and 12 weeks follow-up visits, graded as mild [1] moderate [2] and severe [3].

Study Timeline

Visit No	**0**	**1**	2	**3**	**4**	**5**	**6**
	Day 1		Week 4 (±2 days) (Injection 2)/ Follow-up of subjects with a satisfactory response who do not require further treatment	Week 8 (±4 days) (Injection 3)/ Follow-up of subjects with a satisfactory response who do not require further treatment	Week 12±4 day	Week 16±4 day (In subjects with 2 injections)	Week 20±4 day (In subjects with 3 injections)
Time	Baseline	Injection 1					
Screening	X						
eligibility control	X						
Consent	X						
Demographic data	X						
Injection		X	X	X			
Pain assessment		X	X	X			
Digital Photography	X		X	X	X	X	X
Measurement of submental fat	X		X	X	X	X	X
Patients' satisfaction			X	X	X	X	X
Physicians' assessment According to SMF	X		X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

Study Visits:

Visit 0: Screening & eligibility control

The following screening procedures will be conducted to determine eligibility: The investigator will evaluate each patient against the inclusion and exclusion criteria. If the patient is eligible to participate in the study, the study process will be explained to them in an understandable and verbal manner, and a consent form will be provided. Once the information presented to the patient has been thoroughly reviewed and understood by them, and they have received the necessary explanations, the patient will be asked to write their full name on the consent form and sign it. Following the completion of these steps, the following actions will be carried out:

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter

Visit 1 (day 1):

- Solution injection by the physician
- Monitor the patient for up to half an hour after injection
- Reporting and recording adverse events
- Pain assessment

Visit 2 (4 weeks±2 days):
In case of complete recovery with the physician's opinion:

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter
- Reporting and recording adverse events
- Evaluation the patient satisfaction

If re-injection is needed:

- Solution injection by the physician
- Monitor the patient for up to half an hour after injection
- Digital AP and lateral photography of the patient's neck
- Pain assessment
- Reporting and recording adverse events

Visit 3 (8 weeks±4 days):
In case of complete recovery with the physician's opinion:

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter
- Reporting and recording adverse events
- Evaluation the patient satisfaction

If re-injection is needed:

- Solution injection by the physician
- Monitor the patient for up to half an hour after injection
- Digital AP and lateral photography of the patient's neck
- Pain assessment
- Reporting and recording adverse events

Visit 4 (12 weeks±4 days):

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter
- Reporting and recording adverse events
- Evaluation the patient satisfaction

Visit 5 (16 weeks±4 days) (In subjectswith 2 injections):

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter
- Reporting and recording adverse events
- Evaluation the patient satisfaction

Visit 6 (20 weeks±4 days) (In subjectswith 3 injections):

- Digital AP and lateral photography of the patient's neck
- Grading of submental fat based on SMF
- Measurement of submental fat diameter
- Reporting and recording adverse events
- Evaluation the patient satisfaction

Participants:

This study will be conducted in 20 eligible participants.

Early Termination Policy: The decision to terminate the study early, due to safety concerns or to protect patient health, will be made by the Principal Investigator (PI) or the sponsor, with mutual agreement from both parties.

Withdrawal of Subjects

- The patients were allowed and free to refuse to cooperate with the study and follow-up whenever they want, but the researchers try to collect the maximum information, including the reasons for leaving the study and, if possible, the final results of the treatment.

- If a patient missed 2 or more consecutively scheduled visits, he/she was dismissed from the study.
- Occurrence of any of the exclusion criteria
- Occurrence of serious adverse event (SAE).

Data Collection

All required data will be recorded on the (paper) CRFs for this study, which will be designed and provided by PI. The reason for any missing data will be explained. All entries must be in permanent, blue ink. Errors will have single lines drawn through them with the correct data, recorder's initials, and date entered above the error. All errors must remain legible. Erasure or obliteration of errors in the CRF or other permanent study records are strictly prohibited.

Statistical analysis:
For statistical analysis, we performed descriptive statistics (mean, standard deviation or median and range, frequency and percentages). The efficacy of the treatment was assessed by comparing the mean/median value of each parameter among visits, using the Paired Sample T-test or the nonparametric equivalent, Wilcoxson test. SPSS 24 statistical software was used for data analysis. The statistical significance level was defined as $p<0.05$.

Adverse Events

Adverse Event (AE) is described as any medical event that occurs in patients participating in a study, which differs from the clinical manifestations of the underlying disease progression and does not necessarily have a causal relationship with the treatment used in the study. Clinical manifestations that will be reported as adverse events include any symptoms, signs (such as any abnormal laboratory results), or temporary illness related to the use of the product being studied, whether or not these effects are causally related to the product under study.
Very common adverse events of DCA include:

- Pain
- Edema
- Numbness, tingling,
- Swelling
- Bruising
- Redness of the skin (erythema)
- Itching

Common adverse events of DCA include:

- Injection site reaction
- Bleeding
- Pain and discomfort
- Flushing
- Change of skin color
- Nerve injury around the jaw
- Skin tightness
- Difficulties in swallowing (dysphagia)
- Feeling sick (nausea)
- Headache

Uncommon adverse events of DCA include:

- Unusual taste in the mouth

- Difficulties in speaking
- Hair loss (alopecia)
- Hives (urticarial)
- Skin sores (ulcer)
- Scar

Adverse events of DCA where the frequency is not known include (frequency cannot be estimated from the available data) :

- Reduced or abnormal sensation in the area of the mouth (e.q. lip, tongue)
- Reduced sense of touch or altered sensation in the cheek
- Tissue damage and cell-death (necrosis) around the treatment area
- Injury of blood vessels if injected accidentally into artery or vein

The medical conditions that existed prior to the start of the study are only considered as adverse events if they have worsened during the course of the study and cannot be attributed to the natural progression of the disease.
Serious Adverse Reaction (SAR) is described as a harmful response to an intervention and includes:

•result in death.

•pose a risk of death.

•require hospitalization.

•prolong the duration of hospitalization.

•cause persistent or significant disability.

•result in congenital anomalies or birth defects.

• require medical or surgical intervention to prevent permanent damage

Recording and Reporting of Adverse Events:
All adverse events and adverse drug reactions will be recorded in the patient's medical file as well as in the designated section of the CRF. They will be classified based on severity, relevance, and relation to the treatment used in the study, and in accordance with the investigator's criteria and the guidelines outlined below.
Classification of adverse events based on severity:
Adverse events will be classified according to their severity into three categories: mild [1], moderate [2], and severe [3], based on the following definitions:
Mild: Any reaction, sign, or symptom that the individual can recognize but does not influence performance or functioning.
Moderate: Any reaction, sign, or symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. This may require medical intervention.

Severe: Any reaction, sign, or symptom(s) of a sufficient severity to cause the subject severe discomfort. Performance of daily activities/functioning is compromised and causes disability and/or poses a specific risk to health. This usually requires medical intervention..
Note: Severe AEs are not necessarily serious unless one of the serious outcomes has occurred.
Classification of Adverse Events Based on Association with the Treatment Used in the Study: To determine the association between an adverse event or adverse drug reaction and the treatment used in the study, the following definitions will be considered:

-Certain: A clinical event involving changes in laboratory tests that are associated with a timely logical change in drug administration, and its occurrence cannot be explained by the person's current illness or other medications and substances. The response to drug reduction (dechallenge) should be clinically acceptable. This should be done from a pharmacological point of view and, if necessary, the drug re-exposure information (rechallenge) should be used .
-Probable: A clinical event involving changes in laboratory tests that are associated with a timely logical change in drug administration, and it is unlikely to be associated with a person's current illness or other medications and substances, and a reasonable clinical response is observed when the dose is reduced. There is no need for a rechallenge to put an undesirable event in this group.
-Possible: A clinical event involving changes in laboratory tests that are associated with a timely logical change in drug administration, but it can be justified by the person's current illness or other medications and substances. Drug reduction information maybe not available or may be ambiguous.
Unlikely: A clinical event involving changes in laboratory tests that are associated with a timely logical change in drug administration, and it is acceptable to justify its occurrence through current illness of the individual or other drugs and substances.
Conditional/Unclassified: A clinical event involving changes in laboratory tests, which is declared as an adverse reaction and it is necessary to obtain more data or more data are being evaluated for its correct evaluation.
Unassessable/Unclassifiable: A symptom that is probably an adverse reaction, but because the information about it is insufficient or inconsistent and related data cannot be confirmed or completed, it cannot be judged.

Quality Assurance:

This study and the accuracy of the tests at intervals were evaluated by Dr. Taraneh Yazdanparast; the quality assurance manager based on the relevant SOPs.

Accordance with GCP:

The study was conducted according to the principles provided by Good Clinical Practice (GCP) and the Declaration of Helsinki

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