STATISTICAL ANALYSIS PLAN

Evaluating the efficacy and safety of Embella® (Deoxycholic acid, produced by Espad Pharmed Darou Company) for the treatment of flank fat

NCT Number: NCT07004010

Date: 24 January 2024

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Name of Test Drug:	Embella®
Phase:	IV
Methodology:	Single-arm, open-label clinical trial
Sponsor:	Espad Pharmed Darou 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:	24 January 2024
Statistical Analysis Plan Version:	Version 1.1

Contents

Synopsis

Title	Evaluating the efficacy and safety of Embella (Deoxycholic acid, produced by Espad Pharmed Co.) for the treatment of flank fat
Aim of Study (Primary endpoint)	The primary objective of this study is to assess the efficacy of Embella (produced by Espad Pharmed Co.) by assessing the investigator's Global Aesthetic Improvement Scale (GAIS)
Secondary objectives	The secondary objectives of this study are to assess other efficacy parameters and the safety of Embella
Study Design	The present study is an interventional, single-arm, open-label study conducted in Iran, to evaluate efficacy and safety of Embella (Deoxycholic acid, produced by Espad Pharmed Co.) for the treatment of flank fat
Sponsor	Espad Pharmed Company
Principal Investigator	Investigator: Kamran Balighi, MD Affiliation: Tehran University for Medical Sciences, Department of Dermatology, Pemphigus Research Unit, Razi Hospital, Tehran, Iran
Co-investigators	Dr. Faezeh Khorasanizadeh Tehran University of Medical Sciences, Cancer Research Center
Investigational Drug	Embella (Deoxycholic acid, produced by Espad Pharmed Co.)
Sample size	The sample size is not determined based on a statistical power calculation. 30 subjects will be studied.
Eligibility criteria	<u>Inclusion Criteria:</u> 1. Men and women aging between 21 to 65 years 2. Having mild to moderate flank fat assessed by the investigator and sonography and/or caliper (≥2cm thickness of the fat tissue in posterior axillary lines at the level of ASIS) 3. Signing informed consent by the subject 4. Ability to follow study instructions and likely to complete all required visits 5. Agreement to abstain from any treatment to the flank region, including botulinum toxins, hyaluronic acid fillers, cosmetic

	surgery, laser/light therapy, chemical peels, etc., during the study <u>Exclusion criteria:</u> 1. Planning to change lifestyle within the projected duration of the trial 2. History of liposuction surgery or laser lipolysis in the past 12 months or planning to have these procedures 3. Significant weight reduction in the past 6 months or planning for weight reduction within the projected duration of the trial 4. BMI > 30 kg/m^2 5. Waist circumference > 105 cm 6. Uncontrolled systemic diseases 7. Severe cardiovascular diseases 8. Known allergy or sensitivity to the study medication or its components 9. Females who are pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial 10. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study and for the duration of the study. 11. Previous treatment to the flanks with hyaluronic acid fillers or semi-permanent filler in the past 12 months 12. Use of any permanent filler materials or silicone in the flanks 13. Subjects planning a cosmetic procedure in the treatment area during the study or with prior cosmetic procedures (i.e., surgery) in the treatment area or visible scars that may affect the evaluation 14. Subjects with volume deficit due to trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease 15. Infection or dermatoses at the injection site 16. Evidence of recent alcohol or drug abuse

	17. Medical and/or psychiatric problems that are severe enough to interfere with the study results 18. Known bleeding disorder or receiving medication that will likely increase the risk of bleeding after injection 19. Having hair that would interfere with evaluation and treatment of the flank area 20. Being prone to develop hypertrophic scarring 21. Having a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), hyaluronic acid products, or Streptococcal protein 22. Having porphyria 23. Having an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound in the flank area 24. Having a condition or being in a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
Randomization	The subjects will not be randomly allocated because the study is single arm and all subjects will receive Embella.
Blinding	This study is open-label and there is no blinding in this study
Intervention	Deoxycholic acid, SC, 0.15 ml each injection, up to 2-4 ml in each site (2 ml at visit 1 for everyone, and 2 ml at visit 2 unless the patient does not agree)
Efficacy and Safety outcomes	*Primary endpoint:* The proportion of participants with grade 1 or higher ("improved, much improved, very much improved") in investigator-assessed Global Aesthetic Improvement Scale (GAIS) at Week 12 *Secondary endpoints:* Secondary endpoints: 1. Safety assessment by evaluation of adverse events (AEs) 2. The proportion of participants with grade 1 or higher ("improved, much improved, very much improved") in

	investigator-assessed Global Aesthetic Improvement Scale (GAIS) at Week 6 3. Change from Baseline in ultrasonographic measurement of dermal and hypodermal thickness on both flanks at weeks 6 and 12 4. Changes from Baseline in the bodyweight (Kg) at Weeks 6 and 12 5. Changes from Baseline in right and left thigh circumference at Weeks 6 and 12 using a flexible tape measure 6. Changes from Baseline in caliper measurement (mm) of flank fat on each side at Weeks 6 and 12 7. Changes from Baseline in waist circumference at Weeks 6 and 12 using a flexible tape measure 8. Subject's satisfaction at Weeks 6 and 12 using a 10-point Likert scale
Statistical Plan	The data analysis procedure will cover the cleaning, inspecting, and transforming process. Also, the descriptive analysis will be performed using frequency and percentage, mean and standard deviation (SD) or median and interquartile range (IQR) regarding the type of the variables. **Primary Endpoint:** The primary effectiveness endpoint will be reported as the number and percentage of participants with a ≥ 1-point improvement from baseline in the investigator's GAIS at week 12 **Secondary Endpoints:** The secondary effectiveness endpoints will be reported as the number and percentage of participants with a ≥ 1-point improvement from baseline in the investigator's GAIS and the subject's GAIS at week 6, the number and percentage of participants with a ≥ 1-point improvement from baseline in the subject's GAIS at week 12, the number and percentage of patient satisfaction status at week 12 and mean and SD or median and IQR of patient satisfaction score and changes in derma and hypoderm thickness at weeks 6 and 12 compared to baseline.

	Safety: The safety data will be analyzed primarily using incidence and frequency. Adverse events' severity, seriousness, and causality assessment will be reported.
Withdrawal Criteria	1. Withdrawal of consent by the patient 2. Noncompliance, including refusal of study medical requirements, refusal of procedures as stated in the study protocol, or use of prohibited medications 3. Not possible to follow the patient's condition (loss to follow-up) 4. Treatment to the flanks with hyaluronic acid fillers or semi-permanent filler throughout the study 5. Use of any permanent filler materials or silicone in the flanks throughout the study 6. Performing any cosmetic procedure in the treatment area during the study period (i.e., surgery) 7. Having a condition that, in the investigator's opinion, may interfere with the efficacy assessment

Study Timeline

	Study Duration			
	Screening	**Intervention**	**Follow-up**	
Time Point	Screening Visit	Visit 1	Visit 2	Visit 3
Time	Day -7 to -1	Day 0	Week 6 ± 1 week	Week 12 ± 1 week
Informed Consent Form	×			
Assessment of Inclusion and Exclusion Criteria	×			
Medical History	×			
Physical Examination and Vital Signs		×	×	
Concomitant Medications	×	×	×	×
Skin Ultrasonography	×		×	×
Photography		×*	×	×
Intervention		×	×**	
GAIS Assessment			×	×
Assessment of Participant Satisfaction				×
Adverse Event Assessment	×	×	×	×

* Photography must be performed prior to injection.

** In case a touch-up injection is deemed necessary by the physician.

List of Abbreviations and Definition of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
ASIS	Anterior Superior Iliac Spine
BMI	Body Mass Index
CD36	Cluster of Differentiation 36
CRP	C-reactive protein
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IQR	Interquartile Range
IRCT	Iranian Registry of Clinical Trials
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation

Section 1: Administrative information

Title and Trial registration

Evaluating the efficacy and safety of Embella (Deoxycholic acid, produced by Espad Pharmed Darou Company) for the treatment of flank fat

Study Registration Code in the Iranian Registry of Clinical Trials (IRCT):
IRCT20240416061507N1

Ethics Approval Number

IR.TUMS.MEDICINE.REC.1402.700

SAP Version (SAP version number with dates)

Version: 1.1, Date: 24 January 2024

Section 2: Introduction

Introduction

With the increasing demand for body contouring, non-invasive or minimally invasive methods for reducing localized fat in various areas of the body have gained growing popularity over the past decade (1). Localized adipose deposits are typically found in regions such as the abdomen, flanks, thighs, inner knee, arms, and others. Although diet, exercise, and bariatric surgery may be effective in controlling obesity, aesthetic procedures remain necessary for the removal or reduction of localized fat deposits in areas resistant to these interventions, such as the flanks and abdomen. Liposuction is the most common method for reducing excess localized fat; however, as an invasive surgical technique, it is associated with complications such as pain, infection, prolonged recovery, scarring, hematoma, deep vein thrombosis, pulmonary embolism, and anesthesia-related adverse effects. These complications, along with the extended recovery period, have led patients to seek alternative, less invasive methods for body contouring. Currently, non-invasive fat reduction techniques include low-level lasers, radiofrequency, ultrasound, infrared light, cryolipolysis, and the use of injectable solutions containing fat-dissolving agents. Treatments that are minimally invasive and not accompanied by the aforementioned complications are ideal for patients seeking reduction of localized fat for body contouring (2).

Multiple clinical trial studies have been reported in the field of adipose tissue reduction through subcutaneous injection of solutions containing phosphatidylcholine and bile salts, specifically sodium deoxycholate, and consequently, these treatments have gained significant popularity. Studies have demonstrated that deoxycholate is the primary active ingredient in the aforementioned injectable solutions and is responsible for the clinical reduction of adipose tissue (3).

Synthetic purified deoxycholic acid has been introduced as the first pharmacological intervention approved by the FDA for the reduction of submental fat. Deoxycholic acid is a type of bile acid which, due to its ability to induce non-selective cell lysis and disruption of adipocyte membranes (adipocytolysis), leads to the emulsification of fat in the intestine (4,5).

Deoxycholic acid has been used for the reduction of localized fat for three decades. Its mechanism of action involves the emulsification of phospholipids and subsequent dissolution of biological membranes, which leads to adipocyte necrosis. In a prospective study conducted in 2017, the efficacy and safety of a 1.25% sodium deoxycholate solution were evaluated in 221 patients with various forms and degrees of localized fat. Injections were administered into the adipose tissue at 6-week intervals and continued until clinical results were achieved. Outcomes were assessed using before-and-after photographs and patient satisfaction was measured by completion of an anonymous form, while adverse events (AEs) were reported by the treating physician. Among 185 patients eligible for final evaluation, the mean treatment efficacy score reported by patients was 7.4, and medical assessment indicated treatment success in 93.5% of cases. AEs were mainly mild and localized at the injection site, with the incidence of severe complications being very rare. The results of this study confirm the efficacy and safety of deoxycholic acid injections for the reduction of localized fat (6).

In another study, the efficacy and safety of deoxycholic acid injection in the abdominal area were evaluated in 7 female patients. The results indicate that its mechanism of action is through the increase of crown-like structures and macrophage infiltration, as well as the reduction of leptin expression, hormone-sensitive lipase, triglyceride lipase, and CD36, ultimately resulting in adipose tissue necrosis. In the evaluation of systemic inflammatory markers, including CRP, lipid profile, and blood glucose, no significant changes were observed (7).

In another study, with an emphasis on the effect of deoxycholic acid in reducing the volume of submental adipose tissue, new sites for its injection were proposed. This study reported that deoxycholic acid can be used as an alternative method in areas where other interventions, such as liposuction, do not have acceptable efficacy or safety. In this study, smaller areas of fat accumulation, such as the axilla, upper arm, and around the knee, were suggested for further investigation in future studies. Additionally, the injection of modified concentrations of deoxycholic acid in larger areas, such as superficial abdominal fat, may be beneficial (8).

In a study aimed at reducing local pain and inflammation caused by deoxycholic acid injection, a combination of deoxycholic acid with lidocaine and triamcinolone was used. The resulting solution was injected at one-centimeter intervals into the medial aspect of the right thigh of one patient and the distal regions of both arms of a second patient. Additionally, undiluted deoxycholic acid solution was injected as a control into the medial aspect of the left thigh of the first patient. The results of the evaluation in two cases indicated that the use of this method was effective for larger areas by increasing the spreadability and tolerability, and was associated with lower consumption of deoxycholic acid and fewer side effects (9).

The first successful case report of deoxycholic acid injection for the reduction of flank fat in the United States was published in 2018. In this study, a 39-year-old male received deoxycholic acid injections with a total volume of 4 cc (2 cc on each side) in the flank fat area. Follow-up at 12 weeks demonstrated a gradual reduction of fat in this region, and no recurrence of fat accumulation was observed at the 12-month follow-up. The patient was completely satisfied with the outcome (10).

Given that non-invasive methods have subtle effects that are not immediately observable, various objective and subjective techniques are utilized to assess their efficacy. In most studies, measurement of the circumference of the target area before and after the intervention is reported as an indicator. Other objective techniques, such as the use of calipers, ultrasound, MRI, and three-dimensional photography, have also been employed. Common subjective methods include the evaluation of standardized photographs by a blinded assessor and patient satisfaction surveys. All existing methods for quantifying non-invasive fat reduction have significant limitations and cannot be relied upon independently (11).

Objectives

The injectable solution containing deoxycholic acid (Embella, manufactured by Espad Pharmed Darou Company) demonstrates appropriate efficacy and safety in the reduction of lateral abdominal fat.

Primary objective

The aim of this study is to determine the efficacy and safety of the injectable solution containing deoxycholic acid (Embella, manufactured by Espad Pharmed Darou Company) in reducing fat in the flank area.

Secondary objectives

- The proportion of participants who, at week 6, according to the investigator's assessment on the GAIS score, have achieved a score of 1 or higher (improved, much improved, or very much improved).
- Changes from baseline in waist circumference at weeks 6 and 12 using a flexible measuring tape.
- Changes from baseline in body weight at weeks 6 and 12.
- Changes from baseline in right and left thigh circumference at weeks 6 and 12 using a flexible measuring tape.
- Changes from baseline in flank fat on each side measured by caliper at weeks 6 and 12.
- Assessment of the trend in dermal and hypodermal thickness changes on both sides by measurement with ultrasonography from baseline to weeks 6 and 12
- Assessment of participants' satisfaction at weeks 6 and 12
- Assessment of the incidence of AEs following treatment

Section 3: Research Methods

Study Design

This is a single- arm, open-label clinical trial evaluating the efficacy and safety of Embella® (Deoxycholic acid, produced by Espad Pharmed Darou Company) for the treatment of flank fat

Randomization

There is no randomization.

Blinding

The study is an open-label clinical trial.

Sample size

In this study, 30 participants will be enrolled.

Study Population Criteria

Inclusion Criteria

1. Men and women aged between 21 and 65 years

2. Presence of mild to moderate flank fat, as assessed by the investigator and ultrasound and/or caliper (with a thickness of ≥2 cm of adipose tissue at the posterior axillary lines at the level of the ASIS).
3. Signing of the informed consent form by the participants
4. Ability to comply with study instructions and likelihood of completing all required visits
5. Agreement to abstain from any treatment in the flank area, including botulinum toxin, hyaluronic acid fillers, cosmetic surgery, laser/light therapy, chemical peels, etc., throughout the study period.

Exclusion Criteria

1. Planning for lifestyle modification during the predicted duration of the study
2. History of liposuction or laser lipolysis surgery within the past 12 months, or intention to undergo these procedures
3. Significant weight loss in the past 6 months or planned weight loss during the anticipated duration of the study
4. Body mass index (BMI) greater than 30 kg/m^2
5. Waist circumference greater than 105 centimeters
6. Affliction with uncontrolled systemic diseases
7. Severe cardiovascular diseases
8. Known hypersensitivity or allergy to the study product or its components
9. Pregnant women, breastfeeding women, or women who are expected to become pregnant during the anticipated duration of the study
10. Current enrollment in a drug or investigational device study, or participation in such a study within the past 30 days, as well as during the course of the study.
11. Previous treatment of the flank area with hyaluronic acid fillers or semi-permanent fillers within the past 12 months
12. Use of permanent fillers or silicone in the flank area

13. Individuals who intend to undergo cosmetic procedures in the treatment area during the study, or who have a history of cosmetic procedures (such as surgery) or visible scars in that area that may affect the assessment.
14. Individuals with volume loss due to trauma, adipose tissue disorders associated with autoimmune diseases such as generalized lipodystrophy (e.g., in juvenile dermatomyositis), localized lipodystrophy (such as Barraquer-Simons syndrome), hereditary diseases, or HIV-associated disease
15. Infection or skin diseases at the injection site
16. Evidence of recent alcohol or drug abuse
17. Medical and/or psychiatric conditions of such severity that they may interfere with the outcomes of the study
18. Having a known bleeding disorder or the use of medications that increase the likelihood of bleeding after injection
19. Presence of hair in the flank area that interferes with assessment or treatment
20. Predisposition to hypertrophic scar formation
21. History of anaphylaxis or allergy to lidocaine (or other amide anesthetics), hyaluronic acid products, or streptococcal proteins
22. Affliction with Porphyria
23. Presence of active inflammation, infection, malignant or premalignant lesion, or non-healed ulcer in the flank region
24. Having a condition or being in a situation which, in the opinion of the investigator, may place the individual at significant risk, disrupt the study results, or interfere with the individual's participation in the study.

Withdrawal Criteria

1. Withdrawal of participant from informed consent
2. Non-compliance, including refusal to adhere to the medical requirements of the study, failure to undergo procedures specified in the study protocol, or use of prohibited medications.

3. Inability to follow up on the participant's status
4. Treatment of the flank area with hyaluronic acid fillers or semi-permanent fillers during the course of the study
5. The use of any permanent filler or silicone materials in the flank area during the course of the study
6. Undergoing any cosmetic procedures in the treatment area during the study period (such as surgery)
7. Having conditions that, in the opinion of the investigator, may interfere with the assessment of efficacy

Section 4: Outcome Variables

Primary Outcomes

The proportion of participants who, at week 12, according to the investigator's assessment on the GAIS score, have achieved a score of 1 or higher (improved, much improved, or very much improved).

Secondary Outcomes

- The proportion of participants who, at week 6 based on the investigator's assessment on the GAIS score, have achieved a score of 1 or higher (improved, much improved, or very much improved).
- Changes from baseline in waist circumference at weeks 6 and 12 using a flexible measuring tape.
- Changes from baseline in body weight at weeks 6 and 12.
- Changes from baseline in right and left thigh circumference at weeks 6 and 12 using a flexible measuring tape.
- Changes from baseline in flank fat on each side measured by caliper at weeks 6 and 12.
- Assessment of the trend in dermal and hypodermal thickness changes on both sides by measurement with ultrasonography from baseline to weeks 6 and 12
- Assessment of participant satisfaction at weeks 6 and 12
- Assessment of the incidence of AEs following treatment

Section 5: Descriptive statistics

Baseline characteristics

Baseline characteristics	Categories
Age	-
Sex	Male/Female

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 6: 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.

Study Profile

All participants who sign the informed consent form will be included in the final statistical report. The participants flow throughout the study, reasons for withdrawal from the study, and major deviations and violations of the protocol will be reported.

Statistical Software

The analysis will be carried out using R statistical software.

Missing Data

No imputation will be done.

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.

Primary Endpoint Analysis

Participants who, in the GAIS score assessment by the investigator, received a score of 1 or higher will be reported with the number and percentage.

Secondary Endpoint Analysis

Descriptive analysis of data for quantitative variables will be reported as mean and standard deviation (SD) or median and interquartile range (IQR), based on the data distribution, and for qualitative variables as the number and percentage. Changes over time will be analyzed using repeated measures analysis of variance (repeated measures ANOVA) or the Friedman test, depending on the data distribution. Comparisons between baseline and subsequent timepoints will also be performed using the paired t-test or the Wilcoxon test, as appropriate. The significance level for the tests will be considered as 0.05.

Adverse Events' Analysis

AEs will be classified according to the MedDRA dictionary based on the Preferred Term (PT) and analyzed in terms of frequency and percentage. The severity and seriousness of each event will also 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.

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