

**SAFETY AND EFFICACY OF DEOXYCHOLIC ACID INJECTION FOR
REDUCTION OF UPPER INNER THIGH FAT**

Detailed Protocol

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I. Background and Significance

A. Historical background

Deoxycholic acid (ATX-101; Kybella) is an FDA-approved injectable for the treatment of submental fat. Unwanted upper inner thigh fat is a common aesthetic complaint from patients, and current treatment options include liposuction and cryolipolysis (CoolSculpting, Allergan, Irvine, CA). Liposuction is an invasive surgical procedure, with rare but serious risks including nerve damage, bleeding, fat embolization, and complications from anesthesia.¹ Cryolipolysis is a non-invasive option, but adverse effects include up to two weeks of pain and aching; temporary redness, swelling, or bruising; and very rarely, paradoxical adipose hyperplasia.² At this time, it is not known if deoxycholic acid may be a safe and effective treatment for upper inner thigh fat.

Phosphatidylcholine, a fat-emulsifying soybean lecithin, was initially developed for adipocytolysis. It was combined with deoxycholic acid, a secondary bile acid, to increase solubility.³ *In vitro* and *ex vivo* studies later suggested deoxycholic acid, rather than phosphatidylcholine, as the major active compound.³⁻⁵ Deoxycholic acid is thought to cause direct adipocyte cell membrane damage.^{3,4} Histologically, it appears that deoxycholic acid causes adipocytolysis by inducing an inflammatory reaction, which involves predominantly neutrophils, followed by T-cells. Debris is digested by macrophages, and delayed fibrosis is also present.^{3,6-8}

Phosphatidylcholine with deoxycholic acid (PC/DC) has been studied as an agent for injection lipolysis in animal and human studies.⁶⁻⁸ Lipostabil, a PC/DC formulation, has been advertised in South America, South Africa, and Europe for several decades.⁹ However, high-quality clinical trials are lacking, and PC/DC has not been developed by the pharmaceutical industry in the United States.³ On the other hand, deoxycholic acid for reduction of submental fat has been studied extensively; with four double-blind, multi-center, randomized clinical trials, enrolling about 1800 patients, demonstrating its safety and efficacy.^{3,10-13} It is marketed as Kybella (Allergan, Irvine, CA), and is a popular FDA-approved cosmetic treatment. Deoxycholic acid has been proposed for use in body contouring in areas other than submental fat.¹⁴ There are no studies in the literature on the use of deoxycholic acid (Kybella) for the treatment of unwanted upper inner thigh fat.

B. Previous preclinical or clinical studies

Deoxycholic acid (ATX-101, Kybella) has been found in several large double-blind, randomized clinical trials to be safe and effective for the treatment of submental fat.^{3,10-13} In phase 3 trials, doses of deoxycholic acid 1 mg/cm² and 2 mg/cm² were evaluated.¹⁰ Subjects were treated with a maximum of four treatment sessions, spaced approximately 28 days apart, and follow-up was performed at 12 weeks. At each treatment session, patients were treated with a maximum of 50 injections. Maximum deoxycholic acid per injection was 0.2 mL, for a total maximum dose of 10 mL per treatment session.¹⁰ Efficacy was quantitatively demonstrated through caliper measurements, a subject self-rating scale (0 to 6), a clinician-reported submental fat rating scale, patient-reported submental fat rating scale, and assessment of skin laxity.¹⁰ Both 1 mg/cm² and 2 mg/cm² doses were safe and well-tolerated, and more effective than placebo in reducing submental fat.¹⁰ At 12-week follow-up, patient satisfaction with appearance was 65.4% with deoxycholic acid 2 mg/cm², compared with 60.8% with deoxycholic acid 1 mg/cm², and 29.0% with placebo.¹⁰ Common side effects were mild-to-moderate pain, swelling, ecchymosis, numbness, bleeding, and induration including fibrosis.^{3,10-13} Moderate-to-severe pain was reported in 60% of deoxycholic acid patients, but lasted a median of only 1 day.¹⁰ Temporary nerve injury, affecting the marginal mandibular nerve and resulting in asymmetric smile, occurred in 2.1% of patients treated with deoxycholic acid, and all occurred with the 2 mg/cm² dose. All nerve injury resolved without sequelae during the study period.¹⁰ There were no clinically significant changes in laboratory values or vital signs. No deaths were reported in association with deoxycholic acid.^{3,10-13}

Treatment of localized fat deposits with phosphatidylcholine injection was performed in 50 patients for body contouring; treated areas varied by patient, and included abdomen, arms, and thighs. Subjects received one to four treatments of 5 mL (250 mg/5 mL) phosphatidylcholine in an 80 cm² area. Pre-procedure and post-procedure photographs showed that the treatment was effective in reducing localized fat deposits. With no weight gain, no recurrence was noted in fat deposits over 2-year follow-up. Side effects were bruising, edema, and erythema, lasting 48 to 72 hours. Post-inflammatory

nodules were sometimes noted, resolving within 30 days at most. Otherwise, no atrophy or other side effects were noted.¹⁵

One pilot study of PC/DC for injection lipolysis of the hips and upper lateral thigh showed favorable safety and efficacy results. Fifteen women were treated. Fat reduction was confirmed with circumferential measurements and ultrasound. Treatment with PC/DC was well-tolerated, with side effects limited to local injection-site reactions, including pain, erythema, and edema; itching and bruising occurred in one subject. Reduction in cholesterol, triglycerides, and low-density lipoprotein was noted; this was attributed to phosphatidylcholine. There were no significant adverse lab abnormalities associated with the procedure, including in renal and liver function. The procedure was well tolerated and 73% of patients reported satisfaction.¹⁶

There are no previous reports of deoxycholic acid injection alone as a treatment for upper inner thigh fat.

C. Rationale behind the proposed research, and potential benefits to patients and/or society

The use of deoxycholic acid injection for treatment of upper inner thigh fat has not been previously studied. Deoxycholic acid injection has been studied extensively for submental fat. The proposed doses of deoxycholic acid in the present clinical trial have been shown to be systemically safe based on previous large clinical trials.^{3,10-13} The concept of an injectable treatment for body contouring has been present for years,¹⁵ but high-quality studies are lacking. A pilot study of phosphatidylcholine together with deoxycholic acid in the region of the hips and thighs has yielded safe and favorable results.¹⁶ Due to the safety and effectiveness of deoxycholic acid for submental fat, we hypothesize that deoxycholic acid is a safe and effective treatment for upper inner thigh fat. The results of the present clinical trial may lead to development of a new treatment option for upper inner thigh fat.

II. Specific Aims

A. Specific objectives and hypotheses to be tested in the research project

This prospective, open-label, single-arm, single-center clinical study at the University of California, San Diego Department of Dermatology is designed primarily to investigate the safety and efficacy of deoxycholic acid injection for the treatment of upper inner thigh fat. The secondary objective of this study is evaluation of patient-reported satisfaction outcomes after treatment of upper inner thigh fat with deoxycholic acid injection.

III. Subject Selection

A. Inclusion/Exclusion criteria

Inclusion

1. Adults aged 18 to 65
2. Discrete area of mild-to-moderate excess upper inner thigh fat, amenable to treatment at the discretion of the investigator
3. Subjects who score 0 (extremely dissatisfied) to 2 (slightly dissatisfied) on a Subject Self-Rating Scale, pertaining to upper inner thigh fat, with the scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied)
4. Body mass index (BMI) less than 30 kg/m²
5. Stable body weight for previous 6 months (weight within 10 pounds of baseline)
6. Subjects must be in stable health, as confirmed by medical history, per investigator judgment
7. Subjects must be able to read, sign, and understand the informed consent
8. Subjects must be willing to avoid any other treatments to the inner thigh, including cryolipolysis and liposuction, during the study period.
9. Subjects must be willing to avoid changes in diet or exercise, any weight loss program, and any weight loss supplements, during the study period.
10. Subjects must be able and willing to avoid anticoagulation (aspirin, warfarin, heparin, rivaroxaban) for 1 week prior to each study treatment

Exclusion:

1. History of treatment for inner thigh fat, including cryolipolysis, noninvasive body contouring or liposuction in the last year

2. Previous trauma or surgery to pelvis or thighs
3. Subjects with an unstable medical condition, as deemed by the investigator
4. Women who are pregnant or lactating or plan to become pregnant during the study period
5. Lymphedema or edema of thigh
6. Excessive skin laxity in the treatment area, as judged by the investigator
7. Severe thigh cellulite
8. Subjects with any disease in the treatment area, such as dermatologic disease, that may be exacerbated by the study treatment
9. Subjects with any condition that may impair the evaluation of inner thigh fat
10. Subjects with known bleeding diathesis
11. Subjects with any known hypersensitivity to Kybella (deoxycholic acid) or any of the inactive ingredients: benzyl alcohol, dibasic sodium phosphate, sodium chloride, sodium hydroxide, hydrochloric acid

B. Source of subjects and recruitment methods

Subjects will be recruited by flyers and handouts placed in the UCSD Dermatology clinic. Eligible patients will be determined from the inclusion and exclusion criteria. Eligible patients will be informed of the proposed study and its purpose and given the opportunity to ask any questions.

Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

C. Equitable Selection of Subjects

The risks and benefits of the research are fairly distributed among the populations that stand to benefit from it. Although the risk of this study is minimal, to be prudent, pregnant women will be excluded because of the potential harm posed to the fetus.

IV. Subject Enrollment

A. Number of subjects

15 subjects will be enrolled in the study.

B. Methods of enrollment

Subjects interested in participating in the study may contact one of the investigators. The study objectives, inclusion and exclusion criteria, possible risks and benefits of the study, and the information included in the informed consent form shall be discussed with prospective study participants. Subjects who believe they meet the exclusion and inclusion criteria and remain interested in the study shall be invited to come in for their screening visit. During the screening visit, the investigator will interview the subject and perform a simple clinical examination, particularly examining the thighs. Following the investigator's determination that the inclusion and exclusion criteria are met, the subject be invited to participate in the study.

C. Procedures for obtaining informed consent

Written informed consent must be obtained from each subject prior to enrollment in the study (see attached). The investigator will explain the nature of the study, its purpose and associated procedures, the expected duration and the potential benefits and risks of participation to each subject prior to his/her entry into the study. The information given will be based on a subject informed consent document approved for this study. Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign and date the subject informed consent document (attached). Only if the subject voluntarily signs the informed consent document may he/she enter the study.

The subject will receive a copy of the signed and dated document. No study related procedures shall commence prior to obtaining subject informed consent.

The informed consent sheet is to remain in the investigator's files. By signing the informed consent, the investigator (or his/her representative) provides support that he/she has participated in the consent process with the subject.

The subject informed consent document will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol which necessitates a change to the content of the subject

information/informed consent document. Any revision to the informed consent document, and written information must receive the IRB/IEC's approval prior to use. The investigator will inform the subject of changes in timely manner and will ask the subject to confirm his/her interest in continued study participation by his/her signature on the revised informed consent document.

In addition, Non-English speaking subjects will be given an approved translation of the consent form and the Experimental Subject's Bill of Rights in their native language to sign. Unless the researchers are fluent in the subject's language, a qualified translator will be included in the consent process and will sign his or her name at the end of the approved translated consent form.

D. Treatment assignment and randomization

There will be no randomization. Study participants will be treated with deoxycholic acid (Kybella) 10 mg/ mL injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial). Subjects will receive deoxycholic acid 2 mg/cm², with injections of 0.2 mL spaced evenly 1 cm apart within the treatment area. Bilateral upper inner thighs will be treated. Each treatment will consist of a maximum of 8 mL (40 injection sites) of the study drug, with a maximum of 4 mL (20 injection sites) of the study drug for each thigh. All treatments will be performed by a study physician. Subjects will receive 1 to 4 treatment sessions, each spaced 6 weeks +/- 1 week. Treatment #2, #3, or #4 will be pursued if patient desires more treatment, and if there is sufficient fat for treatment, per investigator's judgment.

V. Study Procedures

a) Study visits and parameters to be measured

All visits in this study will be performed at the UCSD Dermatology Clinic, 3rd floor, 8899 University Center Ln., San Diego, CA 92122.

Screening/ Baseline Visit (Visit 1, Day -14 to 1)

This visit is expected to take approximately 1 hour. The following describes the procedures performed at this visit.

1. Prior to any screening assessments, informed consent will be obtained by the investigator. When the subject fully understands the nature of the study and its risks, the subject will be asked to sign and date the informed consent form. The investigator will then sign and date the form.
2. A detailed medical history of information pertaining to treatment will be obtained.
3. The investigator will perform a relevant physical examination.
4. Patient's weight will be obtained.
5. The subject will be asked to complete the Subject Self-Rating Scale (0 to 6 scale).
6. If the subject meets the criteria for the study, the subject will be assigned the next consecutive subject number.
7. Females of childbearing age will undergo a urine pregnancy test
8. The investigator will determine the patient's eligibility for the study.

First treatment (*Visit 2, Day 1*)

The treatment visit is expected to take approximately 1 hour. The first treatment may be combined with Screening/ Baseline.

Prior to Kybella treatment:

1. Patient will be asked to complete the Subject Self-Rating Scale, rated from 0 to 6.
2. Patient's weight will be obtained.
3. Concomitant medications and procedures will be confirmed and recorded.
4. The investigator will perform a relevant physical examination.
5. Thigh circumference measurement will be obtained with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
6. Caliper measurement of inner thigh skin-fold thickness will be obtained.

- Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
7. Thigh gap measurement will be obtained.
 - Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
 8. Pre-treatment photographs will be taken.
 - Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

Treatment:

9. Deoxycholic acid (Kybella) 10 mg/ mL will be injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial). Subjects will receive deoxycholic acid 2 mg/ cm², with injections of 0.2 mL spaced evenly 1 cm apart within the treatment area. Bilateral thighs will be treated. Each treatment will consist of a maximum of 8 mL (40 injection sites) of the study drug, with a maximum of 4 mL (20 injection sites) of the study drug for each thigh. All treatments will be performed by a study physician.

Post-Treatment Phone Call #1 (*Day 3*)

Phone call expected to take 5-10 minutes.

1. Two days after treatment, patient will be called and asked to report adverse events since last treatment. All adverse events will be recorded.

Second treatment (+/-) (*Day 36 to 50*)

The treatment visit is expected to take approximately 1 hour.

Prior to Kybella treatment:

1. Patient will be asked to complete the Subject Self-Rating Scale, rated from 0 to 6.
2. Patient's weight will be obtained.
3. Concomitant medications and procedures will be confirmed and recorded.
4. Adverse events will be recorded.
5. The investigator will perform a relevant physical examination.
6. Thigh circumference measurement will be obtained with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
7. Caliper measurement of inner thigh skin-fold thickness will be obtained.
 - Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
8. Thigh gap measurement will be obtained.
 - Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
9. Pre-treatment photographs will be taken.
 - Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

Treatment:

10. Deoxycholic acid (Kybella) 10 mg/ mL will be injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial). Subjects will receive deoxycholic acid 2 mg/ cm², with injections of 0.2 mL spaced evenly 1 cm apart within the treatment area. Bilateral thighs will be treated. Each treatment will consist of a maximum of 8 mL (40 injection sites) of the study drug, with a maximum of 4

mL (20 injection sites) of the study drug for each thigh. All treatments will be performed by a study physician.

Post-Treatment Phone Call #2 (*Day 38 to 52*)

Phone call expected to take 5-10 minutes.

1. Two days after treatment, patient will be called and asked to report adverse events since last treatment. All adverse events will be recorded.

Third Treatment (+/-) (*Day 71 to 99*)

The treatment visit is expected to take approximately 1 hour.

Prior to Kybella treatment:

1. Patient will be asked to complete the Subject Self-Rating Scale, rated from 0 to 6.
2. Patient's weight will be obtained.
3. Concomitant medications and procedures will be confirmed and recorded.
4. Adverse events will be recorded.
5. The investigator will perform a relevant physical examination.
6. Thigh circumference measurement will be obtained with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
7. Caliper measurement of inner thigh skin-fold thickness will be obtained.
 - Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
8. Thigh gap measurement will be obtained.
 - Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical

- distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
9. Pre-treatment photographs will be taken.
 - Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

Treatment:

10. Deoxycholic acid (Kybella) 10 mg/ mL will be injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial). Subjects will receive deoxycholic acid 2 mg/ cm², with injections of 0.2 mL spaced evenly 1 cm apart within the treatment area. Bilateral thighs will be treated. Each treatment will consist of a maximum of 8 mL (40 injection sites) of the study drug, with a maximum of 4 mL (20 injection sites) of the study drug for each thigh. All treatments will be performed by a study physician.

Post-Treatment Phone Call #3 (~Day 73 to 101)

Phone call expected to take 5-10 minutes.

1. Two days after treatment, patient will be called and asked to report adverse events since last treatment. All adverse events will be recorded.

Fourth Treatment (+/-) (Day 106 to 148)

The treatment visit is expected to take approximately 1 hour.

Prior to Kybella treatment:

1. Patient will be asked to complete the Subject Self-Rating Scale, rated from 0 to 6.
2. Patient's weight will be obtained.
3. Concomitant medications and procedures will be confirmed and recorded.
4. Adverse events will be recorded.
5. The investigator will perform a relevant physical examination.
6. Thigh circumference measurement will be obtained with anthropometric tape

measure.

- Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
7. Caliper measurement of inner thigh skin-fold thickness will be obtained.
- Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
8. Thigh gap measurement will be obtained.
- Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
9. Pre-treatment photographs will be taken.
- Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

Treatment:

10. Deoxycholic acid (Kybella) 10 mg/ mL will be injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial). Subjects will receive deoxycholic acid 2 mg/ cm², with injections of 0.2 mL spaced evenly 1 cm apart within the treatment area. Bilateral thighs will be treated. Each treatment will consist of a maximum of 8 mL (40 injection sites) of the study drug, with a maximum of 4 mL (20 injection sites) of the study drug for each thigh. All treatments will be performed by a study physician.

Post-Treatment Phone Call #4 (~Day 108 to 150)

Phone call expected to take 5-10 minutes.

1. Two days after treatment, patient will be called and asked to report adverse events since last treatment. All adverse events will be recorded.

Week 4 Follow Up (~Day 134 to 176)

Visit expected to take 1 hour. The visit will take place 4 weeks after the last treatment.

1. Patient will be asked to complete Subject Self-Rating Scale, rated from 0 to 6.
2. Patient will be asked to complete Post-Treatment Satisfaction Questionnaire.
3. Concomitant meds and procedures will be confirmed and recorded.
4. Adverse events will be confirmed and recorded.
5. Patient weight will be obtained.
6. A relevant physical exam will be performed by the investigator.
7. Thigh circumference measurement will be obtained with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
8. Caliper measurement of inner thigh skin-fold thickness will be obtained.
 - Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
9. Thigh gap measurement will be obtained.
 - Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
10. Follow-up photographs will be taken.
 - Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

Week 12 Follow Up (~Day 190 to 232)

Visit expected to take 1 hour. The visit will take place 12 weeks after the last treatment.

1. Patient will be asked to complete Subject Self-Rating Scale, rated from 0 to 6.
2. Patient will be asked to complete Post-Treatment Satisfaction Questionnaire.
3. Concomitant meds and procedures will be confirmed and recorded.
4. Adverse events will be confirmed and recorded.
5. Patient weight will be obtained.
6. A relevant physical exam will be performed by the investigator.
7. Thigh circumference measurement will be obtained with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
8. Caliper measurement of inner thigh skin-fold thickness will be obtained.
 - Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
9. Thigh gap measurement will be obtained.
 - Patient will be asked to stand with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap measurements at all following study assessments are performed at the same sites.
10. Follow-up photographs will be taken.
 - Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

b) Drugs to be used

Deoxycholic acid (Kybella) 10 mg/ mL will be injected subcutaneously, targeting the medial thigh deep fat compartment (pre-fascial).

c) Data to be collected and when data is to be collected

Data to be collected throughout the study includes the items listed in Schedule of Events.

VI. Biostatistical Analysis

A. Study endpoints

1. Primary Endpoint:

The primary endpoint will be safety endpoint, as defined by the incidence rate of patients who experience:

- a) Any adverse event (AE) ascertained by patient report or physician evaluation
- b) One or more serious adverse events (SAE) as defined by CTCAEv4
- c) Adverse events leading to study drug discontinuation.

2. Secondary Endpoints:

- a) Efficacy, defined as reduction in inner thigh fat, measured as follows:
 - i. Change in thigh circumference, as recorded with anthropometric tape measure.
 - Thigh circumference will be measured at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that thigh circumference measurements at all following study assessments are performed at the same site.
 - ii. Change in inner thigh skin-fold thickness, as measured by calipers
 - Caliper measurement will be performed at site of maximum bulge at Screening. Vertical distance of this site from the floor will be measured, such that caliper measurements at all following study assessments are performed at the same site.
 - iii. Increase in “thigh gap,” measured with patient standing with legs at a fixed distance apart. Measurement will be performed between sites of maximum bulge at Screening. Vertical distance of these sites from the floor will be measured, such that thigh gap

measurements at all following study assessments are performed at the same sites.

iv. Percent accuracy by three blinded physicians in correctly identifying baseline photographs, upon independent review of before-and-after clinical photographs of the treatment area.

- Patients will be asked to stand with feet apart at a uniform distance. Anteroposterior and posteroanterior photos will be taken.

b) Patient satisfaction related to study treatment:

- i. Improvement in patient satisfaction, as measured by Subject Self-Rating Scale, a 0 (extremely dissatisfied) to 6 (extremely satisfied) scale
- ii. Scores on additional post-treatment patient satisfaction questionnaire

B. Statistical methods

This is a small descriptive study, with the primary safety endpoint of the incidence rate of patients who experience:

- 1) Any adverse event (AE) ascertained by patient report, physician evaluation, or laboratory value
- 2) One or more serious adverse events (SAE) as defined by CTCAEv4
- 3) Adverse events leading to study drug discontinuation.

The safety analysis will be based on the safety population, which is defined as all patients who have received at least one dose of study medication and who have had at least one post-baseline safety evaluation.

Adverse events will be explored for trends.

The efficacy analysis will be based on the intent-to-treat (ITT) population. In the ITT population, patients will be counted in the treatment group upon informed consent and completion of Baseline measurements, regardless of receiving any dose of study medication.

In the case of a subject's early termination from study, missing values will be imputed using last observation carried forward (LOCF) method.

Baseline values will be those values measured on day of screening, which may be combined with Day 1.

Reduction in inner thigh fat, as measured by tape measure and calipers, will be presented as change in millimeters or centimeters, and presented descriptively. Percent accuracy by three independent blinded physicians in correctly identifying baseline photographs, when comparing before-and-after clinical photographs of the treatment area, will be reported. Patient satisfaction scores on Subject Self-Rating scale and post-treatment patient satisfaction questionnaire will be presented descriptively.

VII. Risks and Discomforts

A. Complications of treatment procedure/ drug side effects and toxicities

Deoxycholic acid will be injected subcutaneously in the treatment area by the principal investigator Dr. Arisa Ortiz, or by a member of the study team who is a UCSD Dermatology resident physician, under direction of Dr. Arisa Ortiz.

Common side effects of deoxycholic acid injection are injection site reactions, including swelling, pain, numbness, redness, and hardness of treatment area. Bruising, itching, warmth, hardness, tingling or burning sensation, skin tightness, hair loss, open sores (ulcers), damage, and tissue cell-death (necrosis) around the injection site are other possible side effects.

Deoxycholic acid injection in submental fat has been rarely associated with nerve injury, headache, mouth or throat pain, hypertension, nausea, or difficulty swallowing.

Patients will be asked regarding allergy to medications. Allergic reaction may occur with any medication.

Subjects will be provided post-treatment instructions (see attached).

B. Psychosocial (non-medical) risks

We do not anticipate any psychosocial risks due to this study. However, if any participants experience emotional distress during the study we will assist them to resolve this stress with appropriate referrals. Steps to prevent this outcome will include detailed explanation of the study and what to expect from the study treatment.

VIII. Potential Benefits

A. Potential benefits to participating individuals

Subjects participating in the study may receive the benefit of reduced inner thigh fat due to the study treatment.

B. Potential benefits to society

The results of this study will help us acquire information that may lead to the development of a new treatment for reduction of inner thigh fat.

IX. Cost and Remuneration

a. Remuneration

Subjects will receive financial compensation for their participation in the study. Screening and treatment visits will not be compensated. Subjects will receive \$50 per in-person follow-up visit. Therefore, subjects will receive a total of \$100 for completing the entire study.

b. Cost

There will be no cost to the patient to participate in this study.

X. Monitoring and Quality Assurance

A. Independent monitoring of source data

At this time, we do not anticipate a need for an independent monitor as our monitoring of the data will be sufficient to ensure the validity and integrity of the data and adherence to the IRB-approved protocol.

Recruitment flyers and handouts will be placed in UCSD Dermatology clinic. Subjects interested in participating in the study may contact one of the investigators. The study objectives, inclusion and exclusion criteria, possible risks and benefits of the study, and the information included in the informed consent form shall be discussed with

prospective study participants. Subjects who believe they meet the inclusion and exclusion criteria and remain interested in the study shall be invited to come in for their screening visit. During the screening visit, the investigator will interview the subject and perform a simple clinical examination, particularly examining the thighs. Following the investigator's determination that the inclusion and exclusion criteria are met, the subject will be invited to participate in the study.

We will make every effort to accurately document all data on study case report forms. All source data will be organized and filed into individual subject binders. Any pertinent notes to file regarding the subject shall be documented by a study investigator and kept in the applicable subject binder. The principal investigator shall review data on an ongoing and consistent basis throughout the duration of the study. Study numbers will be used to deidentify patients. All subjects must be assigned a study identification number that is the only item that appears on the subject binder and photographs. Electronic digital images, labeled with the study identification number, will be stored both in the patient binders and on a secured hospital server. Only investigators involved in the study will have access to this data. Even with these precautions, there is a risk of loss of confidentiality. If this occurs, the subject will be notified immediately.

This study shall be performed in accordance with all applicable federal, state and local laws and regulations, including without limitation 21 CFR Parts 50 and 56 and the Health Insurance portability and Accountability Act of 1996 (“HIPAA”) and any regulations and official guidance promulgated thereunder.

B. Safety monitoring

Safety data will be collected at each visit of the study by study investigators and will be monitored by the Principal Investigator (Dr. Ortiz). Investigators will perform overall efficacy assessments of this study. The Principal Investigator will be reviewing data on an ongoing and consistent basis throughout the duration of the study. Dr. Ortiz will ensure that the study is conducted according to the protocol and that the data was accurately recorded. The Principal Investigator (Dr. Ortiz) is responsible for protecting the rights, safety, and welfare of subjects under his/her care. The Principal Investigator will be responsible for this review and for determining whether the research should be

altered or stopped. If any severe adverse effect or death directly related to the procedure proposed occurs, Principal Investigator will report to the IRB.

XI. Outcomes monitoring

Any adverse events will be reviewed and analyzed by the Principal Investigator as soon as the event occurs and will be documented in the subject's binder. Any unexpected adverse reactions will be reported by telephone to the IRB within 48 hours of observing the event. If a unexpected side effect occurs, Principal Investigator will also report adverse events to the FDA.

XII. Adverse event reporting guidelines

The principal investigator will follow the UCSD Human Research Committee guidelines for Adverse Event Reporting.

XIII. References

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APPENDIX I. Subject Self-Rating Scale

How satisfied are you with the current appearance of your upper inner thighs?

Extremely satisfied (6)
Somewhat satisfied (5)
Slightly satisfied (4)
Neither satisfied nor dissatisfied (3)
Slightly dissatisfied (2)
Somewhat dissatisfied (1)
Extremely dissatisfied (0)

APPENDIX II. Post-Treatment Satisfaction Questionnaire

1. Were you satisfied with the Kybella treatments you received for reduction of inner thigh fat?
Yes/ No

2. Have you noticed a reduction in inner thigh fat, compared to prior to treatments?

No improvement
0-25% improvement
25-50% improvement
50-75% improvement
75-100% improvement

3. Would you recommend Kybella treatments to a friend interested in reducing inner thigh fat?
Yes/ No

4. Considering the side effects and disadvantages, would you undergo Kybella treatment for reduction of inner thigh fat again?
Yes/ No