Protocol Title: A randomized, double-blind, dose-ranging trial of subcutaneous sodium deoxycholate injections with or without low dose triamcinolone and low dose lidocaine for reduction of submental fat with reduction of pain and swelling

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PROTOCOL VERSION: 8-3-2017

The study will be conducted according to the protocol and in compliance with International Conference of Harmonization Good Clinical Practice Guidelines and all other applicable regulatory requirements.

1. Background and Rationale

Submental fat accumulation is a common concern amongst patients presenting for a cosmetic dermatologic consultation. Liposuction was employed previously for aesthetic improvement. However, alternative non-invasive techniques such as cryolipolysis, focused ultrasound, radiofrequency, and injectable sodium deoxycholate (SDOC) have been developed to meet the increasing demand for minimal downtime procedures. Patient experience with SDOC has been less than optimal, however, with approximately only 1in 4 patients returning for more than one treatment.

Subcutaneous pure synthetic SDOC (Kybella™, Allergan) gained FDA approval for reduction of submental fat in June 2015. When injected into submental fat, Kybella(TM) ultimately results in focal adipocytolysis and focal destruction of fat cells. An excellent pharmacokinetic safety profile has been demonstrated, with no measurable increases in serum cholesterol, triglycerides, or free fatty acids detected 24 hours following injection [1, 2]. Furthermore, four large phase III clinical trials to date have demonstrated the efficacy of Kybella(TM) in the reduction of submental fat [3].

Despite the documented safety and efficacy of Kybella(TM), many patients experience a variable degree of edema and pain following subcutaneous injection which can sometimes last for several days to weeks and can be a significant cause for concern. The mechanism of edema and pain secondary to Kybella(TM) injection is unknown but *thought to be an irritant response directly related to deoxycholate and not subsequent adipocyte lysis and death*. This edema and pain is thought to be a major factor contributing to the relatively small percentage of patients returning to complete the full treatment regimen. This study proposes to answer the question of whether immediate swelling and pain can be reduced to increase patient tolerance and improve patient experience without reducing the longer term low level inflammatory component which results in visible and measurable submental fat reduction.

A previous study was performed using high doses of a corticosteroid. This double-blind, randomized study utilized triamcinolone acetonide (TMC), a corticosteroid compound, in conjunction with Kybella(TM) showed that the addition of TMC reduced the incidence of early edema and tenderness, but negatively impacted long term efficacy and produced cutaneous changes of steroid atrophy in 7 (47%) of the 15 patients treated with TMC [4]. In the study, 2.0 mL of 2 mg/cm2 of Kybella(TM) was mixed with 0.05 mL of 40 mg/mL of TMC, and was delivered in up to 50 injections spaced 1.0 cm apart at 0.25 mL/injection for a total dose of up to 100 mg of Kybella(TM). As the tolerability of Kybella(TM) remains a significant issue in patient care, perhaps lower concentrations of TMC would be effective in reducing side effects without compromising treatment efficacy and causing steroid atrophy.

2. Study Objective & Hypothesis

The primary objective of this study is to evaluate the efficacy, edema and pain associated with Kybella(TM) injections of the upper neck in the treatment of submental fat with low concentrations of triamcinolone acetonide plus low doses of lidocaine. An evaluator blinded to the study will grade the level of improvement of the submental fat. Safety will also be assessed.

The Working Hypothesis: The combination of Kybella(TM) and with very low dose triamcinolone acetonide is effective in the reduction of immediate edema associated with Kybella(TM) injections and does not adversely affect the previously demonstrated long term reduction of submental fat. Addition of 0.1% lidocaine will provide immediate pain relief for a better patient experience. As 1% lidocaine is already injected just prior to Kybella injection as per current treatment protocol, there is no anticipated effect from low dose 0.1% lidocaine other than anesthesia.

3. Study Design

This is a two-site randomized, double-blind comparison trial of Kybella(TM) injections with or without triamcinolone acetate for the reduction of submental fat. 30 subjects will be enrolled into the trial (15 subjects per site). At each site, 5 will be randomized to receive Kybella(TM) injections alone whereas 10 will receive Kybella(TM) plus differing doses of triamcinolone acetate in the following way:

1. Group 1 (5 patients per site): Kybella(TM) alone: 2 mg/cm^2 of Kybella(TM) with **0.2 mL of 1% lidocaine with no epinephrine** plus 0.2cc saline to the non-TMC group to maintain equal concentrations in each injection so that the final Kybella concentration per vial will be 10mg/1.2mls or 1.6mg per 0.2 cc injection point will be delivered in up to 50 injections spaced 1.0 cm apart at 0.2 mL/injection for a total maximal dose of up to 100 mg of SDOC.
2. Group 2 (10 patients per site): Kybella(TM)+TMC at **1.0 mg/mL**: 2.0 mL of 2 mg/cm^2 of Kybella(TM) will be mixed with **0.2 mL of 10 mg/mL** of triamcinolone acetate, **0.2 mL of 1% lidocaine with no epinephrine** and then delivered in up to 50 injections spaced 1.0 cm apart at 0.2 mL/injection for a total dose of up to 100 mg of SDOC using a 30 gauge (or smaller) 0.5-inch needle. The final Kybella concentration per vial will be 10mg/1.2mls or 1.6mg per 0.2 cc injection point

The treatment area will be bounded superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone. The subjects and evaluating investigator will be blinded to the treatment, thus maintaining double-blind status. By nature of the varying volumes of injection, the treating investigator will be unblinded to the treatment. A series of 3 injection sessions will be performed spaced 4 weeks apart. No lidocaine will be injected prior to injections to prevent further dilution of injected Kybella™ as it will be

premixed with Kybella™. Chilling with cold will be the method of pain reduction for needle insertion.

Canfield Vectra 3D imaging will be performed at baseline and final visit (Appendix C) with analysis and calculation of volumetric changes performed at baseline and final visit. Photos will also be taken with the Intellistudio at all other visits. Follow up visits will be performed 3 and 5 days after each injection session to assess for side effect and tolerability profile. After the final injection session, additional follow up visits will be performed at days 90 and 180 to assess for efficacy. Subject weight will be recorded at baseline and at end of study.

4. STUDY POPULATION

4.1 NUMBER

Thirty (30), who satisfy all study inclusion criteria, and do not meet exclusion criteria, will be considered for entry into the study.

4.2 Study Endpoints

a. Investigator Evaluations (Appendix A)

- The Clinician-Reported Submental Fat Rating Scale will be completed by a blinded-investigator on Visit Days 1, 30, 60, 90 and 180.

- The Submental Skin Laxity Grade (SMSLG) will be completed by a blinded-investigator on Visit Days 1, 30, 60, 90, and 180.

- A Side Effects Scale will be completed by a blinded-investigator at all follow-up visits. The side effects evaluated will include Edema, Erythema, Tenderness, Erosion/Ulceration, Steroid Atrophy, Induration, and Marginal Mandibular Palsy.

b. Subject Evaluations (Appendix B)

- The Subject Evaluation of Side Effects Scale will be completed at Visits 2 through 11.

- The Subject Satisfaction Rating Scale will be completed by the patient on Visit Day 180.

4.3 INCLUSION CRITERIA

The following are requirements for a potential subject's inclusion into the study:

1. Females or Males in good general health age 18 - 65 years of age
2. Fitzpatrick skin types I-VI
3. Must be willing to give and sign a HIPAA form and informed consent form
4. Must be willing and able to comply with all study protocols and schedules
5. Must have submental fat graded by the investigator as 2 or 3 using the Clinician-Reported Submental Fat Rating Scale (PR-SMFRS)
6. Negative urine pregnancy test prior to each treatment (if applicable)

7. Female patients will be either of **non-childbearing potential** defined as:
    7.1 Having no uterus
    7.2 No menses for at least 12 months.

Or;

(WOCBP) women of childbearing potential must agree to use an effective method of birth control during the course of the study, such as:

    7.3 Oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine device
    7.4 Intrauterine coil
    7.5 Bilateral tubal ligation
    7.6 Barrier method used with an additional form of contraception (e.g., sponge, spermicide or condom)
    7.7 Abstinence (If practicing abstinence must agree to use barrier method described above (7.6) if becomes sexually active)
    7.8 Vasectomized partner (must agree to use barrier method described above (7.6) if becomes sexually active with unvasectomized partner)

8. Males must be willing to be clean shaven for all study visits
9. The patient must have had a stable weight (no fluctuation of >15 pounds in a year), diet, and physical activity for the previous 6 months

4.4EXCLUSION CRITERIA

The following are exclusion criteria for subjects in this study:

1. Pregnancy, currently breast feeding or planning pregnancy for the duration of the trial
2. Any **UNCONTROLLED** systemic disease -a potential patient in whom therapy for a systemic disease is not yet stabilized will not be considered for entry into the study
3. Treatment with botulinum toxin injections in the neck or chin area within 6 months before randomization
4. Any Scars, unshaven hair, tattoos or jewelry on or near the proposed treatment area
5. Significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would preclude enrollment into the study
6. An active dermatitis or open wound in the proposed treatment area
7. An active bacterial, fungal, or viral infection in the proposed treatment area
8. Pre-existing skin condition to the submental region that may confound evaluation or analysis, at investigator discretion
9. Previously treated with subcutaneous sodium deoxycholate to the submental region
10. Previously treated with focused ultrasound, radiofrequency, cryolipolysis or liposuction to the submental region within the previous 6 months
11. Any other laser, light energy device, or chemical peel treatment to the submental region within the previous 3 months
12. Pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia or facial nerve palsy

13. Pre-existing medical condition other than increased submental fat that may result in increased submental fullness such as but not limited to thyroid enlargement, goiter, cervical lymphadenopathy etc., at investigator discretion
14. Must not have a planned fat reduction procedure of any variety to the submental region for the duration of the study
15. Must not have planned significant alterations in diet or physical activity that may result in significant fluctuations in weight
16. Current participation or participation within 30 days prior to the start of this study in a drug or other investigational research study.

5. MATERIALS AND METHODS

5.1 WASHOUT PERIOD

- A patient must not have been previously treated with focused ultrasound, radiofrequency, cryolipolysis or liposuction to the submental region within the previous 6 months.
- The patient must not have had any other laser, light, energy device, or chemical peel treatment to the submental region within the previous 3 months.
- The patient must not have participated in a drug or other investigational research study involving the proposed treatment area within 30 days prior to the start of this study.

6. STUDY PERIOD

Visit 1 (Day 1, Baseline)

- Obtain written Informed Consent and HIPPA
- Record Medical History and Concomitant Medication
- Review Inclusion and Exclusion
- Record Subjects weight
- Randomization
- Pregnancy Test (If applicable)
- Photographs
- Blinded-Investigator Grade (CR-SMFRS) and (SMSLG)
- Treatment #1with either Kybella(TM) alone or varying doses of TMC

Visit 2 (Day 3 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 3 (Day 5 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 4 (Day 30 [+/- 3 days])

- Pregnancy Test (If applicable)
- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects, CR-SMFRS and SMSLG
- Subject Evaluation of Side Effects Scale
- Treatment #2 with either Kybella(TM) alone or varying doses of TMC
- Review Con Meds
- Review Adverse Events

Visit 5 (Day 33 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 6 (Day 35 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 7 (Day 60[+/- 3 days])

- Pregnancy Test (If applicable)
- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects, CR-SMFRS and SMSLG
- Subject Evaluation of Side Effects Scale
- Treatment #3 with either Kybella(TM) alone or varying doses of TMC
- Review Con Meds
- Review Adverse Events

Visit 8 (Day 63 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale

- Review Con Meds
- Review Adverse Events

Visit 9 (Day 65 [+/- 1 day])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 10 (Day 90[+/- 5 days])

- Photographs
- Blinded-Investigator Evaluation of Treatment Side Effects, CR-SMFRS and SMSLG
- Subject Evaluation of Side Effects Scale
- Review Con Meds
- Review Adverse Events

Visit 11 (Day 180[+/- 5 days])

- Photographs
- Record Subject weight
- Blinded-Investigator Evaluation of Treatment Side Effects, CR-SMFRS and SMSLG
- Subject Evaluation of Side Effects Scale
- Subject Satisfaction Rating Scale
- Review Con Meds
- Review Adverse Events

An exit form will be completed at the final examination, or whenever the patient completes or leaves the study for any reason.

6.4 STUDY ENDPOINT CRITERIA

A. Subject Completion of Study

If a subject has completed the final visit (Visit 180) of the study, they are considered to have completed the study.

B. Subject Discontinuation

Each subject may voluntarily discontinue the study at any time they choose. Subjects who cannot complete the study for administrative reasons (e.g., non-compliance, failure to meet visit schedule, etc.) will be discontinued from the study**.** These patients will be asked to return for completion of visit 11**.**

C. Subject Termination

A study subject will be terminated if the subject develops signs or symptoms of moderate to severe irritation or any severe adverse event that may be related to the study protocol. A subject will receive appropriate treatment at the discretion of the investigator and will be terminated

from using the treatment regimen. **Notification of termination** will be clearly documented on the appropriate Case Report Form. **These subjects are considered to have completed the study and will not be replaced.**

D. Study Termination

The investigator with appropriate notification may terminate the study. If, after clinical observations, the investigator feels that it may be unwise to continue the study, he or she may stop the study.

E. Study Completion

The study will be complete when 30 subjects have completed Visit 11 or have been terminated from the study.

7. Adverse Events

7.1 Potential Risks

Possible adverse events from **Kybella(TM)** Injections include:

- Raised red areas at the treatment site(s)
- Bruising
- Itching
- Pain/tenderness
- Edema
- Headache
- Paresthesia
- Ulcerations
- Erythema
- Nausea
- Infection
- Induration
- Skin discoloration
- Foreign body granuloma
- Persistent discoloration
- Scarring
- Dysesthesia
- Post-inflammatory hyperpigmentation
- Numbness of treatment site

The potential risks associated with **Triamcinolone acetate**, a commercially available injectable, include:

- Nausea
- Bloating
- Appetite changes
- Stomach or side pain

- Headache
- Sleep problems (insomnia)
- Acne or other skin changes
- Slow-healing wounds
- Thinning hair
- Bruising or swelling
- Sweating
- Irregular menstrual periods

The potential risks associated with **0.1% lidocaine**, a commercially available injectable, include:

- drowsiness, dizziness;
- feeling hot or cold;
- numbness in places where the medicine is accidentally applied

7.2 Unknown/Unforeseeable Risks

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with Triamcinolone and/or Kybella(TM) injections. Patients will be informed both verbally and in writing in a timely manner of any new information, findings or changes to the way the research will be performed that might influence their willingness to continue their participation in this study.

***Pregnancy/Fetal Risks*:** The effects of Triamcinolone and/or Kybella(TM) injections have not been studied in pregnancy and therefore **may be hazardous.**

If a patient thinks that you may be pregnant or have become pregnant during the study the patient is to inform the study doctor immediately. If a patient becomes pregnant or thinks they may be pregnant, they will be removed from the study and the study doctor will refer the patient to seek obstetric care and may request to track their pregnancy and will report the pregnancy to the IRB.

8. RESPONSIBILITIES OF THE INVESTIGATOR

8.1 Adherence to the Study Protocol

The Investigator must ensure adherence to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: "Guideline for Good Clinical Practice." Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

8.2 Data Handling and Record Keeping

The Investigator must ensure that proper source documentation for all study activities are diligently maintained and securely kept. The Investigator will transfer all relevant data to the

Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. The Investigator will maintain reliable study records and will store study supplies in a secure, locked location. In addition, the Investigator will ensure that all Case Report Forms will be maintained for a period of two years after the conclusion of the study.

9. REGULATORY OBLIGATIONS

9.1 Institutional Review Board

The study protocol, informed consent forms (all versions), and any specific advertising will be submitted to and approved by Independent Investigational Review Board before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to Allergan.

9.2 Protocol

The Investigator signing the protocol signature page will act as the Principal Investigator at this site. Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator's Signature Page. Copies of the IRB approved protocol and informed consents will be provided to Allergan.

9.3 Informed Consent

An Informed Consent (IC) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study patient at screening and before enrollment into the study. The type and method of study, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator of designee. Once the Investigator is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the Informed Consent form. The Investigator or Designee will also sign and date the form. A copy of the IRB approved IC form will also be provided to Allergan.

9.4 Protocol and Informed Consent Changes

Changes to the protocol or Informed Consent form(s) will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and IC amendments/revisions, along with letters noting IRB approval, will be submitted to Allergan, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study.

9.5 Study Monitoring

All monitoring activities are the responsibility of the clinical site. Monitoring is for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The site will be responsible for internal verification of data throughout the study.

10. Confidentiality of Records

Information about the subject's health taken during this study may be used and given to others by the study coordinators, the medical staff, the respective study center and by the subject's doctors and their other health care providers (together, they are called "providers"). These providers may share health information about the subject with the study coordinator. The study coordinator and the providers may share that information with researchers participating in this Study laboratories conducting tests for this Study; a final study report will be shared with the U.S. Food and Drug Administration (FDA); Department of Health and Human Services (DHHS) agencies; Other U.S. and foreign government agencies that watch over quality, safety, and effectiveness of research.

11. Delegation of Investigator Responsibilities

The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant trial-related duties.

12. Direct Access to Source Data/Documents

The Investigator must ensure that institutional regulations, the Informed Consent Form, and the HIPAA Authorization clearly permit study-related monitoring, audits, REB review, and regulatory inspections providing direct access to source data and documents.

13. Adverse Events and Reporting

Serious and/or Adverse Event and Reporting

A ***serious adverse event*** is any untoward medical occurrence, that, at any dose:

- Results in death;
- is life-threatening;
- requires in-subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

An ***unexpected adverse event*** is any treatment-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test product.

Any serious adverse event occurring in this study must be reported to the IRB within 24 hours of awareness of the event. Initial reports must be made by telephone, followed by the completion of a Serious Adverse Event Report and submission by facsimile.

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An ***adverse event*** is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.
All adverse events, including serious and treatment related or unexpected adverse events, must be recorded by the Investigator. In the event of an adverse event or serious adverse event, the physician will provide optimal patient care.

Subjects who have had a serious adverse event must be followed clinically until all parameters have either returned to normal or are otherwise explained. If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

14. DATA ANALYSIS

A blinded investigator will grade the side effects on a scale of 0-4 to assess erythema, edema, tenderness, and erosion/ulceration at each follow-up visit and utilize the Clinician-Reported Submental Fat Rating Scale of 0-4 will be completed on Visit Days 1, 30, 60, 90 and 180.

The subject will evaluate the side effects of bruising, pain, swelling, tolerability, and interference in daily function on a scale of 0-4 at all follow-up visits and complete the Subject Satisfaction Rating Scale of 0-6 on Visit Day 180 (See Appendix B). The investigator will also evaluate the side effects of bruising, pain, swelling, tolerability, and interference in daily function on a scale of 0-4 at all follow up visits.

A p value of 0.05 or less will be considered significant.

15. References

1. Walker, P., J. Fellmann, and P.F. Lizzul, *A phase I safety and pharmacokinetic study of ATX-101: injectable, synthetic deoxycholic acid for submental contouring.* J Drugs Dermatol, 2015. **14**(3): p. 279-87.
2. Walker, P. and D. Lee, *A phase 1 pharmacokinetic study of ATX-101: serum lipids and adipokines following synthetic deoxycholic acid injections.* J Cosmet Dermatol, 2015. **14**(1): p. 33-9.
3. Wollina, U. and A. Goldman, *ATX-101 for reduction of submental fat.* Expert Opin Pharmacother, 2015. **16**(5): p. 755-62.
4. Goldman, M.P., Vanaman Wilson, M.J., Jones, I.T., Bolton JL, Zaleski-Larsen LA, Wu, D.C. A randomized, double-blind comparison trial of subcutaneous sodium deoxycholate injections with or without triamcinolone for reduction of submental fat. [In production].

APPENDIX A

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

Score	SMF Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

Clinician Evaluation: Submental Skin Laxity Grade (SMSLG)

Grade	Laxity Description

1
None
	• No or minimal superficial wrinkling
	• Skin well opposed to deeper neck structures
	• No skin redundancy
	  • No skin draping (vertical folds)
	  • No skin sagging (horizontal folds)

2
Mild
	• Mild superficial wrinkling
	• Skin well opposed to deeper neck structures
	• Minimal skin redundancy
	  • Slight skin draping (vertical folds)
	  • No skin sagging (horizontal folds)

3
Moderate
	• May have moderate superficial wrinkling
	• Skin has mild to moderate separation from deeper neck structures
	• Moderate skin redundancy
	  • Moderate skin draping (vertical folds)
	  • Minimal to mild skin sagging (horizontal folds)

4
Severe
	• Superficial wrinkling present, may be marked
	• Loose skin separated from deeper neck structures
	• Marked skin redundancy
	  • Marked skin draping (vertical folds)
	  • Marked skin sagging (horizontal folds)

Assessment Procedures

The SMSLG is an integration of three features: skin wrinkling, adherence to underlying neck structures (bone and muscle) and redundancy (horizontal and vertical folds). Each grade (none, mild, moderate and severe) defines the maximal allowed limit for skin wrinkling, adherence to underlying structures and redundancy.

SMSLG is based on assessor's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head. The score is determined using the definitions in the rating scale and representative photographs associated with each score. The final determination of the score will be made while the subject's head is in the Frankfort plane posture. The score will be recorded as a whole number.

Clinician Evaluation of Side Effects Scale

	Edema	**Erythema**	**Tenderness**	**Erosion/ Ulceration**	**Steroid Atrophy**	**Induration**	**Marginal Mandibular Palsy**
0	None	None	No tenderness	No erosion/ulceration	None	None	Not Present
1	Very slight (barely perceptible)	Very slight	Very slight	Very slight (barely perceptible)	Very slight (barely perceptible)	Very slight (barely perceptible)	Present
2	Slight	Well-defined	Slight	Slight	Slight	Slight	
3	Moderate (raised approximately 1mm)	Moderate to severe	Moderate	Moderate	Moderate	Moderate	
4	Severe (raised more than 1mm and exceeding beyond area of exposure)	Severe (beet red to slight eschar formation)	Severe	Severe	Severe	Severe	

Appendix B

Subject Evaluation of Side Effects Scale

	Swelling	**Bruising**	**Pain**	**Overall Tolerability**	**Interference in Daily Function**
0	None	None	None	Very Tolerable	None
1	Very slight (barely perceptible)	Very slight	Very slight	Very Slightly Intolerable	Very Slightly Interferes
2	Slight	Slight	Slight	Slightly Intolerable	Slightly Interferes
3	Moderate (raised approximately 1mm)	Moderate to severe	Moderate	Moderately Intolerable	Moderately Interferes
4	Severe (raised more than 1mm and exceeding beyond area of exposure)	Severe	Severe	Severely Intolerable	Severely Interferes

Subject Satisfaction Rating Scale (SSRS)

0 - Extremely dissatisfied

1 - Dissatisfied

2 - Slightly dissatisfied

3 - Neither satisfied nor dissatisfied

4 - Slightly satisfied

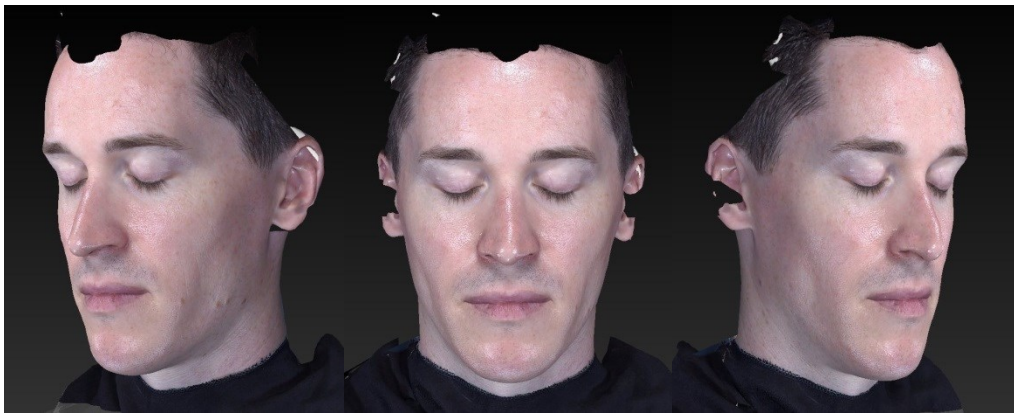
5 - Satisfied

6 - Extremely satisfied

Appendix C

Standardized Vectra Photography

Photos will be taken in a standardized fashion:
*Standard lighting and camera positioning to ensure comparable before and after treatment photographs of the face (VECTRA photos are always done in the same room) approximately 2 feet away from base of system.



Please ensure the following for consistent before and after photos:

1. Subjects removal of makeup and face washed at least 20 minutes prior to having their photograph taken to ensure makeup, lotions and/or sunscreens will not interfere with any evaluations (Males must be clean shaven).
2. Please ensure that subjects jewelry is removed from ears/neck and hair is pushed back away from the face with a black headband (any stray hairs will cause the VECTRA system to crop the face). A black drape will be placed around the subjects neck to ensure photo consistency.
One (1) photo will be taken with eyes closed one (1) image will allow us to capture (5) views (frontal, left oblique, right oblique, left profile and right profile views). The camera we will be using is a Canfield VECTRA. Photos will be captured at ALL visits (on treatment visits day 1, 30 and 60 photos will be captured pre-treatment).