

Study Title: Open, Label, Single-Center study, Evaluating the Efficacy and Safety of JUVÉDERM VOLUMA™ XC for the facial temporal regions

Study #: Voluma Temporal 2014

Sponsor: Baumann Cosmetic & Research Institute

Document: Study Protocol and Statistical Analysis Plan

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STUDY PROTOCOL

TITLE: Open Label, Single-Center study, Evaluating the Efficacy and Safety of JUVÉDERM VOLUMA™ XC for the Facial Temporal Regions

PROTOCOL NO.: Voluma Temporal 2014

PROTOCOL VERSION: August 7, 2015 (version 1.0 Amended Protocol)
Correlates with ICF version 3 dated 08/07/15

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BACKGROUND

Volume deficit in the temporal area (the side of the forehead) of the face is a common sign of aging. It can occur in younger people as well that have a low body fat percentage and can make them look older than their age. Most individuals who start developing age-related volume deficit in the temple area are those over 30 years of age.

JUVÉDERM VOLUMA™ XC is a dermal filler, which was FDA-approved in October 2013 for the improvement and correction of age-related volume deficit in the mid-face area. JUVÉDERM VOLUMA™ XC is a gel implant composed of 20 mg/mL hyaluronic acid (HA) formulation, produced by *Streptococcus equi* bacteria, and 0.3 w/w lidocaine. JUVÉDERM VOLUMA™ XC is a clear, sterile, and biodegradable gel indicated for subcutaneous and/or supraperiosteal injection.

History of use of fillers in the temple area-

Temples have been treated with various filler substances including fatⁱ, HAⁱⁱ, and polylactic acid for over a decade.ⁱⁱⁱ Dermatologists and aesthetic surgeons lecture about using HA fillers, including VOLUMA™, in the temples at international meetings. “How to” injection videos appear on Youtube.^{iv} Aesthetic physicians frequently teach these injection techniques and discuss them on panels.^v Allergan, the company that sells VOLUMA™, reports that approximately 8 % of VOLUMA™ is used off-label in the temples.^{vi} Unfortunately, there is limited standardized data on the safety of hyaluronic acid temple injections and no guidance on injection technique. Dr. Baumann (The PI in this study) has treated approximately 40 patients in the temple with VOLUMA™, and approximately 80 in the temple, with JUVÉDERM over the last 2 years with the only side effect being mild and temporary swelling and bruising.

Moradi^{vii} did an Investigational Device Exemption (IDE) approved-study evaluating a HA product known as Restylane® for use in the temple area. He reported no serious adverse events and nor occurrences of visual side effects. Dr. Moradi reports that he has treated “a few thousand” patients in the temple and has not seen severe adverse events nor visual disturbances in his patients.^{viii} Dr. Moradi’s technique^{ix} to inject the temple area is similar to the technique that will be used in this study. (see Figure 1). There are no published studies on the use of JUVÉDERM VOLUMA™ XC in the temples.

Anatomy-

The temporal zone is bordered by the zygomatic arch inferiorly, the orbital bone anteriorly and the temporal line of the skull superficially. HA fillers are injected superficial to the temporoparietal fascia.^x

Figure 1- Anatomy of temporal area and plane of injection

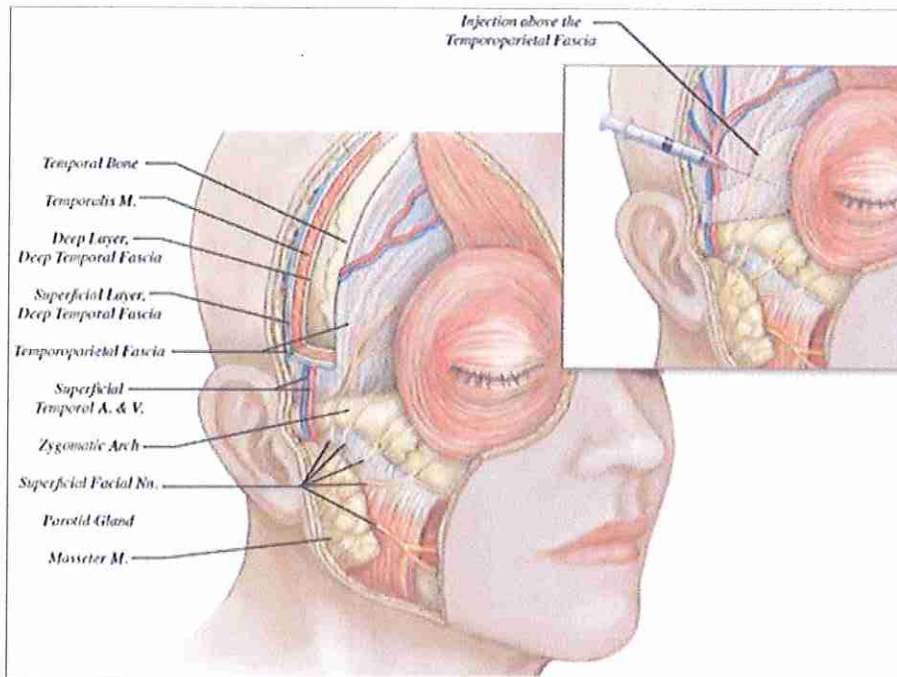
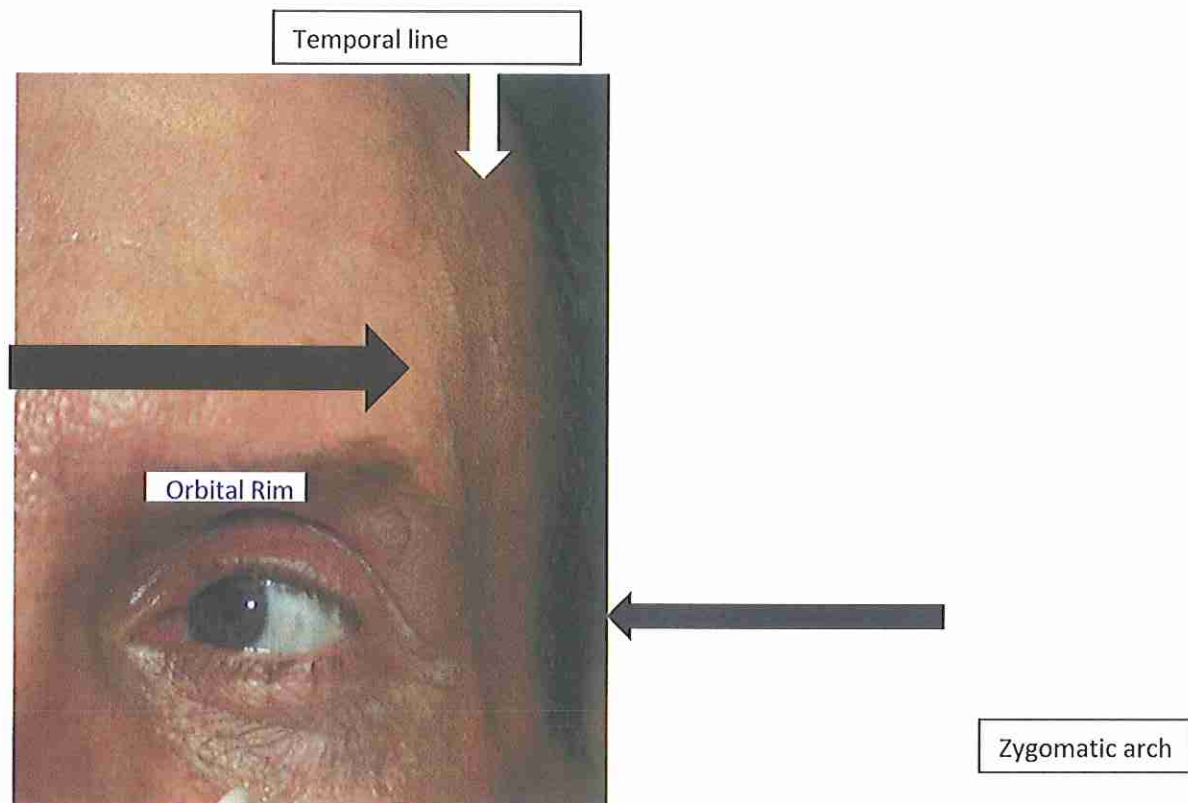


Figure 2- Temporal region



Injection technique-

Figure 3- The injection technique for this trial will begin with careful palpation of the temple area for aberrant arterial vessels. Subjects with any palpable arterials in the area of injection will be excluded from the study.



Figure 4 - The injection will be oriented at an 85 to 95 degree angle to the plane of the temple.

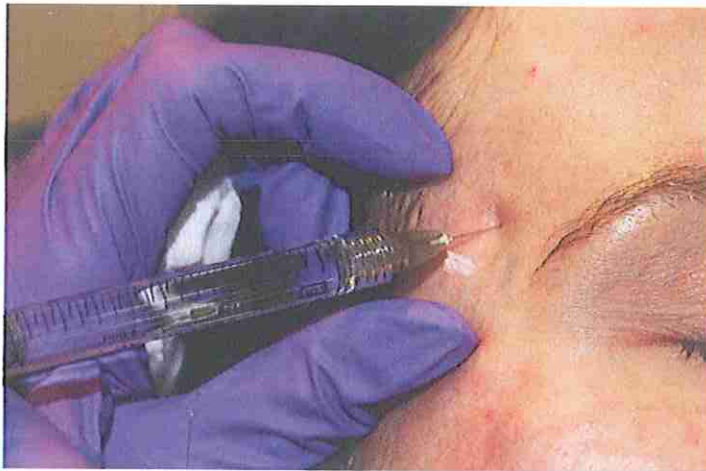


Figure 5- The needle is very slowly advanced until it reaches the periosteum. If any resistance is felt, the needle is withdrawn and re-oriented. The plane of injections is superficial to the temporoparietal fascia.

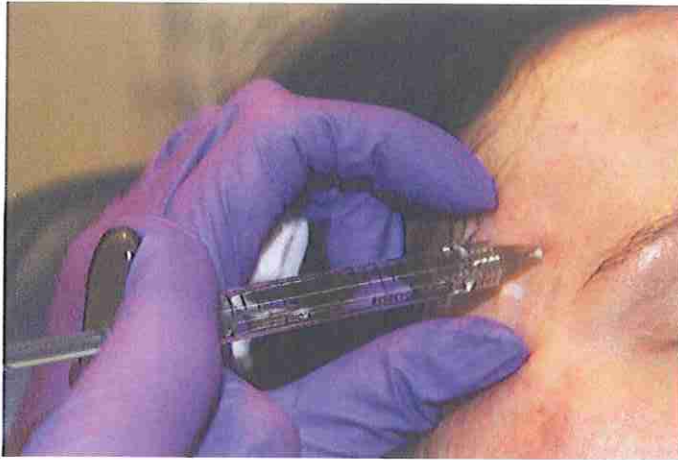


Figure 6- Once the periosteum has been reached without any resistance, the needle is withdrawn 1-2 mm away from the bone. The needle is aspirated. If no blood is in the needle, a small amount of HA is injected slowly (0.01cc). Then the needle is slowly retracted with 0.01cc aliquots injected along the way until the desired correction is achieved.

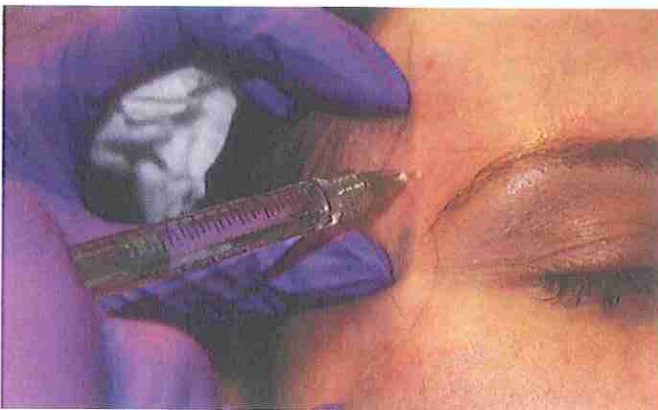


Figure 7- Proper injection technique results in minimal bleeding, swelling or bruising. This photo is taken immediately after injection.



Adverse events-

Common adverse events-

Bruising, erythema, tenderness, lumps and bumps, and swelling are the most common adverse events seen with HA filler injections. These can be minimized by avoiding ibuprofen, aspirin, and omega 3 fatty acids for 10 days prior to injection, and by minimizing exercise and heat exposure for 24 hours after injection. The temple area tends to have less bruising and swelling than other areas such as the nasolabial folds and the lips.^{xi}

Uncommon adverse events-

Arterial occlusion can occur if the HA filler is injected intra-arterially, but this occurs in less than 2 % of patients.^{xii} This is most often seen in injections in the nasolabial and glabellar area. The PI has never seen this occur in the temporal area. Arterial occlusion is heralded by intense pain in the distribution of the branches of the affected artery and a reticulated vascular pattern following the distribution of the affected artery and its anastomoses. The treatment consists of topical nitropaste, and hyaluronidase injection in the area of suspected arterial blockage. If the arterial occlusion results in blockage of a branch of the ophthalmic artery, timolol 0.5% is placed in the affected eye to lower intraocular pressure (IOP) to allow increased perfusion to the ophthalmic arteries. Massage of the globe will also decrease IOP.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

Temple injections have rarely been associated with visual disturbances and blindness. Most of these have been reported with the use of fat or with HA treated in the glabellar or nasolabial fold area. Yanyuan et al.^{xiii} reported 13 cases of visual disturbance in Beijing China after facial filler injections; 4 of these were treated in the temple area with fat injections and none were treated with HA in the temple area. Park et al.^{xiv} reported 12 patients that developed retinal artery occlusion after facial filler injections; 4 of these were treated with HA, but none in the temple. (The glabella and nasolabial folds were treated). Lazzeri et al.^{xv} reviewed twenty- nine articles that described 32 patients that developed blindness after facial injections. Only 2 of these were treated with HA and neither was treated in the temple (The glabella, cheek and nasal tip were treated.) In all reports, eye pain occurred immediately after injection and was often accompanied by dizziness and nausea. Blindness has been reported to the FDA as an adverse event to HA fillers injected near the eye.^{xvi} For this reason, patients will be closely monitored post injection and visual assessments will be conducted at baseline and at the end of each injection visit using the “Vision Test” application on the iPad.

These unanticipated AEs will be reported to the FDA and IRB no later than 10 working days after the UADE onset.

If any of these UADE events occur, enrollment of this trial will be halted immediately. The patient will be sent to Bascom Palmer Eye Institute for Evaluation.

- Blindness
- Loss of visual field noted on exam by PI

Loss of Visual Acuity confirmed by iPad app or Snellen Visual Chart Mitigation of Risk

When reviewing the literature about visual disturbances caused by facial injections, it appears that the highest risk areas are injections of the glabella and nasolabial fold areas, which will not be treated in this study. Loss of visual acuity from injections in the temporal area likely occurs from retrograde embolism of ophthalmic arterial system. Multiple authors^{xvii} have discussed the ways of preventing retrograde embolism and mitigating the risk of visual disturbances and they include:

- 1) Aspiration prior to injection
- 2) Injecting slowly and with minimal pressure
- 3) Stop injection if resistance is felt
- 4) Fractionated incremental injections avoiding bolus injections
- 5) Limited total volume of substance injected
- 6) Use of small syringes (1cc or less) to minimize injection pressure
- 7) Use of smaller needles (27.5 or smaller) to slow injection speed

These precautions will be used in this study.

Vision Assessments:

An application on the iPad called “vision test” will be used to assess visual acuity. The “visual acuity” tab will be used. If for some reason the application is unavailable, a Snellen vision test will be used with the patient standing 20 feet away from the chart and one eye covered. If the iPad app is used, the iPad or iPhone will be held at arm’s length and one eye will be covered according to the application instructions. The iPad program has a disclaimer that it does not replace an eye exam from a doctor, but this test will be used to track changes from baseline so it will be sensitive enough to suit the purpose of identifying a visual deficit induced by filler which is more likely to be manifested as a visual field defect than a change in visual acuity.

Treatment Plan for Unexpected Adverse Events

Arterial occlusion with no visual disturbance

All subjects will remain in the clinic for observation for 15 minutes after injections. The study team will be instructed to watch for the signs of arterial occlusion, which include intense skin pain, blanching of the skin, and a reticulated vascular pattern in the area of injection. This usually occurs within 15 minutes of treatment. Subjects will be instructed to call the office if they experience moderate to severe pain or skin blanching. If signs of arterial occlusion occur, the treatment plan is as follows:

- 1) Injections of hyaluronidase into the area that HA was placed prior to the symptoms
- 2) Use of anticoagulative therapy, i.e. aspirin, ibuprofen
- 3) Application of nitropaste to the treated area to encourage vasodilation for 10 minutes
- 4) Follow up as determined necessary by the investigator

Treatment Plan for Unanticipated Adverse Device Effect

Visual Disturbance:

These unanticipated AEs will be reported to the FDA and IRB no later than 10 working days after the UADE onset. If any of these UADE events occur, enrollment of this trial will be halted immediately. The patient will be sent to Bascom Palmer Eye Institute for Evaluation.

In all of the reports about facial fillers causing visual acuity including those reported about fat and silicone injections, the patients reported eye pain immediately after injection. Many also reported dizziness and nausea. If these symptoms are noted then authors^{xviii} have suggested the following treatments:

- 1) Lowering of intraocular pressure with
 - a. Use of one drop of timolol 0.5% in the affected eye
 - b. Globe massage
- 2) Injections of hyaluronidase into the area that HA was placed prior to the symptoms
- 3) Referral to Dr. Wendy Lee (oculoplastic surgeon) or colleague at the Bascom Palmer Eye Institute ER which is about 10 minutes away.

Use of hyaluronidase

Hyaluronic acid is rapidly dissolved by hyaluronidase injections. It is injected in the site of HA placement and can mitigate vascular occlusion when placed near- rather than in- the artery. Studies^{xix} have shown that cross-linked HA is susceptible to hydrolysis by hyaluronidase when contained within the intact facial artery in a cadaver model, indicating that direct intra-arterial injection of hyaluronidase is not necessary to help restore the circulation of ischemic tissues. Multiple authors^{xx} recommend hyaluronidase injections to treat vascular occlusion after HA fillers. In the reports that review the cases of HA facial injections leading to blindness, hyaluronidase was not used in any of the patients. It is unknown if use of hyaluronidase would have improved outcomes, but the common belief is that it would have improve outcomes if it had been used.

Hyaluronidase will be injected into the temple area in the area of Voluma injection or ischemia. 0.5- 1.0 cc will be used per ischemic site. Only the affected areas will be treated. After injection of hyaluronidase, the injected area will be massaged. If the filler has migrated to a distant location, the hyaluronidase will be injected in the area where the vessel appears to be ischemic and the surrounding vascular area will be massaged for 2 minutes to encourage penetration of the hyaluronidase into the vessel. A warm compress may be used to increase blood flow to the area. Nitropaste should only be used in patients with no history of heart disease. After application of nitropaste, if the patient feels dizzy, vital signs should be taken and the patient should be given juice. If blood pressure drops below 90/60, the nitropaste should be removed immediately and the patient's blood pressure should be closely monitored. If it does not rise in 5 minutes and the patient continues to feel dizzy or unwell, 911 will be called. If visual disturbances persist- the patient will be transferred to the Bascom Palmer ER. If the ischemia persists, the PI will decide if the patient needs to go to the ER or if the ischemia is mild (and not affecting vision) the patient will be placed on one aspirin every 4 hours, and warm compresses and seen within 18 hours by the PI to check for revascularization. NOTE: THE PATIENT WILL NOT BE PLACED ON ASPIRIN IF A VISUAL DISTURBANCE OCCURS IN CASE SURGICAL INTERVENTION IS NECESSARY.

Summary of background

Hyaluronic acid injections have been used safely in the temples in many patients by many physicians, including Dr. Baumann. Risks, however, do exist but do not seem to be as common as in patients treated with HA fillers in the nasolabial folds. Clinical studies using JUVÉDERM VOLUMA™ XC have demonstrated efficacy, safety and duration of the dermal filler in the mid-facial area. Many doctors are advocating the use of VOLUMA™ in the temples, therefore, there is a need to conduct clinical studies of augmentation in the temporal regions of the face in order to develop an approach that mitigates risk and management of adverse events. The purpose of this study is to evaluate efficacy and safety using a cautious injection technique with a clear plan for recording and treating adverse events.

STUDY DESIGN

CLINICAL HYPOTHESIS

The use of JUVÉDERM VOLUMA™ XC in the temporal areas of the face will show an improvement of ≥ 1 grade as compared to pre-treatment by a trained investigator and the subject's satisfaction with their appearance will improve by ≥ 1 grade as compared to pre-treatment scores. The investigator will assess the treated patients using the Temporal Fossa Rating scale (see Appendix A). The risk of mild adverse side effects is expected to be less than 5 percent, with no expected incidences of moderate to severe adverse events.

DESIGN

This study will be an open label, single center study, composed of a treating investigator and 30 subjects.

30 subjects will be injected with JUVÉDERM VOLUMA™ XC to their right and left facial temporal regions at the baseline visit. Subjects will receive up to 4, 1mL syringes of JUVÉDERM VOLUMA™ XC for their initial injection and a maximum of 6, 1mL syringes of JUVÉDERM VOLUMA™ XC for the study. Subjects will undergo one touch-up injection approximately 2 weeks post initial treatment, and will continue to be evaluated at month 1, month 3, and month 6. All treated subjects with the study product may exit the trial at month 6.

The baseline visit will consist of completion of the informed consent, medical history, concomitant medications and procedures, pregnancy screen via urine pregnancy test (females of child bearing potential only), and evaluation of both inclusion and exclusion criteria. Upon determination of qualification for study participation, subject's assessments (see Appendices C and E), investigator assessments, and photography will be completed. Subjects will proceed to

the initial injection, if no wash out is required. The treating investigator will inject a maximum of 4, 1mL syringes of JUVÉDERM VOLUMA™ XC into the subject's facial temporal area (see Figure 1). Treating investigator may use ice packs to diminish swelling prior to; or post injection. After the initial treatment, subjects will receive a treatment diary (see Appendix F) spanning from initial treatment to touch up treatment in order to monitor treatment site, patient reaction to study product and comments. The diary will be completed daily post-injection for 14 days post each injection. Treated subjects will undergo photos post-treatment as well. Subjects will receive a phone call three days post-treatment for a follow up.

Subjects will return two weeks post initial injection for a possible touch up. The treating investigator will determine whether a touch up treatment is necessary. Prior to treatment, subject diaries will be collected and reviewed. All AEs/SAEs, changes in concomitant medications and concomitant procedures will be documented. Per the treating investigator's discretion, the subject may or may not qualify for a touch up. The subject will undergo photos. If treatment is necessary, subject will undergo same procedures as the initial injection visit. Post-treatment photos will be taken and subject will receive another diary and 3 day post injection phone call.

Follow up visits will consist of documentation of AEs/SAEs, changes in concomitant medications and changes in concomitant procedures at the beginning of the visit. The investigator and subject will complete their respective assessments and photos will be taken.

ENDPOINTS

The primary endpoint of this study is to determine the efficacy and safety of JUVÉDERM VOLUMA™ XC when used in the facial temporal regions based on the change in the score of the investigator's Temporal Fossa Scale. The secondary endpoints are the 2-point change in the scale of Subject's Satisfaction of Facial Appearance and Investigator's Satisfaction Scale.

STUDY PROCEDURES

PROCESS OF CONSENT/SUBJECT COMPREHENSION

All subjects will first be given the informed consent to read over by themselves. One of the investigators and a qualified member of the research staff will then review the informed consent with the prospective subject. The subject will then be allowed ample time to ask any questions about the study, and all questions will be answered. The person obtaining consent will ensure that the subject has a clear understanding of the study procedures. Once all questions are answered and the subject chooses to enroll in the study, the subject will be asked to sign the IRB-approved informed consent document. No study procedures will be conducted prior to signing the informed consent. Each subject will receive a copy of their signed informed consent for their information.

CONSENT FORMS

IRB approval will be obtained prior to use of the consent form.

INCLUSION CRITERIA

Subjects must meet the following inclusion criteria to be enrolled in this study:

Be willing and able to read and sign the informed consent and other study documents.

Male or female, 35- 75 years old.
Willing and able to read and sign the informed consent and other study documents.
Treating investigator's score of 3, 4, or 5 on the Temporal Fossa Rating Scale.
Written informed consent has been obtained prior to any study-related procedures.
Written Authorization for Use and Release of Health and Research Study Information has been signed.
Ability to follow study instructions and complete study assessment tools including the subject diary
Female patients of childbearing potential must have a negative urine pregnancy test result and not be lactating.
Likely to complete all required visits with no plans to move from Miami in the next 12 months
Agree to not undergo other treatments or cosmetic procedures in the treatment area during the study such as facial laser treatments, botulinum toxin, hyaluronic acid injections, subcutaneous fat injections, any other permanent or semi-permanent facial fillers.

EXCLUSION CRITERIA

Subjects will be excluded from this study if they do not meet the specific inclusion criteria or if they have:

Any uncontrolled systemic disease
History of any of the following conditions: vision loss not corrected by lenses or LASIX surgery; glaucoma, retinal detachment, macular degeneration, history of multiple sclerosis or optic neuritis, or any uncontrolled eye disease.
Have a history of severe allergic/anaphylactic reactions or multiple allergies.
Conditions within the treatment area including acne, scarring, acute lupus erythematosus, dermatitis, or melasma.
Females planning to become pregnant, are pregnant, or are breast-feeding.
History or current evidence of drug or alcohol abuse within 12 months prior to the screening visit

Have severe thin skin, in the treatment area as determined by the PI.
Have undergone temporary facial dermal filler injections with hyaluronic acid-based fillers within 12 months in the treatment area. Have had neuromodulator injections, mesotherapy, or resurfacing (laser or other ablative or non-ablative procedures) within 5 months prior to entry in the study or be planning to undergo any of these procedures at any time during the study.
Have undergone facial plastic surgery (with the exception of rhinoplasty or a brow lift), tissue grafting, or tissue augmentation with silicone, fat, or other permanent or semi-permanent dermal fillers or be planning to undergo any of these procedures affecting the treatment area, at any time during the study.
Unwilling to undergo injections in the temple area.
Have a history of migraines or frequent headaches, as determined by the PI.
Have blindness or partial vision loss in either eye.
Have received any other therapy, which, in the opinion of the investigator, could interfere with safety or efficacy evaluations.
Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.
Patient who has a condition or is in a situation that, in the investigator's opinion, may put the patient at significant risk, or may significantly interfere with the patient's participation in the study.
Have received anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (NSAIDs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time from 10 days pre- to 3 days post injection. A wash out period of 10 days is allowed.
Have undergone immunosuppressive therapy, chemotherapy, biologics or systemic corticosteroids within 3 months prior to each study visit.

DRUG DISPENSING

A total of 30 subjects will be treated with JUVÉDERM VOLUMA™ XC.

The JUVÉDERM VOLUMA™ XC study products will be placed in a locked temperature monitored study cabinet for the duration of the trial. On treatment day, Baseline/Visit 1, subjects will receive a treatment of a maximum of 4 total, 1 mL syringes of JUVÉDERM VOLUMA™ XC. Maximum drug allotted per subject including initial treatment and touch up treatment will be 6, 1 mL syringes.

SCREENING/ VISIT 0

Before enrollment into the study, subjects must sign the informed consent form and the HIPAA form. Once the subject has signed the informed consent and HIPAA, the following procedures will be conducted:

- Inclusion and exclusion criteria will be reviewed.
- Demographic information will be recorded.
- Medical/surgical history and concomitant medications will be obtained from the subject and recorded.
- Physical exam will be performed including vital signs and visual assessments
- The investigator will rate the subject's facial temporal areas using a scale with photo guide as follows (1 = Convexity, 2 = Flat, 3 = Mild Concavity, 4 = Moderate Concavity, and 5 =Severe Concavity). This scale will be referred to as the Frontal Temporal Fossa Rating Scale.
- Inclusion and exclusion criteria will be reconfirmed
- Subjects who do not meet the inclusion and exclusion criteria will be marked as screen failures
- Enrolled subjects will continue with the baseline visit or enter a washout period for 10 days if needed (ex. use of anticoagulants) and then continue to baseline visit.

VISIT 1/DAY 0/ Baseline

Subjects who meet the criteria to enter into the study and who score a 3, 4, or 5 on the Temporal Fossa Rating by the investigator's assessments qualify for injection. Subjects may have the baseline visit the same day as the screening visit.

- If the baseline visit is a different day than screening visit, investigator will again review inclusion and exclusion criteria to ensure that subject is still eligible.
- Baseline photos using the Canfield VISIA Camera System will be taken.
- A urine pregnancy test will be completed for women of childbearing potential.
- Subject will complete their self-assessments.
- The subject will be administered the "Vision Test" on the iPad.
- If the subject qualifies for injection, the following procedures will also be conducted.
- Subjects will receive up to 4, 1 mL syringes of JUVÉDERM VOLUMA™ XC, by the Treating Investigator.
 - Subjects may receive ice packs to reduce swelling and bruising post-treatment. Any actions taken will be documented.
 - Monitor treatment subject for at least 15 minutes post injection.

- Post injection, the subject will be again be administered the “Vision Test” on the iPad
- Physical exam will include a visual field analysis assessed as follows:
 - The examiner should be nose to nose with the patient, separated by approximately 8 to 12 inches.
 - Each eye is checked separately. The examiner closes one eye and the patient closes the one opposite. The open eyes should then be staring directly at one another.
 - The examiner should move their hand out towards the periphery of his/her visual field on the side where the eyes are open. The finger should be equidistant from both persons.
 - The examiner should then move the wiggling finger in towards them, along an imaginary line drawn between the two persons. The patient and examiner should detect the finger at more or less the same time.
 - The finger is then moved out to the diagonal corners of the field and moved inwards from each of these directions. Testing is then done starting at a point in front of the closed eyes. The wiggling finger is moved towards the open eyes.
 - The other eye is then tested
- A diary will be dispensed for subjects to record any reaction to study product or comments prior to Visit 2. Subjects will be instructed on diary completion
- The treating investigator will review the Vision Test results, compare to baseline and examine the patient prior to dismissal.
- Subjects will be instructed to contact the office if they experience any unexpected side effects including intense pain of the skin, eye pain, or visual disturbances. In case of an emergency, subjects will be instructed to call 911.

DAY 3 POST INITIAL TREATMENT FOLLOW UP PHONE CALL (±1 DAY)

- Subjects who received treatment will be called and questioned about AEs, SAEs, changes in concomitant medications, or concomitant procedures.
- Subjects will be reminded to complete study diary and call the office if any issues may arise.
- Subjects will be reminded of exclusionary concomitant medications/procedures.

VISIT 2/WEEK 2 FOLLOW UP/ POSSIBLE TOUCH UP/ (±3 DAYS)

Treated subjects will come for a follow up at week 2 (±3 days) after initial injection. The following procedures will be conducted:

- Study diary will be collected and reviewed.
- Changes in adverse events and concomitant medications/procedures will be documented.
- Subject’s vitals and weight will be documented.
- The Vision Test will be administered on the iPad.

- Physical exam will include a visual field analysis
- Photos using the Canfield VISIA camera will be taken.
- Treatment subjects will complete the assessments.
- If Treating Investigator determines a touch-up is indicated, then perform the following:
 - Subjects' vital signs will be taken
 - Touch up will be performed by the treating investigator. The combined initial treatment and touch up treatment drug total per subject will not exceed 6cc (six 1 mL syringes) of JUVÉDERM VOLUMA™ XC.
- Subjects may receive ice packs to reduce swelling and bruising post-treatment. Any actions taken will be documented.
- Monitor treatment subject for at least 15 minutes post injection.
- The Treating Investigator will review the Vision Test results, visual field exam and compare to baseline results and examine the patient prior to dismissal.
- A diary will be dispensed to subjects to record any reaction to study product or comments for collection at the month 1 visit.

Subjects will be scheduled for the next visit and reminded to complete their diaries and return them at the next visit

If subjects report any unexpected side effects at this visit or at any time after injection, they will be scheduled to come to the office for evaluation.

DAY 3 POST TOUCH-UP TREATMENT FOLLOW UP PHONE CALL (±1 DAY)

- Subjects will be called and questioned about AEs, SAEs, changes in concomitant medications, or concomitant procedures.
- Subjects will be reminded to complete study diary and call the office if any issues may arise.
- Subjects will be reminded of exclusionary concomitant medications and procedures.

VISIT3 /MONTH 1(±7 DAYS)

At this visit(s), the following procedures will be conducted:

- Changes in adverse events and concomitant medications will be documented.
- Subject's vitals and weight will be documented.
- Photos using the VISIA will be taken.
- Subject will complete the following assessments:
 - Subject's Satisfaction with Temple Appearance
 - Subject Self-Perception of Age
- Treating investigator will rate the subject's treatment area using the Temporal Fossa Rating Scale, Investigator's Satisfaction with the Appearance of the Temporal Regions, and the Subject Global Aesthetic Improvement Scale (GAIS)
- Subjects will be scheduled for next visit.

- Subjects will be scheduled for next visit.

VISITS 4,5,6 /MONTH 3,6,and 9 (±7 DAYS)

At this visit, the following procedures will be conducted:

- Changes in adverse events and concomitant medications will be documented.
- Subject's vitals and weight will be documented.
- Photos using the VISIA will be taken.
- Subject will complete the following assessments:
 - Subject's Satisfaction with Temple Appearance
 - Subject Self-Perception of Age
- Treating investigator will rate the subject's treatment area using the Temporal Fossa Rating Scale, Investigator's Satisfaction with the Appearance of the Temporal Regions, and the Subject Global Aesthetic Improvement Scale (GAIS)
- Subjects will be scheduled for next visit.

If subjects report any unexpected side effects at these visits or at any time after injection, they will be scheduled to come to the office for evaluation.

VISIT 7/MONTH 12- STUDY EXIT (±7 DAYS)

At this visit, the following procedures will be conducted:

- Changes in adverse events and concomitant medications will be documented.
- Subject's vitals and weight will be documented.
- Photos using the VISIA will be taken.
- Subject will complete the following assessments:
 - Subject's Satisfaction with Temple Appearance
 - Subject Self-Perception of Age
- Treating investigator will rate the subject's treatment area using the Temporal Fossa Rating Scale, Investigator's Satisfaction with the Appearance of the Temporal Regions, and the Subject Global Aesthetic Improvement Scale (GAIS)
- Subjects will exit the study

DATA ANALYSIS, MONITORING, AND STORAGE

Data analysis and monitoring will be performed on safety and efficacy of all subjects who are randomized into the study. Descriptive statistical methods will be used to summarize subject population and demographic characteristics.

All study-related documents, such as correspondence, regulatory documents, consent forms and source documents will be kept confidential. Only authorized research staff will have access to the documentation, which will be stored in a secure area.

ANTICIPATED ADVERSE EVENTS

Any adverse events that occur during the study that may or may not have a relationship with the study treatment must be reported for all subjects. Some adverse events that have been observed or reported after JUVÉDERM VOLUMA™ XC injections consist of the following:

- Itching
- Redness
- Pain
- Lumps/Bumps
- Infection at injection site
- Allergic reaction
- Unsatisfactory/unsymmetrical result
- Nausea
- Headache
- Blood vessel injury
- Skin ulceration or necrosis
- Telangiectasia
- Vision disturbances as serious as blindness

In addition, the following adverse reactions have been observed at the injection site:

- Redness
- Nodules
- Bruising
- Pain
- Inflammation
- Numbness
- Needle marks
- Infection

All adverse events will be recorded in source (see Appendix F) and will be assessed by the principal investigator. The investigator will document any actions required. The principal investigator will also determine the severity and causality for adverse events. All adverse events which remain “ongoing” at the exit visit will be followed-up as appropriate.

Information about adverse events reported in the study will be aggregated and summarized. Adverse events information will be collected via subject report and investigator observation at each visit and monitored by the investigator. The rates of adverse events in each treatment group will be compared. An investigator will determine causality of adverse events, and all adverse events will be reported to the Institutional Review Board (IRB) according to policies and procedures.

SERIOUS ADVERSE EVENTS

A serious adverse event will consist of any medical condition with the following outcomes:

- Resulted in death
- Life-threatening
- Resulted in hospitalization or prolongation of hospitalization
- Resulted in a persistent or significant disability or incapacity
- Resulted in congenital anomaly or birth defect
- Important medical events or conditions such as cancer adverse events and spontaneous or nonspontaneous abortions, or others that may require medical intervention

Serious adverse events will be reported to the product manufacturer and the IRB in the time periods required by regulations and policies and procedures.

PHOTOGRAPHY

Facial photographs at 45° (right and left temporal regions) and 90° (front face) will be captured using a Canfield Imaging System, VISIA-CR 2.0, with Mirror software. Patients will be notified in their informed consent form about the collection and use of their photographs for research purposes. Photographs may be used for regulatory purposes, scientific or educational presentations, and publications. Subjects not willing to allow the research team and sponsor to use their facial photographs as described in their informed consent will be excluded from the trial. Photographs will be taken before and after JUVÉDERM VOLUMA™ XC injections and at each consequent follow-up visits.

RISK/BENEFIT ASSESSMENT

RISK CATEGORY

Moderate risk

PROTECTION AGAINST RISKS

The following measures have been taken to protect subjects against risks:

- Strict inclusion and exclusion criteria.
- Monitoring of all subjects for at least 15 minutes after injection.
- Follow up phone calls 3 days after treatment and a follow up visit 2 weeks after initial injection.
- Voluntary participation in the study and allowing subjects to withdraw at any time.

- Participation may be stopped at any time by an investigator if it is necessary for the health or safety of subjects.
- All subjects are encouraged to call the site at any time with questions, or if they experience any adverse effects from treatment. Each study subject will be given information regarding emergency contacts. This information will contain numbers for the research staff and the doctor.
- A licensed physician will administer all treatments with experience injecting hyaluronic acid for temporal deficit.
- Injection technique will be used as discussed in the “mitigation of risk” section.
- Serious device related adverse events will be handled in the manner discussed in the “Mitigation of risk section. The PI has experience dealing with the uncommon adverse events of vascular occlusion because many of these patient have been referred to her and treated successfully by her. None of them have had long term effects.

BENEFITS

Subjects may observe a temporary improvement in the appearance of the volume deficit in the facial temporal area. Subjects may not benefit from their participation in the study and may not observe a desired cosmetic result.

COSTS TO THE SUBJECT

Study treatments will be provided free of charge. Subjects will be paid \$40 for each completed study visit. Subjects will be responsible for opportunity costs related to their participation, such as transportation and parking fees.

ALTERNATIVES TO PARTICIPATION

Subjects do not have to participate in this study to achieve correction of their facial deficit. Subjects may receive treatment with another FDA-approved hyaluronic acid, semi-permanent, or permanent filler. Other treatment methods may include surgical treatments. Subjects may also choose not to treat their facial deficit. These treatment options will be discussed with each subject.

SUBJECT DISCONTINUATION

The investigator may discontinue an individual study subject from the study at any time. Subjects may also withdraw from the study at any time. If a subject decides to withdraw, he/she will be encouraged to return to the study site for an exit visit. If a subject withdraws or is discontinued from the study before completion, every effort will be made to complete the scheduled visits.

If a subject suffers an adverse event or develops a concurrent illness that, in the opinion of the investigator, presents an unacceptable consequence or risk to the subject continuation in the study, the investigator may discontinue the subject from the study. The subject may be followed until the resolution or stabilization of the adverse event.

A subject may also be discontinued from the study for a failure to return for follow-up visits. Reasonable efforts will be made to encourage subjects to comply with study requirements, including returning for follow-up visits.

APPENDICES

Appendix A

Frontal Temporal Fossa Rating Scale

Please grade severity of the temporal line of the frontal bone (TLFB) using the Frontal Temporal Fossa Rating Scale: (these will have a picture assigned to each score. Pictures are currently being collected).

Score (Circle One)	Description	
5	Severe Concavity	Severe recess of the tissue below the temporal line of the frontal bone; TLFB very prominent
4	Moderate Concavity	Moderate recess of the tissue below the place of the temporal line of the frontal bone; easily visualized; TLFB mildly prominent
3	Mild Concavity	Mild recess of the tissue below the plane of temporal line of the frontal bone; TLFB visible
2	Flat	Temporal line of the frontal bone not visible or slightly visible
1	Convexity	Tissue extends beyond the plane of the temporal line of the frontal bone (TLFB); TLFB not visible

Appendix B

Investigator's Satisfaction with the Appearance of the Temporal Regions

Please grade the level of satisfaction with the current appearance of the temporal region making certain that you are looking at the patient's right side and not the investigator's right side.

Patient's Right Side

Patient's Left Side

Score	Grade		Score	Grade
-3	Very Dissatisfied		-3	Very Dissatisfied
-2	Moderately Dissatisfied		-2	Moderately Dissatisfied
-1	Somewhat Dissatisfied		-1	Somewhat Dissatisfied
0	Neither Satisfied nor Dissatisfied		0	Neither Satisfied nor Dissatisfied
1	Somewhat Satisfied		1	Somewhat Satisfied
2	Moderately Satisfied		2	Moderately Satisfied
3	Very Satisfied		3	Very Satisfied

Appendix C

Subject's Satisfaction with Temple Appearance

Patient's Right Side

Patient's Left Side

Score	Grade		Score	Grade
-3	Very Dissatisfied		-3	Very Dissatisfied
-2	Moderately Dissatisfied		-2	Moderately Dissatisfied
-1	Somewhat Dissatisfied		-1	Somewhat Dissatisfied
0	Neither Satisfied nor Dissatisfied		0	Neither Satisfied nor Dissatisfied
1	Somewhat Satisfied		1	Somewhat Satisfied
2	Moderately Satisfied		2	Moderately Satisfied
3	Very Satisfied		3	Very Satisfied

Appendix D

Subject Global Aesthetic Improvement Scale (GAIS)

Please grade the improvement of the temporal line of the frontal bone (TLFB) using the global aesthetic improvement scale:

Score (Circle one)	Grade	Description
3	Very Much Improved	Very marked improvement in appearance
2	Much Improved	Marked improvement in appearance
1	Improved	Improvement in appearance, but a touch-up or retreatment is indicated
0	No Change	The appearance is essentially the same as the original condition
-1	Worse	The appearance is worse than the original condition
-2	Much Worse	The appearance is much worse than the original condition
-3	Very Much Worse	The appearance is very much worse than the original condition

Appendix E

Subject Self-Perception of Age

What is my perception of age when I look at my temples (right & left temporal areas)? (Please check only one box, and write in the number of years if necessary):

☐ I look my age.

☐ I look _____ years younger.

☐ I look _____ years older.

Appendix F

Subject Diary Day 0-14

Day _____ Date _____

Treatment Response Events	Left Side				Right Side				Comments
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
Redness/ dermatitis									
Pain / tenderness of skin									
Skin discoloration									
Lumps/ Bumps									
Swelling of injection site									
Bruising									
Itching									
Nausea									
Headache									
Dizziness									
Eye Pain									
Blurred vision									
Decreased vision									
Other (specify)									

Key to terms:

None = not present

Mild = noticeable but does not interfere with daily activity and did not require medication or treatment

Moderate = bothersome and/ or required medication or treatment or was disruptive to normal routine

Severe = sought medical attention and was disruptive to normal routine

Appendix G: Telephone Visit Script

Have you noticed any of the following?	Yes	No	Comments			
			Date	Side	Severity	Was treatment required? (medications)
Redness				L R (Circle)	Mild Moderate Severe	
Pain / tenderness of skin				L R	Mild Moderate Severe	
Skin discoloration				L R	Mild Moderate Severe	
Lumps/ Bumps				L R	Mild Moderate Severe	
Swelling of injection site				L R	Mild Moderate Severe	
Bruising				L R	Mild Moderate Severe	
Itching				L R	Mild Moderate Severe	
Nausea					Mild Moderate Severe	
Headache					Mild Moderate Severe	
Dizziness					Mild Moderate Severe	
Eye Pain				L R	Mild Moderate Severe	
Blurred or decreased vision				L R	Mild Moderate Severe	
Other (specify)				L R N/A	Mild Moderate Severe	

Appendix H: Telephone Visit Script

Key to terms:

None = not present

Mild = noticeable but does not interfere with daily activity and did not require medication or treatment

Moderate = bothersome and/ or required medication or treatment

Severe = sought medical attention and was disruptive to normal routine

REFERENCES

-
- ⁱ Kranendonk S¹, Obagi S. Autologous Fat Transfer for Periorbital Rejuvenation: Indications, Technique, and Complications: *Dermatol Surg.* 2007 May;33(5):572-8.
- ⁱⁱ Moradi A., Shirazi A, Moradi J. A 12-Month, Prospective, Evaluator-Blinded Study of Small Gel Particle Hyaluronic Acid Filler in the Correction of Temporal Fossa Volume Loss. *J Drugs Dermatol.* 2013;12(4):470-475
- ⁱⁱⁱ Current Concepts in Utilization of Collagen Stimulators *J Drugs Dermatol.* 2009;8 (10S):S1-S15.
- ^{iv} <http://www.youtube.com/watch?v=aZr-reZgR9Y>
- ^v <http://dermatologytimes.modernmedicine.com/dermatology-times/news/best-practices-temple-rejuvenation?page=full>
- ^{vi} Personal communication with Allergan representative.
- ^{vii} Moradi A., Shirazi A, Moradi J. A 12-Month, Prospective, Evaluator-Blinded Study of Small Gel Particle Hyaluronic Acid Filler in the Correction of Temporal Fossa Volume Loss. *J Drugs Dermatol.* 2013;12(4):470-475
- ^{viii} Personal communication with Dr Moradi
- ^{ix} Moradi A., Shirazi A, Perez V. A Guide to Temporal Fossa Augmentation With Small Gel Particle Hyaluronic Acid Dermal Filler *J Drugs Dermatol.* 2011;10(6):673-676.
- ^x Moradi A et al. A Guide to Temporal Fossa Augmentation With Small Gel Particle Hyaluronic Acid Dermal Filler *J Drugs Dermatol.* 2011;10(6):673-676.
- ^{xi} PI personal experience.
- ^{xii} PI personal experience as an expert injector
- ^{xiii} Yanyun, C; Wenying, ;, Jipeng L, Yajie Y; Lin L; Ning L Fundus artery Occlusion Caused by Cosmetic Injections *Chin Med J* 2014;127 (8): 1434-1437.
- ^{xiv} Park S; Woo S; Park K; Huh J; Jung C; Kwon O; Iatrogenic Retinal Artery occlusion Caused by Cosmetic Facial Filler Injections. *Am J Ophthalmol.* 2012 Oct;154(4):653-662
- ^{xv} Lazerri D; Agostini T; Figus M; Nardi M; Pantaloni M; Lazzeri S; Blindness Following Cosmetic Injections of the Face. *Plast. Reconstr. Surg* 129:995,2012.
- ^{xvi} June 13, 2014 FDA response to NDA application G140071.
- ^{xvii} Lazerri D; Agostini T; Figus M; Nardi M; Pantaloni M; Lazzeri S; Blindness Following Cosmetic Injections of the Face. *Plast. Reconstr. Surg* 129:995,2012.
- ^{xviii} McCleve DE, Goldstein JC. Blindness Secondary to injections in the nose, mouth and face: Cause and prevention. *Ear, Nose and Throat J.* 1995;74:182-188.
- ^{xix} DeLorenzi C. Transarterial degradation of hyaluronic Acid filler by hyaluronidase. *Dermatol Surg.* 2014 Aug;40(8):832-41
- ^{xx} Funt D, Pavicic T, Dermal Fillers in Aesthetics: An overview of adverse events and treatment approaches. *Clinical, Cosmetic and Investigational Dermatology* 2013;6, 295-316.