Sutura Medical Technology, Inc

Statistical Analysis Plan

A Pivotal, Blinded Multi-Center Study to show the safety and effectiveness of the Demetech Barbed PDO Suture

(Device Post-Market)

CF-CLT-PRT

Version 1

Date: 06 DEC 2023

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Intervals
CTR	Common Treatment Response
CFR	Code of Federal Regulations
CRF	Clinical Research Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FACE-Q	FACE-Q Appraisal of Cheeks and Age Appraisal Questionnaires
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic Acid
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	Investigational Product
IPL	Intense Pulsed Light
ITT	Intention to Treat
IRB	Institutional Review Board
PASS	Power Analysis and Sample Size (software)
PHI	Personal Health Information
PI	Principal Investigator
PDO	Polydioxanone
PMA	Pre-Market Approval
PP	Per Protocol
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (software)
SES	Safety Evaluation Set
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
UADE	Unexpected Adverse Device Effect

1. GENERAL AND TECHNICAL ASPECTS

This Statistical Analysis Plan (SAP) is intended to act as an outline for the statistical interpretation of the data resulting from the CF-CLT-PRT trial, titled: *A Pivotal, Blinded, Multi-center Study to show the safety and effectiveness of the Demetech Barbed PDO*. This statistical analysis plan is based on the clinical study protocol version 1.0, dated 21-DEC-2022.

The objective of this statistical analysis plan is to specify the statistical analyses in more detail than stated in the clinical study protocol (CSP) and to be precise enough to serve as a guideline for statistical programming and creation of tables, figures and listings (TFLs).

[redacted]

[redacted]

A complete table of contents for all planned analyses can be found in Appendix 1.

2. CLINICAL STUDY DESIGN AND OBJECTIVES

Demetech Barbed PDO Suture is an absorbable polydioxanone (PDO) suture with barbed sutures along the surface indicated for the treatment of midface wrinkles. This study will evaluate the safety and effectiveness of Demetech Barbed PDO Sutures for the temporary correction of mid face wrinkles. The rationale for the study is to demonstrate that treatment with Demetech Barbed PDO Sutures improves the appearance of mid face wrinkles as demonstrated by ≥1 point improvement on the Lemperle Classification Facial Wrinkle Scale at 6 months compared to baseline, as rated by a panel of three blinded evaluators.

2.1. CLINICAL STUDY DESIGN

The study is a pivotal, blinded, multi-center study to evaluate the safety and effectiveness of Demetech Barbed PDO Suture for the treatment of mid face wrinkles. Subjects who meet Inclusion/Exclusion criteria will receive treatment with Demetech Barbed PDO Sutures. Fifty-seven subjects will be treated. In addition, up to 2 run-in subjects may be treated with Demetech Barbed PDO Sutures by the investigator to allow the investigator to become familiar with Demetech Barbed PDO Suture characteristics. This run-in cohort will be required to meet all study inclusion/exclusion criteria and will be followed in the same manner as the non-run-in cohort.

Primary effectiveness will be assessed at 6 months. All subjects will be followed for a minimum of 12 months after treatment. Subjects will be followed up for safety via telephone or email at 72 hours after receiving treatment.

2.1.1.Photography Protocol

To ensure valid photograph comparability, standardized photos will be taken at each site. To this end, the same camera will be used at each site along with the same background. The images will be taken with controlled lighting and positioning of the subjects to ensure consistency between subjects and the photos taken at different time points throughout the study. Hair ties and make-up removers will be available to the subjects in order to help with capturing an accurate depiction of the mid-face area.

2.1.2. Patient Population

The patient population for this study is all adult subjects with age-related midface wrinkles who fulfill the entry criteria (inclusion and exclusion) will be considered for study recruitment. The study will seek to enroll approximately 20% of subjects of Fitzpatrick Skin Types IV – VI.

2.1.3. Study flow chart



2.2. Clinical Study Objectives

The primary effectiveness endpoint will be determined by the proportion of subjects with ≥1 point improvement on the Lemperle Classification of Facial Wrinkles Scale at 6 months compared to baseline as rated by a panel of three blinded evaluators. The Lemperle Scale will be used for photographic assessment by the blinded panel. Assessment of the secondary effectiveness endpoints will include the use of the Lemperle Scale by photograph by the blinded panel and live by the Investigator, as well as Investigator- and Subject-rated GAIS, and FACE-Q.

2.2.1. Effectiveness Endpoints

[redacted]

The secondary effectiveness endpoints include:

1. Individual endpoints at each timepoint of 6 weeks, 3, 9, and 12 months for the proportion of subjects with ≥1 point improvement from baseline on the Lemperle Scale, as rated by a panel of three blinded evaluators.

2. Change from baseline at each timepoint of 6 weeks, 3, 6, 9, and 12 months on the Lemperle Scale, as rated by a panel of three blinded evaluators.

3. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for the proportion of subjects with ≥1 point improvement from baseline on the Lemperle Scale, as rated by the Investigator.

4. Change from baseline at each timepoint of 6 weeks, 3, 6, 9, and 12 months on the Lemperle Scale, as rated by the Investigator.

5. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement in Investigator-rated GAIS.

6. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement in Subject-rated GAIS.

7. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement from baseline on each of the validated FACE-Q Satisfaction with Cheeks and Age Appraisal scales as rated by the Subject.

2.2.2. Safety Endpoints

The safety endpoint is to assess the rate of adverse events (AEs) from initial treatment through the last study visit. All AEs that occur throughout the duration of the study will be captured. Adverse events will be categorized by type, duration, severity, relationship to the study device and need for treatment. This will be done using a subject take-home diary as well as live follow-up visits.

An Immediate Visual Disturbance Incidence Reporting process will be in place. Any incidence of visual disturbance (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes, etc.) will be reported to the FDA.

Protocol Stopping Rules will be in place to halt further subject enrollment if the following serious adverse events are observed: vascular embolic event leading to skin necrosis, vision loss, and stroke.

Safety will be assessed at each follow-up visit. Subjects will be seen for follow up visits at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months from treatment.

[redacted]

4. ANALYSIS SETS

The following analysis sets will be defined for the statistical analysis of this clinical study:

4.1. Safety Evaluation Set (SES)

The SES consists of all subjects who receive study treatment. The SES will consist of all treated subjects regardless of protocol compliance and will be analyzed according to the treatment received. The SES will be used for all safety analysis.

4.2. Intent to treat (ITT)

The Intent to Treat (ITT) population consists of all subjects who were enrolled and treated, regardless of adherence to the protocol, and will exclude subjects who are not treated. This population is the same as the SES. Sensitivity analysis for effectiveness endpoints will use the ITT.

4.3. Per Protocol Set (PPS)

The PPS will be a subset of the ITT population, consisting of all treated subjects whom the 6-month assessment was completed per protocol with no major protocol deviations.

A major protocol deviation is defined to be a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Examples of major protocol deviations may include but are not limited to an inclusion/exclusion criteria violation, or informed consent violation.

The PPS will be a subset of the ITT population, consisting of all treated subjects for whom the 6-month assessment was completed per protocol with no major protocol deviations. The PPS will have had the primary effectiveness variable recorded. The PPS will be used for primary effectiveness analysis.

A major protocol deviation is defined to be a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. [redacted]

5. VARIABLES FOR ANALYSIS

5.1. Effectiveness Variables

5.1.1. Lemperle Classification Facial Wrinkle Scale

The Lemperle Scale is a 6-point wrinkle classification scale with classification values of 0 to 5. It was originally developed for objective measurements of dermal filler effectiveness to assess the changes resulting from injecting filler materials in patients. The scale has been validated for use in live assessment as well as photographic assessment (Lemperle, 2001). This study will utilize this scale as a photographic assessment for primary effectiveness and a live evaluation scale (as rated by the investigator) as a secondary assessment.

Table 5-X: Lemperle Classification Facial Wrinkle Scale

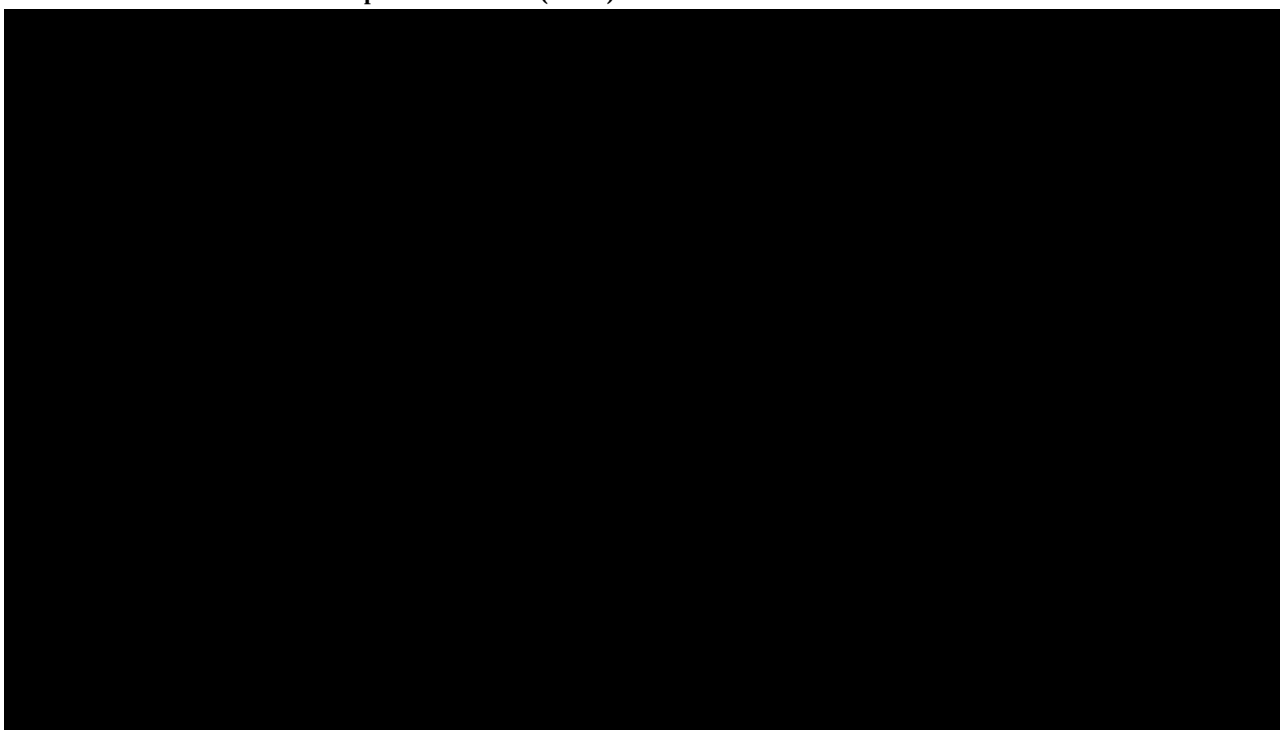


Raters score each side of the face separately; a global score will also be derived using the mean of the two sides. For photographic evaluations, the median score of the raters will be used per side as the side score and then the mean global score will be calculated.

5.1.2. GAIS

The Global Aesthetic Improvement Scale (GAIS) is a non-validated subjective measurement tool that rates the relative appearance compared to baseline using photographs taken prior to treatment. There are 7 points on the GAIS used for this study, associated with values ranging from -3 (Very Much Worse) to 3 (Very Much Improved, see Table 5-1). Raters score each side of the face separately; a global score will also be derived using the mean of the two sides.

Table 5-1: Global Aesthetic Improvement Scale (GAIS)

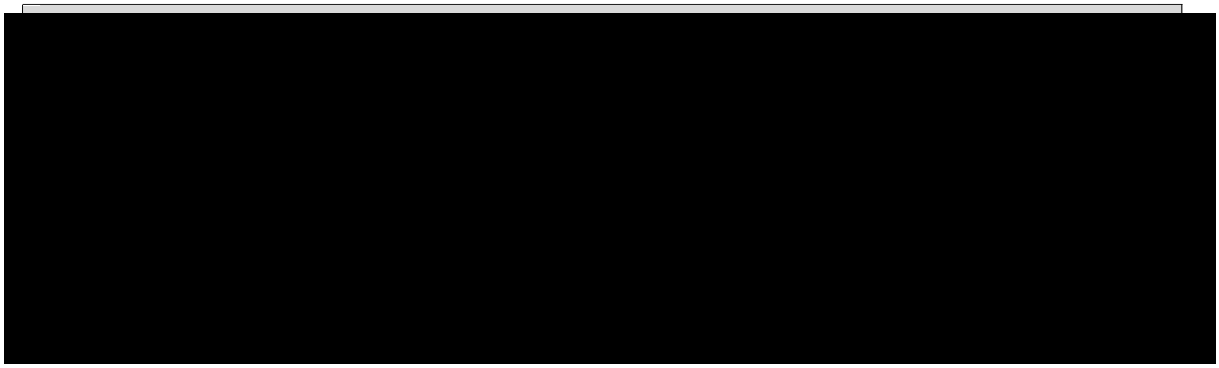


GAIS score responder rates as rated by the live, masked evaluator, treating investigator, and the study subject are secondary effectiveness endpoints. Treated subjects with GAIS ratings of Improved, Much Improved, or Very Much Improved will be considered responders for tested analyses. For global assessment, subjects must have an average score of ≥1, e.g., if Left scores 2 and Right scores 0, the mean would still be '1: Improved', but if one side has a score of 1 and the other 0, that person would not be a responder.

5.1.3. FACE-Q

FACE-Q Satisfaction with Cheeks and Age Appraisal scales as rated by the subject are also secondary effectiveness variables. FACE-Q is a patient-reported outcome measure; in this study the Age Visual Analog Scale (VAS) and Patient Satisfaction with Outcome (patient Satisfaction with Cheeks) are the only FACE-Q instruments used. The Age Appraisal VAS asks patients to select how many years older or younger they think they look than their actual age, ranging from -15 years to +15 years in increments of 1, with 0 'I look my age' at the center (Figure 5-2). The subject is instructed to circle only one number, and that number circled by the patient is the number used in analysis with no further derivation required.

Figure 5-1: Age Appraisal VAS from FACE-Q



The Satisfaction with Cheeks instrument consists of 5 questions pertaining to different aspects of cheek appearance. Each is evaluated on a scale of 1 to 4, with 1 being Very Dissatisfied and 4 being Very Satisfied (Table 5-3).

Table 5-1: Satisfaction with Cheeks from FACE-Q



The raw scores for items that make up a scale are added to provide a total score. The total score is converted to a score from 0 to 100. The official instructions for FACE-Q total score calculation are as follows (written for excel):

a) Using Excel, enter the numerical value of the response selected for each question.
b) Once all of your data has been entered into an excel template, sum the values within each scale and place that value in the last column of that row labeled "Sum."
c) For items missing data*, insert the mean of the completed items into the total sum score. If less than 50% of the questions have been answered, then the scale cannot be scored.
d) Using the score conversion table provided, locate your sum score and insert the equivalent rasch transformed score (see Table 5-4).

*Missing data refers to responses where more than one answer choice was selected, non-applicable (N/A) was selected, or a question was skipped.

Table 5-2: FACE-Q Score Conversion Table



To clarify the official instructions further, a missing score will have the average of the other questions imputed as its value prior to total score calculation or score transformation.

5.2. Pharmacodynamic Variables

Not Applicable.

5.3. Pharmacokinetic Variables

Not Applicable.

5.4. Pharmacogenetic Variables

Not Applicable.

5.5. Safety Variables

Evaluable safety variables will include subject reported common treatment site responses (CTRs) from subject diaries, investigator reported events (adverse events), pregnancy test results, and concomitant medications. The general definition for an adverse event (AE) is an untoward medical occurrence which does not necessarily have a causal relationship to the study device. Only treatment-emergent adverse events (TEAE) will be analyzed, which are defined as AEs with onset

or worsening after the initial treatment through the last study visit. Only TEAEs will be captured in the EDC.

Pain and bleeding adverse events will be summarized as a secondary safety endpoint, both by total frequency and frequency by subject.

CTRs will be analyzed separately from TEAEs. CTRs are expected side effects that result from study treatment. For 30 days after treatment, subjects will record CTRs on a take-home diary. [redacted] Any CTR that extends beyond the diary collection period of 30 days or is evaluated by the PI as an SAE will be defined as an AE and recorded on an Adverse Event form as well as documented on a CRF by the study staff. Any CTR that is also recorded as an AE will appear in analysis of both event types.

Adverse events and common treatment responses will be summarized descriptively and in listings by type, duration, severity, and for AEs only, relationship to study device and need for treatment. TEAEs will be summarized by MedDRA system organ class and preferred term, CTRs will be summarized by MedDRA system organ class and lowest level term as some pre-specified diary events map to the same preferred term. Adverse event summary overview tables will be further broken down by the defined planned subgroups (see Examination of Subgroups).

5.5.1. Serious adverse events

An SAE is an AE that meets at least one of the following 6 criteria:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization, or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or disability.
- Is a congenital anomaly or birth defect.
- Requires intervention to prevent permanent impairment or damage.

5.5.2. Related events

An AE is considered to be "related" to the study device if a causal relationship between the study device and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

The expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline). Otherwise, the relationship should be considered as "not related."

CRF selections of 'Possibly Related' or 'Related' will be classified as 'Related' in analysis, while 'Unlikely Related' and 'Unrelated' will be classified as 'Unrelated'. Any event without a selection (unknown) will be classified as 'Related'.

5.5.3. Treatment Emergent Events of Special Interest

TEAEs of special interest will be defined by MedDRA preferred terms, including: Vision loss, Unilateral vision loss, Visual disturbance, Visual field tests abnormal.

5.5.4. Event Duration

Duration of events will be summarized in categories of [redacted]
Event duration will be measured in days and be calculated using the standard end date – start date +1.

As CTRs are collected as daily events, composite events will be created to allow calculation of maximum severity and event duration. Event duration will be imputed as continuous for up to two days of missing diary reporting, if an event was occurring before the missing days and is also present afterwards. If the event is no longer occurring after the missing days, the event duration will only extend to the last day of event reporting.

5.5.5. Pregnancy test results

Pregnancy test results or reasons for non-childbearing status for all enrolled subjects will be presented in listings only.

5.5.6. Concomitant Medications

Concomitant medications will be presented only in subject listings, and will include reported term, indication, dose, ongoing at enrollment, and duration data.

5.5.7. Facial Nerve Assessments

Facial nerve assessment results will be presented only in subject listings and will be presented by visit.

5.6. Other Variables

Other collected variables will be presented as part of subject disposition and baseline characteristics. Issues with the study product and subject exposure will also be summarized. Medical history will be described using reported term categories for the ITT and PPS.

5.6.1. Demographics

The following demographic variables will be presented in analysis. Categorical subgroups will be presented as frequency and percent.

5.6.1.1. Sex

Sex will be summarized categorically by collected eCRF terms.

5.6.1.2. Race

Race will be summarized categorically by collected eCRF CDISC-compliant terms. If more than one race is checked for a subject, they will appear in tabulation as 'Multiple' and all options checked on the eCRF will be provided in the demographics listing. If 'Other' is the only option selected, the subject will appear as 'Other' in tabulation and the specification will be provided in the demographics listing.

5.6.1.3. Ethnicity

Ethnicity will be summarized categorically by collected eCRF terms.

5.6.1.4. Fitzpatrick Skin Type

The frequency and percent of subjects in each of the six Fitzpatrick Skin Types will be computed in the demographics table.

For the purpose of subgroup analysis, Fitzpatrick Skin Type groups will be defined as 'Type I – III' and 'Type IV – VI'.

5.6.1.5. Age

Subject age will be presented using summary statistics in demographics analysis. Age will be calculated using the subject's date of birth and the informed consent date (year difference between informed consent date and date of birth, rounded down). It will be reported with one decimal place only for the mean, median (if applicable), and standard deviation, and will otherwise be reported as an integer.

[redacted]

5.6.1.6. Weight

Weight will be converted to lbs and will be presented using summary statistics. Weight recorded as kg in the EDC will be derived using the equation:

Weight lbs = kg*2.20462

Weight will be rounded to the nearest integer on the subject-level and will be reported with one decimal place only for the mean, median (if applicable), and standard deviation.

5.6.1.7. Height

Height will be converted to inches and reported as summary statistics. Height recorded as cm in the EDC will be derived using the equation:

Height in = cm*0.393701

Height will be rounded to the nearest integer on the subject-level and will be reported with one decimal place only for the mean, median (if applicable), and standard deviation.

5.6.1.8. BMI

BMI will be calculated using weight and height in kilograms and centimeters using the equation:

$$BMI = \text{weight (kg)} / (\text{height (cm)}/100)^2$$

BMI will be rounded to one decimal place.

5.6.1.9. Baseline Lemperle Scale score

Subjects will be presented with their baseline investigator-rated Lemperle Scale scores reported by frequency and percent, as well as summary statistics. A subject's baseline score will be a global score derived as the mean of both sides.

5.6.2. Protocol Deviations

Protocol deviations will be summarized by Major or Minor, category (Safety, Informed Consent, Eligibility, Protocol Implementation), and reported term as selected on the eCRF. Protocol deviations will be presented as total events and total subjects per category or term. Missed and out of visit deviations will provide relevant visit and 'Other' deviations will provide specifications only in the protocol deviations listing.

5.6.3. Device Exposure

Treatment variables such as number of devices used per patient, cannula and insertion needle size, and anesthetic use will be summarized categorically using counts and percentages.

5.6.4. Issues with the Study Device

Whether there was an issue with the study device is collected as a yes/no binomial question followed by a written description of any issue. Issues will be presented as counts out of the total number by subject. Categorical questions from the Ease of Use CRF will also be summarized. Descriptions of issues will be reported in listings.

Issues will be mapped to the FDA Device Problem Code Hierarchy (see FDA Coding Resources for Medical Device Reports). All device event assignations will be reviewed and approved by the Sponsor.

5.6.5. Subject Withdrawal

Reason for subject withdrawal will be summarized categorically with counts using the terms reported on the eCRF. As subjects may be withdrawn for multiple reasons, they may appear more than once in the table under different terms. A total 'subjects withdrawn' summary will be provided with percentages out of the ITT population.

6. STATISTICAL ANALYSIS METHODS

All collected data will be presented in listings, and all analysis will be presented using summary statistics for continuous and categorical data. The study population will be described using summary statistics for continuous data (n, mean, standard deviation, median, minimum, maximum) and categorical data (counts, percentages).

6.1. Effectiveness Variables

[redacted]

6.1.1. Primary Effectiveness Variable

[redacted]

The null and alternative superiority hypotheses are:

H_0: **π**Demetech Barbed PDO Suture ≤ 60%

H_a: **π**Demetech Barbed PDO Suture > 60%

[redacted]

6.1.2. Secondary Effectiveness Variables

[redacted]

The secondary effectiveness endpoints are:

1. Individual endpoints at each timepoint of 6 weeks, 3, 9, and 12 months for the proportion of subjects with ≥1 point improvement from baseline on the Lemperle Classification Facial Wrinkle Scale, as rated by a panel of three blinded evaluators.

2. Change from baseline at each timepoint of 6 weeks, 3, 6, 9, and 12 months on the Lemperle Scale, as rated by a panel of three blinded evaluators.

3. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for the proportion of subjects with ≥1 point improvement from baseline on the Lemperle Scale, as rated by the Investigator.

4. Change from baseline at each timepoint of 6 weeks, 3, 6, 9, and 12 months on the Lemperle Scale, as rated by the Investigator.

5. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement in Investigator-rated GAIS.

6. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement in Subject-rated GAIS.

7. Individual endpoints at each timepoint of 6 weeks, 3, 6, 9, and 12 months for improvement from baseline on each of the validated FACE-Q Satisfaction with Cheeks and Age Appraisal scales as rated by the Subject.

6.1.2.1. Improvement on the Lemperle Scale

[redacted]

6.1.2.2. Change from baseline on the Lemperle Scale

[redacted]

[redacted]

6.1.2.3. Improvement on the Lemperle Scale, Live Investigator Rating

[redacted]

6.1.2.4. Change from baseline on the Lemperle Scale, Live Investigator Rating

[redacted]

6.1.2.5. GAIS Improvement, Investigator Rating

[redacted]

[redacted]

6.1.2.6. GAIS Improvement, Subject Rating

[redacted]

6.1.2.7. Improvement from Baseline in FACE-Q

[redacted]

[redacted]

6.2. Pharmacodynamic Variables

Not Applicable.

6.3. Pharmacokinetic Variables

Not Applicable.

6.4. Pharmacogenetic Variables

Not Applicable.

6.5. Safety Variables

All safety analyses will be performed on the SES.

[redacted]

6.6. Other Variables

[redacted]

6.7. Special Statistical/Analytical Issues

Not Applicable.

6.7.1. Discontinuations and Missing Data

[redacted]

6.7.2. Interim Analyses

The Sponsor plans to perform an analysis, prior to study completion, when all subjects have completed the 6 Month visit. The data will be monitored and cleaned and is intended for use in submission to FDA in support of a 510k. No statistical adjustments will be made as the primary endpoint will be complete. Secondary effectiveness endpoints for 9 and 12 Months will not be analyzed until all subjects have completed the study. There are no necessary unblinding precautions.

6.7.3. Data Monitoring Committee

This study will be monitored regularly by a qualified monitor in accordance with applicable regulations and SOPs.

The monitor for this study is:

Health Policy Associates, Inc.
3 Allied Drive, Suite 210
Dedham, MA 02026
Phone: +1-781-329-2993

For more details on the Data Monitoring plan, please consult the CSP. All data through the 6 month visit and all safety data to the cutoff date will be fully monitored and cleaned prior to the production of the interim analysis. All protocol deviations to the cutoff date for the interim analysis will be considered for inclusion into the Per Protocol Set.

6.7.4. Multiple Comparisons/Multiplicity

Not Applicable.

6.7.5. Examination of Subgroups

The following preoperative characteristics will be evaluated for potential association with outcomes: sex, race, ethnicity, age group, Fitzpatrick Skin Scale type, baseline Lemperle Classification Facial Wrinkle Scale score, number of threads used, and investigational site.

[redacted]

[redacted]

7. CHANGES IN THE PLANNED ANALYSES

All secondary endpoints will be analyzed at the 6 Week interval; this was specified in 11.3.1 of the CSP but not listed within all individual secondary endpoints.

An interim analysis has been added; no statistical adjustment is necessary as the primary endpoint will be complete.

The ANOVA test for homogeneity of sites and investigators as a sensitivity analysis has been removed; site responses and 95% confidence intervals will be presented. Next observation carried forward has been added to the sensitivity analysis.

8. REFERENCES

Lemperle, Gottfried, Ralph Holmes, Steven Cohen, and Stefan Lemperle. “A Classification of Facial Wrinkles.” *Plastic & Reconstructive Surgery* 108, no. 6 (2001): 1735–50.

9. APPENDIX 1: LIST OF TABLES, FIGURES, AND LISTINGS



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