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

Development phase:	Device Post-Market
Study protocol number:	CF-CLT-PRT
Indication:	Temporary correction of midface wrinkles
Planned study period:	First subject first visit: Q1 2022 Last subject first visit: Q2 2022 Last subject last visit: Q2 2023
Investigational product(s):	Demetech Barbed PDO Suture
Sponsor:	Sutura Medical Technology, Inc. [redacted]
Version Date:	21 December 2022

PROTOCOL APPROVAL PAGE

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

Version Date: 21 December 2022

Study Sponsor: Sutura Medical Technology, Inc.

We, the undersigned, have read and approve this protocol and agree on its content.

Sponsor Representative:

Name: [redacted]

Title: [redacted]

[redacted]

Signature and Date

Sponsor Medical Expert:

Name: [redacted]

Title:

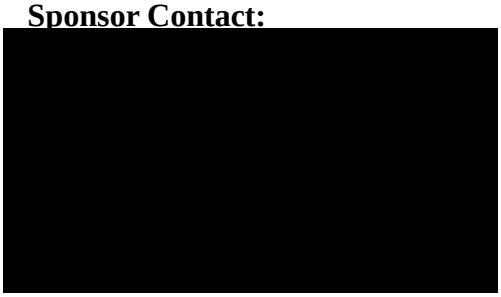
Address:

Phone:

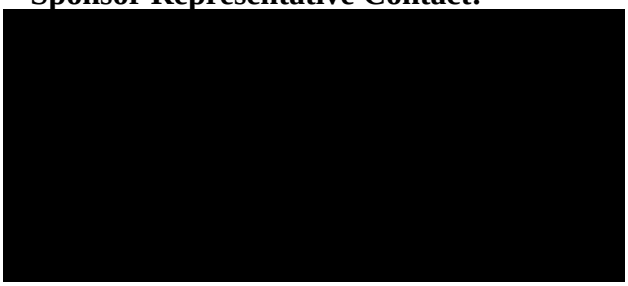
[redacted]

STUDY CONTACT INFORMATION

Sponsor Contact:



Sponsor Representative Contact:



Study Monitor:



Protocol Version and Amendment Tracking

Version #/Date	Description
v.A/ 02Oct2020	Original
v.B/ 09Apr2021	• Correction of minor typos and grammar • [redacted] • Sample size calculation adjusted to 15% attrition and one-sided test; greater explanation provided in protocol text (sections 4.1 and 11.1) • Clarifying language throughout regarding the use of photographs for the primary endpoint, and of the derivation of a subject's Lemperle score • [redacted] • Addition of Justification for Investigation (section 3.2), Risk Mitigation Strategy (section 3.4), Photograph Protocol (section 5.2) and Patient Population (section 5.3) • Update to SAEs triggering study stopping rules • Updates to Inclusion and Exclusion criteria • Addition of 'There is no loss of benefit if the subject decides to not participate in the study' to section 6.2.1 • Blinding procedure updated to include non-chronological order of Lemperle photo reviewing • Facial nerve function test added to follow-up visits and addition of motor nerve assessment added post treatment • Common treatment site responses list updated • Addition of secondary safety endpoint for adverse events of pain and bleeding • Edits made to suture instructions
Rev.0/ 10Nov2021	• Added footnote number three (3) to Table 8-1 providing greater clarity to order of events • Updated protocol specific identification code • Sponsor contact information updated • Removed inclusion 11 as it was redundant with inclusion 2 • Further specified notification of serious adverse events • Added the approximate enrolling time for patients to synopsis • Added planned study period with quarter and year • Altered classification and naming of version of previous protocols per sponsors document system to allow this final version as Rev 0 and therefore switched prior versions to lettered versions
Rev 1/21Dec2022	• Add clarification to Inclusion/Exclusion criteria while maintaining intent of target population without trauma, prior surgeries or present fillers in the target area (as opposed to whole body) • Minor formatting corrections

Table of Contents

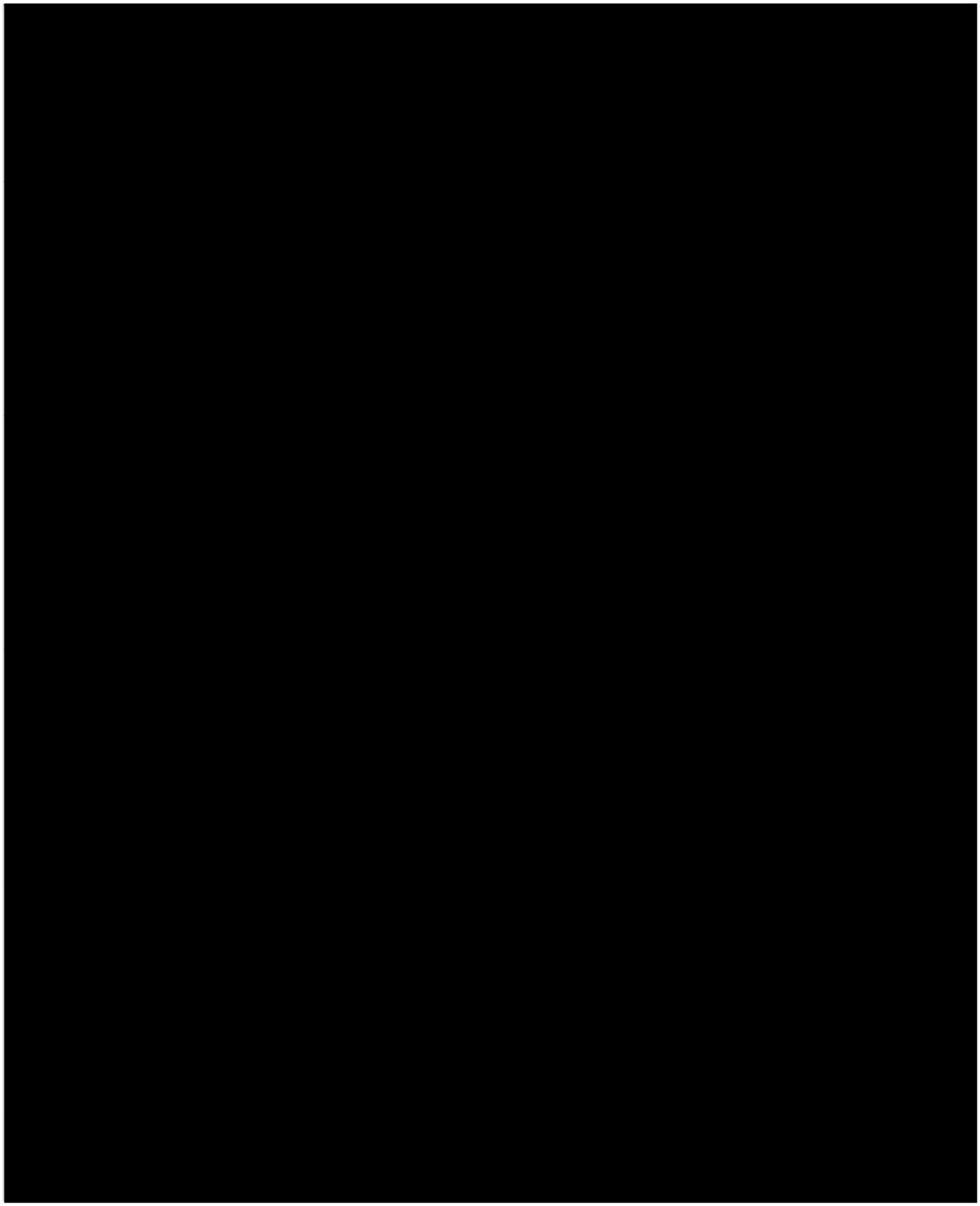
Protocol Version and Amendment Tracking 4
Investigator Statement of Compliance 9
1 SYNOPSIS 10
2 ETHICS 15
2.1 Institutional Review Board / Ethics Committees 15
2.2 Ethical conduct of the study 15
2.3 Informed consent 15
3 INTRODUCTION 16
3.1 Study rationale 16
3.2 Justification for Investigation 16
3.3 Risk-benefit assessment 16
3.4 Risk Mitigation Strategy 16
4 STUDY OBJECTIVES 17
4.1 Effectiveness Endpoints 17
4.2 Safety Endpoint 18
5 Investigational PLAN 19
5.1 Overall study design 19
5.2 Photography Protocol 19
5.3 Patient Population 19
5.3.1 Study flow chart 20
6 STUDY POPULATION 21
6.1 Inclusion criteria 21
6.2 Exclusion criteria 21
6.2.1 Discontinuation of subjects 23
6.2.2 Premature termination or suspension of the study or a study site 23
7 TREATMENTS 24
7.1 Investigational product(s) 24
7.1.1 Description of investigational product(s) 24
7.1.2 Disposition of investigational product(s) 24
7.2 Treatment administration 25
7.2.1 Randomization Procedures 25
7.2.2 Treatment method 25

7.3 Restrictions during the study 25
7.4 Blinding Procedures 25
8 STUDY ASSESSMENTS 26
8.1 Screening / Enrollment 26
8.2 Treatment 26
8.3 Follow Up Visits 26
9 SAFETY ASSESSMENTS 28
9.1 Definition of intensity 28
9.2 Definition of causal relationship 28
9.3 Definition of type 29
9.3.1 Adverse event 29
9.3.2 Serious adverse event 29
9.3.3 Unanticipated adverse device effect 29
9.3.4 Common Treatment Site Responses 29
9.4 Recording Adverse Events 30
9.5 Reporting Adverse Events 30
10 QUALITY CONTROL AND QUALITY ASSURANCE 32
10.1 Monitoring 32
10.2 Audits / Inspections 32
11 STATISTICAL METHODS 33
11.1 Determination of sample size 33
11.2 Analysis sets 33
11.3 Statistical analysis methods 34
11.3.1 Effectiveness variables 34
11.3.1.1 Primary effectiveness variable 34
11.3.1.2 Secondary effectiveness variables 35
11.3.2 Safety variables 38
11.3.3 Other statistical / analytical issues 38
11.3.3.1 Discontinuations and missing data 38
11.3.3.2 Interim analyses 39
11.3.3.3 Exploratory analyses 39
11.3.3.4 Significance Level 39
12 DATA HANDLING AND RECORDKEEPING 40
12.1 Confidentiality 40
12.2 Source Documents 40
12.3 Data Capture 40
12.4 Record Retention and Availability 41
13 PUBLICATION POLICY 42
14 REFERENCES 43
15 APPENDICES 44
15.1 Lemperle Classification of Facial Wrinkles Scale 44

15.2 Informed Consent....44
15.3 Case Report Forms (CRFs)....44
15.4 PASS Output of Sample Size Calculation....44
15.5 Treatment Method....44
Appendix 15.1....45
Lemperle Classification of Facial Wrinkles Scale....45
Appendix 15.2....46
Informed Consent....46
Appendix 15.3....47
Case Report Forms....47
Appendix 15.4....48
PASS Output of Sample Size Calculations....48
Appendix 15.5....49
Treatment Method....49

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
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	Investigational Product
IPL	Intense Pulsed Light
ITT	Intention to Treat
IDE	Investigational Device Exemption
IRB	Institutional Review Board
[redacted]	[redacted]
[redacted]	[redacted]
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
[redacted]	[redacted]
SES	Safety Evaluation Set
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
UADE	Unexpected Adverse Device Effect

Investigator Statement of Compliance



1 SYNOPSIS

Protocol Title	A Pivotal, Blinded, Multi-center Study to show the safety and effectiveness of the Demetech Barbed PDO Suture
Protocol Number	CL-CLT-PRT
Study Sponsor	Sutura Medical Technology, Inc.
Study Device	Demetech Barbed PDO Suture is a 510k approved absorbable Polydioxanone (PDO) suture with barbed sutures along the surface. Demetech Barbed PDO Suture is manufactured by Demetech Corp., Miami Lakes, FL
Study Indication	Demetech Barbed PDO Suture is indicated for placement in the subcutaneous plane for the temporary treatment of midface wrinkles.
Study Rationale	Treatment with Demetech Barbed PDO Suture will result in temporary correction of midface wrinkles, as determined by a one-point improvement on the five-point Lemperle Classification Facial Wrinkle Scale by a panel of three blinded evaluators at 6 months.
Study Design	The study will be a pivotal, blinded, multi-center study to show the safety and effectiveness of the Demetech Barbed PDO Suture in the treatment of midface wrinkles.
Study Duration	The study will last approximately 12 months. All subjects will be recruited within approximately six months and followed for 12 months.
Follow Up Schedule	Subjects will receive a 72-hour post-treatment phone call for general assessment of subject well-being and of adverse events. Subjects will return for in-office follow up visits at 2 weeks, 6 weeks, 3, 6, 9, and 12 months.
Number of Subjects	57 subjects will be enrolled. This enrollment number accounts for a 15% attrition rate to ensure an ITT population of 48 subjects. In addition, up to two run-in subjects may be treated by each 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.
Number of Sites	Up to 4 sites will participate
Patient Population	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.
Inclusion Criteria	1. Male and female subjects, 22+ years of age 2. Subject received a rating, in each cheek, by PI of at least Class 1 or more for wrinkling in the midface according to the Lemperle Scale Classification of Facial Wrinkling. 3. If a woman is of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile), then she must have a confirmed negative urine pregnancy test result at screening. If treatment is not provided at the screening visit, a negative urine pregnancy test result is required within 7 days before treatment. 4. If a woman of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile), subject confirms she will utilize at least one form of contraception throughout the duration of the study. 5. Subjects who desire cheek lifting to correct age-related wrinkles in the mid-face as recommended by the treating investigator. 6. Subjects who are able to understand the study requirements, including the obligation not to receive any other facial procedures or treatments affecting mid-face at any time during the study. These include procedures or treatments done at home or with a professional. Facial treatments include lasers, facial massages, and anything beyond common skincare routine.

	7. Subjects who are willing to participate in the study and to sign a witnessed/informed consent form. 8. Subjects who are logistically able to present for all study visits and meet all study requirements. 9. Subjects who are willing to complete the 30-day diary. 10. Subjects who pass the pinprick and/or cotton swab facial nerve assessment.
Exclusion Criteria	1. Abnormal rating in midface sensation, with inability to feel a 0.4 G monofilament or a cotton wisp at any site on the midface. 2. Active acne or prominent acne scars in the treatment area. 3. Active inflammatory or infectious conditions 4. Allergy or foreign body sensitivities to plastic biomaterials 5. Known bleeding disorder 6. Breast feeding, pregnant, or not on/willing to use contraception if of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile), 7. Collagen skin disorder 8. Pre-existing facial asymmetry 9. History of any device use on the mid-face in the prior 6 months (laser, IPL, radiofrequency, ultrasound, micro needling, micro needle RF, or cool based treatments). 10. History of autoimmune or connective tissue disease 11. History of facelift, midface lift, lower facelift. Neck lift that changes the facial structure and anchor points would be exclusionary. 12. History of fat transfer to the midface. 13. History of injectable fillers other than temporary fillers such as Hyaluronic Acid or Radiesse to the midface at any time. Permanent and semi-permanent fillers are not allowed (PLLA, Sculptra) 14. History of Kybella in the prior 6 months 15. History of facial trauma in the mid-face 16. History of facial surgical procedures 17. Inability to chew, puff cheek, or smile broadly 18. Metabolism irregularities 19. On immunosuppressive therapy 20. Recent weight loss or intention to lose a significant amount of weight during the study period (2 BMI Points) 21. Subjects who have undergone cosmetic facial plastic surgery (with the exception of rhinoplasty or upper blepharoplasty, more than 2 years prior to enrollment), tissue grafting, or tissue lifting or augmentation with any permanent or semi-permanent filler. 22. Subjects who have had temporary facial dermal filler injections below the orbital rim with HA-based fillers or Radiesse within 18 months, porcine-based collagen fillers within 24 months, or neuromodulator injections to the midface or lateral canthal lines, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months of entry in the study or who were planning to undergo any of these procedures at any time during the study. 23. Subjects who have very thin skin in the mid-face region, who have the tendency to accumulate fluid in the lower eyelids, or who have large infraorbital fat pads (i.e., significant convexity or projection from the infraorbital fat pads). 24. Subjects who have mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial

	lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease. 25. Subjects who have serious concurrent illness which may lead to problems with wound healing (e.g., uncontrolled diabetes or vascular disease). 26. Subjects with known or suspected family history of problems with keloid scarring. 27. Subjects with serious neurological or psychological conditions which could prevent the subject from cooperating with treatment or post-procedure care and assessment. 28. Smokers, since this may compromise wound healing. 29. Subjects who have a current or prior history within the last 3 years of neoplasm and/or any active neoplasm in the face or that in the opinion of the Investigator may make then not a suitable candidate. 30. Subjects currently enrolled in other clinical trials. 31. Subjects taking Warfarin or other anticoagulants. These subjects may experience a significant risk of problems with post-operative bleeding. 32. Subjects who have taken, in the last 2 weeks, ad-lib medication or herbal supplements that may increase risk of bleeding. This includes aspirin or other herbal supplements known to increase risk of bleeding. 33. Subjects with significant co-morbidities e.g., heart disease, strokes, or angina) that in the opinion of the Investigator may prevent the subject from completing the study. 34. Subjects with planned cosmetic procedures, facial or dental surgery during the follow-up period. 11. Other concerning health issue in the opinion of the Investigator.
Dosage/Dose Regimen	Subjects who meet Inclusion/Exclusion criteria will receive treatment to correct mid face wrinkles using the Demetech Barbed Suture. The number of sutures used will be determined by the treating investigator.
Effectiveness Endpoints	The primary effectiveness endpoint is the proportion of subjects with ≥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. The median score as rated by the blinded panel using subject photographs will be used to determine if a subject is a responder. Clinical effectiveness will be demonstrated by superiority of this 6-month response rate over a target rate of 60%. Secondary effectiveness endpoints include: 1. Individual endpoints at each timepoint of 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 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 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 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. 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.

Safety Endpoints	7. 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. Pain and bleeding adverse events will be summarized as a secondary safety endpoint, both by total frequency and frequency by subject.
Sample Size Calculation	For this study, a successful outcome is defined as a one-point improvement from baseline at 6 months on the five-point Lemperle Classification Facial Wrinkle Scale, as rated by a panel of three blinded evaluators. The median score as rated by the blinded panel will be used to determine if a subject is a responder. Sample size calculations were estimated [redacted] Statistical power calculations were conducted based on the primary effectiveness targets of previously approved studies. PMA P050047 used a target rate of 60% to demonstrate device superiority over a minimal clinically meaningful response. [redacted] Although only 48 subjects are required, 57 subjects will be enrolled and treated to collect additional safety data and to account for an attrition rate of 15%.
Statistical Methods	Effectiveness analyses will be based on the Intention to Treat (ITT) population, defined as all enrolled subjects. Analysis of the primary effectiveness endpoint will use an [redacted] To investigate the robustness of the effectiveness results, this analysis will be [redacted] In sensitivity analyses, [redacted] Safety analyses will be performed on the [redacted] All collected data will be presented in listings, and all analysis will be presented [redacted] The study population will be described using [redacted] and [redacted]

	[redacted] Further details on the statistical and analytical aspects will be presented in the Statistical Analysis Plan (SAP).

2 ETHICS

2.1 Institutional Review Board / Ethics Committees

The following documents must be submitted to the responsible IRB and approval obtained:

- The clinical study protocol
- Subject information and informed consent forms
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable)
- Any other IRB-required documents

2.2 Ethical conduct of the study

This study will be conducted in accordance with all applicable regulations. This includes the Protection of Human Subjects regulations in 21 CFR part 50, the Institutional Review Boards regulations in 21 CFR part 56, and the Investigational Device Exemption regulations in 21 CFR part 812.

2.3 Informed consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH guidelines for GCP, US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), if applicable, and local regulations. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the Institutional Review Board for the study. A blank copy of the IRB-approved form must be kept on-site and by the Sponsor and Investigator.

The ICF will be reviewed with the prospective study subject (and/or legal representative) by the Investigator or qualified designee who will be available to answer questions about procedures, risks, and alternatives. Once the appropriate essential information has been provided to the subject and fully explained, and it is felt that the subject understands the implications of participating, the subject and qualified designee reviewing the consent will sign and date the IRB-approved paper ICF. The subject will receive a copy of the signed ICF. The original signed and dated ICF will be kept in the site's regulatory file. Documentation of informed consent for participation in this trial will be noted in the subject's medical record at the site.

The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. Communication of this information to the subject will be recorded.

3 INTRODUCTION

3.1 Study rationale

Midface wrinkles are often the result of the natural aging process and involve sagging of the facial structures and loss of subcutaneous fat. The majority of subjects interested in facial aesthetic correction are aged 45 through 60 years. A number of treatment options are available including surgical procedures, fat transfer, and injection of various dermal fillers. Each of these options having varying levels of effectiveness and durability and, as with any medical procedure have safety risks.

Demetech Barbed PDO Suture is an absorbable polydioxanone (PDO) suture with barbed sutures along the surface indicated for the treatment of midface wrinkles.

3.2 Justification for Investigation

PDO sutures have long been used for tissue approximation and have been shown to be safe to use. However, there have been no sutures approved in the U.S for a mid-face wrinkle reduction indication. Therefore, we wish to conduct this prospective study in order to observe safety and effectiveness of PDO suture use in reducing mid-face wrinkles. Risk-benefit assessment has been completed as well as risk analysis and using PDO sutures for midface wrinkles creates an acceptable risk profile.

3.3 Risk-benefit assessment

The potential benefit of treatment with Demetech Barbed PDO Suture include temporary facial aesthetic correction of mid face wrinkles through a minimally invasive method.

The potential risk associated with Demetech Barbed PDO Suture include:

- Bleeding, pain/tenderness, edema, ecchymosis/bruising, tightness, bumps/puckering, contour irregularity in the skin from aberrant placement of the suture in the subcutaneous plane, asymmetry, foreign body reaction, allergic reaction, broken thread, loss of correction, discoloration, extrusion, hematoma, infection, chronic inflammation, and cellulitis, motor and sensory nerve injury.

- As with any medical intervention, adverse events, other than those mentioned above, can occur.

3.4 Risk Mitigation Strategy

Device based risked have been demonstrated to be acceptable via approval of the device in the 510k K191361. Additional risks for this investigation have been addressed in Attachment A: Additional Risk Analysis. Risks will be mitigated by providing a descriptive Instructions for Use to prevent process-based risks. As seen in K191361, devices had bench, biocompatibility, sterilization, and shelf-life testing performed in order to minimize device functionality risks.

4 STUDY OBJECTIVES

This study will evaluate the safety and effectiveness of Demetech Barbed PDO Sutures for the temporary correction of mid face wrinkles.

4.1 Effectiveness Endpoints

The primary effectiveness endpoint is the proportion of subjects with ≥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. The median score as rated by the blinded panel using subject photographs will be used to determine if a subject is a responder. As PMA P050047 used a target rate of 60% to demonstrate device superiority over a minimal clinically meaningful response, clinical effectiveness will be demonstrated by superiority of this 6-month response rate over a target rate of 60%.

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.

The secondary effectiveness endpoints include:

1. Individual endpoints at each timepoint of 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 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 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 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.

4.2 Safety Endpoint

The safety endpoint of the study is to assess the rate and severity of adverse events (AEs) from initial treatment through 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. Events will be recorded using a subject take-home diary as well as at live follow up visits. Pain and bleeding adverse events will be summarized as a secondary safety endpoint, both by total frequency and frequency by subject.

In addition, an Immediate Visual Disturbance Incidence Reporting process will be in place. Any incidence of visual disturbances (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 recorded on the diary.

Protocol Stopping Rules will be in place to halt further subject enrollment if the following serious adverse events are observed: motor nerve injury, arterial injury, parotid gland injury, or vision loss, (refer to section 9.5 for additional details).

5 INVESTIGATIONAL PLAN

5.1 Overall study design

The study will be 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.

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.

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.

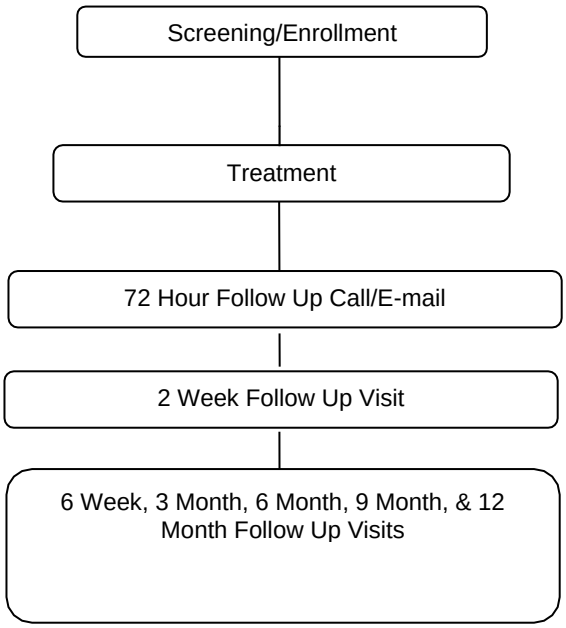
5.2 Photography Protocol

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.

5.3 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.

5.3.1 Study flow chart



6 STUDY POPULATION

6.1 Inclusion criteria

Only subjects meeting all of the following inclusion criteria will be considered for study enrollment:

1. Male and female subjects, 22+ years of age.
2. Subject received a rating, in each cheek, by PI of at least Class 1 or more for wrinkling in the midface according to the Lemperle Scale Classification of Facial Wrinkling.
3. If a woman is of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile), then she must have a confirmed negative urine pregnancy test result at screening. If treatment is not provided at the screening visit, a negative urine pregnancy test result is required within 7 days before treatment.
4. If a woman of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile), subject confirms she will utilize at least one form of contraception throughout the duration of the study.
5. Subjects who desire cheek lifting to correct age-related wrinkles in the mid-face as recommended by the treating investigator.
6. Subjects who are able to understand the study requirements, including the obligation not to receive any other facial procedures or treatments affecting mid-face at any time during the study. These include procedures or treatments done at home or with a professional. Facial treatments include lasers, facial massages, and anything beyond common skincare routine.
7. Subjects who are willing to participate in the study and to sign a witnessed/informed consent form.
8. Subjects who are logistically able to present for all study visits and meet all study requirements.
9. Subjects who are willing to complete the 30-day diary.
10. Subjects who pass the pinprick and/or cotton swab facial nerve assessment.

6.2 Exclusion criteria

Subjects having any of the following criteria, either at screening or at baseline, will not be included in the study:

35.

36. Abnormal rating in midface sensation, with inability to feel a 0.4 G monofilament or a cotton wisp at any site on the midface.
37. Active acne or prominent acne scars in the treatment area.
38. Active inflammatory or infectious conditions
39. Allergy or foreign body sensitivities to plastic biomaterials
40. Known bleeding disorder
41. Breast feeding, pregnant, or not on/willing to use contraception if of childbearing potential (not amenorrheic for the previous 24 months or not surgically sterile),
42. Collagen skin disorder
43. Pre-existing facial asymmetry

44. History of any device use on the mid-face in the prior 6 months (laser, IPL, radiofrequency, ultrasound, micro needling, micro needle RF, or cool based treatments).
45. History of autoimmune or connective tissue disease
46. History of facelift, midface lift, lower facelift. Neck lift that changes the facial structure and anchor points would be exclusionary.
47. History of fat transfer to the midface.
48. History of injectable fillers other than temporary fillers such as Hyaluronic Acid or Radiesse to the midface at any time. Permanent and semi-permanent fillers are not allowed (PLLA, Sculptra)
49. History of Kybella in the prior 6 months
50. History of facial trauma in the mid-face
51. History of facial surgical procedures
52. Inability to chew, puff cheek, or smile broadly
53. Metabolism irregularities
54. On immunosuppressive therapy
55. Recent weight loss or intention to lose a significant amount of weight during the study period (2 BMI Points)
56. Subjects who have undergone cosmetic facial plastic surgery (with the exception of rhinoplasty or upper blepharoplasty, more than 2 years prior to enrollment), tissue grafting, or tissue lifting or augmentation with any permanent or semi-permanent filler.
57. Subjects who have had temporary facial dermal filler injections below the orbital rim with HA-based fillers or Radiesse within 18 months, porcine-based collagen fillers within 24 months, or neuromodulator injections to the midface or lateral canthal lines, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months of entry in the study or who were planning to undergo any of these procedures at any time during the study.
58. Subjects who have very thin skin in the mid-face region, who have the tendency to accumulate fluid in the lower eyelids, or who have large infraorbital fat pads (i.e., significant convexity or projection from the infraorbital fat pads).
59. Subjects who have mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease.
60. Subjects who have serious concurrent illness which may lead to problems with wound healing (e.g., uncontrolled diabetes or vascular disease).
61. Subjects with known or suspected family history of problems with keloid scarring.
62. Subjects with serious neurological or psychological conditions which could prevent the subject from cooperating with treatment or post-procedure care and assessment.
63. Smokers, since this may compromise wound healing.
64. Subjects who have a current or prior history within the last 3 years of neoplasm and/or any active neoplasm in the face or that in the opinion of the Investigator may make then not a suitable candidate.
65. Subjects currently enrolled in other clinical trials.
66. Subjects taking Warfarin or other anticoagulants. These subjects may experience a significant risk of problems with post-operative bleeding.
67. Subjects who have taken, in the last 2 weeks, ad-lib medication or herbal supplements that may increase risk of bleeding. This includes aspirin or other herbal supplements known to increase risk of bleeding.
68. Subjects with significant co-morbidities e.g., heart disease, strokes, or angina) that in the opinion of the Investigator may prevent the subject from completing the study.
69. Subjects with planned cosmetic procedures, facial or dental surgery during the follow-up period.
12. Other concerning health issue in the opinion of the Investigator.

6.2.1 Discontinuation of subjects

The subject may discontinue from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled. There is no loss of benefit if the subject decides to not participate in the study. Date and discontinuation circumstances should be stated.
Subjects must be discontinued from the study by the investigator at any time for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject
- Failure to comply with requirements
- Investigator discretion that study is no longer in subject's best interest
- Repeated non-compliance

Before discontinuation, every effort should be made to ensure that the subject returned for a final study visit. In the case of loss to follow-up subjects, every effort should be made to contact subjects lost to follow-up, and all such efforts should be documented in the subject file.

6.2.2 Premature termination or suspension of the study or a study site

The study or a study site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the study or a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.
- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data do not justify a continuation of the study.
- The investigator or study site exhibit serious and/or persistent non-adherence to the clinical study protocol and/or applicable regulatory requirements.
- The sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the IRB has decided to terminate or suspend approval for the study, the study site, or the investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as appropriate.

7 TREATMENTS

7.1 Investigational product(s)

7.1.1 Description of investigational product(s)

Demetech Barbed PDO Suture is a 510k approved absorbable polydioxanone (PDO) suture with barbed sutures along the surface.

7.1.2 Disposition of investigational product(s)

The Sponsor will provide the Investigator with a supply of study devices for conduct of the study. The devices will be packed in containers labeled as clinical investigational devices according to the regulatory requirements under which they are shipped. Investigational devices will be logged into the device accountability log. If a device is used in the investigation, it will be documented in the device accountability log. Devices returned to the Sponsor will be noted as such in the device accountability log.

The Investigator shall permit an investigational device to be used only in subjects enrolled in the study. The Investigator shall not supply an investigational device to any person not authorized to receive it.

The Investigator or designee shall document receipt, use, and disposition of the device as it relates to:

- The quantity of the device, dates of receipt, catalogue and lot numbers.
- The names of all persons who received each device; and
- Why and how many units of the device have been returned to Sponsor or otherwise have left the possession of the Investigator.

The devices must be stored separately from other clinical supplies. Opened, unused devices must be returned to the Sponsor or destroyed on site as directed by the Sponsor.

The use of the study product outside of this protocol is prohibited. Each investigational site will identify a designee who will be held responsible for controlling the product and ensuring that the product is dispensed only for the purposes of this study. This designee will be expected to retain all unused study supplies until the completion of the study and/or until a representative of the Sponsor has inventoried and made arrangements to return the supplies to the Sponsor. Upon completion or termination of this investigation or the Investigator's part of this investigation, or at the request of the Sponsor, the Investigator shall return any remaining supply of the device or otherwise dispose of the device as directed by the Sponsor.

7.2 Treatment administration

7.2.1 Randomization Procedures

All subjects will receive the Demetech Barbed PDO Suture. There are no randomization procedures for this study. Up to two run-in subjects may be treated with the Demetech Barbed PDO Suture per investigator in order to become familiar with study device characteristics.

7.2.2 Treatment method

PDO threads are placed in a subcutaneous plane which is the tissue right under the skin in the fat layer. See attachment 15.5 for treatment method details.

7.3 Restrictions during the study

Subjects in this study are restricted from the following for the duration of their participation in this study.

- Surgery in mid-face areas.
- Any medication which, in the judgement of the investigator, may interfere with the study objectives.
- High-dose Vitamin E, aspirin, anti-inflammatories, antiplatelets, or thrombolytics up to 1 month after treatment.
- Dermabrasion, facelift, or Botox, or tissue augmentation for facial wrinkles and scars in mid-face areas.
- Any injections outside of those in the study protocol including non-permanent fillers (e.g., hyaluronic acid, CaHA) or neurotoxin on the face below the orbital rim (forehead is acceptable).
- Dermal resurfacing procedures or non-invasive skin tightening on the face.
- Prescription facial wrinkle therapies (tretinoin), topical steroids, skin irritating topical preparations, or self-tanning agents on the face.
- Participation in a weight loss/gain during (for a change of 5% of body weight).

7.4 Blinding Procedures

The treating investigator, the subject, and study staff will not be blinded. There will be a panel of the three evaluators who will be blinded. Keeping the panel of three evaluators blind will be accomplished by:

- The treating physician, study staff, and office staff do not inform the panel of three blinded evaluators of whom they are viewing or of the chronological timepoint of the photograph.
- The panel of three blinded evaluators will record ratings on a source document that is maintained separately from the study subject’s main source document binder.

8 STUDY ASSESSMENTS

8.1 Screening / Enrollment

Each subject will present for a Screening/Enrollment Visit. At this visit, subjects will be provided with an informed consent form to review. Prior to conducting any activities specifically related to the study, written informed consent from the subject will be obtained.

After a subject consents to participation in the study, they will be assessed for the study inclusion/exclusion criteria. For the inclusion criterion a rating, in each cheek, of at least Class 1 or more for wrinkling in the midface according to the Lemperle Classification Facial Wrinkle Scale as determined by the treating investigator is required for the subject to be eligible. The treating investigator will be specifically trained and qualified on the Lemperle Scale by the study sponsor.

If all criteria are met, the subject will be enrolled and assigned a study ID number via an electronic data capture system. Females of childbearing potential will receive a urine pregnancy test and if the result is positive, will be withdrawn from the study. For enrolled subjects, demographics, weight, medical history, and concomitant medication[1] information will be collected. In addition, subjects will complete the FACE-Q Satisfaction with Cheeks and Age Appraisal scales and standardized photographs will be taken.

8.2 Treatment

If desired, screening/enrollment and treatment can occur at the same visit. However, these visits cannot occur more than 14 days apart.

For the procedure, the treating investigator will follow the respective Instructions For Use for the Demetech Barbed PDO Suture.

Procedure details and details regarding any adverse events observed will be recorded. In addition, subjects will receive a 30-day take-home diary on which to record any adverse events experienced post treatment. The investigator will also assess facial nerve function via motor exam. Subjects will be followed up for safety via telephone or email at 72 hours after the procedure.

8.3 Follow Up Visits

All subjects will return for follow-up visit 2 weeks after the procedure. At this visit, subjects will be assessed for adverse events and completed pages of the take-home diary will be collected. Subject weight will be recorded.

All subjects will return for additional follow-up visits at 6 weeks, 3 months, 6 months, 9 months and 12 months after the initial treatment.

The following will be performed at each of these follow-up visits:

[1] Any medication necessary to support the vital functions of the subject or which are part of the standard treatment of the subject, which can and must be administered during the period of the study, must be recorded.

[redacted]

9 SAFETY ASSESSMENTS

All adverse events (AEs) and common treatment site responses (CTRs) observed by study subjects, investigators or other study staff from first exposure to the study product through last study follow up visit will be recorded. This will include use of a subject take-home diary on which to record any side effects experienced for 30 days after any injection.

The following information, at minimum, must be recorded for AEs:

- Description
- Type (serious, expected, unexpected) – Refer to definitions below
- Start and Stop Dates
- Intensity (mild, moderate, severe) – Refer to definitions below
- Causal relationship (not related, related) – Refer to definitions below
- Treatment description, if any

The following information will be recorded on subject diaries for CTRs:

- Description
- Start and Stop Dates
- Intensity (mild, moderate, severe) – Refer to definitions below
- Treatment description, if any

9.1 Definition of intensity

The clinical intensity of an AE or CTR will be classified as:

Mild: Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.

Moderate: Signs and symptoms that cause discomfort and interfere with normal functioning, but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.

Severe: Signs and symptoms that affect usual daily activity and incapacitate the subject, thereby interrupting his/her daily activities.

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the CRF AE report form). In such situations, the investigator should make a judgment based on personal experience.

9.2 Definition of causal relationship

An AE is considered to be "related" to IP(s) if a causal relationship between the IP(s) 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."

9.3 Definition of type

9.3.1 Adverse event

The general definition for an adverse event (AE) is an untoward medical occurrence which does not necessarily have a causal relationship to the investigational product.

9.3.2 Serious adverse event

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

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

All SAEs that occur during the study period, whether considered to be related to the investigational product or not must be reported within 24 hours of knowledge of the event to the sponsor via an EDC notification.

Although all information required for completion of an SAE report form may not be available within the specified time period, the following minimal initial information should be reported: Subject ID #, Site #, an identifiable reporting source name and contact information (e.g., investigator/study coordinator), which of the 6 SAE criteria identified above resulted in the event being deemed “serious”.

IRB reporting requirements may also apply for SAEs.

9.3.3 Unanticipated adverse device effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the IDE investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. FDA, IRB, and investigator reporting requirements apply.

9.3.4 Common Treatment Site Responses

Common treatment site responses (CTRs) are expected side effects that result from study treatment. These include but are not limited to bleeding, pain/tenderness, edema, ecchymosis, tightness, bumps/puckering, contour irregularity in the skin from aberrant placement of the suture in the subcutaneous plane, asymmetry, foreign body reaction, broken thread, hematoma, and chronic inflammation. For 30 days after treatment, subjects will record CTRs on a take-home diary. Any CTR that extends beyond the diary collection period of 30 days will be defined as an Adverse Event and recorded on an Adverse Event form.

9.4 Recording Adverse Events

All AEs and CTRs occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause.

Events that are ongoing at the time subjects return their diaries will be reported as an adverse event.

The investigator will promptly review documented adverse events and abnormal test findings to determine:

- If the abnormal test finding should be classified as an adverse event.
- If there is a reasonable possibility that the adverse event was caused by the investigational device or other study treatments or diagnostic product(s), if applicable.
- If the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)," the adverse event will be classified as associated with the use of the investigational device or study treatment or diagnostic drug product(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)," the determination and the rationale for the determination will be documented in the respective subject's case history.

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study device will be recorded in the eCRFs.

9.5 Reporting Adverse Events

Any adverse event that results in serious injury or death and any type of unanticipated adverse device effect, regardless of seriousness or severity, must be reported to the study Sponsor within 24 hours of the site becoming aware of the event. Initial reports may be partial and should be updated as additional information becomes available.

All unanticipated adverse device effects and all adverse events resulting in research subject death or injury reported by the Investigator to the study Sponsor should also be reported to the Investigator's local IRB in accordance with their reporting requirements.

Subjects will be provided with a study site contact name and phone number to report any concerns about adverse events.

Stopping Rules will be as follows to halt further subject enrollment if the following serious adverse events are observed - vision loss, motor nerve injury, arterial injury, or parotid gland injury.

- Enrollment and treatment will be suspended at the investigational site at which the event occurs.

- A root cause investigation will be conducted to determine whether the outcome was anticipated (the investigator did not properly follow the treatment procedure) or unanticipated (the investigator did properly follow the treatment procedure).
- If the investigator did properly follow the treatment procedure, the entire study will be immediately suspended, and no subjects will be enrolled until the event can be properly characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

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

The monitor for this study is:

[redacted]

Monitoring procedures will include one or more visits prior to study initiation as well as periodic monitoring visits during the study on a regular basis according to a mutually agreed schedule. During these visits, the monitor will check for compliance with the study protocol and applicable regulations including but not limited to assessing integrity of the source data with the CRF entries; proper reporting of adverse events; subject eligibility and consent; and proper handling and disposition of the investigational product.

In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required. Monitors will confirm product accountability and disposition. Additionally, the ongoing ability of site staff to continue the conduct of the study in a compliant manner will be assessed.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits.

10.2 Audits / Inspections

Audits may be performed, including the possibility that a member of the sponsor's quality assurance function or their representative may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there.

Inspections by regulatory authority representatives and IRBs are possible at any time, even after the end of study. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IRB and/or regulatory authorities, and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

11 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study planning. Further details on the statistical and analytical aspects will be presented in the Statistical Analysis Plan (SAP).

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close or unblinding, respectively, will be described in amendments to the clinical study protocol or the SAP. All deviations and/or alterations will be summarized in the clinical study report.

11.1 Determination of sample size

For this study, a successful outcome is defined as ≥1 improvement from baseline at 6 months on the five-point Lemperle Classification Facial Wrinkle Scale, as rated by a panel of three blinded evaluators using subject photographs. The median score as rated by the blinded panel will be used to determine if a subject is a responder. As PMA P050047 used a target rate of 60% to demonstrate device superiority over a minimal clinically meaningful response, clinical effectiveness will be demonstrated by superiority of this 6-month response rate over a target rate of 60%.

Sample size calculations were estimated using [redacted] Statistical power calculations were conducted based on the primary effectiveness targets of previously approved studies. PMA P050047 used a target rate of 60% to demonstrate device superiority over a minimal clinically meaningful response. [redacted]

Although only 48 subjects are required, 57 subjects will be treated in the study to collect additional safety data and to account for an attrition rate of 15%.

11.2 Analysis sets

Performance data will be analyzed on the Intention to Treat (ITT) population. Further analyses will be performed on the Per Protocol Set (PPS).

The ITT population will consist of all subjects who were enrolled, regardless of adherence to the protocol.

The PPS will be a subset of the ITT population, consisting of all treated subjects for whom defined as treated subjects for 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.

Safety data (such as AEs) will be analyzed using the Safety Evaluation Set (SES). The SES will consist of all treated subjects regardless of protocol compliance.

11.3 Statistical analysis methods

All collected data will be presented in listings, and all analysis will be presented using summary statistics for [redacted] as appropriate. The study population will be described using summary statistics for [redacted] Computation for all results will be performed using the [redacted]

Further details on the statistical and analytical aspects will be presented in the Statistical Analysis Plan (SAP).

11.3.1 Effectiveness variables

The primary effectiveness variable is the responder rate or proportion of responders of ≥ 1 point improvement from baseline on the Lemperle Classification Facial Wrinkle Scale at 6 months, as rated by a panel of three blinded evaluators using photographs for assessment. Each subject will be classified as a success (improvement by ≥1 point compared to baseline) or a failure (improvement by <1 compared to baseline) at 6 months. A subject's responder status is derived from the score as rated per side. A subject must have at least 1 point improvement on both sides to be classified as a responder. A subject's by-side score is the median value as rated by the panel of three blinded evaluators.

The responder rate of ≥ 1 point improvement from baseline and change from baseline as rated by a panel of three blinded evaluators at each individual timepoint of 3, 9, and 12 months, as well as by the Investigator at 3, 6, 9, and 12 months, is also a secondary effectiveness variable. Change from baseline uses the average of by-side scores to derive the subject's global score.

Other effectiveness variables include GAIS score responder rates as rated by the treating investigator and the study subject, and FACE-Q Satisfaction with Cheeks and Age Appraisal scales as rated by the subject. These will be evaluated at 6 weeks, 3, 6, 9, and 12 months.

11.3.1.1 Primary effectiveness variable

[redacted]

The null and alternative superiority hypotheses are:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.3.1.2 Secondary effectiveness variables

Each timepoint and each rater will be analyzed as an individual endpoint for all secondary endpoints. The secondary endpoints will be [redacted] as appropriate. Secondary effectiveness responder analyses are compared against a [redacted]

The secondary effectiveness endpoints are:

1. Individual endpoints at each timepoint of 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 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 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 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.

11.3.1.2.1 Improvement on the Lemperle Scale

At 3, 9, and 12 months, responders with ≥1 point improvement from baseline on the Lemperle Scale, as rated by a panel of three blinded evaluators will be summarized. [redacted]

The null and alternative hypotheses are:

[redacted]

11.3.1.2.2 Change from baseline on the Lemperle Scale

Summary statistics will be used for change from baseline at 3, 6, 9, and 12 months on the Lemperle Scale, as rated by a panel of three blinded evaluators. [redacted]

The null and alternative hypotheses are:

[redacted]

11.3.1.2.3 Improvement on the Lemperle Scale, Live Investigator Rating

At 3, 6, 9, and 12 months, responders with ≥1 point improvement from baseline on the Lemperle Scale, as rated by the investigator, will be summarized. [redacted]

The null and alternative hypotheses are:

[redacted]

[redacted]

[redacted]

11.3.1.2.4 Change from baseline on the Lemperle Scale, Live Investigator Rating

Summary statistics will be used for change from baseline at 3, 6, 9, and 12 months on the Lemperle Scale, as rated by the Investigator. [redacted]

The null and alternative hypotheses are:

[redacted]

[redacted]

[redacted]

11.3.1.2.5 GAIS Improvement, Investigator Rating

GAIS scores at 6 weeks, 6, 9, and 12 months as rated by the Investigator will be summarized as counts by each subject, [redacted]

The null and alternative hypotheses are:

[redacted]

[redacted]

[redacted]

11.3.1.2.6 GAIS Improvement, Subject Rating

GAIS scores at 6 weeks, 6, 9, and 12 months as rated by the Subject will be summarized as counts by each subject, [redacted]

The null and alternative hypotheses are:

[redacted]

[redacted]

[redacted]

11.3.1.2.7 Improvement from Baseline in FACE-Q

Summary statistics will be used for improvement from baseline on the validated FACE-Q Appraisal of Satisfaction with Cheeks and Age Appraisal scales at 6 weeks, 6, 9, and 12 months as rated by the study subject. [redacted]

The null and alternative hypotheses are:

[redacted]

[redacted]

[redacted]

11.3.2 Safety variables

Adverse events (AEs) and common treatment responses (CTRs) will be categorized and summarized descriptively by type, duration, severity, relationship to study device and need for treatment. Pain and bleeding adverse events will be summarized as a secondary safety endpoint, both by total frequency and frequency by subject. The adverse event summary tables will be broken down by age category, Fitzpatrick Skin Type (I-III v. IV-VI) and other subgroups of interest. Categories will be further defined in the SAP.

Safety analyses will be performed on the Safety Evaluation Set (SES). Only treatment emergent AEs [TEAEs], which are defined as AEs with onset or worsening after the initial treatment through the last study visit. [redacted]

11.3.3 Other statistical / analytical issues

11.3.3.1 Discontinuations and missing data

Procedures for discontinuations and missing data may be performed in accordance with the SAP, as appropriate. For the primary efficacy analysis, [redacted]

[redacted]

11.3.3.2 Interim analyses

There are no plans for interim analyses.

11.3.3.3 Exploratory analyses

Pre-planned exploratory analyses will be specified in the SAP. Additional ad hoc exploratory analyses may be performed at the discretion of the Sponsor and results will be presented as such.

11.3.3.4 Significance Level

The primary endpoint analysis and sensitivity analyses of the primary endpoint will be performed based on [redacted] All other statistical tests will be performed based on [redacted]

12 DATA HANDLING AND RECORDKEEPING

12.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

1. What protected health information (PHI) will be collected from subjects in this study.
2. Who will have access to that information and why
3. Who will use or disclose that information.
4. The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

12.2 Source Documents

The full dataset should be collected for all subjects randomized. All required data for this study will be collected in the eCRFs. The collected data will be entered into a validated database. Database lock will occur once quality assurance procedures have been completed.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, memoranda, evaluation checklists, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays and subject files.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

12.3 Data Capture

Electronic Data Capture (EDC) is the primary data collection instrument for the study. All data requested on the EDC's electronic Case Report Forms (eCRF) must be recorded and missing data noted. The EDC system has pre-set logic checks for all required fields, forcing an explanation for each omitted field. The EDC system also allows for data corrections, noting the change as well as who made it and at what time. All data collected for the study and entered into the EDC must be traceable to a source document.

eCRFs will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and electronically sign the completed eCRF for each subject; the Investigator's electronic signature will serve as a testament of the Investigator's responsibility for ensuring that all clinical data entered on the eCRFs are complete, accurate and authentic.

12.4 Record Retention and Availability

It is the Investigator's responsibility to retain study-essential documents for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed informed consent form (ICF), HIPAA authorization and assent form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information in the eCRFs was derived.

13 PUBLICATION POLICY

The study sites and Investigator each acknowledge that the study is part of a multi-center study, and an independent, joint publication is anticipated to be authored by Investigators in the multi-center study, including the Principal Investigator. Therefore, the clinical site and Investigator each agree not to publish or present the results of the Study before the publication of the multi-center Investigator paper, but in no event shall any site or Investigator be so restricted after the expiration of twelve (12) months from completion of the study at all sites.

If a site or Investigator prepares any presentation or publication, the Sponsor must be sent a draft of the same for the Sponsor's review and comment. The site or Investigator must give these comments due consideration. The Sponsor shall return comments to the site or Investigator within thirty (30) days after initial receipt. In the event that the site or Investigator and the Sponsor differ in their opinion or interpretation of data in the publication, the parties shall resolve such differences in good faith through appropriate scientific debate. In addition, the site or Investigator shall delay any proposed publication/presentation an additional sixty (60) days in the event the Sponsor requests to secure a patent or other proprietary protection.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between Sutura Medical Technology, Inc. and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act.

14 REFERENCES

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