CLINICAL INVESTIGATION PLAN

Evaluation of Safety and Effectiveness of APTOS Threads – Absorbable Surgical Sutures Excellence Product Line Models for Mid-face Suspension by Mini-Invasive Surgery to Temporarily Fixate the Cheek Sub-dermis in a Repositioned Site for the Treatment of Moderate to Severe Nasolabial Fold

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STUDY SYNOPSIS

Clinical Investigation Title	Evaluation of Safety and Effectiveness of APTOS Threads – Absorbable Surgical Sutures Excellence Product Line Models for Mid-Face Suspension by Mini-Invasive Surgery to Temporarily Fixate the Cheek Sub-dermis in a Repositioned Site for the Treatment of Moderate to Severe Nasolabial Fold
Short Title	Evaluation of Safety and Effectiveness of APTOS Threads - Excellence Product Line Models for Treatment of Nasolabial Folds
Reference Number	EXCELLENCE-001
Version of the CIP	Version 4.0, 25 February 2026
Sponsor name and address	Aptos LLC 15 Givi Amilakhvari Street 0109 Tbilisi, Georgia
Participating locations and country	**Principal Investigators (PIs)** 1) Nino Nishnianidze, "Total Charm" LTD, Tbilisi, Georgia 2) Albina Kajaia, "Total Charm Vake" LTD, Tbilisi, Georgia 3) Ketevan Kavtaradze, "Total Charm Piazza" LTD, Batumi, Georgia **Independent Blinded Evaluators (IBEs):** Three (3) independent board-certified dermatologists and plastic surgeons will be assigned as IBEs for each scale: Wrinkle Severity Rating Scale (WSRS), Global Aesthetic Improvement Scale (GAIS), Canfield Jawline Definition Scale (CJDS).
Name of Investigational Medical Device (IMD)	**APTOS Threads – Absorbable Surgical Sutures (APTOS THREADS-ABSORBABLE – POLY (L-LACTIDE-co-ε-CAPROLACTONE), P(LA/CL)):** Excellence Product Line Models: • Visage Excellence Method (EV) • Visage Excellence Method S (EVS) • Visage Excellence Method HA (EVHA) • Visage Excellence Method S HA (EVSHA) • Nano Excellence Method (NE) • Nano Excellence Method HA (NEHA)
Investigational Medical Device indication and intended purpose:	**Intended purpose:** APTOS Threads - Excellence Product Line models are single use implantable devices, intended to be totally introduced into the human's subcutaneous tissue by dermatologists and plastic surgeons for the purpose of temporary modifying anatomy of subcutaneous tissue and skin through repositioning of the subcutaneous tissue and its temporary fixation in repositioned site in adult male and female patients having moderate and severe facial (mid face – nasolabial fold) skin laxity. **Indication:**

	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe nasolabial folds.
Clinical investigation purpose and background	Attractiveness of the midfacial features is a key component to facial aesthetics, and treatment of midfacial aging, together with rejuvenation of the lower third of the face, is therefore key to eliminating the signs of facial aging [1-5]. Most of the facial aging changes occur in the middle and lower face as a consequence of gravity, and solutions for facial aging include lifting drooping soft tissues, augmenting shrunken areas with fat grafts or implants, and antigravitational lifting procedures [6]. Historically, facial aging was primarily addressed with face lift surgery (rhytidectomy) [7], however there is currently an increasing demand for less invasive antiaging interventions that have a shorter procedure duration, easier technical execution, faster postoperative recovery, fewer complications and durable effect [8,9]. Thread lifting techniques are therefore becoming more attractive than traditional surgical lifting procedures for facial augmentation [6-8]. Thread lifting involves the passage of sutures under the skin to counteract the descent and laxity of the tissues [9, 10]. Face lifting with absorbable threads with barbs/cones has been shown to be an effective and tolerable procedure for facial rejuvenation [6,8-15]. Specifically, satisfaction with nasolabial fold, marionettes, lower face, and jawline appearance was shown to be significantly improved 6 and 12 months after thread lifting [12]. It has been demonstrated tissue repositioning can last up to 12 months for the correction of mild to moderate ptosis of the jawline and midface [11,18]. Aptos LLC has developed APTOS Absorbable Threads, a sterile, implantable, fully resorbable device intended for adult patients, which also includes threads coated with hyaluronic acid (HA), a biodegradable, non-immunogenic, and non-toxic glycosaminoglycan, which is an essential component of the extracellular matrix. APTOS Absorbable Threads are used in aesthetic surgery for fixation, repositioning, and approximation of soft tissues and skin of the face and body. This Clinical Investigation Plan (CIP) describes the investigation of application of APTOS Absorbable Threads (Excellence models) for mid-facial laxity – nasolabial folds correction. Although there is no generally accepted standard treatment, there are several other alternatives for the improvement of nasolabial fold. Current treatment options for improvement of facial wrinkles or folds include the use of soft tissue fillers, plastic surgery (i.e., facelift), botulinum toxin or deoxycholic acid injections, fat removal, radiofrequency / ultrasound skin tightening. The medical device under investigation (IMD) has been CE-marked since 2014 under EU MDD (directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001). According to Article 120 (3a), Medical Device Regulation (MDR) European Union (EU) 2017/745 these products are recognized as Legacy Devices. The prospective post-market clinical study Excellence-001 (Part 1 and 2) is conducted to provide pivotal data on the

	effectiveness and safety of APTOS Threads - Excellence Product Line models in nasolabial fold improvement and is intended to confirm the new IMD intended use according to Common Specifications (CS) of Annex XVI, Medical Device Regulation (MDR) European Union (EU) 2017/745. Biostimulation refers to the stimulation of dermal fibroblasts, promoting replication, protein synthesis, and production of extracellular matrix (ECM) components, primarily collagen and elastin [19]. Lifting threads are known to stimulate collagen production, with various effects depending on thread material [18,19]. APTOS (P(LA/CL) and P(LA/CL)-HA) threads combine three biostimulatory agents: PLLA, PCL, and non-crosslinked HA in one device. PLLA and PCL promote long-term collagen regeneration, and the breakdown of threads generates low molecular weight molecules that gradually prompt the skin to produce collagen and HA [20-31]. Non-crosslinked HA is the natural component of the extracellular matrix which stimulates fibroblast proliferation, synthesis of collagen and elastin, endogenous HA, resulting in increased moisture, revitalization, and firmness of the skin [32,33]. The animal studies performed for both types of APTOS threads (P(LA/CL) and P(LA/CL)-HA) showed collagen and elastin stimulation [20,21] that clinically manifests as improvement of skin quality. This study was aimed to provide exploratory data within the optional biopsy Substudy on biostimulation and skin quality improvement capabilities of APTOS threads implanted in the mid-face. Midface and jawline improvement in case of thread lifting are interrelated due to the anatomical interconnection of facial tissues, which was previously investigated [11]. Jawline Substudy of this CIP retrospectively evaluates the potential added benefit of APTOS Excellence threads for jawline contouring through midface suspension.
Comparator	N/A
Clinical development stage	Post-market
Amendments	**Amendment 1:** from version 1.0 dated 15 April 2024 to version 2.0 dated 14 March 2025. Statistical analysis and endpoint wording updated. Collection of Fitzpatrick skin type added to procedures. Interim analysis removed. **Amendment 2**: from version 2.0 dated 14 March 2025 to version 3.0 dated 10 July 2025. Retrospective Jawline Substudy added. Visit window for Part II Day 720 extended. **Amendment 3**: from version 3.0 dated 10 July 2025 to version 4.0 dated 25 February 2026. PI list updated, visit window for Part II Day 720 extended. Expected sample size for Part 2 updated.
Overall study design	This is a multicenter, prospective study consisting of two prospective parts (Part 1 and Part 2) and one retrospective part – Jawline Substudy. Part 1 is short / mid-term study (the main study) that includes an optional two-arm biopsy Substudy, and Part 2 is an optional long-term follow-up study where safety, effectiveness, and user satisfaction of a midface thread implantation device are

	evaluated over two years. Jawline Substudy is a retrospective study utilizing the data (subjects' photos) collected during Part 1 for evaluation of the effect of the device under study on jawline definition. After signing Informed Consent for Part 1, all subjects will undergo screening procedures to assess their eligibility for study enrollment. The enrolled patients will undergo one-time treatment – implantation of the non-HA or HA-variants Excellence Aptos absorbable threads in the mid–face area and will further be followed up for 180 days in Part 1 and up to 720 days in Part 2**.** The retrospective Jawline Substudy will use the data collected in Part 1, will be conducted during Part 2 and will not involve any additional visits of subjects to the clinic or any procedures. **Key procedures at study visits:** **Part 1** *Screening Visit (Day -14 to Day 0)* • Receiving informed consent • Patient selection according to inclusion and exclusion criteria • Collection of patient medical history, demographic data, baseline characteristics • Documentation of concomitant medications • Urine pregnancy test is administered for female participants • 2D photo images are taken • Physical examination, including measurements of height, weight, and BMI • Nasolabial fold (NLF) severity assessment with WSRS • Facial nerve assessment (pinprick or cotton swab). *Procedure Day (Day 0)* • **Baseline assessments**: Face-Q™ Satisfaction with Skin questionnaire for patients participating in the biopsy Substudy, NLF severity assessment (WSRS) • **Imaging:** 2D photo images collection • **Randomization** (HA/non-HA) and **assignment of the model** from the Excellence Product line based on thread trajectory measurements • **Thread Implantation** • **Punch biopsy** for patients participating in the biopsy Substudy • **Safety assessments**: urine pregnancy test, physical examination including vital signs (blood pressure, heart rate, and temperature), adverse events assessment, collection of concomitant medications' information *Follow-up Visits: regular evaluations on Day 5 (±1 day), Day 14 (±2 days), Day 30 (±2 days), Day 90 (±7 days), and Day 180 (±7 days)* • **Imaging**: 2D photos collection (Day 30, Day 90, Day 180)

	• **Effectiveness assessments**: NLF severity assessment, GAIS assessment by subjects and blinded evaluators, Face-Q™ Satisfaction with Outcome questionnaire (Day 30, Day 90, Day 180), Face-Q™ Satisfaction with Skin questionnaire (for biopsy Substudy only) (Day 5, Day 30, Day 90, Day 180) • **Safety assessments**: adverse event assessment (diary review), physical examination • Punch biopsy for patients participating in the biopsy Substudy (Day 5, Day 90, Day 180) *End of Study (Day 180)*: patients who complete the six-month main study are offered participation in the extended follow-up study (Part 2). **Part 2** *Screening (Day 180 (±7 days)*: • patient selection and signing informed consent *Follow-up visits on Day 360 (±14 days), Day 540 (±14 days), Day 720 (±60 days)* • **Imaging**: 2D images collection • **Effectiveness assessments**: o NLF severity assessment (WSRS), o GAIS assessment by blinded evaluators and by patients o Face-Q™ Satisfaction with Outcome questionnaire • **Safety assessments**: physical examination, collection of concomitant medications' information, adverse events assessment **Jawline Substudy** This is a retrospective study which will include data obtained in study Excellence-001, Part 1. Subjects' face photos made before and 1, 3 and 6 months after thread implantation will be analyzed. Using these photos, changes in jawline definition after midface thread implantation will be assessed using Canfield Jawline Definition Scale (CJDS) on each side of the jawline by 3 blinded evaluators who will be not aware of the timepoint when each subject's photo was taken. Data from all subjects, participating in the study Excellence-001 by the time of data selection for the Jawline Substudy, with mild to very severe jawline definition loss, will be included in the retrospective analysis. Assessment of eligibility for this study will include evaluation of the degree of jawline definition loss with CJDS by Investigator using subjects' face photos collected at baseline of study Excellence-001. Assessment will be done for each face side, further CJDS assessments will be performed by IBEs.
Number of Subjects	**Part 1:** 140 subjects, with a 1:1 ratio of subjects receiving HA threads to subjects receiving non-HA threads. **Part 1, Biopsy Substudy:** 48 subjects, with at least 24 receiving HA threads and 24 receiving non-HA threads.

	Part 2: all patients who completed the main study, are eligible for the extension follow-up study, and agree to participate in Part 2 (**CIP amendment 3:** expected 70 subjects to complete Part 2 based on the number enrolled in Part 2 with expected 15% drop-out during Part 2). **Jawline Substudy**: all subjects of the Excellence-001 study, eligible according to the selection criteria for Jawline Substudy.
Number of Study Arms	**Parts 1, 2, 3:** Single-arm studies. **Part 1, Biopsy Substudy:** Two-arm study, in which results will be compared between HA threads and non-HA threads.
Duration and follow up of the clinical investigation	**Part 1 and Biopsy Substudy:** Twelve (12) months, comprising 4 months for enrollment, 6 months for patient short and mid-term follow-up, and 2 months for study close-out, data analysis and writing of the final study report. **Part 2:** One year and 8 months, comprising 1.5 years for patient follow-up, and 2 months for study close-out, data analysis and writing of the final study report. Patient enrollment will be optional and will take place at the Day 180 (Month 6) follow-up visit during Part 1. **Jawline Substudy:** 12 months
Part 1 (Main Study): <u>Six (6)-month evaluation of safety and effectiveness</u> of APTOS Threads - Excellence Product Line models for mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe NLFs.	
Study Objectives	1. Primary Objectives: 1.1. To demonstrate safety of the investigational medical device (IMD) models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through Day 30 (Month 1) after the implantation procedure. 1.2. To demonstrate effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 90 (Month 3) after the implantation procedure. 2. Secondary Objectives: 2.1. To assess safety of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through Day 180 (Month 6) after the implantation procedure. 2.2. To assess effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 30 (Month 1), Day 90 (Month 3), and Day 180 (Month 6) after the implantation procedure.
Study Endpoints	**Primary Endpoints** <u>Primary safety endpoints</u> Incidence of device and procedure related serious adverse events by Day 30 (Month 1) after the implantation procedure.

	Primary effectiveness endpoint Reduction in NLF severity at Day 90 (Month 3) after the implantation procedure in comparison with baseline grading, as assessed by blinded evaluators using the Wrinkles Severity Rating Scale (WSRS). **Secondary Endpoints** Secondary safety endpoints 1. Incidence of all adverse events after implantation of threads throughout the whole study (through Day 180 [Month 6] after the implantation procedure). 2. Incidence of early recovery symptoms (as listed in section 6.1.1) related to the treatment (threads implantation) among adverse events reported by both patients and treating physician(s) up to Day 14 after the implantation procedure. Secondary effectiveness endpoints 1. Observed values and change from baseline in WSRS on Day 30 and Day 180. 2. The proportion of subjects with improvement of ≥1 WSRS score at each visit 3. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 30, Day 90, and Day 180. 4. Mean GAIS value assessed by subject with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) 5. Patient satisfaction with the procedure outcome assessed using the mean total Face-Q™ Satisfaction with Outcome score at Day 30 (Month 1), Day 90 (Month 3), and Day 180 (Month 6) after the implantation procedure.
Inclusion Criteria	1. Male and female subjects, 22+ years of age. 2. Subjects who desire cheek lifting to correct age-related wrinkles in the mid-face as recommended by the treating investigator. 3. Subject received a rating, in each cheek, by Investigator of at least Grade 3 or Grade 4 for wrinkling of the NLF in the mid-face according to the WSRS. 4. 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. 5. 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 (6 months). 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 a 30-day diary. 10. Subjects who pass the pinprick and/or cotton swab facial nerve assessment.
Exclusion Criteria	1. Abnormal rating in mid-face sensation, with inability to feel a 0.4 G monofilament or a cotton wisp at any site on the mid-face. 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. Known collagen skin disorder. 8. Pre-existing facial asymmetry. 9. History of any device use on the mid-face in the prior 6 months (laser, Intense Pulsed Light [IPL], radiofrequency (RF), ultrasound, micro needling, micro needle RF, or cool based treatments). 10. History of autoimmune or connective tissue disease. 11. History of facelift, mid-face lift, lower facelift or neck lift that changes the facial structure and anchor points. 12. History of fat transfer to the mid-face. 13. History of injectable fillers other than temporary fillers such as HA or Radiesse to the mid-face at any time. Permanent and semi-permanent fillers are not allowed (Poly-L-lactic acids [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. Receiving immunosuppressive therapy. 20. Recent weight loss or intention to lose a significant amount of weight during the study period (2 body mass index [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 mid-face 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 a 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 are included to list of vulnerable populations (pediatric, pregnant, elderly individuals with visual or hearing impairments, mentally ill subjects).
Sample size justification	The sample size of the main study was calculated for each sub-group (i.e., HA threads and non-HA threads) separately. Hypothesis: H0: Delta≤0 H1: Delta>0 *Delta* is the mean difference from baseline to Day 90 in mean WSRS. The sample size assumptions are expected mean difference in WSRS score of 1 by Day 90 and its standard deviation SD=1.5 and customary significance and power of $\alpha = 0.01$ and $(1-\beta) = 0.9$. The total number of patients required for each group (HA threads and non-HA threads), including 5% expected drop out is 70. Thus, total sample size is 140.
Part 1 Biopsy Substudy *(Optional):* Histological assessment of the bio-stimulation effect (collagen and elastin stimulation effect) of APTOS Threads - Excellence Product Line with and without HA.	
Study Objectives	1. To assess the change over time in bio-stimulation effect of APTOS Threads - Excellence Product Line models in terms of collagen and elastin content. 2. To compare the bio-stimulation effect of APTOS Threads - Excellence Product Line models in terms of collagen and elastin content in non-HA threads versus HA threads. 3. To assess the change over time in patient-reported satisfaction with facial skin.

Study Endpoints	1. Difference between the HA and non-HA groups in change over time in biostimulation (collagen types 1,3 and elastin measurements before procedure and on Day 90). 2. Change in collagen types 1,3 and elastin percentage (%) in areas adjacent to implanted sutures by assessing collagen and elastin content using collagen and elastin polyclonal antibodies in the 3-mm biopsy sections obtained through punch biopsy on Day 5 and Day 180 in comparison with baseline (Day 0) 3. Degree/thickness of fibrosis (% / mm) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180. 4. Inflammatory cells (number / 400XHPF) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180. 5. Blood vessel proliferation (number / 400XHPF) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180. 6. Observed values and change from baseline in skin satisfaction score assessed using the Face-Q™ Satisfaction with Skin questionnaire collected from patients at Day 0, Day 30, Day 90 and Day 180.
Inclusion Criteria	1. Eligible for Part 1 Excellence-001 study. 2. Subject agrees to participate in the biopsy Substudy, i.e. signs the Substudy informed consent form.
Sample size justification	The sample size of the Substudy, i.e., to demonstrate the comparison of the HA and non-HA groups, was calculated using the independent t-test. Hypothesis: H_0: Delta ≤ 0% H_1: Delta > 0% *Delta* is the mean difference in collagen and elastin measurements between the HA and non-HA groups. For a difference of 5% between the two groups (HA and non-HA), we need 24 patients in each group, assuming as SD of 6%. The sample size assumptions are customary significance and power of $\alpha = 0.01$ and $(1-\beta) = 0.8$.
Part 2 Study *(Optional)*: Evaluation of <u>safety and effectiveness</u> of APTOS Threads - Excellence Product Line models for mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe NLFs <u>for an extended follow-up period up to 2 years</u>.	
Study Objectives	1. Primary Objective 1.1. To demonstrate effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site

	for NLF treatment at Day 360 (Year 1) after the implantation procedure. 2. Secondary Objectives 2.1. To assess safety of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through the study at Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure. 2.2. To assess effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure.
Study Endpoints	**Primary Endpoints** Primary effectiveness endpoint Reduction of NLF severity at Day 360 (Year 1) after the implantation procedure in comparison with baseline grading, assessed by the blinded evaluators using the WSRS. **Secondary Endpoints** Secondary safety endpoints: Incidence of all adverse events after implantation of threads throughout the whole study (to Day 720 [Year 2] after the implantation procedure). Secondary effectiveness endpoints 1. Observed values and change from baseline in WSRS on Day 540 (Year 1.5) and Day 720 (Year 2). 2. The proportion of subjects with improvement of ≥1 WSRS score at each visit 3. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2). 4. Mean GAIS value for subjects with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2). 5. Patient satisfaction with the procedure outcome assessed using the mean total Face-Q™ Satisfaction with Outcome questionnaire at Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure.
Inclusion Criteria	1. Subject completed Part 1 of the Excellence-001 study and attended the Day 180 (Month 6) visit. 2. Subjects who are willing to participate in the study and to sign a witnessed/informed consent form for Part 2. 3. 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. 4. Subjects who are logistically able to present for all study visits and meet all study requirements.
Exclusion Criteria	1. Recent weight loss or intention to lose a significant amount of weight during the study period (2 BMI points)
Sample size justification	The sample size of the Part 2 study will be based on subjects who completed the main study, are eligible for the extension follow-up study, and agree to participate in Part 2 (**CIP amendment 3**: expected 70 subjects to complete Part 2 based on the number enrolled in Part 2 with expected 15% drop-out during Part 2).
Jawline Substudy *(Retrospective)*: Evaluation of Jawline Definition in Subjects Who Had Midface Suspension with Excellence Product Line Models of APTOS Threads – Absorbable Surgical Sutures for Treatment of Nasolabial Fold	
Jawline Substudy Objectives	To assess retrospectively the changes in jawline definition for up to 6 months after thread implantation using CJDS in subjects who had undergone midface suspension with Excellence product line models of APTOS Threads – Absorbable Surgical Sutures for treatment of nasolabial fold in study Excellence-001.
Jawline Substudy Endpoints	**Primary endpoint in Jawline Substudy:** Improvement in jawline definition on Day 90 (Month 3) after the implantation procedure in comparison with baseline grading, as assessed by blinded evaluators using the Canfield Jawline Definition Scale **Secondary endpoints in Jawline Substudy:** 1. Proportion of subjects with improvement in CJDS score ≥1 point for both sides from baseline to Day 30, Day 90, Day 180 after IMD application. Subjects will be considered responders if improvement in CJDS scale ≥1 point is demonstrated for both face sides. 2. Improvement in jawline definition in comparison with baseline grading, as assessed with CJDS, and observed CJDS values on Day 30 and Day 180 after the implantation procedure 3. Improvement in jawline definition (mean change from baseline) ≥1 point on Day 30, Day 90, Day 180 after the implantation procedure in comparison with baseline grading, as assessed with CJDS 4. Correlation of improvement in NLFs and jawline definition on Day 30, Day 90, Day 180 after thread application
Jawline Substudy Inclusion Criteria	Data obtained in study Excellence-001 of the following subjects will be collected and analyzed:

	1. Subject underwent the IMD application procedure in Study Excellence-001. 2. Subject currently participates in study Excellence-001. 3. Subject has amenable photos for jawline definition assessment on each face side at baseline (prior to thread implantation) and at least one amenable photo for jawline definition assessment on each face side from follow-up visits of Excellence-001 study, Part 1 (Day 30, Day 90, or Day 180 after thread implantation). 4. Subject who had jawline definition loss from mild to very severe (CJDS score from 2 to 5) on both face sides at enrollment to study Excellence-001. 5. Subject who signed the informed consent form and agreed that his/her data obtained in study Ecellence-001 Part 1 will be used in current retrospective Substudy.
Jawline Substudy Exclusion Criteria	None
Jawline Substudy Sample size	As this is a retrospective analysis, all available data from subjects enrolled in the EXCELLENCE-001 study that meet the inclusion criteria will be included.
Statistical considerations	A comprehensive statistical analysis plan will be drafted and approved by the Sponsor before commencing data analysis. The following populations will be used for analysis: • **All subject analysis set:** Includes all screened patients. This set will be used for the disposition table and for the summary of reasons for premature termination or withdrawal. • **Intent-to-treat analysis set (ITT):** Includes all randomized patients. The set will be used for all effectiveness analyses, for summarizing and listing subject demographics and baseline characteristics, medical history, medications and therapies (prior and concomitant) and CIP deviations. Subjects will be analyzed according to randomized assignment to non-HA threads/HA threads group. • **Safety analysis set:** Includes all patients who undergo the procedure. The set will be used for all safety analyses. All safety endpoints will be analyzed according to actual type of implanted threads (with or without HA). • **Effectiveness analysis set:** Includes all patients who undergo the procedure and have non-missing effectiveness endpoint data collected at the Day 90. The set will be used for a sensitivity analysis of the primary effectiveness endpoint. • **Biopsy Substudy analysis set:** Includes subjects who agreed to participate in the biopsy Substudy, signed the Substudy informed consent form and have baseline biopsy results and at least one post-baseline result. The set will be used only for the biopsy Substudy analysis and subjects will be analyzed according to the implanted threads (with and without HA).

- **Jawline analysis set:** Includes all patients who underwent the procedure and have amenable photos for jawline assessment on both sides from baseline and any visit after the thread implantation procedure of the following: Day 30, Day 90 or Day 180. The set will be used only for the jawline Substudy analysis and subjects will be analyzed according to the implanted threads (with and without HA).

Primary endpoint

Part I

For the primary safety endpoint, serious adverse events will be point estimated along with the exact Binomial 95% CI.

For the primary effectiveness endpoint, WSRS score will be reported as mean change from baseline, and difference from baseline to Day 90 will be tested with the paired t-test with a significance level of $\alpha = 1.67\%$ separately for each group (HA/non-HA/total).

Biopsy Substudy

The primary endpoint for biopsy Substudy is difference between the HA and non-HA groups in change over time in biostimulation (collagen types 1,3 and elastin measurements before procedure and on Day 90) which will be tested by the Mann-Whitney non-parametric test with a significance level of $\alpha = 5\%$.

Part II

WSRS score will be reported as mean change from baseline, and difference from baseline to Day 360 will be tested with the paired t-test with a significance level of $\alpha = 1.67\%$ separately for each group (HA/non-HA/total).

Jawline Substudy

CJDS score will be reported as mean change from baseline, and difference from baseline to Day 90 will be tested with the paired t-test with a significance level of $\alpha=1.67\%$ separately for each group (HA/non-HA/total) in the Jawline analysis set.

Secondary endpoints

Main Study Part I and Part II

For the analysis of the secondary safety endpoints, the rate of all adverse events and the incidence of early recovery symptoms will be point estimated along with the exact Binomial 95% CI.

Change from baseline in WSRS will be tested by the paired t-test with a significance level of $\alpha = 1.67\%$ separately for each group (HA/non-HA/total). The proportion of subjects with improvement of ≥ 1 WSRS score at each visit will be tested by the McNemar test for repeatedly measured proportions with comparison to "baseline improvement assessment" = 0 with a significance level of $\alpha = 1.67\%$. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 30, 90, 180, 360, 540, 720 will be summarized for

	NLF. Mean total score of the Face-Q™ Satisfaction with Outcome questionnaire will be summarized on Day 30, 90, 180, 360, 540, 720. *Substudies* In the Jawline Substudy, change from baseline in CJDS will be tested by the paired t-test with a significance level of α=1.67% separately for each group (HA/non-HA/total) in the Jawline analysis set. The proportion of subjects with improvement in CJDS score ≥1 point for both sides at each visit will be tested by the McNemar test for repeatedly measured proportions with comparison to "baseline improvement assessment" = 0 with a significance level of α = 1.67% separately for each group (HA/non-HA/total) in the Jawline analysis set. In the Biopsy Substudy, the difference of the means between baseline and each post-baseline collagen and elastin measurements will be tested by the Wilcoxon signed-rank non-parametric test with a significance level of α = 5%. The difference in mean content of collagen types 1,3 and elastin (%) in tissue samples obtained from subjects treated with non-HA threads versus HA threads will be tested by the Mann-Whitney non-parametric test with a significance level of α = 5%. In both Substudies, the analysis will include Spearman's correlation: in the Biopsy Substudy between patient satisfaction with skin and change in collagen and elastin measurements, in the Jawline Substudy between WSRS and CJDS scoring at study visits and corresponding WSRS and CJDS changes from baseline. *Evaluation of IBEs' assessments* In Part 1 and Part 2, for the correlation analysis between the different WSRS blinded evaluators and correlation analysis between different GAIS evaluators the interrater reliability will be assessed by using Intraclass Correlation Coefficients (ICC). ICC estimates and their 95% confident intervals will be calculated based on a mean-rating (k = 3), absolute-agreement, 2-way mixed-effects model. The ICC scores will be interpreted as follows: < 0.5 – poor reliability; 0.5-0.75 – moderate reliability; 0.75-0.9 – good reliability; > 0.9 – excellent reliability. Similarly, in the Jawline Substudy the correlation analysis between different CJDS blinded evaluators using ICC will be performed. *Adjustment for multiplicity* Bonferroni correction will be used as an adjustment for multiplicity for all effectiveness endpoints in the main study Part 1 and Part 2, as well as in the Jawline Substudy, to control type I error due to testing in three groups (HA threads group, non-HA threads group, total group). In Parts 1 and 2, as well as in the Jawline Substudy, all effectiveness endpoints will be tested with a significance level of α = 5/3 % = 1.67%. In the Biopsy Substudy, a significance level of α = 5% will be used. *Safety reporting* Adverse events will be coded with MedDRA dictionary (current version for the time of coding) and summarized by system organ class (SOC) and preferred term

	(PT). The number of events (AE, SAE), AE term, AE severity, the relationship to the investigational devices or procedure (not related, unlikely, possible, probable, causal relationship), incidence of early recovery symptoms (overall and for each symptom), procedure-related and device-related AEs, unresolved events, and time to event resolution will be summarized in the Safety analysis set for each group (non-HA/HA threads) and their total.

SPONSOR SIGNATORY

CLINICAL INVESTIGATION PLAN TITLE:

Evaluation of Safety and Effectiveness of APTOS Threads – Absorbable Surgical Sutures Excellence Product Line Models for Mid-face Suspension by Mini-Invasive Surgery to Temporarily Fixate the Cheek Sub-dermis in a Repositioned Site for the Treatment of Moderate to Severe Nasolabial Fold.

I agree to conduct this trial in accordance with the requirements of this Clinical Investigation Plan and in accordance with the following:

- Declaration of Helsinki
- Established principles of Good Clinical Practice (GCP) as outlined by the International Council for Harmonization (ICH) E6, ISO 14155:2020
- Applicable federal, state, and/or local laws and regulations in the country where the clinical trial will be conducted
- Clinical trial contractual obligations

Anna Kadzhaya, MD
Head of Clinical Development,
Aptos, LLC

25 Feb 2026
Signature, Date

George Sulamanidze, MD, PhD
Chief Executive Officer
Aptos, LLC

25. Feb. 2026
Signature, Date

Tamara Beshidze, PhD
Head of QA/QC
Aptos, LLC.

25.02.2026
Signature, Date

PRINCIPAL INVESTIGATOR AGREEMENT

CLINICAL INVESTIGATION PLAN TITLE:

Evaluation of Safety and Effectiveness of APTOS Threads – Absorbable Surgical Sutures Excellence Product Line Models for Mid-face Suspension by Mini-Invasive Surgery to Temporarily Fixate the Cheek Sub-dermis in a Repositioned Site for the Treatment of Moderate to Severe Nasolabial Fold.

This Clinical Investigation Plan was subjected to critical review and has been released by the Sponsor.

I agree to conduct this trial in accordance with the requirements of this protocol and in accordance with the following:

• Declaration of Helsinki

• Established principles of Good Clinical Practice (GCP) as outlined by the International Council for Harmonization (ICH) E6, ISO 14155:2020

• Applicable federal, state, and/or local laws and regulations in the country where the clinical trial will be conducted

• Clinical trial contractual obligations

Principal Investigator Printed Name: _____

Principal Investigator Signature and Date: _____

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1 GENERAL

1.1 History of changes

Version	Date	Comment
1.0	15-Apr-2024	Initial version
2.0	14-Mar-2025	Statistical analysis and endpoint wording updated. Collection of Fitzpatrick skin type added. Interim analyses removed from study plan.
3.0	10-Jul-2025	Retrospective Jawline Substudy added. Document reformatted according to MDCG 24-3 guideline. Visit window for Part II Day 720 extended.
4.0	25-Feb-2026	PI list updated. Visit window for Part II Day 720 extended. Expected sample size for Part 2 updated.

1.2 Amendments Summary

Amendment 1: from version 1.0 dated 15 April 2024 to version 2.0 dated 14 March 2025

Summary of updates:

Collection of Fitzpatrick skin type added to procedures. Interim analyses removed from study plan. Statistical analysis updated and endpoints detailed:

- Wording for study endpoints in Part 1, Part 2 and Biopsy Substudy added and detailed
- Correction for multiplicity updated
- Hypothesis updated with corresponding update in the wording for the primary endpoint and claims
- Statistical tests for secondary endpoints updated
- Intraclass Correlation Coefficients (ICC) added for GAIS and WSRS
- Synopsis moved to the beginning of the document and added with information on sample size justification and statistical considerations

Amendment 2: from version 2.0 dated 14 March 2025 to version 3.0 dated 10 July 2025

Summary of updates: Full description of the retrospective Jawline Substudy added. Document structure updated according to MDCG 2024-3 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices. Visit window for Part II Day 720 extended to Day 720±30 days.

Amendment 3: from version 3.0 dated 10 July 2025 to version 4.0 dated 25 February 2026. PI list updated. Visit window for Part II Day 720 extended to Day 720±60 days to enhance subject

retention and ensure completion of the study. This adjustment accounts for potential scheduling challenges during the summer vacation period and does not affect the scientific integrity of the study. Expected sample size for Part 2 was updated based on available information on enrollment to Part 2. Other minor misprints and inconsistencies corrected.

1.3 Abbreviations

Acronym	Acronym Definition
ADE	Adverse Device Effect
AE	Adverse Event
ANOVA	Analysis of Variance
AoR	Acknowledgment of Receipt
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
C&Q	Commissioning and Qualification
CE	Conformité Européenne
CI	Confidence Interval
CIP	Clinical Investigation Plan
CJDS	Canfield Jawline Definition Scale
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Clinical Research Organization
CV	Curriculum Vitae
DD	Device Deficiency
DSMB	Data and Safety Monitoring Board
ECM	Extracellular Matrix
eCRF	electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HA	Hyaluronic Acid
ICC	Intraclass Correlation Coefficient
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IMD	Investigational Medical Device
IPL	Intense Pulsed Light
IQR	Interquartile Range

Acronym	Acronym Definition
IRB	Institutional Review Board
ISO	International Organization for Standardization
MD	Medical Doctor
MDR	Medical Device Regulation
MoH	Ministry of Health
NLF	Nasolabial Fold
P(LA/CL)	Poly(L-lactide-co-ε-caprolactone)
P(LA/CL)-HA	Poly(L-lactide-co-ε-caprolactone)-Hyaluronic Acid
PCL	Polycaprolactone
PDO	Polydioxanone
PGA	Polyglycolic Acid
PLA	Polylactic Acid
PLLA	Poly-L-lactic acid
QMS	Quality Management System
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SIC	Subject Informed Consent
SOP	Standard Operational Procedure
SOTA	State-of-the-Art
UDI	Unique Device Identification
USADE	Unanticipated Serious Adverse Device Effect
WSRS	Wrinkles Severity Rating Scale

1.4 Sponsor/Manufacturer Information

Sponsor/Manufacturer of Investigational Device Details

Name	Aptos LLC
Address	15 Givi Amilakhvari Str., 0109, Tbilisi, Georgia
Sponsor Representative	Anna Kadzhaya, MD Head of Scientific and Clinical Development Department
Contact Information	Email: Anna.Kadzhaya@aptos.ge Phone: +995597119525

1.5 Clinical Research Organization

Clinical Accelerator Ltd, whose registered address is located at the 19-21 Circular Road, Douglas, Isle of Man, IM1 1AF, Great Britain represented by LTD Clinical Accelerator Georgia in Georgia, with legal address at 11 Saakadze Descent "LTD Panorama", Floor 4, Office 405, Tbilisi 0160, Georgia, collectively further referred to as Clinical Accelerator Georgia.

1.6 Regional Laboratory

Laboratory of pathology, Tbilisi State Medical University, Administrative Building, 33, Vazha-Pshavela Ave. 0186, Tbilisi, Georgia. This laboratory will be used within the biopsy Substudy for histological assessments.

1.7 Principal Investigator, Coordinating Investigator and Investigation Site(s)

There are three (3) investigation sites, as detailed in Table 1.

Table 1: Investigation Sites and Investigators.

	Investigation Site Name	Investigation Site Location	Type of clinic	Principal Investigator	Coordinating or Sub Investigators
1	"Total Charm" LTD	Orbeliani Str #18, Tbilisi, Georgia	Clinic of Plastic and Aesthetic Surgery	Dr. Nino Nishnianidze (Dermatologist)	Sub-Investigator: Dr. Murat Tsintsadze (Plastic Surgeon)
2	"Total Charm Vake" LTD	Phaliashvili Str #87 "B" Block, Entrance 3, floor 2, Flat 1 Tbilisi, Georgia	Clinic of Aesthetic Medicine	Dr. Albina Kajaia (Dermatologist)	Sub-Investigator: Dr. Tatyana Paikidze (Dermatologist)
3	"Total Charm Piazza" LTD	Gorgasali Str #15, Batumi Georgia	Clinic of Aesthetic Medicine	Dr. Ketevan Kavtaradze (Dermatologist)	-

All three sites were chosen as they meet the following criteria: adequate facility, over 20 years' experience in thread lifting, the Principal Investigator and Sub-Investigator at the clinics have been trained and are qualified to perform thread lifting procedures, and there is a sufficient patient pool that is representative of the intended target population of APTOS Absorbable Threads Excellence Product Line models.

1.8 Study Flow Chart

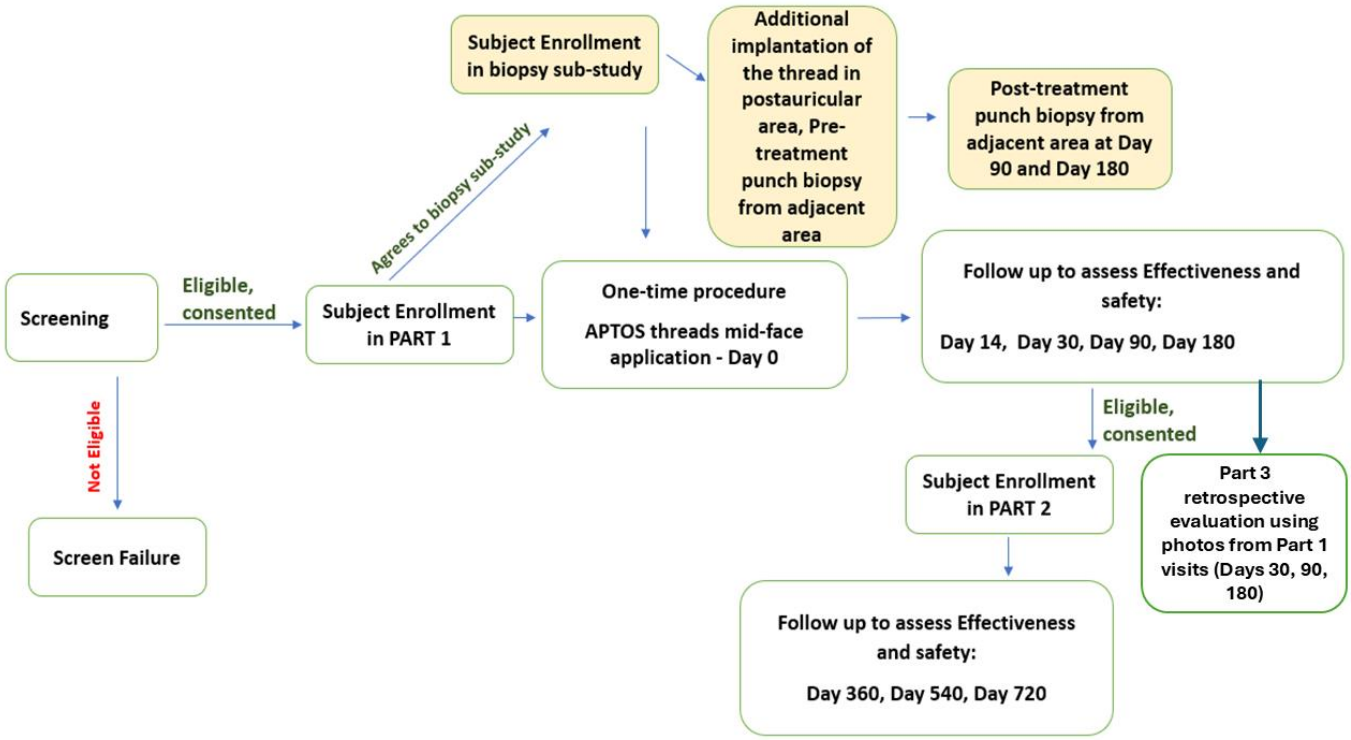


Figure 1: Study Flow Chart

1.9 Financial Considerations and Agreements

This Clinical Investigation is financed by the Sponsor, Aptos LLC, which is also the IMD manufacturer.

Three-partite agreement between the Sponsor and the participating sites will be arranged, comprising the following parties: the Investigation Site, the Principal Investigator and the Sponsor. The Investigation Site will ensure payment to site staff who conduct activities for this clinical trial as per the agreement.

2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE & PROCEDURE

2.1 Device Description Summary

APTOS Absorbable Threads are made of Poly(L-lactide-co-ε-caprolactone) (P(LA/CL)) and are with or without Hyaluronic Acid coating. P(LA/CL is a biocompatible and biodegradable material that is commonly used for biomedical purposes. P(LA/CL) has been approved by the Food and Drug Administration (FDA). HA used for coating is non-stabilized hyaluronic acid known as natural component of the body. HA is a biodegradable, non-immunogenic, and non-toxic glycosaminoglycan, which is an essential component of the extracellular matrix [14]. APTOS Threads - Absorbable Surgical Sutures include threads without barbs as well as threads with multidirectional and bi-directional barbs situated along the entire length of the thread, which help to adhere to tissue underneath the skin and to support fixating the tissue in a repositioned site. The absorbable sutures work at the level of subcutaneous adipose tissue, not in the dermis or in the muscles, which is essential to ensure the desired effect and to avoid complications. Specifically, the safety of APTOS Absorbable Threads is achieved by working within the superficial fatty layer, as this layer is free of major neurovascular structures like arteries, motor nerves, or veins.

2.2 Manufacturer Details

Aptos LLC

Address:15 Givi Amilakhvari str., 0109, Tbilisi, Georgia

E-mail: info@aptos.ge

Tel.: +99532 2920372

2.3 Device Models

- Visage Excellence Method (EV)
- Visage Excellence Method S (EVS)
- Visage Excellence Method HA (EVHA)
- Visage Excellence Method S HA (EVSHA)
- Nano Excellence Method (NE)
- Nano Excellence Method HA (NEHA)

2.4 Device traceability

The investigational device models can be tracked from manufacturing to end-use in a healthcare setting. The devices will be assigned with lot numbers. A packing slip will list devices identifiers and will accompany the products. Before release for use, the Investigation Site will provide acknowledgment of receipt (AoR) to the Clinical Research organization (CRO) or Sponsor. Device accountability logs will be used, including master accountability and subject accountability logs.

Unused devices will be returned to the Sponsor directly. The investigation Site will maintain the unused devices in their original packaging, unopened, undamaged and return to the Sponsor.

2.5 Intended Purpose

APTOS Threads - Excellence Product Line models are single use implantable devices, intended to be totally introduced into the human's subcutaneous tissue by dermatologists and plastic surgeons for the purpose of temporary modifying anatomy of subcutaneous tissue and skin through repositioning of the subcutaneous tissue and its temporary fixation in repositioned site in adult male and female patients having moderate and severe facial (mid face – nasolabial fold) skin laxity.

**The devices are CE marked since 2014 under EU MDD (directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001). According to Article 120 (3a), Medical Device Regulation (MDR) European Union (EU) 2017/745 these products are recognized as Legacy Devices. The intended use of the devices that are currently marketed is: Fixation, repositioning and approximation of soft tissues and skin. This clinical trial is intended to confirm a new intended use according to Common Specifications (CS) of Annex XVI, Medical Device Regulation (MDR) European Union (EU) 2017/745.*

2.6 Population

Female and male patients 22+ years of age who present at the clinics for correction of age-related changes of the face and who meet the inclusion and exclusion criteria of this study plan.

2.7 Indication

For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe NLFs.

2.8 Full Device Description

APTOS Absorbable Threads are made of P(LA/CL), a biocompatible and biodegradable material that is commonly used for biomedical purposes. P(LA/CL) has been approved by the FDA. APTOS Absorbable Surgical Sutures include threads without barbs as well as threads with multidirectional and bi-directional barbs situated along the entire length of the thread, which help to adhere to tissue underneath the skin and to support fixating the tissue in a repositioned site. The absorbable sutures work at the level of subcutaneous adipose tissue, not in the dermis or in the muscles, which is essential to ensure the desired effect and to avoid complications. Specifically, the safety of APTOS Absorbable Threads is achieved by working within the superficial fatty layer, as this layer is free of major neurovascular structures like arteries, motor nerves, or veins.

APTOS Threads - Excellence Product Line includes six different device models which are indicated for aesthetic dermatology and plastic surgery (Table 2). The products differ in terms of thread

length (size) and the diameter of cannulas (needles) which are used to introduce the threads into the subcutaneous tissue. Threads of different lengths are important to allow the most appropriate product to be used based on the size of the treated area, as wider faces would require longer threads. The different diameters of the cannulas have only a technical purpose for the physician when implanting the threads. A larger diameter is used for threads which are longer (namely, EV/EVHA threads which are 19 cm), as this allows the threads to smoothly pass the soft tissues during the application trajectory where there is a longer distance from the entry point to the endpoint. In addition, some Excellence model threads are coated with non-stabilized HA. HA is a biodegradable, non-immunogenic, and non-toxic glycosaminoglycan, which is an essential component of the extracellular matrix [14]. HA stimulates elastin and collagen, speeds up wound healing, and also reduces inflammation [14]. A recent study of patients receiving P(LA/CL) threads with and without HA found notably higher long-term improvement in aging appearance and satisfaction in the group treated with HA-containing threads compared to the treatment arm without HA, with less skin-related adverse effects during the recovery period (1 week post-treatment) [14]. The APTOS Excellence models thus support personalized treatment and enhanced bio-stimulation to maximize effectiveness and safety of facial thread lift procedures.

Table 2: APTOS Threads - Excellence Product Line Models

Ref.	Name	Components*	Description	Indication and treatment area
EV	Visage Excellence Method	Straight round tip hollow needle – 20G x 150 mm Straight round tip hollow needle – 23G x 80 mm Straight lancet point needle – 18G x 40 mm Thread – 190 mm P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%.	Visage Excellence Method contains 10 pcs P(LA / CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue underneath the skin. The threads are placed inside the needle 20G x 150mm. beside is put the needle 23Gx80mm for infiltration and 18Gx40mm for puncture out. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe nasolabial folds.
EVS	Visage Excellence Method S	Straight round tip hollow needle – 21G x 100 mm Straight round tip hollow needle – 23G x 80 mm Straight lancet point needle – 18G x 40 mm Thread – 100 mm	Visage Excellence Method S Threads contains 10 pcs P(LA /CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue underneath the skin. The threads are placed inside the needle 21G x 100mm. beside is put the needle	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of

Ref.	Name	Components*	Description	Indication and treatment area
		P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%.	23G x 80mm for infiltration and 18G x 40mm for puncture out. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	moderate to severe nasolabial folds.
NE	Nano Excellence Method	Straight round tip hollow needle – 21G x 70 mm Thread – 80 mm P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%.	Nano Excellence Method contains 5 pcs P(LA / CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue underneath the skin. The threads are placed inside the needle 21G x 70mm. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe nasolabial folds.
EVHA	Visage Excellence Method HA	Straight round tip hollow needle – 20G x 150 mm Straight round tip hollow needle – 23G x 80 mm Straight lancet point needle – 18G x 40 mm Thread – 190 mm P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%. Non-stabilized hyaluronic acid coating – Sodium Hyaluronate, non-animal origin.	Visage Excellence Method contains 10 pcs P(LA / CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue underneath the skin. The threads are placed inside the needle 20G x 150mm. beside is put the needle 23G x 80mm for infiltration and 18G x 40mm for puncture out. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe nasolabial folds.
EVSHA	Visage Excellence Method S HA	Straight round tip hollow needle – 21G x 100 mm Straight round tip hollow needle – 23G x 80 mm	Visage Excellence Method S HA Threads contains 10 pcs P(LA / CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-

Ref.	Name	Components*	Description	Indication and treatment area
		Straight lancet point needle – 18G x 40 mm Thread – 100 mm P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%. Non-stabilized hyaluronic acid coating – Sodium Hyaluronate, non-animal origin.	underneath the skin. The threads are placed inside the needle 21G x 100mm. beside is put the needle 23G x 80mm for infiltration and 18G x 40mm for puncture out. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	dermis in a repositioned site for the treatment of moderate to severe nasolabial folds.
NEHA	Nano Excellence Method HA	Straight round tip hollow needle – 21G x 70 mm Straight round tip hollow needle – 23G x 80 mm Straight lancet point needle – 18G x 40 mm Thread – 80 mm P(LA/CL) [Poly(L-lactide-co-ε-caprolactone); monofilament undyed Suture, the approximate percentage data of co-caprolactone and poly L-lactide. In the P(LA / CL): Caprolactone 25%, L-Lactide 75%. Non-stabilized hyaluronic acid coating – Sodium Hyaluronate, non-animal origin.	Nano Excellence Method HA Threads contains 10 pcs P(LA / CL) opposing multidirectional barbs situated along the entire length, which help to adhere to tissue underneath the skin. The threads are placed inside the needle 21G x 70 mm. beside is put the needle 23G x 80mm for infiltration and 18G x4 0mm for puncture out. The threads are replaced by a fibrous bridle which forms due to threads and gradual liberation of microscopic quantities of Lactic acid. The threads have specific barbs arrangement. Non-Standard Needle Attachment.	For mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe nasolabial folds. .

*All thread materials are in contact with tissues as derma and subcutaneous tissue.

2.9 Training

For the purpose of this study, the physicians will be expert plastic surgeons or expert dermatologists in the aesthetic medicine field. Each physician involved in the study must be trained on APTOS threads methods and have at least 1 year of experience of using APTOS threads. Should a new team who has not before been trained or had experience in APTOS threads methods be involved in the study, they will undergo 2 days of training, including didactic presentations regarding the operation of the APTOS Threads Implantation in the study-defined zone (mid-face, cheek, and

NLFs). Hands-on experience operating the system in a model will also be provided prior to initiating the study.

2.10 Procedure Description Summary

All study subjects will undergo a one-time procedure, namely APTOS threads application using the Excellence Method for NLF improvement. The thread implantation will be performed by the Principal Investigators or dedicated Sub-Investigator(s) who are trained in APTOS methods application. During the procedure, one of the following six device models from the APTOS Threads - Excellence Product Line models will be used:

- Visage Excellence Method (EV)
- Visage Excellence Method S (EVS)
- Visage Excellence Method HA (EVHA)
- Visage Excellence Method S HA (EVSHA)
- Nano Excellence Method (NE)
- Nano Excellence Method HA (NEHA)

These six device models differ from each other only by the length of the threads. Therefore, device model assignment will be based on a single criterion: the length of the longest trajectory of the thread implantation from I entry point (projection of zygomaticus arche) to the projection of the mental ligament, as this will define the size of the thread that is needed (Table 10 in Appendix A). Assignment of non-HA and HA threads will be performed using a randomization block design of 4 patients, with a ratio of 1:1 at each Investigation Site, meaning that each patient will be randomly assigned to either the non-HA or HA sub-group, with an equal number of patients in the sub-groups at each site. The model of the product line (namely EV/EVHA or EVS/EVSHA or NE/NEHA) for each sub-group will be assigned according to the criterion for appropriate thread length. (Appendix A). The threads allocation will be according to corresponding subsequent number of site-specific sealed envelopes provided to the site during site initiation visit. The allocation of threads with or without HA will be blinded for patients. The investigator receives the sterile packs without outer boxes from applicable study team immediately before the treatment. During the study the investigational team will maintain the blinding of the thread type for patients. During the procedure, threads will be inserted into the subcutaneous tissue along pre-marked areas of the face using a needle. After each needle has reached its endpoint, the tissues will be moved toward the injection point. Thereafter, it will be necessary to pull the tissues away from the injection point, as close as possible to the start point. The needle will then be carefully removed, assuring that the thread remains in the tissue. Once sutures are placed, the barbs will be engaged by gently massaging the application areas. When the barbs of the threads are engaged, they gain purchase in the fatty fibrous adipose tissues, transferring the force to elevate the overlying dermis

and skin [9]. The barbed suture therefore sets anchor in the tissues and maintains the suspension [9]. The procedure avoids large incisions, which reduces post-surgery recovery time [9] and allows for use of local anesthesia without the need for hospitalization [10].

2.11 Reference to Investigator's Brochure and Instructions For Use

Investigator Brochure for APTOS Absorbable Excellence model threads, Edition 1.0 dd 12 APR 2024. Instructions For Use Version# IFU/EXCELLENCE/REV00/2024-04-05.

2.11.1 Biopsy Substudy procedure

Subjects eligible for the **Biopsy Substudy** and who consent to the Substudy will be enrolled in the biopsy Substudy. For subjects enrolled in the Substudy, at the time of suture placement (the primary procedure), a 2-2.5 -cm section of the suture will be implanted in the subcutaneous plane in the posterior auricular area. In addition, punch biopsies (3 mm) will be collected from the area adjacent to the suture implantation area that was placed in the posterior auricular area (approximately 2 mm from the thread) at Day 5, Days 90 and 180.

The investigators who will perform threads implantation will be trained on the requirement to apply the 2-2.5 cm additional thread in postauricular area for punch biopsy purposes during the primary procedure. Investigators performing punch biopsy will be trained on Substudy specific surgical guide and punch biopsy manual. The additional package of threads will be provided to the site for Substudy purposes will be Nano Excellence Method and Nano Excellence Method HA with labeling as for Substudy.

2.12 Background

Facial aging is a multifactorial process that results in skeletal and soft tissue changes at all anatomical levels, including bones, ligaments, muscles, fasciae, subcutaneous fat, and skin [1]. It has been suggested that most of the facial aging changes occur in the middle and lower face as a consequence of gravity [1–5]. Visible signs of facial aging in the mid-lower third of the face can include sagging cheeks; downward sliding of the zygomatic, malar region (middle face); the loss of elasticity and descent of fat in the jowl region; development of perioral rhytids, deep nasolabial folds (NLFs), and marionette lines; the loss of definition of the lips; and laxity of the neck skin, muscle, and fat [5,6]. Given our increased life expectancy and the active promotion of youth and beauty, there has been a surge of interest in aesthetic procedures to eliminate the external signs of aging, particularly by supporting and reinforcing the soft tissues of the face and neck [7]. A substantial number of face and neck cosmetic surgeries are therefore conducted worldwide [6], with rejuvenation of the lower third of the face becoming part of routine aesthetic practice that is essential for a good overall result [2].

Solutions for facial aging include lifting drooping soft tissues, augmenting shrunken areas with fat grafts or implants, and antigravitational lifting procedures [6]. Historically, facial aging was primarily addressed with face lift surgery (rhytidectomy) [7]. However, such surgery entails skin incisions, suturing, risk of infection, postoperative scars, and long rehabilitation times [7]. There is currently an increasing demand for less invasive antiaging interventions that have a shorter procedure duration, easier technical execution, faster postoperative recovery, fewer complications and durable effect [7]. Thread lifting techniques are therefore becoming more attractive than traditional surgical lifting procedures for facial augmentation [6-8].

Thread lifting involves the passage of sutures under the skin to counteract the descent and laxity of the tissues [9]. Threads may be either absorbable or nonabsorbable, and if nonabsorbable materials are used, the threads will remain permanently in the tissue [6]. In addition, barbed sutures, which have small projections that radiate outward from the center of the suture, may be used [9]. Thread lifting with absorbable threads with barbs/cones has been shown to be an effective and tolerable procedure for facial rejuvenation [8-18]. Specifically, satisfaction with NLF, marionettes, lower face, and jawline appearance was shown to be significantly improved 6 and 12 months after thread lifting [12,14]. A chart review of 193 patients who underwent thread lifting of the face and/or neck, which was most commonly performed for the jawline (46%) and mid-face (34%), demonstrated similar findings, with increasing patient and surgeon satisfaction over time (98-99% by 6 months after surgery) [6].

Aptos LLC has developed APTOS Absorbable Threads, a sterile, implantable, fully resorbable device intended for adult patients, which includes both hyaluronic acid (HA) coated threads and threads without HA. These are used in aesthetic surgery for fixation, repositioning, and approximation of soft tissues and skin of the face and body. This Clinical Investigation Plan (CIP) describes the application of APTOS Absorbable Threads (Excellence models) for mid-facial laxity – nasolabial folds correction.

3 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURES AND CLINICAL INVESTIGATION

Risks

1. Anticipated clinical performance of the investigational device models:

The anticipated clinical performance of the device models includes aesthetic improvement (i.e., improved WSRS and GAIS score) and patient's satisfaction with the result (Face-Q questionnaires).

2. Anticipated adverse effects of the investigational device models:

The Absorbable P(LA/CL) Surgical Sutures are associated with the following adverse reactions:

- Transient local irritation at the wound of entry point site
- Transient inflammatory response symptoms to foreign body (swelling, pain, discomfort, erythema, feeling of warmness)
- Bruising
- Tightness

3. Residual risks associated with the investigational device models:

With regard to both general absorbable sutures and HA-coated sutures, all but two risks were deemed to be acceptable after risk mitigation. Mitigated risks that were deemed to be acceptable were associated with barbed thread production, production of twisted threads, production of spiral threads, primary and secondary packaging, sterilization, final packaging and warehouse storage, sales and usage, and the post-usage stage. The two risks that were deemed to be unacceptable were associated with the surgeon lacking overall experience, lack of familiarity with facial anatomy, unskilled/poor surgical operation practice, or severe infection leading to wound dehiscence and scarring. The likelihood of occurrence of these risks was nevertheless deemed to be improbable.

With regard to the design of the APTOS Absorbable Threads (both general absorbable sutures and HA-coated sutures), residual risks were all deemed to be acceptable, except for one risk linked to environmental impact which was also deemed to be improbable.

4. Risks associated with participation in the clinical investigation:

Subjects who participate in this study would be exposed to the risks that are normally associated with the use of the Absorbable Threads, as specified above. There are no additional risks to subjects who participate in this study. Subject privacy and confidentiality will be strictly guarded, and no additional risk will be posed to subjects in this regard. In addition, there are no risks for health care personnel, family members or caregivers.

5. Possible interactions with concomitant medical treatments:

No interactions with concomitant medications is known.

6. Risk mitigation strategies:

Risk mitigation strategies for this study include designing the clinical investigation in accordance with relevant standards, guidelines, and good clinical practice (GCP), and performing the study at Investigation Sites with expertise in facial thread lifting. In addition, the following mitigation strategies have been implemented for APTOS threads:

- All raw materials compatibility with company & standard requirements is tested according to Quality Management System (QMS)-WI-14 Incoming Control.
- Environmental monitoring and Contamination Control are performed according to QMS-Standard Operational Procedure (SOP)-45 Work Environment and Contamination Control.
- Effective cleaning is performed according to procedure QMS-SOP-16 Cleaning.
- Personnel Training & Instructions provided are lined up to internal procedure QMS-SOP-02 Training.
- Barbs making processes are performed according to QMS-WI-32 Procedural Instruction for Cutting the Barbs off the Thread and Filament Cutting.
- In-process and final control are performed according to QMS-WI-15 In-process and final control.
- Production is accomplished according to QMS-PD-10 Production.
- Equipment commissioning, qualification and validation is performed according to QMS-SOP-50 Commissioning and Qualification (C&Q) Activities for New Areas, Equipment and Systems.
- Waste Disposal is performed according to QMS-PD-16 Destruction.
- Disposal of damaged product or unused parts is detailed in the Instructions for Use, according to QMS SOP-06-Labelling templates.
- Sterilization process and maintenance of sterilizer are managed according to QMS-SOP-72 Sterilization process and QMS-WI-49 Sterilization, respectively.
- Validation of sterilization process is provided by APT-TCF-MD-06-A06-GE Sterilization Validation.
- Final Products release is managed according to QMS-SOP-38 Preparation of the product for sale and QMS-SOP-44 Product release.
- All raw materials and final product storage accomplishes QMS-SOP-47 Receiving/Dispatching and Storage of Finished Products and Raw Materials in Warehouses.
- Qualification of all suppliers is performed according to QMS-PD-07 Purchase, par. 6.2.
- Packaging and sealing are validated.

- Packaging and shipping is performed according to QMS-SOP-25 Packaging and transportation of sterile and non-sterile products.
- Labelling is performed according to QMS-SOP-06 Labelling.
- Post-Marketing system including PMS, PMCF, Clinical Evaluation, and Vigilance processes is managed according to relevant SOPs.
- Biocompatibility Certificates of raw material and packaging are collected. Biocompatibility Evaluation Plan and Report are set according to ISO 10933: 1 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.
- Training of user (doctor) is provided by APTOS certified Doctors, along with Aptos support, Aptos videos transmission and surgical guides. Periodical evaluation of training.
- Training of user (doctor) to provide patients with proper instructions for post-procedure care of the application area.

7. Risk threshold and degree of distress:

Each risk is defined separately. Risk is assessed by identifying the associated risk acceptance rating for each combination of probability (Table 3) and severity (Table 4), using the matrix presented in Table 5. Table 5 thus depicts risk thresholds, where green represents an acceptable risk and red an unacceptable risk. Risks that are not acceptable have all been mitigated. The degree of distress is directly linked to the severity/possible consequence of the risk. The level of distress will be higher if the harm is injury or impairment requiring professional intervention than the level of distress from inconvenience or temporary discomfort. The risks and degree of distress will be constantly monitored throughout the study.

Table 3: Occurrence Scorings

Score	Criteria	Frequency of Occurrence (Per Application)
O5	Frequent	Greater than or equal to 1 : 1,000 ($\geq 10^{-3}$)
O4	Probable	Less than 1 : 1,000, greater than or equal to 1 : 10,000 ($< 10^{-3}$ to $\geq 10^{-4}$)
O3	Occasional	Less than 1 in 10,000, greater than or equal to 1 : 100,000 ($< 10^{-4}$ to $\geq 10^{-5}$)
O2	Remote	Less than 1 : 100,000, greater than or equal to 1 : 1,000,000 ($< 10^{-5}$ to $\geq 10^{-6}$)

O1	Improbable	Less than 1 in 1,000,000 ($< 10^{-6}$)

Table 4: Severity Scorings

Ranking	Severity of Harm	Possible Consequences
5	Catastrophic	Results in death.
4	Critical	Results in permanent impairment or life-threatening injury
3	Serious	Results in injury or impairment requiring professional medical intervention
2	Minor	Results in temporary injury or impairment not requiring professional medical intervention
1	Negligible	Inconvenience or temporary discomfort
0	No Harm	No effect

Table 5: Risk Acceptability Matrix

SEVERITY ↑						
S5	Catastrophic	5	10	15	20	25
S4	Critical	4	8	12	16	20
S3	Major	3	6	9	12	15
S2	Minor	2	4	6	8	10
S1	Marginal	1	2	3	4	5
		O1	O2	O3	O4	O5

→ OCCURRENCE

Benefits

According to the European Medical Device Regulation (EU MDR) (chapter VI, article 61, section 9), in the case of products without an intended medical purpose, the requirement to demonstrate a clinical benefit is understood as a requirement to demonstrate the performance of the device. This applies to APTOS Threads - Excellence Product Line models which only have an aesthetic indication. As such, no intended clinical benefits are claimed for APTOS Threads - Excellence Product Line models.

Risk/Benefit Rationale

The risk/benefit assessment is based on State-of-the-Art (SOTA) publications of facial rejuvenation (publications and current edition of clinical evaluation report can be provided upon request). The clinical evaluation of APTOS Absorbable Threads found that these products were safe and effective. They are accepted in current medical practice and present risks within acceptable limits. Potential adverse events from the device models are all expected. The aesthetic and quality-of-life gains of the APTOS threads – Absorbable P(LA/CL) surgical sutures outweigh the residual risks, thus presenting an acceptable risk/benefit ratio. The primary endpoints for the main study, namely reduction of NLF (WSRS) severity grading and incidence of serious adverse events, are clinically relevant.

4 RELEVANCE OF THE CLINICAL INVESTIGATION

Evaluation of preclinical data

Pre-clinical testing was performed using Visage Excellence Method, which are threads composed of P(LA/CL) that are intended for single use implantable devices, intended to be totally introduced into the human's subcutaneous tissue by dermatologists and plastic surgeons for the purpose of modifying anatomy of subcutaneous tissue and skin through repositioning of the subcutaneous tissue and its temporary fixation in repositioned site.

Since the Excellence threads are made of the same material, i.e., P(LA/CL), have the same structure, and have the same intended purpose, the pre-clinical results are applicable for all Excellence models.

Pre-clinical testing demonstrated that the threads have the following characteristics: non-mutagenic, non-cytotoxic, non-pyrogenic, non-sensitizer, non-hemolytic for both the direct and extract methods, no signs of infections associated with any of the injection sites, no systemic toxic effects in animals, align with ISO 10993-6, and non-irritant. Animal testing was performed, including the investigation of irritation score, material mediated pyrogenicity test, and Ames bacterial reverse mutation assay. Another animal study determined the effectiveness of collagen genesis due to resorbing and permanent implants on the basis of study pathomorphological changes in the skin. The latter study supports the conclusion that the threads induce a mild inflammatory reaction which leads to collagen production and that this stimulation will last until full degradation of the thread. Specifically, animal studies have been performed for both types of APTOS threads (P(LA/CL) and P(LA/CL)-HA) and show collagen and elastin stimulation [20,21] that clinically manifests as improvement of skin quality.

In summary, the pre-clinical data support the safety and effectiveness of the APTOS Threads - Excellence Product Line models, and therefore justify the use of these device models in human subjects.

Evaluation of Clinical Data

This study will assess the safety and effectiveness of APTOS Threads - Excellence Product Line for the treatment of one of the mid-facial laxity symptoms – nasolabial folds. A clinical evaluation of APTOS Threads – Absorbable Surgical Sutures has been performed, which included the six device models in this CIP. The clinical evaluation included data from biocompatibility testing, techno vigilance alerts of similar devices, scientific

literature, and a real-world evidence clinical study. The evaluation confirmed that the analyzed products demonstrated adequate safety and efficacy outcomes. Safety endpoints, including the incidence of adverse events, were analyzed – all adverse events were mild and resolved within the study follow-up, with no serious adverse events having been reported in any study. There were also no techno vigilance alerts. The efficacy analysis included outcomes of satisfaction, improvement after treatment through WSRS and aesthetic improvement scale (GAIS), and quality of life. APTOS Threads Surgical Sutures were thus shown to have an acceptable risk-benefit profile (see 'Risk/Benefit Rationale' in Section 4), and clinical investigations using these products are therefore justifiable.

The study proposed in this CIP will be a multicenter, prospective study (single-arm study for Part 1 and Part 2, and two-arm study for the Part 1 Biopsy Substudy) with a retrospective Substudy for jawline evaluation (Jawline Substudy). A multicenter study will be performed to maximize the number of eligible subjects who can be recruited for the study. Study subjects will be followed up for six (6) months. A six (6)-month follow-up period was chosen for short and mid-term safety and effectiveness assessment in order to align with other studies, including studies on similar devices [6,15]. Patients in the optional extended follow-up study (Part 2) may be followed for up to 2 years after the procedure. This extended follow-up time was chosen as it aligns with another applicable study [8] and with the degradation profile for P(LA/CL) polymer received from the pre-clinical animal implantation study. The retrospective Jawline Substudy will provide new data for interrelation of jawline and midface effects of midface thread lifting. Jawline Substudy brings no additional risks for subjects due to its retrospective nature.

Clinical Development Stage of the Hypothesis

Six (6)-Month Main Study (Part 1): This is a confirmatory, post-market, pivotal clinical investigation. The hypothesis of this study is that the investigational device models (APTOS Threads - Excellence Product Line models) are safe through Day 30 (Month 1) after the implantation procedure and are effective for mid-facial suspension surgery (NLF correction) at Day 90 (Month 3) after the implantation procedure.

Part 1 Biopsy Substudy: This study has exploratory goals. The hypothesis is that APTOS Threads - Excellence Product Line models with and without

HA provide a bio-stimulation effect in terms of collagen and elastin stimulation, as well as skin improvement, at Day 5, at Day 90 (Month 3) and Day 180 (Month 6) post-procedure in addition to a lifting effect.

Optional Extended Follow-Up Study (Part 2): This is a confirmatory, post-market, pivotal clinical investigation. The hypothesis is that APTOS Threads - Excellence Product Line models are effective for mid-facial suspension surgery (NLF correction) at Day 360 (Year 1) after the implantation procedure.

Retrospective Jawline Substudy: This is an exploratory post-market study. The hypothesis, based on anatomical knowledge, thread lifting experience and literature [11], is that effects of thread lifting in the midface and jawline are interconnected and midface thread lifting will produce improvement in the jawline definition.

5 OBJECTIVES & HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 Six-Month Main Study (Part 1)

Purpose

This study aims to assess the safety and effectiveness of APTOS Absorbable Threads for treatment of NLFs. Specifically, the primary endpoints of the main study are to monitor serious adverse events by Day 30, and to demonstrate a reduction in NLF severity grading at Day 90 in comparison with baseline grading assessed by the blinded evaluators.

Objectives

1. Primary Objectives:

1.1 To demonstrate safety of the investigational medical device (IMD) models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through Day 30 (Month 1) after the implantation procedure.

1.2 To demonstrate effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 90 (Month 3) after the implantation procedure.

2. Secondary Objectives:

2.1 To assess safety of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through Day 180 (Month 6) after the implantation procedure.

2.2 To assess effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 30 (Month 1), Day 90 (Month 3), and Day 180 (Month 6) after the implantation procedure.

Scientific Justification

Most changes associated with facial aging occur in the middle and lower face [1–4]. Attractiveness of the midfacial features is a key component to facial aesthetics, and treatment of midfacial aging, together with rejuvenation of the lower third of the face, is therefore key to eliminating the signs of facial aging [2-4,7,8]. Atrophy of adipose tissue causes facial tissue involution, with loss of malar prominence, hollowing of the tear trough, and deepening of the NLFs, resulting in a tired appearance of the face [18]. These changes result in subsequent gravitational ptosis of depleted facial volumes [18]. Although fat, HA and alloplastic implants can restore lost malar volume, these are associated with limitations in terms of structure, durability and suitability for

all patients [18]. Inappropriate placement and excessive amounts of injected fillers have also led to facial distortion and lack of results [18]. Absorbable sutures can create a suspension system that addresses ptotic skin located primarily in the mid-face [18]. A quantitative assessment has demonstrated that it is possible to achieve tissue repositioning which lasts up to 12 months for the correction of mild to moderate ptosis of the mid-face [18]. This study, which investigates absorbable sutures for thread lifting of the mid-face to treat NLFs is therefore clinically relevant and scientifically justified.

Claims and Performance

The performance claims to be supported by this study are:

- APTOS Absorbable Threads and the implantation procedure should not result in any serious adverse device effect by Day 30 (Month 1) post-procedure.
- APTOS Absorbable Threads reduce the NLF severity grading at Day 90 (Month 3) in comparison with baseline grading.

Risks and Adverse Effects

All serious adverse events and unexpected adverse events, as well as adverse device effects, will be evaluated in the course of this study.

5.2 Biopsy Substudy

Purpose

This Substudy aims to histologically assess bio-stimulation of APTOS Threads - Excellence Product Line models in humans in terms of collagen and elastin stimulation effects, and to assess patient-reported satisfaction with clinical improvement of their skin.

Objectives

1. To assess the change over time in bio-stimulation effect of APTOS Threads - Excellence Product Line models in terms of collagen and elastin content.
2. To compare the bio-stimulation effect of APTOS Threads - Excellence Product Line models in terms of collagen and elastin content in non-HA threads versus HA threads.
3. To assess the change over time in patient-reported satisfaction with facial skin.

Scientific Justification

The term bio-stimulation indicates stimulation of the anabolic functions of dermal fibroblasts such as replication, protein synthesis and production of extracellular matrix (ECM) components [19].

Collagen and elastin are the main fibers that form the extracellular matrix. Both are formed by fibroblasts. Collagen is responsible for tensile strength, and

elastin provides elasticity to the skin [34-37]. The main collagens involved in skin architecture and physiology are the fibril-forming types, predominantly Type I and Type III [34].

The threads are the inducers of bio-stimulation among the other materials and products that are currently available on the market providing the bio-stimulation effect [20-29,34]. Histological pre-clinical studies show that regardless of the type of threads material (Polypropylene, Polydioxanone [PDO], Polyglycolic Acid [PGA], Polylactic Acid [PLA], Polycaprolactone [PCL], P(LA/CL), P(LA/CL)-HA), they induce a collagen stimulation effect [20-30,34] but with different intensity. This similar reaction to different agents is explained by the capability of the body to provide a foreign body reaction to the biomaterial implant [29,30].

APTOS threads consist of PLA, PCL and HA that gives the presence of three biostimulator agents in one device. PLLA is composed of a biocompatible polymer derived from lactic acid, are extensively utilized in various applications, are resorbable and promote collagen regeneration over a more extended period compared to PDO threads. Utilizing cones to engage with tissue, PLA threads augment volume in saggy areas, aiding in facial contour restoration and lifting [31]. PCL stimulates collagen regeneration for an extended duration compared to PDO and PLLA threads, as the breakdown of threads generates low molecular weight molecules that gradually prompt the skin to produce collagen and HA, resulting in increased moisture, revitalization, and firmness of the skin [26]. Non-crosslinked HA is the natural component of the ECM - a natural polysaccharide which is largely biocompatible. Cosmetic non-crosslinked HA formulation stimulates fibroblast proliferation; mechanical effect on fibroblasts due to increase of water in ECM (attraction of water by HA) stimulates synthesis of collagen and elastin. Exogenous HA serves as a stimulator for endogenous HA synthesis [32,33].

The animal studies performed for both types of APTOS threads (P(LA/CL) and P(LA/CL)-HA) showed collagen and elastin stimulation [20,21] that clinically manifests as improvement of skin quality. There is clinical research with a limited study design performed to provide clinical evidence of bio-stimulation effects of P(LA/CL) and P(LA/CL)-HA threads [16]. Therefore, collection of wider clinical evidence is required to confirm, both histologically and clinically, the bio-stimulation and skin quality improvement capabilities of

APTOS Threads - Excellence Product Line models. The main study (Part 1), which will investigate absorbable sutures for thread lifting of the mid-face to treat NLFs, and will allow to collect the exploratory data within the optional Biopsy Substudy on bio stimulation and skin quality improvement capabilities of APTOS threads implanted in mid-face.

Claims and Performance

The performance claim to be supported by the Substudy is:

- The implantation of APTOS Absorbable Threads with and without HA provides a bio-stimulation effect (collagen and elastin stimulation) and skin improvement at Day 90 (Month 3) and Day 180 (Month 6) post-procedure in addition to a lifting effect.

Risks and Adverse Effects

All serious adverse events and unexpected adverse events, as well as adverse device effects, will be evaluated in the course of this study.

5.3 Optional Extended Follow-Up Study (Part 2)

Purpose

This study aims to assess the safety and effectiveness of APTOS Absorbable Threads for treatment of NLFs for an extended follow-up period of up to 2 years after the implantation procedure. Specifically, the primary endpoint of the study is to assess the capability of APTOS Threads to reduce the NLF severity grading at Day 360 (Year 1) in comparison with baseline grading assessed by the blinded evaluators.

Objectives

1. Primary Objective

    1. To demonstrate effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day 360 (Year 1) after the implantation procedure.

2. Secondary Objectives

2.1. To assess safety of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment through the study at Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure.

2.2. To assess effectiveness of the IMD models for mid-facial suspension surgery to fixate the cheek sub dermis in a repositioned site for NLF treatment at Day

360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure.

Scientific Justification

Most changes associated with facial aging occur in the middle and lower face [1–5]. Attractiveness of the midfacial features is a key component to facial aesthetics, and treatment of midfacial aging, together with rejuvenation of the lower third of the face, is therefore key to eliminating the signs of facial aging [2,18]. Atrophy of adipose tissue causes facial tissue involution, with loss of malar prominence, hollowing of the tear trough, and deepening of the NLFs, resulting in a tired appearance of the face [18]. These changes result in subsequent gravitational ptosis of depleted facial volumes [18]. Although fat, HA and alloplastic implants can restore lost malar volume, these are associated with limitations in terms of structure, durability and suitability for all patients [18]. Inappropriate placement and excessive amounts of injected fillers have also led to facial distortion and lack of results [18]. Absorbable sutures can create a suspension system that addresses ptotic skin located primarily in the mid-face [18]. A quantitative assessment has demonstrated that it is possible to achieve tissue repositioning which lasts up to 12 months for the correction of mild to moderate ptosis of the mid-face [18]. This study, which investigates absorbable sutures for thread lifting of the mid-face to treat NLFs is therefore clinically relevant and scientifically justified.

Claims and Performance

The performance claims to be supported by this study are:

- APTOS Absorbable Threads and the implantation procedure should not result in any long-term safety concerns, as determined by incidence of Adverse Events from Day 180 (Month 6) to Day 720 (Year 2) post-procedure.
- APTOS Absorbable Threads reduce the NLF severity grading at Day 360 (Year 1) in comparison with baseline grading.

Risks and Adverse Effects

All serious adverse events and unexpected adverse events, as well as adverse device effects, will be evaluated in the course of this study.

5.4 Retrospective Jawline Substudy

Purpose

To evaluate retrospectively the improvement in jawline definition after midface thread lifting with APTOS Threads – Absorbable Surgical Sutures, Excellence Visage models

Objectives

To assess retrospectively the changes in jawline definition for up to 6 months after thread implantation using CJDS in subjects who had undergone midface suspension with Excellence product line models of APTOS Threads – Absorbable Surgical Sutures for treatment of nasolabial fold in study Excellence-001, Part 1.

Scientific Justification

This retrospective study will use the data and images collected in study Excellence-001 (Part 1) to provide additional assessment if the midface thread lifting can cause improvement in jawline definition. This can be supposed based on anatomical considerations due to the interconnected nature of facial muscles, fat pads, and ligaments:

- The *platysma* is indirectly affected by changes in midface tissue tension. When midfacial tissues are lifted, it can relieve the downward pull on the platysma, improving jawline definition.
- The *depressor anguli oris* and *depressor labii inferioris* pull the corners of the mouth and lower lip downward. Lifting the midface reduces strain on these muscles, subtly enhancing jaw contour.
- Malar fat pad, major contributor to the youthful fullness of the cheeks, descends with age. Lifting the malar fat pad can redistribute volume upward, indirectly reducing jowls and sharpening the jawline.
- Jowl fat pads accumulate at the jawline due to gravitational descent of the midfacial fat. Elevating midface tissues can alleviate the accumulation of jowl fat, creating a more defined jawline.
- Buccal fat pad, which extends from the midface toward the lower cheek, may shift slightly when midface lifting is performed, further influencing the jawline's appearance.
- Midface lift repositions the SMAS upward, which can indirectly tighten the skin along the jawline.
- Ligaments such as the zygomatic and mandibular retaining ligaments anchor skin and fat to the underlying bone. Lifting midfacial tissues can reduce the strain on these ligaments, which may improve the lower face's appearance.

The interconnection of midface and jawline improvement in case of thread lifting has been demonstrated by the study [11]: efficacy and safety of absorbable barbed threads (Definisse™) for reshaping the lower face in 27 subjects with mild to moderate facial laxity was investigated. The threads were implanted

along the mandibular angle to enhance the jawline contour and address soft tissue laxity. Significant improvement in jawline volume was observed immediately after treatment and maintained over 12 months. Despite the focus on the lower face, a positive effect on the nasolabial folds and midface areas was documented. Improved midface volume was likely due to the redistribution of soft tissue following thread suspension. No data has been published on the jawline definition changes after midface thread lifting, this study (Jawline Substudy) will provide new data on the interconnection of NLF and jawline improvement after thread lifting.

Claims and Performance	The anticipated clinical performance of the device models includes aesthetic improvement, i.e., improvement in CJDS score.
Risks and Adverse Effects	Due to the retrospective nature of the study no risks for study subjects are expected.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 General

This is a multicenter, prospective study consisting of two prospective parts (Part 1 and Part 2) and one retrospective part – Jawline Substudy. Part 1 is short / mid-term study (the main study) that includes an optional two-arm Biopsy Substudy, and Part 2 is an optional long-term follow-up study where safety, effectiveness, and user satisfaction of a midface thread implantation device are evaluated over two years. Jawline Substudy is a retrospective study utilizing the data (subjects' photos) collected during Part 1 for evaluation of the potential effect of the device under study on jawline definition.

The study will include subjects from 22+ years of age who present to the Investigation Sites for correction of age-related facial changes. After signing informed consent, all subjects will undergo screening procedures to assess their eligibility for study enrollment that will be carried out by Principal Investigator and/or authorized qualified sub-investigator at investigation sites. Subjects who meet the inclusion and exclusion criteria of this clinical trial plan and agree to participate in the study will be enrolled in **Part 1** of the study, namely the Six (6)-Month Main study. Subjects will further be followed up to 720 days in **Part 2.** The retrospective **Jawline Substudy** includes jawline assessment and does not involve any procedures with study subjects.

6.1.1 Six-Month Main Study (Part 1) and Biopsy Substudy

After eligible subjects are enrolled, they will undergo a one-time procedure, namely APTOS threads application with the Excellence Method for NLF treatment. The thread implantation will be performed by the Principal Investigators or dedicated Sub-Investigator(s) who are trained in APTOS methods application. During the procedure, one of six device models from the Excellence Absorbable Threads models will be used, namely:

- Visage Excellence Method (EV)
- Visage Excellence Method S (EVS)
- Visage Excellence Method HA (EVHA)
- Visage Excellence Method S HA (EVSHA)
- Nano Excellence Method (NE)
- Nano Excellence Method HA (NEHA)

These six device models are made from the same material and are applied using the same surgical technique. They differ from each other only by the length of the thread. Therefore, device model assignment will be based on a single criterion: the length of the longest trajectory of the thread implantation from the entry point (projection of zygomaticus arche) to the projection of the mental ligament, as this will define the size of the thread that is needed (Appendix A).

Assignment of non-HA and HA threads will be performed using a randomization block design of 4 patients, with a ratio of 1:1 at each Investigation Site, meaning that each patient will be randomly assigned to either the non-HA or HA sub-group, with an equal number of patients in the sub-groups at each site. The model of the product line (namely EV/EVHA or EVS/EVSHA or NE/NEHA) for each sub-group will be assigned according to the criterion for appropriate thread length. (Appendix A). The treads allocation will be according to corresponding subsequent number of site-specific sealed envelopes provided to the site during site initiation visit. The allocation of threads with or without HA will be blinded for patients. The investigator receives the sterile packs without outer boxes from applicable study team immediately before the treatment. During the study the investigational team will maintain the blinding of the thread type for patients.

Ten threads will be implanted in a single subject, with five threads on each side (Surgical Guide, Appendix C).

After implantation of the device, the patient will be provided with an Implant Card. The Implant Card will contain the following information: identification of the device, including the device name, lot number, the Unique Device Identification (UDI), the device model, as well as the name, address, and website of the manufacturer; warnings and precautions; information about the expected lifetime of the device and any necessary follow-up.

Safety and effectiveness of the APTOS threads application procedure will be monitored for up to 6 months, including a total of five follow-up visits, in Part 1. Subjects will be followed up at the following time points after the procedure: Day 0 (post-procedure), Day 14, Day 30, Day 90, and Day 180.

The safety assessments will be performed by investigator(s) throughout the entire study, and will take into account:

- Incidence of serious adverse events after thread implantation up to Day 30 (Month 1).
- Incidence of all adverse events after implantation of threads throughout the whole study (through Day 180 [Month 6]).
- Incidence of early recovery symptoms related to the thread implantation procedure, where early symptoms are defined as transient symptoms related to foreseeable reaction of the tissue to irritation caused by foreign body (implantation of threads in case of the study treatment method) up to 2 weeks. The early recovery symptoms are presented in Table 6.

Table 6: Early Recovery Symptoms after Thread Implantation

Early recovery symptoms after the APTOS thread implantation procedure
Swelling (Edema)
Pain
Discomfort

Early recovery symptoms after the APTOS thread implantation procedure
Redness (Erythema)
Feeling of Warmness
Bruising (Ecchymosis)

Photographing of subjects to assess the effectiveness of the procedure will be carried out before the procedure and post-procedure from the Day 30 follow-up visit onwards or at unscheduled visits performed due to adverse effects. The effectiveness of the thread implantation will be assessed by board-certified plastic surgeons or dermatologists who were not involved in the procedure by assessing photographs of the subjects, i.e., a blinded evaluation will be performed. Different blinded evaluators will be used for each assessment tool to increase the reliability of the assessment. The assessment will entail:

- Visual determination of the severity of NLFs on each side of face for each subject. This will be assessed using the WSRS (Appendix B) at the Day 30, Day 90, and Day 180 follow-up visits after the implantation procedure.
- Visual determination of aesthetic improvement by comparing photographs of subjects before the procedure and at Day 30, Day 90 and Day 180 follow-up visits after the procedure using the GAIS (Appendix B) for investigators.

In addition, effectiveness will be evaluated by the enrolled subjects who will provide a rating on their improvement according to the GAIS for subjects at Day 30, Day 90, and Day 180 after the procedure. Enrolled subjects will also provide an assessment of satisfaction using the Face-Q™ Satisfaction with Outcome questionnaire (Appendix B) at Day 30, Day 90, and Day 180 follow-up visits after the procedure.

Subjects eligible for the **Biopsy Substudy** and who consent to the Substudy will be enrolled in the Biopsy Substudy. For subjects enrolled in the Substudy, at the time of suture placement (the primary procedure), 2-2.5 -cm section of the suture will be implanted in the subcutaneous plane in the posterior auricular area. In addition, punch biopsies (3 mm) will be collected from the area adjacent to the suture implantation area that was placed in the posterior auricular area (approximately 2 mm from the thread) at Day 5, Days 90 and 180. As the dermis in this area is thinner than in the mid-face, this will allow the suture to be palpated and marked, to ensure that the distance from the suture is consistently 2 mm. Biopsy sites will be noted to ensure that subsequent biopsies are taken from the same area. The 3-mm biopsy sections will be assessed for the quantitative analysis of Type I and III collagen employing immunohistochemistry; evaluation of elastic fiber density in preparations stained with Weigert's method, observed at 10 High Power

Fields (HPF) under 400x magnification; measurement of fibrosis thickness through micromorphometric techniques at 10 HPF (400x magnification) and standard assessments of tissue biopsy as quantification of inflammatory cells, calculating the average cell count per 10 HPF (400x magnification); enumeration of blood vessels, determining the average vessel count per 10 HPF (400x magnification).

The collagen and elastin content will be assessed with a type I collagen and type III polyclonal antibody and an elastin polyclonal antibody. Tissue sections will be evaluated by a blinded histopathologist.

Bio-stimulating effects of APTOS threads with HA and without HA coating will be assessed by measuring collagen and elastin content in areas adjacent to implanted sutures in comparison with baseline. The bio-stimulation effects will be compared in the two groups (non-HA versus HA threads).

In addition, subjects will provide an assessment of satisfaction using the Face-Q™ Satisfaction with Skin questionnaire (Appendix B) at the follow-up visits on Day 30, Day 90, and Day 180 after the implantation procedure.

The schedule of events for Part 1 main study and the optional Biopsy Substudy is presented in Table 7.

Table 7: Schedule of Events for Part 1 (Six-Month Study) and the Biopsy Substudy

Procedures	Screening[a] (Day -14 - 0)	Day 0 (procedure day)*	Follow-up visits					
			Day 0 (after procedure)	Day 5 (+/-1 day)	Day 14 (+/- 2 days)	Day 30 (+/- 2 days) (Month 1)	Day 90 (+\- 7 days) (Month 3)	Day 180 (+\- 7 days) (Month 6)[g]
Selection of patients according to inclusion and exclusion criteria	X							
Signing the consent form	X							
Medical history, demographics and skin type*	X							
Collection of Concomitant Medications' information	X[a]	X	X		X	X	X	X
2D photo images collection [e, f]	X[a]	X				X	X	X
Urine Pregnancy test	X[a]	X						
Randomization/assignment to non-HA/HA sub-group		X						
Assignment of the Model from Excellence Product line using the measurement of longest thread's (1st) trajectory length (Appendix A)		X						
Thread implantation procedure		X						
Punch biopsy for patients participating in the Substudy		X		X			X	X
NLF severity assessment (WSRS)	X[a]	X				X[h]	X[h]	X[h]
GAIS assessment by blinded evaluators						X	X	X
GAIS assessment by patients						X	X	X
Face-Q™ Satisfaction with Outcome questionnaire for all patients in Part 1						X	X	X
Face-Q™ Satisfaction with Skin questionnaire for patients participating in the Biopsy Substudy		X		X		X	X	X
Patient adverse events diary administration			X		X			
Physical examination (including vital signs (blood pressure, heart rate, and temperature))	X[a,b]	X[b]	X[c]		X[c]	X[c]	X[c]	X[c,]
Adverse events assessment (including patient's diary review and assessment**)	X[a]	X	X		X[d]	X[d]	X	X

[a] Screening and Day 0 visits can be combined on the same day. In such cases, Day 0 (pre-procedure) procedures already performed for screening do not need to be repeated. If the Threads implantation procedure is not provided at the screening visit, a negative urine pregnancy test result is required within 7 days before Threads implantation procedure.

[b] At screening visit/Day 0 pre-treatment standard physical examination (including height, weight and BMI measurements) and the pinprick and/or cotton swab facial nerve assessment to be performed.

[c] During these follow-up visits, physical examination may be limited to examination of treatment area only (face) if extension of the examination is not required per patient's medical condition except Day 180 when weight, height/BMI assessment to be performed to confirm Part 2 Exclusion criteria.

[d] At Day 14 and Day 30, the adverse events assessment will include adverse events assessment reported by patient in patient's diary.

[e] 2D photo images to be collected according to the study photo guide provided to the site (Appendix D).

[f] In case of adverse event-related unscheduled visit, 2D photos to be taken.

[g] Patients who complete the 6-Month main study, i.e., who attend the follow-up visit at Day 180 of the study, will be offered to participate in the extended follow- up study – Part 2.[h] Change in NLF severity after the implantation procedure in comparison with baseline grading, will be assessed by the blinded evaluators using the WSRS.

* Information on skin type can be collected at subsequent visits

6.1.2 Optional Extended Follow-Up Study (Part 2)

Patients who consent to participate in **Part 2** will be followed up to 2 years after the thread placement (Part 2 of Excellence-001 study). Safety and effectiveness of the APTOS threads application procedure will be monitored up to Day 720 (Year 2), including a total of three follow-up visits. Subjects will be followed up at the following time points after the procedure: Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2).

The safety assessments will be performed by investigator(s) throughout the entire study, and will take into account:

- Incidence of all adverse events after implantation of threads throughout the whole study (to Day 720 [Year 2]).

Photographing of subjects to assess the effectiveness of the procedure will be carried out post-procedure at Day 360, Day 540 and Day 720 or at unscheduled visits performed due to adverse effects. The effectiveness of the thread implantation will be assessed by board-certified plastic surgeons or dermatologists who were not involved in the procedure by assessing photographs of the subjects, i.e., a blinded evaluation will be performed. Different blinded evaluators will be used for each assessment tool to increase the reliability of the assessment. The assessment will entail:

- Visual determination of the severity of NLFs on each side of face for each subject. This will be assessed using the WSRS (Appendix B) at Day 360, Day 540, and Day 720 follow-up visits after the procedure.

- Visual determination of aesthetic improvement by comparing photographs of subjects before the procedure and at Day 360, Day 540 and Day 720 follow-up visits after the procedure using the GAIS (Appendix B) for investigators.

In addition, effectiveness will be evaluated by the enrolled subjects who will provide a rating on their improvement according to the GAIS for subjects, and who will provide an assessment of satisfaction using the Face-Q™ Satisfaction with Outcome questionnaire (Appendix B) at Day 360, Day 540 and Day 720 follow-up visits after the procedure .

Details regarding the schedule of events for the 2-year follow-up study (Part 2) are presented in Table 8.

Table 8: Schedule of Events for Part 2 - Extended Follow-up Study

Procedures	**Day 180 (+\- 7 days) (Month 6)[a]**	**Day 360 (+\- 14 days) (Month 12/Year 1)**	**Day 540 (+\- 14 days) (Month 18/Year 1.5)**	**Day 720 (±60 days) (Month 24 / Year 2)**
Selection of patients according to inclusion and exclusion criteria for Part 2	X	X		
Signing the consent form	X	X		
2D images collection		X*	X	X
NLF severity assessment (WSRS)		X	X	X
GAIS assessment by blinded evaluators		X	X	X
GAIS assessment by patients		X	X	X
Face-Q™ Satisfaction with Outcome questionnaire		X	X	X
Physical examination		X[b]	X[b]	X
Collection of Concomitant Medications' information		X	X	X
Adverse events assessment		X	X	X

[a] Patients who complete the 6-Month main study, i.e., who attend the follow-up visit at Day 180 of the study, will be offered to participate in the extended follow- up study – Part 2.

[b] During these follow up visits, physical examination may be limited to examination of treatment area only (face) if extension of the examination is not required per patient's medical condition.

6.1.3 Retrospective Jawline Substudy

6.1.3.1 Data source

The source documents / data used will be:

- the clinical database from study Excellence-001, Part 1 (verified by the time of analysis in Jawline Substudy),
- subjects' 2D face photos.

Special paper CRF will be designed for data collection in the retrospective Jawline Substudy.

6.1.3.2 Study variables

Following characteristics from the clinical database of the study Excellence-001 will be used:

- Nasolabial fold severity (WSRS scores) at baseline and follow-up visits.

2D photos from baseline and follow-up visits of study Excellence-001 Part 1 will be used in the study. Following assessments of these photos will be performed:

- Data selection for Jawline Substudy: CJDS assessment of baseline photos by the Investigator for right and for left jawline according to the inclusion criteria for Jawline Substudy
- Assessment of 2D photos from baseline and follow-ups of Part 1 (Days 30, 90, 180) by IBEs with CJDS.

6.1.3.3 Data collection

The data to be collected and analyzed is detailed in Table 9.

Table 9: Data collection and assessment schedule in Jawline Substudy

Data / Variable	Role	Source	Time of source data collection in study Excellence-001	Time of data collection	Operational definition
Subject ID	Selection of subjects' data according to inclusion criteria for Jawline Substudy	Excellence-001 eCRF	Screening	Part II	The Investigator will identify the numbers of subjects who remain in Part II, for ICF signing and selection for Jawline Substudy
Date of informed consent for Jawline Substudy	Selection of subjects' data according to inclusion criteria for Jawline Substudy	Source data, ICF for the Jawline Substudy	N/A	Part II	The Investigator will collect the data from ICF and add to the Jawline Substudy CRF
CJDS score for right jawline at baseline (by Investigator)	Selection of subjects' data according to inclusion criteria for Jawline Substudy	2D photos collected at baseline in Part 1	Baseline (screening)	Any time during Part II, prior to any CJDS assessments by IBEs	The Investigator will assess jawline definition using CJDS and fill the data in the Jawline Substudy CRF.
CJDS score for left jawline at baseline (by Investigator)			Baseline (screening)		
Subject eligible / not eligible for Jawline Substudy	Selection of subjects' data according to inclusion criteria for Jawline Substudy	Excellence-001 eCRF, ICF for the Jawline Substudy, CJDS assessment by Investigator	Baseline (screening)	Any time during Part II, prior to any CJDS assessments by IBEs	The Investigator will record the decision if the subject is eligible or not eligible in the Jawline Substudy CRF.
Nasolabial fold severity (WSRS score) at baseline and Part 1 follow-ups for the right and left sides	Secondary Endpoint in the Jawline Substudy	Excellence-001 eCRF	Screening / baseline, follow-up visits 1, 3, 6 months	Part II, after CJDS assessments	The Investigator will collect the data from clinical database of Excellence-001 study, Part 1
Right jawline CJDS score (assessed by IBEs)	Baseline assessment, primary and secondary effectiveness endpoint assessment in Jawline Substudy	2D photos collected in Part 1	Part I: baseline, follow-up visits 1, 3, 6 months	Any time during Part II, after subject data selection completed by Investigator	The IBE will assess jawline definition using CJDS and provide the corresponding source document
Left jawline CJDS score (assessed by IBEs)					

6.1.4 Study Endpoints and Study Population

6.1.4.1 Primary Endpoints for Part I

Primary safety endpoints:

Incidence of device and procedure related serious adverse events by Day 30 (Month 1) after the implantation procedure.

Primary effectiveness endpoint:

Reduction in NLF severity at Day 90 (Month 3) after the implantation procedure in comparison with baseline grading, as assessed by blinded evaluators using the Wrinkles Severity Rating Scale (WSRS).

6.1.4.2 Secondary Endpoints for Part I

Secondary safety endpoints:

1. Incidence of all adverse events after implantation of threads throughout the whole study (through Day 180 [Month 6] after the implantation procedure).
2. Incidence of early recovery symptoms (as listed in section 6.1.1) related to the treatment (threads implantation) among adverse events reported by both patients and treating physician(s) up to Day 14 after the implantation procedure.

Secondary effectiveness endpoints

1. Observed values and change from baseline in WSRS on Day 30 and Day 180.
2. The proportion of subjects with improvement of ≥1 WSRS score at each visit
3. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 30, Day 90, and Day 180.
4. Mean GAIS value assessed by subject with frequency of each grade and sum of improved subjects (very much improved, much improved, improved)
5. Patient satisfaction with the procedure outcome assessed using the mean total Face-Q™ Satisfaction with Outcome score at Day 30 (Month 1), Day 90 (Month 3), and Day 180 (Month 6) after the implantation procedure.

6.1.4.3 Endpoints for Biopsy Substudy

1. Difference between the HA and non-HA groups in change over time in biostimulation (collagen types 1,3 and elastin measurements before procedure and on Day 90).

2. Change in collagen types 1,3 and elastin percentage (%) in areas adjacent to implanted sutures by assessing collagen and elastin content using collagen and elastin polyclonal antibodies in the 3-mm biopsy sections obtained through punch biopsy on Day 5 and Day 180 in comparison with baseline (Day 0)
3. Degree/thickness of fibrosis (% / mm) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180.
4. Inflammatory cells (number / 400XHPF) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180.
5. Blood vessel proliferation (number / 400XHPF) in tissue samples obtained from subjects treated with non-HA threads and HA threads on Day 5, Day 90 and Day 180.
6. Observed values and change from baseline in skin satisfaction score assessed using the Face-Q™ Satisfaction with Skin questionnaire collected from patients at Day 0, Day 30, Day 90 and Day 180.

6.1.4.4 Primary Endpoints for Part II

Primary effectiveness endpoint:

Reduction of NLF severity at Day 360 (Year 1) after the implantation procedure in comparison with baseline grading, assessed by the blinded evaluators using the WSRS.

6.1.4.5 Secondary Endpoints for Part II

Secondary safety endpoints:

Incidence of all adverse events after implantation of threads throughout the whole study (to Day 720 [Year 2] after the implantation procedure).

Secondary effectiveness endpoints:

1. Observed values and change from baseline in WSRS on Day 540 (Year 1.5) and Day 720 (Year 2).
2. The proportion of subjects with improvement of ≥1 WSRS score at each visit
3. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2).
4. Mean GAIS value for subjects with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2).
5. Patient satisfaction with the procedure outcome assessed using the mean total Face-Q™ Satisfaction with Outcome questionnaire at Day 360 (Year 1), Day 540 (Year 1.5), and Day 720 (Year 2) after the implantation procedure.

6.1.4.6 Study Endpoints for Retrospective Jawline Substudy

Primary endpoint in Jawline Substudy

Improvement in jawline definition on Day 90 (Month 3) after the implantation procedure in comparison with baseline grading, as assessed by blinded evaluators using the Canfield Jawline Definition Scale.

Secondary endpoints in Jawline Substudy

1. Proportion of subjects with improvement in CJDS score ≥1 point for both sides from baseline to Day 30, Day 90, Day 180 after IMD application. Subjects will be considered responders if improvement in CJDS scale ≥1 point is demonstrated for both face sides.

2. Improvement in jawline definition in comparison with baseline grading, as assessed with CJDS, and observed CJDS values on Day 30 and Day 180 after the implantation procedure

3. Improvement in jawline definition (mean change from baseline) ≥1 point on Day 30, Day 90, Day 180 after the implantation procedure in comparison with baseline grading, as assessed with CJDS

4. Correlation of improvement in NLFs and jawline definition on Day 30, Day 90, Day 180 after thread application

6.1.4.7 Endpoint Justification

The primary safety endpoint for the main study (Part 1) is the incidence of device- and procedure-related serious adverse events by Day 30. Safety will be assessed by Day 30, as was done in the real-world evidence study 0322-001, in order to assess the short-term safety profile of the device and device-related procedure. The primary effectiveness endpoint for the main study (Part 1) is the reduction in NLF severity grading at Day 90 in comparison with baseline, as assessed by the blinded evaluator. This endpoint is directly related to the purpose of the procedure, namely correction of nasolabial fold in patients with mid-facial laxity It will be assessed at Day 90, as has previously been done in our real-world evidence study 0322-001 and in a published study [17]. In addition, 90 days is considered the earliest time that effectiveness can be assessed. By this time, all natural healing processes have been completed, meaning that all the recovery symptoms from the procedure have fully resolved and would not interfere with effectiveness. The endpoints for the Substudy include assessment of the bio-stimulation effect of HA and non-HA threads at Day 90 and Day 180. These timepoints were chosen, based on data received from pre-clinical animal studies showing increase of collagen and elastin at 90 and 180 day timepoints.

The primary endpoint of the optional follow-up study (Part 2) is assessing the change in NLF severity at Day 360 (Year 1). This follow-up time was chosen as it aligns with another applicable

study that assesses effectiveness of thread lifting at 1 month, 1 year and 2 years after thread implantation [8].

All subjects who underwent the procedure will be included in the study population and data analysis. If a subject withdraws from the study or is lost to follow-up, the subject will still be included in the study population and data analysis. Since the sample size calculation takes into account a pre-determined drop-out rate, these subjects will not need to be replaced. However, in case of a higher drop-out rate or non-eligible participants or missing data, the sample size will be extended in order to reach the desired sample size. Where subjects are lost to follow-up, every effort will be made to trace the study subject.

Jawline Substudy will use the data and images collected in Part 1 to provide additional assessment if the midface thread lifting can cause improvement in jawline definition. Although this can be supposed based on anatomical considerations and surgical experience, such type of data is not available. Effectiveness of lifting will be assessed for jawline definition improvement by blinded dermatologist/plastic surgeon with a validated instrument - Canfield Jawline Definition Scale. Canfield Scientific, Inc. has conducted a series of scale development and validation activities and demonstrated that the CJDS can be reliably utilized in the clinical setting for evaluation of jawline definition grading and clinically relevant differences on this scale can be detected by raters when evaluating random side-by-side photographs with ≥1 grade difference.

6.2 Investigational Comparator(s)

In the main study (Part 1) and Part 2, the investigational device models (APTOS Threads - Excellence Product Line models) will not be compared to a comparator group. However, the optional Biopsy Substudy will compare collagen and elastin results in HA and non-HA threads.

6.3 Subjects

6.3.1 Six-Month Main Study (Part 1)

Subject Selection

Inclusion Criteria:

1. Male and female subjects, 22+ years of age.
2. Subjects who desire cheek lifting to correct age-related wrinkles in the mid-face as recommended by the treating investigator.
3. Subject received a rating, in each cheek, by Investigator of at least Grade 3 or Grade 4 for wrinkling of the NLF in the mid-face according to the WSRS.
4. 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.

5. 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 (6 months).
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 a 30-day diary.
10. Subjects who pass the pinprick and/or cotton swab facial nerve assessment.

Exclusion Criteria:

1. Abnormal rating in mid-face sensation, with inability to feel a 0.4 G monofilament or a cotton wisp at any site on the mid-face.
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. Known collagen skin disorder.
8. Pre-existing facial asymmetry.

9. History of any device use on the mid-face in the prior 6 months (laser, Intense Pulsed Light [IPL], radiofrequency (RF), ultrasound, micro needling, micro needle RF, or cool based treatments).
10. History of autoimmune or connective tissue disease.
11. History of facelift, mid-face lift, lower facelift or neck lift that changes the facial structure and anchor points.
12. History of fat transfer to the mid-face.
13. History of injectable fillers other than temporary fillers such as HA or Radiesse to the mid-face at any time.
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. Receiving immunosuppressive therapy.
20. Recent weight loss or intention to lose a significant amount of weight during the study period (2 body mass index [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 mid-face 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 a 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 are included to list of vulnerable populations (pediatric, pregnant, elderly individuals with visual or hearing impairments, mentally ill subjects).

Withdrawal

Subjects will be removed from the study whenever it is necessary to safeguard their welfare. Non-compliance with the protocol or occurrence of serious adverse events may also necessitate discontinuation from the study. When a patient is removed from the study, a final physical examination must be performed. Subjects removed from the study because of an adverse event will be followed-up until the adverse event has resolved and will still be considered in the final safety analysis.

Additional reasons for removing a patient from the study:

1 Subjects who express a desire to withdraw from the study.

2 Any medical condition that, in the opinion of the Principal Investigators, warrants discontinuation from the study for the safety of the patient. To reduce bias, this will be reviewed by the Data and Safety Monitoring Board (DSMB) and these subjects will be included in the safety analysis.

3 Patient had new cosmetic face and neck procedures (e.g. dermal filler injections; thread lifting, facial surgeries) during the study duration.

4 Lost to follow-up (i.e., the subject fails to return for three or more study visits).

Since the sample size calculation takes into account a pre-determined drop-out rate, these subjects will not need to be replaced. However, in case of a higher drop-out rate or non-eligible participants or missing data, the sample size will be extended in order to reach the desired sample size.

Point of Enrollment

Subjects will meet with the physician or physician appointed representative (such as a clinical coordinator) and be given ample opportunity to read and review the provided informed consent form and will be asked to sign prior to

performing any study-related procedures. Subjects will be given the opportunity to ask the physicians questions prior to signing the informed consent. Subjects unable to sign prior to the day of procedure will be asked to sign the informed consent form prior to undergoing treatment. A signed copy of the form will be provided for each patient.

Duration

This multi-center study is expected to last no longer than 1 year (12 months). Study enrolment is expected to take 4 months. Each enrolled subject will undergo the APTOS threads application procedure and be followed for up to 6 months involving five (5) in-person follow-up visits at the clinic post treatment. Thereafter, study close-out, data analysis, and writing of the final study report will take 2 months.

Number of Subjects

This study will include a total of 140 subjects at three sites. At least 30 subjects will be included at each site (depending on the number of Sub-Investigators undergoing training). Subjects will be enrolled over a 4-month period at each site and will undergo the once-off procedure and 6-month follow-up at the same site.

6.3.2 Biopsy Substudy

Subject Selection

Inclusion Criteria:

1. Eligible for Part 1 Excellence-001 study.
2. Subject agrees to participate in the biopsy Substudy, i.e. signs the Substudy informed consent form.

Withdrawal

Subjects will be removed from the study whenever it is necessary to safeguard their welfare. Non-compliance with the protocol or occurrence of serious adverse events may also necessitate discontinuation from the study. When a patient is removed from the study, a final physical examination must be performed. Subjects removed from the study because of an adverse event will be followed-up until the adverse event has resolved and will still be considered in the final safety analysis.

Additional reasons for removing a patient from the study:

1. Subjects who express a desire to withdraw from the study.
2. Any medical condition that, in the opinion of the Principal Investigators, warrants discontinuation from the study for the safety of the patient. To

reduce bias, this will be reviewed by the DSMB and these subjects will be included in the safety analysis.

3. Patient has any other withdrawal criteria for the main study. Since the sample size calculation takes into account a pre-determined drop-out rate, these subjects will not need to be replaced. However, in case of a higher drop-out rate or non-eligible participants or missing data, the sample size will be extended in order to reach the desired sample size.

Point of Enrollment

Subjects will meet with the physician or physician appointed representative (such as a clinical coordinator) and be given ample opportunity to read and review the provided informed consent form for the biopsy Substudy and will be asked to sign prior to performing any study-related procedures. Subjects will be given the opportunity to ask the physicians questions prior to signing the informed consent. Subjects unable to sign prior to the day of procedure will be asked to sign the informed consent form prior to undergoing treatment. A signed copy of the form will be provided for each patient.

Duration

The duration of the Substudy aligns with the main Part 1 study, i.e., it is expected to last no longer than 1 year (12 months). Study enrolment is expected to take 4 months. Each enrolled subject will undergo the APTOS threads application procedure and be followed for up to 6 months. Thereafter, study close-out, data analysis, and writing of the final study report will take 2 months.

Number of Subjects

The study will include a total of 48 subjects at three sites, with at least 24 receiving HA threads and 24 receiving non-HA threads. At least 10 subjects will be included at each site (depending on the number of Sub-Investigators undergoing training). Patients who are enrolled in the main study will be offered to participate in the Substudy. Eligible, consented Substudy patients will undergo additional biopsies at Days 0, Day 5, Day 90 and Day 180.

6.3.3 Optional Extended Follow-Up Study (Part 2)

Subject Selection

Inclusion Criteria

1. Subject completed Part 1 of the Excellence-001 study and attended the Day 180 (Month 6) visit.
2. Subjects who are willing to participate in the study and to sign a witnessed/informed consent form for Part 2.

3. 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.
4. Subjects who are logistically able to present for all study visits and meet all study requirements.

Exclusion Criteria

1. Recent significant weight loss or intention to lose a significant amount of weight during the study period (2 BMI points).

Withdrawal

Subjects will be removed from the study whenever it is necessary to safeguard their welfare. Non-compliance with the protocol or occurrence of serious adverse events may also necessitate discontinuation from the study. When a patient is removed from the study, a final physical examination must be performed. Subjects removed from the study because of an adverse event will be followed-up until the adverse event has resolved and will still be considered in the final safety analysis.

Additional reasons for removing a patient from the study:

1. Subjects who express a desire to withdraw from the study.
2. Any medical condition that, in the opinion of the Principal Investigators, warrants discontinuation from the study for the safety of the patient. To reduce bias, this will be reviewed by the DSMB and these subjects will be included in the safety analysis.
3. Patient has any other withdrawal criteria for the main study (Part 1).

Since the sample size calculation takes into account a pre-determined drop-out rate, these subjects will not need to be replaced. However, in case of a higher drop-out rate or non-eligible participants or missing data, the sample size will be extended in order to reach the desired sample size.

Point of Enrollment

Subjects will meet with the physician or physician appointed representative (such as a clinical coordinator) and be given ample opportunity to read and review the provided informed consent form for the extended follow-up study and will be asked to sign prior to performing any study-related procedures. Subjects will be given the opportunity to ask the physicians questions prior to signing the informed consent. A signed copy of the form will be provided

for each patient.

Duration	Part 2: One year and 8 months, comprising 1.5 years for patient follow-up, and 2 months for study close-out, data analysis and writing of the final study report. Patient enrollment will be optional and will take place at the Day 180 (Month 6) follow-up visit during Part 1.
Number of Subjects	Patients who completed the main study, are eligible for the extension follow-up study, and agree to participate in Part 2 (**CIP amendment 3**: expected 70 subjects to complete Part 2 based on the number enrolled in Part 2 with expected 15% drop-out during Part 2).

6.3.4 Retrospective Jawline Substudy

Inclusion Criteria	Data obtained in study Excellence-001 of the following subjects will be collected and analyzed: 1. Subject underwent the IMD application procedure in Study Excellence-001. 2. Subject currently participates in study Excellence-001. 3. Subject has amenable photos for jawline definition assessment on each face side at baseline (prior to thread implantation) and at least one amenable photo for jawline definition assessment on each face side from follow-up visits of Excellence-001 study, Part 1 (Day 30, Day 90, or Day 180 after thread implantation). 4. Subject who had jawline definition loss from mild to very severe (CJDS score from 2 to 5) on both face sides at enrollment to study Excellence-001. 5. Subject who signed the informed consent form and agreed that his/her data obtained in study Ecellence-001 Part 1 will be used in current retrospective Substudy.
Withdrawal	No withdrawal of subjects is expected due to the retrospective nature of the study.
Point of Enrollment	No enrollment procedure for subjects is planned. Subjects' data and 2D photos will be used in the Jawline Substudy.
Duration	12 months
Number of Subjects	Data of all subjects from study Excellence-001, eligible for inclusion in this retrospective analysis, will be used (no less than 70 subjects)

6.3.5 Vulnerable population (pediatric, geriatric, pregnant, mentally ill etc.)

This clinical investigation will be conducted on adult population only. No vulnerable populations (pediatric, pregnant, elderly individuals with visual or hearing impairments, mentally ill subjects) will be included in the study population.

6.4 Measures to minimize bias

Use of validated scales to assess the effectiveness of the procedure, such as WSRS and CJDS, should streamline the assessment and assure uniformity of scoring. Use of validated methodology to assess the collagen and elastin measurements, and use of the validated Face-Q questionnaire should streamline the assessment and assure uniformity of scoring. This is implemented to minimize assessor bias.

6.4.1 Randomization

Assignment of non-HA and HA threads will be performed using a randomization block design of 4 patients, with a ratio of 1:1 at each Investigation Site, meaning that each patient will be randomly assigned to either the non-HA or HA sub-group, with an equal number of patients in the sub-groups at each site.

6.4.2 Blinding

The allocation of threads with or without HA will be blinded for patients.

The effectiveness of the thread implantation will be assessed by board-certified plastic surgeons or dermatologists who were not involved in the procedure by assessing photographs of the subjects, unaware of the thread type, subject's background and timepoint when the photo was taken, i.e., a blinded evaluation will be performed. Different blinded evaluators will be used for each assessment tool to increase the reliability of the assessment. The assessment will entail visual determination of the severity of NLFs using the WSRS on each side of face for each subject on Days 30, 90, 180, 360, Day 540, and Day 720 after the procedure. A similar blinded assessment of jawline with CJDS will be performed within the Jawline Substudy for 2D photos collected in Part 1.

The histopathologist assessing the elastin and collagen measurements will be blinded to the type of thread used during the procedure and to the patient background.

6.4.3 Management of potential confounding factors

For the primary endpoints (Part 1, 2, Jawline Substudy), the effect of the treatment (delta WSRS or CJDS) will be adjusted for the potentially confounding variables (age, sex, and skin type) using linear regression.

6.5 Procedures

The thread implantation procedure is described in detail in Section 19.3. Appendix C. Surgical Guide for APTOS Threads Absorbable Surgical Sutures of this CIP. Subjects indicated for mid-face suspension by mini-invasive surgery to temporarily fixate the cheek sub-dermis in a repositioned site for the treatment of moderate to severe NLF will meet with the physician or clinical coordinator prior to the procedure for a standard pre-procedure evaluation. Following a preliminary evaluation of eligibility, the patient will be informed of the clinical study and offered the opportunity to participate if he/she is an acceptable candidate. Should the subject agree to join the study, they will be provided with a copy of the patient informed consent form and provided ample time to review the form. The point of enrollment will be upon signing the patient informed consent form. Subjects who sign the consent form but do not undergo any treatment will be recorded as screen failures on a separate log and removed from the enrollment roster.

The duration of this multicenter main study (Part 1) is expected to be 1 year (12 months) at each site. Each enrolled subject will participate for up to 180 days (+\- 7 days in case the procedure is not done on the same day as screening), which will include the day of the informed consent signature with a 6-month follow-up period. The subjects will attend five follow-up visits at Day 0 (post-procedure), Day 14, Day 30, Day 90, and Day 180.

At least 30 subjects will be enrolled at each site, with a total of up to 140 subjects overall. The ratio receiving non-HA and HA threads will be 1:1, meaning that at each site, every other patient will be assigned non-HA and HA threads.

Patients eligible for Part 1 will be offered to participate in the biopsy Substudy. Patients who consent to the biopsy Substudy will undergo implantation of additional threads, 2-2.5 -cm section of the suture in the subcutaneous plane in the posterior auricular area at the time of the primary procedure. Punch biopsies (3 mm) will be collected from the area adjacent to the suture implantation area that was placed in the posterior auricular area (approximately 2 mm from the thread) at Day 0, Days 5, Days 90 and 180. As the dermis in this area is thinner than in the mid-face, this will allow the suture to be palpated and marked, to ensure the distance from the suture is consistently 2 mm. Biopsy sites will be noted to ensure subsequent biopsies are taken from the same area. The 3-mm biopsy sections will be assessed for collagen and elastin content with a type

I collagen polyclonal antibody and an elastin polyclonal antibody. Tissue sections will be evaluated by a blinded histopathologist.

Patients who complete the 6-month main study (Part 1) will be offered to continue to Part 2 of the study - the extended follow-up study. Patients who consent to participate in Part 2 will be followed up to 2 years after the procedure and will have three additional follow-up visits as Day 360, Day 540, and Day 720.

Jawline Substudy will not involve participation of subjects and any subject-related procedures.

6.6 Monitoring plan

This clinical investigation will be monitored in accordance with the requirements set forth in the ISO 14155:2020 standard for clinical investigations in human subjects, GCP, and the requirements set forth by the applicable regulatory bodies and ethical review boards, to ensure the protection of study subjects' rights and well-being as well as the integrity of the clinical data collected. Accuracy and completeness of reported data will be verified from source documents in compliance with the approved CIP.

Monitors independent from the investigational site(s) will be provided access to the source documents as agreed upon by the clinical site and the sponsor. This may include remote monitoring; however, this will be arranged in advance prior to initiation of the various clinical sites and in compliance with the local regulations.

A full monitoring plan will be provided upon request.

7 STATISTICAL DESIGN AND ANALYSIS

7.1 Six-Month Main Study (Part 1)

Statistical Analysis Plan:

Population Analysis

The number of participants of each part of the study, as well as the number of drop-out subjects (prematurely terminated or withdrawal from the study) and the number of subjects who completed the study will be illustrated in a flow chart for each group (HA and non-HA).

The following populations will be used for analysis:

- **All subject analysis set:** Includes all screened patients. This set will be used for the disposition table and for the summary of reasons for premature termination or withdrawal.
- **Intent-to-treat analysis set (ITT):** Includes all randomized patients. The set will be used for all effectiveness analyses, for summarizing and listing subject demographics and baseline characteristics, medical history, medications and therapies (prior and concomitant) and CIP deviations. Subjects will be analyzed according to randomized assignment to non-HA threads/HA threads group.
- **Safety analysis set:** Includes all patients who undergo the procedure. The set will be used for all safety analyses. All safety endpoints will be analyzed according to actual type of implanted threads (with or without HA).
- **Effectiveness analysis set:** Includes all patients who undergo the procedure and have non-missing effectiveness endpoint data collected at the Day 90. The set will be used for a sensitivity analysis of the primary effectiveness endpoint.
- **Biopsy Substudy analysis set:** Includes subjects who agreed to participate in the biopsy Substudy, signed the Substudy informed consent form and have baseline biopsy results and at least one post-baseline result. The set will be used only for the biopsy Substudy analysis and subjects will be analyzed according to the implanted threads (with and without HA).

Descriptive statistics

Baseline characteristics, including demographics, clinical background, and Fitzpatrick skin type, will be summarized for all the data. Similarly, procedure data and follow-up data will be summarized with descriptive statistics.

Summary statistics will include mean (standard deviation [SD]), median (interquartile range [IQR]) and total range (minimum and maximum) for continuous measurement such as WSRS, and frequencies and percentage for categorical variables such as serious adverse events, early symptoms etc.

Safety data will summarize the number of events, severity scores, and the relationship to the investigational devices. Rate of serious adverse events will be estimated along with the exact Binomial 95% confidence intervals (CIs). Time to event resolution and the rate of unresolved events will also be estimated followed by 95% CI. A listing of adverse events and the treatments used to resolve the events will be generated. Adverse events will be coded with MedDRA dictionary and categorized by system organ classes (SOCs) and preferred terms (PTs).

Effectiveness data will summarize the scale ratings by estimated mean (SD) of the WSRS and GAIS and their 95% CI. The Face-Q questionnaire scores will be summarized by estimated mean and 95% CI.

Analytical procedures

Primary endpoints analysis:

For the primary safety endpoint, serious adverse events will be point estimated along with the exact Binomial *95% CI*.

All effectiveness analyses will be performed based on the ITT analysis set. For the primary effective*ness* endpoint, *WSRS* score will be reported as mean change from baseline, and difference from baseline to *Day 90* will be tested *with* the paired t-test with a significance level of $\alpha = 1.67\%$ separately for each group (HA/non-HA/total). The primary effectiveness endpoint will also be analyzed in the Effectiveness analysis set in the course of sensitivity analysis. Another sensitivity analysis will be performed by the linear multivariate regression model to adjust for age, sex, and skin type in the ITT analysis set.

Secondary endpoints analysis:

For the analysis of the secondary safety endpoints, the rate of all adverse events and the incidence of early recovery symptoms will be point estimated along with the exact Binomial 95% CI.

The analysis of all secondary effectiveness endpoints will be performed separately for each group (HA/non-HA/total) in the ITT set. Change

	from baseline in WSRS at Day 30 and Day 180, and GAIS at Day 30, Day 90, and Day 180 will be tested with the paired t-test with a significance level of α = 1.67% separately for each group (HA/non-HA/total). The proportion of subjects with improvement of ≥1 WSRS score at each visit will be tested by the McNemar test for repeatedly measured proportions with comparison to "baseline improvement assessment" = 0 with a significance level of α = 1.67%. Mean GAIS value assessed by blinded evaluators with frequency of each grade and sum of improved subjects (very much improved, much improved, improved) on Day 30, Day 90, and Day 180 will be summarized. Mean total score of the Face-Q™ Satisfaction with Outcome questionnaire will be summarized on Day 30, Day 90, and Day 180.
Significance level and power of primary endpoints	Bonferroni correction will be used as an adjustment for multiplicity for all effectiveness endpoints in the main study Part 1 and Part 2 to control type I error due to testing in three groups (HA threads group, non-HA threads group, total group). All effectiveness endpoints will be tested with a significance level of α = 5/3 % = 1.67%. In the optional biopsy Substudy a significance level of α = 5% will be used.
Sample size calculation and justification	The sample size of the main study was calculated for each sub-group (i.e., HA threads and non-HA threads) separately. Hypothesis: H0: Delta≤0 H1: Delta>0 *Delta* is the mean difference from baseline to Day 90 in mean WSRS. The sample size assumptions are expected mean difference in WSRS score of 1 by Day 90 and its standard deviation SD = 1.5 and customary significance and power of α = 0.01 and (1- β) = 0.9. The total number of patients required for each group (HA threads and non-HA threads), including 5% expected drop out is 70. Thus, total sample size is 140.
Rationale for procedures performed by a single operator	Not applicable; the study will be conducted at three different sites.

Pass/Fail criteria applied to investigation results	As a single-arm study which presents significant changes from baseline *to Day 90,* for the treatment group *we expect an improvement > 0 in the mean WSRS.*
Interim Analysis	No interim analysis planned. Safety results will be reviewed and summarized by the monitoring committee and WSRS scale change from baseline to Day 90 will be measures for trend results.
Bias Management	The effectiveness evaluation of facial photos will be conducted by blinded evaluators who are unaware of the type of thread used during the procedure and of the patient background. This is implemented to minimize assessor bias. Use of validated scales to assess the procedure, such as *the WSRS*, should streamline the assessment and assure uniformity of scoring.
Confounding factors	For the primary endpoint of the main study, the effect of the treatment (delta *WSRS*) will be *adjusted* for confounding variables using linear regression (in the course of sensitivity analysis).
Multiplicity control and adjustment of error probabilities	Bonferroni correction will be used as an adjustment for multiplicity for all effectiveness endpoints in the main study Part 1 and Part 2 to control type I error due to testing in three groups (HA threads group, non-HA threads group, total group). All effectiveness endpoints will be tested with a significance level of $\alpha = 5/3\ \% = 1.67\%$.
Specification of sub-groups for analysis	To explore the safety and performance of the treatment in a particular subgroup, post hoc subgroup analysis will be conducted: By age 50+ By sex (F/M), By face size By investigational site
Missing, unused or spurious data	The safety analysis will be conducted using all the available data. Missing data values will not be included in the effectiveness analysis. No imputation for endpoint scales is expected.
Exploratory & sensitivity analysis	The primary effectiveness endpoint will also be analyzed in the Effectiveness analysis set in the course of sensitivity analysis. Another sensitivity analysis will be performed by the linear multivariate

regression model to adjust for age, sex, and skin type in the ITT analysis set.

For the correlation analysis between the different WSRS blinded evaluators and correlation analysis between different GAIS evaluators the interrater reliability will be assessed by using Intraclass Correlation Coefficients (ICC). ICC estimates and their 95% confident intervals will be calculated based on a mean-rating (k = 3), absolute-agreement, 2-way mixed-effects model. The ICC scores would be interpretated as follows:

- < 0.5 – poor reliability
- 0.5-0.75 – moderate reliability
- 0.75-0.9 – good reliability
- > 0.9 – excellent reliability

Procedures for deviation from original statistical plan

A comprehensive statistical analysis plan will be drafted and approved by the *S*ponsor before commencing data analysis. Any deviations from the plan will be documented in an appendix to the statistical report along with a rationale for the deviation. If significant deviations occur, they will be addressed in the risk assessment and the final interpretation of the results.

Strategy for imbalance of subject numbers per site

The study calls for enrollment of at least *30* patients at each Investigation Site. This will eliminate the risk that some Investigation Sites will have too few subjects for per site analysis. Furthermore, the Investigation Site influence on the primary outcome will be explored by means of sub-group analysis.

Pooling data strategy

Since NLF severity will be assessed by WSRS score separately for each side of the face (left and right) by 3 blinded evaluators, a single mean score of left and right sides will be calculated for each blinded evaluator's assessment for each subject. Subsequently, assessments from blinded evaluators will be averaged for each patient in order to get a single averaged value for each subject.

Since GAIS will be assessed by 3 blinded evaluators, mean scores will be calculated for each subject for each assessment and used for effectiveness analyses.

7.2 Biopsy Substudy

Statistical Analysis Plan:

Population Analysis

The Substudy analysis will comprise the sub-sample of 48 (ratio 1:1 for with and without HA). Subjects who agree to participate in the biopsy Substudy, i.e. sign the Substudy informed consent form, will participate in this Substudy.

Descriptive statistics

Baseline characteristics for the Substudy patients, including demographics, clinical background and Fitzpatrick skin type, will be summarized.

Summary statistics will include mean (SD) and median (IQR) for the collagen and elastin measurements (% in μm^2), as well as the Face-Q Satisfaction with Skin questionnaire score.

Biopsy sub-sample data regarding collagen content and elastin results will be reported separately as mean (SD) at each visit where a biopsy was performed, i.e., Day 0, Day 90, and Day 180.

Analytical procedures

The primary endpoint for biopsy Substudy is difference between the HA and non-HA groups in change over time in biostimulation (collagen types 1,3 and elastin measurements before procedure and on Day 90). The difference in change in collagen types 1,3 and elastin levels between the groups will be tested by the Mann-Whitney non-parametric test with a significance level of $\alpha = 5\%$.

Comparison of the HA and non-HA groups with respect to change in collagen and elastin between the groups will be tested by the Mann-Whitney non parametric test.

Change in collagen types 1,3 and elastin percentage (%) from baseline will be summarized and the difference of the means between baseline and each post-baseline collagen and elastin measurements will be tested by the Wilcoxon signed-rank non-parametric test with a significance level of $\alpha = 5\%$.

The difference in mean content of collagen types 1,3 and elastin (%) in tissue samples obtained from subjects treated with non-HA threads versus HA threads on Day 5, Day 90 and Day 180 will be tested by the Mann-Whitney non-parametric test with a significance level of $\alpha = 5\%$.

	Degree/thickness of fibrosis (% / mm), Inflammatory cells (number / 400XHPF), Blood vessel proliferation (number / 400XHPF) in tissue samples will be summarized on Day 5, Day 90 and Day 180 will be summarized by visits. Satisfaction with Skin questionnaire scores and change from baseline will be analyzed with the Wilcoxon signed-rank non-parametric test with a significance level of $\alpha = 5\%$. In addition, the analysis will include Spearman's correlation between patient satisfaction and change in collagen and elastin measurements to investigate the relationship between patient-reported skin satisfaction and histological results of collagenesis and elastogenesis.
Significance level and power of primary endpoints	*Statistical significance for group comparisons, i.e., HA vs non-HA groups, will be conducted at a 5% significance level and will be reported as significant should the p-value be smaller than 5% (p<0.05).*
Sample size calculation and justification	The sample size of the Substudy, i.e., to demonstrate the comparison of the HA and non-HA groups, was calculated using the independent t-test. Hypothesis: H_0: Delta $\leq$ 0% H_1: Delta $>$ 0% *Delta* is the mean difference in collagen and elastin measurements between the HA and non-HA groups. For a difference of 5% between the two groups (HA and non-HA), we need 24 patients in each group, assuming as SD of 6%. The sample size assumptions are customary significance and power of $\alpha = 0.01$ and $(1-\beta) = 0.8$.
Rationale for procedures performed by a single operator	Not applicable; the study will be conducted at three different sites.
Pass/Fail criteria applied to investigation results	For the two-arm Substudy, *we except a change greater than 0%.*
Interim Analysis	No interim analysis planned.

Bias Management	The *histopathologist assessing the elastin and collagen measurements will be blinded to* the type of thread used during the procedure and *to* the patient background. This is implemented to minimize assessor bias. Use of validated methodology to assess the *collagen and elastin measurements*, *and use of the validated Face-Q questionnaire* should streamline the assessment and assure uniformity of scoring.
Confounding factors	The Substudy comparing HA and non-HA groups will utilize linear regressions to control for the cofounding effects of age, sex, and skin type on the group comparison.
Multiplicity control and adjustment of error probabilities	No multiplicity control or adjustment of error probabilities will be used.
Specification of sub-groups for analysis	There will be no sub-group analyses for the Substudy.
Missing, unused or spurious data	Missing data values will not be included in the analysis. No imputation for endpoint scales is expected.
Exploratory & sensitivity analysis	Overall, this Substudy is of exploratory nature. No sensitivity analysis planned.
Procedures for deviation from original statistical plan	A comprehensive statistical analysis plan will be drafted and approved by the *S*ponsor before commencing data analysis. Any deviations from the plan will be documented in an appendix to the statistical report along with a rationale for the deviation. If significant deviations occur, they will be addressed in the risk assessment and the final interpretation of the results.
Strategy for imbalance of subject numbers per site	The same laboratory will analyze all collagen and elastin measurements to avoid differences between Investigation Sites. The statistical analyses will take into account the different Investigation Sites.
Pooling data strategy	Not applicable

7.3 Optional Extended Follow-Up Study (Part 2)

Statistical Analysis Plan: **Population Analysis**	The number of participants of each part of the study, as well as the number of drop-out subjects (prematurely terminated or withdrawal

from the study) and the number of subjects who completed the study will be illustrated in a flow chart for each group (HA and non-HA).

The following populations will be used for analysis:

- **All subject analysis set:** Includes all screened patients. This set will be used for the disposition table and for the summary of reasons for premature termination or withdrawal.
- **Intent-to-treat analysis set (ITT):** Includes all randomized patients. The set will be used for all effectiveness analyses, for summarizing and listing subject demographics and baseline characteristics, medical history, medications and therapies (prior and concomitant) and CIP deviations. Subjects will be analyzed according to randomized assignment to non-HA threads/HA threads group.
- **Safety analysis set:** Includes all patients who undergo the procedure. The set will be used for all safety analyses. All safety endpoints will be analyzed according to actual type of implanted threads (with or without HA).
- **Effectiveness analysis set:** Includes all patients who undergo the procedure and have non-missing effectiveness endpoint data collected at the Day 90. The set will be used for a sensitivity analysis of the primary effectiveness endpoint.
- **Substudy analysis set:** Includes subjects who agreed to participate in the biopsy Substudy, signed the Substudy informed consent form and have baseline biopsy results and at least one post-baseline result. The set will be used only for the biopsy Substudy analysis and subjects will be analyzed according to the implanted threads (with and without HA).

Descriptive statistics

Follow-up data will be summarized with descriptive statistics.

Summary statistics will include mean (SD) and median (IQR) for continuous measurements (such as WSRS, GAIS, and Face-Q questionnaire) and frequencies and percentage for categorical variables (such as serious adverse events).

Safety data will summarize the number of events, severity scores, and the relationship to the investigational devices. Rate of serious adverse events will be estimated along with the exact Binomial 95% CIs. Time to event resolution and the rate of unresolved events will also be

	estimated followed by 95% CI. A listing of adverse events and the treatments used to resolve the events will be generated. Adverse events will be coded with MedDRA dictionary and categorized by system organ classes (SOCs). **Effectiveness data** will summarize the scale ratings as mean (SD) of the WSRS and GAIS by estimate and 95% CI. The Face-Q questionnaire full scale and sub-scales will be summarized by estimated mean and 95% CI.
Analytical procedures	**Primary endpoint analysis:** For the primary effectiveness endpoint, WSRS score will be reported as mean change from baseline, and difference from baseline to Day 360 will be tested with the paired t-test with a significance level of α = 1.67% separately for each group (HA/non-HA/total). All effectiveness analyses will be performed based on the ITT analysis set. The primary effectiveness endpoint will also be analyzed in the Effectiveness analysis set in the course of sensitivity analysis. Another sensitivity analysis will be performed by the linear multivariate regression model to adjust for age, sex, and skin type in the ITT analysis set. **Secondary endpoints analysis:** For the secondary safety endpoint, serious adverse events will be point estimated along with the exact Binomial 95% CI. Change from baseline in WSRS at Day 540 and Day 720 will be tested by the t-test with a significance level of α = 1.67% separately for each group (HA/non-HA/total). The Face-Q questionnaire and GAIS scores will be summarized by frequency distribution as well as mean and SD.
Significance level and power of primary endpoints	Data analysis will be performed with a significance level of α = 1.67% separately for each group (HA/non-HA/total). The level of significance was adjusted for multiple comparisons.
Sample size calculation and justification	The sample size of the Part 2 study will be based on subjects who completed the main study, are eligible for the extension follow-up study, and agree to participate in Part 2 (**CIP amendment 3:** expected 70 subjects to complete Part 2 based on the number enrolled in Part 2 with expected 15% drop-out during Part 2).

Rationale for procedures performed by a single operator	Not applicable; the study will be conducted at three different sites.
Pass/Fail criteria applied to investigation results	No pass / fail criteria applied
Interim Analysis	No interim analysis planned.
Bias Management	The effectiveness evaluation of facial photos will be conducted by blinded evaluators who are unaware of the type of thread used during the procedure and of the patient background. This is implemented to minimize assessor bias. Use of validated scales to assess the procedure, such as the WSRS, should streamline the assessment and assure uniformity of scoring.
Confounding factors	For the primary endpoint of the main study, the effect of the treatment (delta WSRS) will be adjusted for confounding variables using linear regression.
Multiplicity control and adjustment of error probabilities	Bonferroni correction will be used as an adjustment for multiplicity for all effectiveness endpoints in the main study Part 1 and Part 2 to control type I error due to testing in three groups (HA threads group, non-HA threads group, total group). All effectiveness endpoints will be tested with a significance level of $\alpha = 5/3\ \% = 1.67\%$.
Specification of sub-groups for analysis	To explore the safety and performance of the treatment in a particular subgroup, post hoc subgroup analysis will be conducted: By age 50+ By sex (F/M), By face size By investigational site
Missing, unused or spurious data	The safety analysis will be conducted using all the available data. Missing data values will not be included in the effectiveness analysis. No imputation for endpoint scales is expected.
Exploratory & sensitivity analysis	The primary effectiveness endpoint will also be analyzed in the Effectiveness analysis set (Part 2 subset) in course of sensitivity analysis.

Another sensitivity analysis will be performed by the linear multivariate regression model to adjust for age, sex, and skin type in the ITT (Part 2 subset) analysis set.

For the correlation analysis between the different WSRS blinded evaluators and correlation analysis between different GAIS evaluators the interrater reliability will be assessed by using Intraclass Correlation Coefficients (ICC). ICC estimates and their 95% confident intervals will be calculated based on a mean-rating (k = 3), absolute-agreement, 2-way mixed-effects model. The ICC scores would be interpretated as follows:

- < 0.5 – poor reliability
- 0.5-0.75 – moderate reliability
- 0.75-0.9 – good reliability
- > 0.9 – excellent reliability

Procedures for deviation from original statistical plan

A comprehensive statistical analysis plan will be drafted and approved by the Sponsor before commencing data analysis. Any deviations from the plan will be documented in an appendix to the statistical report along with a rationale for the deviation. If significant deviations occur, they will be addressed in the risk assessment and the final interpretation of the results.

Strategy for imbalance of subject numbers per site

At the end of follow-up we expect to have at least 20 patients per Investigation Site. This will eliminate the risk that some Investigation Sites will have too few subjects for per site analysis. Furthermore, the Investigation Sites will be adjusted for outcome by the statistical analysis.

Pooling data strategy

Since NLF severity will be assessed by WSRS score separately for each side of the face (left and right) by 3 blinded evaluators, a single mean score of left and right sides will be calculated for each blinded evaluator's assessment for each subject. Subsequently, assessments from blinded evaluators will be averaged for each patient in order to get a single averaged value for each subject.

Since GAIS will be assessed by 3 blinded evaluators, mean scores will be calculated for each subject for each assessment and used for effectiveness analyses.

7.4 Retrospective Jawline Substudy

Statistical Analysis Plan:

Population Analysis

The following populations will be used for analysis:

Jawline analysis set: all patients' data included in the Jawline Substudy (current participants of the Excellence-001 study who underwent the procedure and have amenable photos for jawline assessment on both sides from baseline and any visit of the following: Day 30, Day 90, Day 180 after thread implantation).

Descriptive statistics

Data will be summarized with descriptive statistics.

Summary statistics will include mean (SD) and median (IQR) for continuous measurements (such as CJDS and GAIS) and frequencies and percentage for categorical variables.

Analytical procedures

Primary endpoint analysis:

All effectiveness analyses will be performed based on the Jawline analysis set. For the primary effectiveness endpoint, CJDS score will be reported as mean change from baseline, and difference from baseline to Day 90 will be tested with the paired t-test with a significance level of $\alpha = 1.67\%$ separately for each group (HA/non-HA/total). A sensitivity analysis will be performed by the linear multivariate regression model to adjust for age, sex, and skin type in the Jawline analysis set.

Secondary endpoints analysis:

The analysis of all secondary effectiveness endpoints will be performed separately for each group (HA/non-HA/total) in the Jawline Analysis Set. The proportion of subjects with improvement in CJDS score ≥1 point for both sides at each visit will be tested by the McNemar test for repeatedly measured proportions with comparison to "baseline improvement assessment" = 0 with a significance level of $\alpha = 1.67\%$.

Change from baseline in CJDS at Day 30 and 180 will be tested by the t-test with a significance level of $\alpha=1.67\%$.

Comparison of the observed change with 1-score improvement on Day 30, Day 90 and Day 180 will be tested by the paired t-test with a significance level of $\alpha = 1.67\%$.

In addition, the analysis will include Spearman's correlation between WSRS and CJDS scores at visits and changes in WSRS in CJDS from baseline for Day 30, Day 90, Day 180. Statistical significance will be

	conducted at a 1.67% significance level and will be reported as significant should the p-value be smaller than 1.67% (p<0.0167). Strength of the association corresponding to the correlation coefficient value would be interpretated as follows: • ≥ 0.7 –strong • 0.4-0.69 – moderate • < 0.4 – weak The sign of the Spearman correlation indicates the direction of association between WSRS and CJDS scores: positive correlation coefficient would mean direct relationship and negative coefficient would mean inverse relationship.
Significance level and power of primary endpoints	Data analysis will be performed with a significance level of α=1.67% for the Jawline analysis set.
Sample size calculation and justification	As this is a retrospective analysis, all available data from subjects enrolled in the EXCELLENCE-001 study that meet the inclusion criteria will be included. Therefore, a formal prospective sample size calculation is not applicable. Nonetheless, to address the potential statistical power of the analysis, it should be noted that if data are available for at least 60% of the EXCELLENCE-001 study population, the analysis will retain a statistical power of ≥90% (β ≤ 0.10) to detect a mean change from baseline to Day 90 in the CJDS score of 1 point, assuming a standard deviation (SD) of 1.5 points with two-sided α=0.01.
Rationale for procedures performed by a single operator	Not applicable.
Pass/Fail criteria applied to investigation results	No pass / fail criteria applied
Interim Analysis	No interim analysis planned.
Bias Management	The effectiveness evaluation of facial photos will be conducted by IBEs with a validated scale (CJDS).

Confounding factors	For the primary endpoint of the Jawline Substudy, the effect of the treatment (delta CJDS) will be adjusted for confounding variables using linear regression.
Multiplicity control and adjustment of error probabilities	Bonferroni correction will be used as an adjustment for multiplicity for all effectiveness endpoints to control type I error due to testing in three groups (HA threads group, non-HA threads group, total group). All effectiveness endpoints will be tested with a significance level of α = 5/3 % = 1.67%.
Specification of sub-groups for analysis	Post hoc subgroup analysis will be conducted: by baseline CJDS score (subgroup 1: CJDS 2-3; subgroup 2: CJDS 4-5).
Missing, unused or spurious data	Missing data values will not be included in the effectiveness analysis. No imputation for endpoint scales is expected.
Exploratory & sensitivity analysis	A sensitivity analysis will be performed by the linear multivariate regression model to adjust for age, sex, and skin type in the Jawline analysis set. For the correlation analysis between the different CJDS blinded evaluators the interrater reliability will be assessed by using Intraclass Correlation Coefficients (ICC). ICC estimates and their 95% confident intervals will be calculated based on a mean-rating (k = 3), absolute-agreement, 2-way mixed-effects model. The ICC scores would be interpretated as follows: • < 0.5 – poor reliability • 0.5-0.75 – moderate reliability • 0.75-0.9 – good reliability • > 0.9 – excellent reliability.
Procedures for deviation from original statistical plan	A comprehensive statistical analysis plan for Jawline Substudy will be drafted and approved by the Sponsor before commencing data analysis. Any deviations from the plan will be documented in the statistical report along with a rationale for the deviation. If significant deviations occur, they will be addressed in the risk assessment and the final interpretation of the results.
Strategy for imbalance of subject numbers per site	No imbalance is expected other than described for Part 1 and Part 2 due to the retrospective nature of this Substudy.

Pooling data strategy

Since jawline definition will be assessed by CJDS score separately for each side of the face (left and right) by 3 IBEs, a single mean score of left and right sides will be calculated for each blinded evaluator's assessment for each subject. Subsequently, assessments from 3 blinded evaluators will be averaged for each patient in order to get a single averaged value for each subject.

8 DATA MANAGEMENT

Data entry & collection methods:

The company will use electronic data capture (in Part 1 and Part 2). Responsible, qualified (including GCP certification), authorized site staff will enter data in the electronic Case Report Form (eCRF). For exploratory Substudies separate CRFs / extraction forms / worksheets will be used.

The data manager and medical reviewer (as applicable) will review the data and query the site staff when applicable. Site monitor will verify data entered and query responses. Verified pages and data will be locked.

Errors may occur in all stages of the clinical investigation; therefore, data cleaning will be implemented during every phase of the data flow. The data points specified in the study protocol and collected on the CRFs will be verified with the source documents at the investigational site during the Interim Monitoring Visits. Any discrepancies, illegible documentation and/or missing data points will be identified and corrected prior to the investigator signing off on the eCRF.

The Clinical Research Associate (CRA) assigned to the investigational site will conduct a targeted adverse event search in the subject's medical records to ensure that all adverse events have been identified and captured. If repeated errors or omissions in data entry occur, corrective and preventative actions plans will be implemented as indicated. Documentation errors and/or missing data identified after retrieval of the CRF will be corrected using the query process.

During the data analysis phase of the research, outlying data will be confirmed through queries and source document verification.

Queries will be generated by the Data Manager and/or the CRA. The query will be sent to the site's Clinical Research Coordinator (CRC) for confirmation or correction. All data queries are tracked as an integral part of the eCRF and study database which are compliant with FDA 21 CFR part 11.

Data management procedures:

The company will utilize the qualified clinical QMS provided by the CRO. This will include SOPs as well as forms and logs used to document the various administrative functions such as subject

	informed consent logs, screening logs, device accountability etc. Procedures will include CRF tracking, data review, database cleaning, and issuing and resolving data queries. Specifically, timely and reliable processes will be used for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.
V&V and securing electronic database procedures:	The eCRF platform used in the study will be Viedoc (Viedoc Technologies), a verified and validated tool meeting all regulatory requirements. All work with the database will be performed in compliance with the applicable SOPs and regulations. Given that electronic CRFs will be used, cybersecurity measures will conform with the FDA 21CFR part 11. In the case of a data security breach, measures taken will be in conformance with the company's SOPs.
Subject privacy protection procedures	The sites will all work in accordance with the EU General Data Protection Regulation (GDPR) laws as applicable and any other local requirements.
Database management procedures:	The database will be automatic, and the platform will include procedures for database management. At a minimum, the database will be password secured and locked for changes. Should the sponsor decide to use an external qualified data management/analysis biostatistician, procedures for data management utilized by the data management center will be implemented.
Data retention procedures:	In Georgia, the requirement is 15 years. Data will be retained in a manner that will protect the privacy of the study subjects in accordance with the local 15-year requirements.
Responsibilities	The **Principal Investigators** for the clinical investigation are responsible for: • Maintaining records to document the compliance of all parties involved in the clinical investigation. • Ensuring that the clinical investigation is correctly documented at the investigation site according to this CIP.

- Ensuring the accuracy, completeness, legibility and timeliness of the data in all required reports during the clinical investigation

The **Site Clinical Coordinator** for the clinical investigation is responsible for:

- Maintaining all of the study related hospital files
    - This includes maintaining all logs such as:
        - CIP Deviation Log
        - Subject Informed Consent (SIC) Signature Log
        - Investigation Team Log
        - Investigation Site Team Training Log
        - Clinical Investigation Document Approval Log
        - CIP Amendment Log
        - CRF completion
        - IMD Log Master and subject
        - Biopsy Samples Log
- Correct CRF & source / live documentation
- Maintaining contact with study subjects, and coordinating visits to the hospital for signing documents and undergoing treatment.
- Maintaining contact with the Principal Investigator for all reportable incidents and general updates.

The **Data Manager** is responsible for: (if applicable)

- Managing CRF receipt and reconciliation of any discrepancies prior to data entry.
- Performing manual review of the CRF to verify completeness and legibility, data content and consistency.
- Ensuring that all serious adverse events have been reported.
- Performing CRF data entry into the clinical database.
- Maintaining the CRF Tracking Form, recording data receipt and reconciliation, manual review, data changes, data queries and data entry.

Clinical Quality Assurance

- At the start of the clinical study, the Clinical Coordinator will prepare the study files for the following:
  - Institutional Review Board (IRB) / Independent Ethics Committee (IEC) documents
    - All IRB/IEC correspondence is on file.
    - The study staff are IRB/IEC approved prior to performing any study procedures.
    - Adverse events and deviation procedures for reporting to IRB / IEC per current guidelines are in place.
    - All versions of the IRB / IEC protocols and informed consent forms are on file.
    - Signed GCP compliance form, financial disclosure and Curriculum Vitae (CV) for the Principal Investigator and Sub-Investigators.
    - Procedures of documentation of serious adverse events that are unexpected and related for reporting are in place.
- Other documents:
  - CVs for all study staff are on file and updated within the last 2 years.
  - Medical licenses for the Sub-Investigators are on file and updated prior to expiration.
  - Delegation Log is updated and procedures for updating the log with new staff are in place.
  - All other essential documents have been prepared and completed as appropriate.

Protocol:

- Confirm that the study staff is conducting the study in compliance with the protocol approved by IRB/IEC.
- The protocol deviations (exceptions and violations) are documented in the subject chart and reported to IRB/IEC.
- Ensure any deviations are logged in a CIP Deviation Form.

Case Report Forms:

- Ensure that the data reported on the CRF is complete and consistent with the CIP requirements.
- Discrepancies between the source documents and CRF are explained in a note to file or captured in a comment in the CRF.

Query Management:

Queries may be generated by the Principal Investigators, Sub-investigators, Data Manager or Clinical Coordinator.

Samples of data queries are as follows:

- Non-compliance to CIP
- Missing data
- Out-of-range data
- Unplanned patient visits
- Data inconsistent with the subject medical files
- Data clarification

9 AMENDMENTS TO THE CIP

Amendments

All subsequent amendments to the CIP must also be agreed and approved by the Principal Investigators. Substantial amendments to CIP must be approved by local ECs and the Ministry of Health (MoH). Non-substantial changes to the protocol do not require local EC and MoH approval but must be provided to the authorities for information.

The Principal Investigators will ensure that:

- Amendments to the CIP are documented.
- Approval is documented and filed.

10 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Deviations

Neither the Principal Investigators nor any of the Sub-Investigators are authorized to deviate from the CIP, except as specified in 5.64 of ISO 14155:2020, which specifically requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the EC/IRB Committee. Such deviations shall be documented and reported to the sponsor and the IEC/IRBas soon as possible.

Notifications

All notifications will be carried out within the time frames specified by local regulatory authorities or as noted in the Clinical Investigation Monitoring Plan (for this CIP)

Other

In the event that responsibilities are not met by participating personnel, the Principal Investigators reserve the right to disqualify the specific parties involved:

- Accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and in all required reports during the clinical investigation are not carried out or are compromised.
- Resources are not provided in order to facilitate the operation of the investigational study.
- Any unethical actions related to the investigation and/or serious deviations from the CIP and/or written procedures.

11 DEVICE ACCOUNTABILITY

Procedures for device accountability

A packing slip will accompany the products. Before release for use, the site will provide an AoR to the CRO or sponsor. Device accountability logs will be used: master accountability and subject accountability logs.

Access to the IMDs will be authorized by the Principal Investigator at each Investigation Site. Adequate storage of the device must be ensured at each Investigation Site. The disposal of waste from the devices used in the clinical investigation (for example, cannulas, part of sutures) must

be performed according to local requirements and treated as medical waste. Unused, expired, or malfunctioning devices must be returned to the Sponsor.

Usage of the opened package of the investigational device is restricted. The IMDs must be used only in the clinical investigation and according to the CIP. Investigators shall keep records to document:

• name(s) of person(s) who received, used, returned, or disposed of the device.

• the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code).

• the expiry date, if applicable;

• the date or dates of use;

• subject identification;

• date on which the investigational device was returned/explanted from subject, if applicable;

• the date of return of unused, expired, or malfunctioning investigational devices, if applicable;

• the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

Instructions for safe return of investigational devices

Unused devices will be returned to the Sponsor directly. The Investigation Site will maintain the unused devices in their original packaging, unopened, undamaged, until the return to the Sponsor.

12 STATEMENTS OF COMPLIANCE

1. This clinical investigation will be conducted in accordance with ethical principles stated in the Declaration of Helsinki and in compliance with all national and local regulatory requirements for the safety and protection of human subjects.

2. This clinical investigation will be conducted in compliance with MDR and with the ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice and will be monitored and audited accordingly.

3. This clinical investigation will be implemented only upon receiving all final notification/authorizations from local and national regulatory authorities and IEC/IRB, as appropriate.

4. This clinical investigation will comply with any additional requirements set forth by the IEC/IRB and/or regulatory authorities.

5. This clinical investigation provides clinical study medical insurance for study participants as required by local and national regulatory authorities.

13 INFORMED CONSENT PROCESS

General process

Subjects interested in participating in the clinical investigation will be screened by the clinical coordinator or participating physician.

Subjects who meet the criteria will then be given a copy of the Patient Informed Consent, with ample time to read and review the document and ask questions prior to signing.

Subjects will meet with one of the investigators to discuss investigational participation and any questions they may have regarding the investigation, the investigational device models, and the informed consent.

The informed consent will be signed during the meeting with one of the participating investigators.

A copy of the signed patient informed consent form will be provided to the patient prior to the procedure.

Subjects requesting to withdraw consent will be discontinued from the investigation at no cost or consequence.

The same consent processes will be utilized for consenting patients for the Biopsy Substudy, Part 2 (the Extended Follow-Up Study) and Jawline Substudy.

Unable subjects

Subjects unable to provide consent on their own behalf will not be recruited into the study.

Emergency treatment

In the event of an emergency resulting from the clinical investigation, all emergency treatment will be provided at no cost to the patient. **Clinical Investigation Insurance** has been provided to ensure all costs are covered if necessary.

14 ADVERSE EVENTS

Definitions

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device (MDR Article 2(57)).

Note: a. This definition includes events that are anticipated as well as unanticipated events

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

An **Adverse Device Effect (ADE) -** Any adverse event related to the use of an IMD.

A **Serious Adverse Event (SAE)** is an adverse event that:

- Leads to death,
- Leads to serious deterioration in the health of the subject, that either results in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

An **Anticipated Serious Adverse Device Effect** (ASADE) - Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

An **Unanticipated Serious Adverse Device Effect** (USADE) - Any serious adverse device effect, the nature, severity or outcome of which is not consistent with the reference safety information.

Severity of all adverse events to be assessed as follows:

A **mild adverse event** is one where the symptoms are barely noticeable to the patient. It does not influence performance, require drug treatment, or prevent the patient from carrying on with normal life activities.

A **moderate adverse event** is one where the symptoms make the patient uncomfortable and causes some impairment to normal life activities and requires treatment for symptom(s).

A **severe adverse events** Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

A **Device deficiency (DD)** - Any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer (MDR Article 2(59)).

Principal Investigator

The Principal Investigators will notify the authorities (within 24 hours) of any serious adverse event. All reports to the appropriate authorities will be made by the Principal Investigators as set forth in the standard clinical practices outlined in the 21 CFR (§ 812.150(a)(1), § 812.46(b) and § 812.150(b)(1))/ MEDDEV 2.7/3 Dec 2010 and International Conference of Harmonization (ICH)-GCP Guidelines.

Adverse Events Report

Adverse Events will be reported and treated as per the standard clinical practices outlined in the 21 CFR (§ 812.150(a)(1), § 812.46(b) and § 812.150(b)(1))/ MEDDEV 2.7/3 Dec 2010 and ICH-GCP Guidelines.

Regardless of the relationship to the investigational device, all moderate to serious adverse events occurring from the time that the informed consent is signed must be recorded in the patient's CRF.

SAEs are to be reported to the Sponsor within 24 hours of awareness by the investigator.

The Sponsor is to report incidents fulfilling reporting criteria to the MoH of Georgia as applicable timelines per local legislation.

SAEs and SADEs are to be reported to Sponsor representative:

	Anna Kadzhaya, MD, Head of Clinical Development, Aptos, LLC Mobile number for 24/7 contact: +995597119525 Email: safety@aptos.ge All local regulatory requirements for reporting to the DSMB will be followed.
Foreseeable Adverse Events	The Absorbable P(LA/CL)/P(LA/CL)-HA Surgical Sutures are associated with the following adverse reactions: • Transient local irritation at the wound of entry point site • Transient inflammatory response symptoms to foreign body (swelling, pain, discomfort, erythema, feeling of warmness) • Bruising • Tightness
Emergency Contact Details	In the event of a serious adverse event and/or a serious adverse device effect, the relevant Principal Investigator should be notified immediately: Site 1: "Total Charm", LTD Name: Nino Nishnianidze Address: 18 Orbeliani street, Tbilisi, Georgia Phone: +995 599006426 Email: m.tsintsadze@ tcc.ge Site 2: "Total Charm Vake", LTD Name: Albina Kajaia Address: Phaliashvili Str #87 "B" Block, Entrance 3, floor 2, Flat 1 Phone: +995597119525 Email: dr.kajaia@tcc.ge Site 3: "Total Charm Piazza", LTD Name: Ketevan Kavtaradze Address: Gorgasali str # 15, Batumi. Phone: +995 598006688 Email: drketikavtaradze@gmail.com

In the event of a SAE and/or a SADE, the relevant Principal Investigator should notify the Sponsor immediately:

Anna Kadzhaya, MD, Head of Clinical Development, Aptos, LLC

Mobile number for 24/7 contact:

+995597119525

Email: safety@aptos.ge

15 EARLY TERMINATION OR SUSPENSION OF THE CLINICAL INVESTIGATION

Suspension or Premature Termination

Grounds for suspension or premature termination of the clinical investigation include, but are not limited to:

- Noncompliance of the investigational site personnel to the CIP and or investigational procedures.
- Severe adverse events that demonstrate danger to the patient population.
- Unethical performance on the part of any of the investigators.
- Procedural adverse effects that demonstrate danger to the patient population or a severe flaw in investigational procedure.
- Other unforeseen events that give the Principal Investigator reasonable doubts to the safety and/or performance of the system which will be referred to the Data Safety Monitoring Committee for review prior to determination of suspension or termination.

Follow-Up

Patients will be followed up for up to 6 months in Part 1 of the study (the main 6-month study) via in-person study visits to each site. The last follow-up visit will take place at Day 180 ± 7 days post-treatment.

Patients will be followed up for up to 2 years in the optional Part 2 study (the extended follow-up study)via in-person study visits to each site. The last follow-up visit will take place at Day 720 ± 60 days post-treatment.

16 PUBLICATION POLICY

The results of this clinical investigation may be published in a mainstream peer reviewed professional journal once analysis and write-up have been completed and pending prior written approval from Aptos LLC. Criteria for authorship will be decided based on the requirements set forth in the journal to which the publication will be submitted. In addition:

- The clinical investigation will be registered in a publicly available database.
- The results of the clinical investigation will be made publicly available.

17 ARRANGEMENTS FOR SUBJECTS FOLLOWING PARTICIPATION

Considering the condition being investigated in this study (aging skin laxity, NLF), subjects enrolled in this study would not normally be considered for additional care after participation in the clinical trial.

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19 APPENDICES

19.1 Appendix A. Investigational Medical Device Model Assignment Rules.

19.1.1 Product model thread length

Product model thread length and the length of the longest threads trajectory in the application area is presented in Table 10.

Table 10: Product Model Thread Length

Excellence Product Line Models	Model Thread Length	Length of Longest Threads Implantation Trajectory in Application Area (distance from projection of zygomaticus arch to mandibular ligament)
- Visage Excellence Method - Visage Excellence Method-HA (EV/EVHA)	190 mm	>100 mm
- Visage Excellence Soft Method - Visage Excellence Soft Method – HA (EVS/EVSHA)	100 mm	80-100 mm
- Nano Excellence Method - Nano Excellence Method-HA (NE/NEHA)	80 mm	< 80 mm

Distance from projection point of zygomatic arch to projection of mandibular ligament will be measured using a digital ruler (Figure 2, Figure 3).

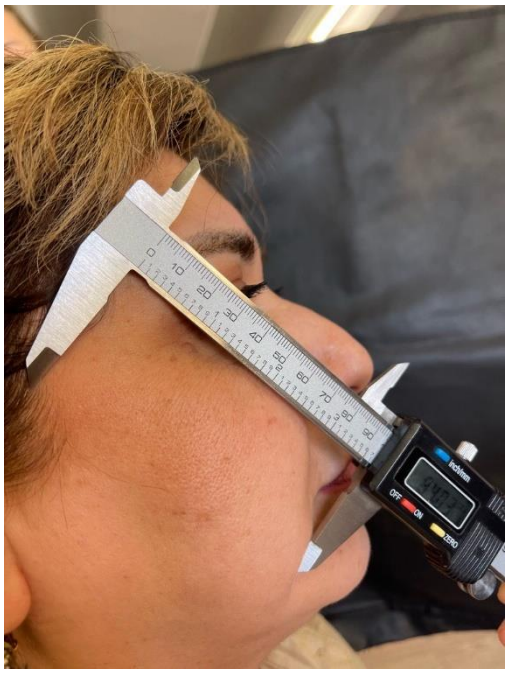


Figure 2: Thread implantation trajectory measurement method on patient.

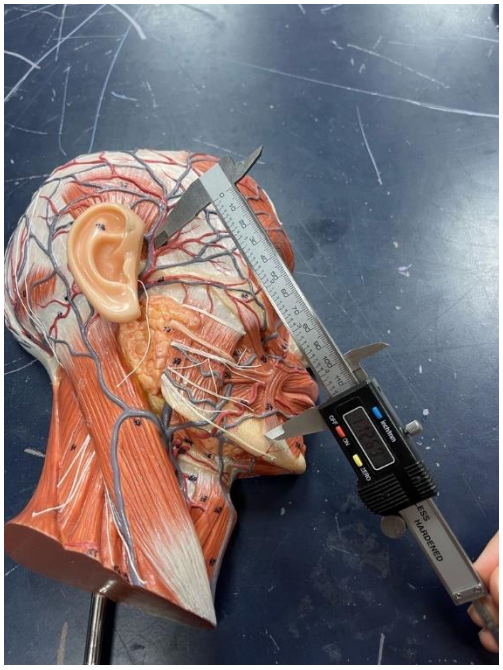


Figure 3: Visualization of anatomical points used for thread implantation trajectory measurement.

19.1.2 Threads with or without HA coating.

Assignment of non-HA and HA threads will be performed using a randomization block design of 4 patients, with a ratio of 1:1 at each Investigation Site, meaning that each patient will be randomly assigned to either the non-HA or HA sub-group, with an equal number of patients in

the sub-groups at each site. The model of the product line (namely EV/EVHA or EVS/EVSHA or NE/NEHA) for each sub-group will be assigned according to the criterion for appropriate thread length. The treads allocation will be according to corresponding subsequent number of site-specific sealed envelopes provided to the site during site initiation visit. The allocation of threads with or without HA will be blinded for patients. The investigator receives the sterile packs without outer boxes from applicable study team immediately before the treatment. During the study the investigational team will maintain the blinding of the thread type for patients

19.2 Appendix B. Study Outcomes Assessment Tools (Scales and Questionnaires)

19.2.1 Wrinkle Severity Rating Scale



Figure 4: Five-point Wrinkle Severity Rating Scale for NLF assessment. Source: Day et al. 2004 [38].

19.2.2 Global Aesthetic Improvement Scale Assessment (for Physicians)

The GAIS assessment for physicians will use the five-point scale presented by Narins et al. 2003 [39] (Table 11), where 1 = Very Much Improved, 2 = Much Improved, 3 = Improved, 4 = No Change and 5 = worse.

Table 11: Global Aesthetic Improvement Scale for Physicians. Source: Narins et al, 2003 [39],

Rating	*Description*
Very much improved	Optimal cosmetic result for the implant in this patient
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition

The GAIS Assessment for Subjects will be the same as for physicians but without the description (Table 12).

Table 12: Global Aesthetic Improvement Scale for Subjects.

Rating	Degree of Improvement
1	Very much improved
2	Much improved
3	Improved
4	Unchanged
5	Worsened

19.2.3 Face-Q Questionnaires

Two different Face-Q Questionnaires will be used in this study – Face-Q Satisfaction with Outcome and Face-Q Satisfaction with Skin, as presented below.

a) Face-Q Satisfaction with Outcome

FACE-Q™ - SATISFACTION WITH OUTCOME

For each statement, circle only one answer. We would like to know how you feel about your most recent procedure. Please indicate how much you agree or disagree with each statement.

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. I am pleased with the result.	1	2	3	4
b. The result turned out great.	1	2	3	4
c. The result was just as I expected.	1	2	3	4
d. I am surprised at how good I look in the mirror.	1	2	3	4
e. The result is fantastic.	1	2	3	4
f. The result is miraculous.	1	2	3	4

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Note to Investigators: This scale can be used independently of the other scales.

Figure 5: Face-Q Satisfaction with Outcome. Source: The FACE-Q, authored by Drs. Andrea Pusic, Anne Klassen and Stefan Cano, is the copyright of Memorial Sloan Kettering Cancer Center (Copyright ©2013, Memorial Sloan Kettering Cancer Center).

b) Face-Q Satisfaction with Skin

FACE-Q™ - SATISFACTION WITH SKIN

For each question, circle only one answer. With your facial skin (complexion) in mind, in the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your facial skin looks at the end of your day?	1	2	3	4
b. How healthy your facial skin looks?	1	2	3	4
c. How attractive your facial skin makes you look?	1	2	3	4
d. How smooth your facial skin looks?	1	2	3	4
e. How clear your facial skin (complexion) looks?	1	2	3	4
f. How refreshed your facial skin makes you look?	1	2	3	4
g. How hydrated your facial skin looks?	1	2	3	4
h. How your facial skin looks when you first wake up?	1	2	3	4
i. How radiant your facial skin looks?	1	2	3	4
j. How the tone (color) of your facial skin looks?	1	2	3	4
k. How your pores look?	1	2	3	4
l. How even-colored your facial skin looks?	1	2	3	4

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Note to Investigators: This scale can be used independently of the other scales.

Figure 6: Face-Q Satisfaction with Skin. Source: The FACE-Q, authored by Drs. Andrea Pusic, Anne Klassen and Stefan Cano, is the copyright of Memorial Sloan Kettering Cancer Center (Copyright ©2013, Memorial Sloan Kettering Cancer Center).

19.2.4 Canfield Jawline Definition Scale

The Canfield Jawline Definition Scale is a 5-point ordinal rating scale. The severity grades are anchored from 1 to 5, with a severity score of a 1 indicating no to minimal jowl formation and a score of 5 indicating a very severe jowl with presence of pre and post jowl sulcus. The images on the scale represent jawlines of males and females of various ages and Fitzpatrick Skin Types. The severity descriptors of the scale are as follows:

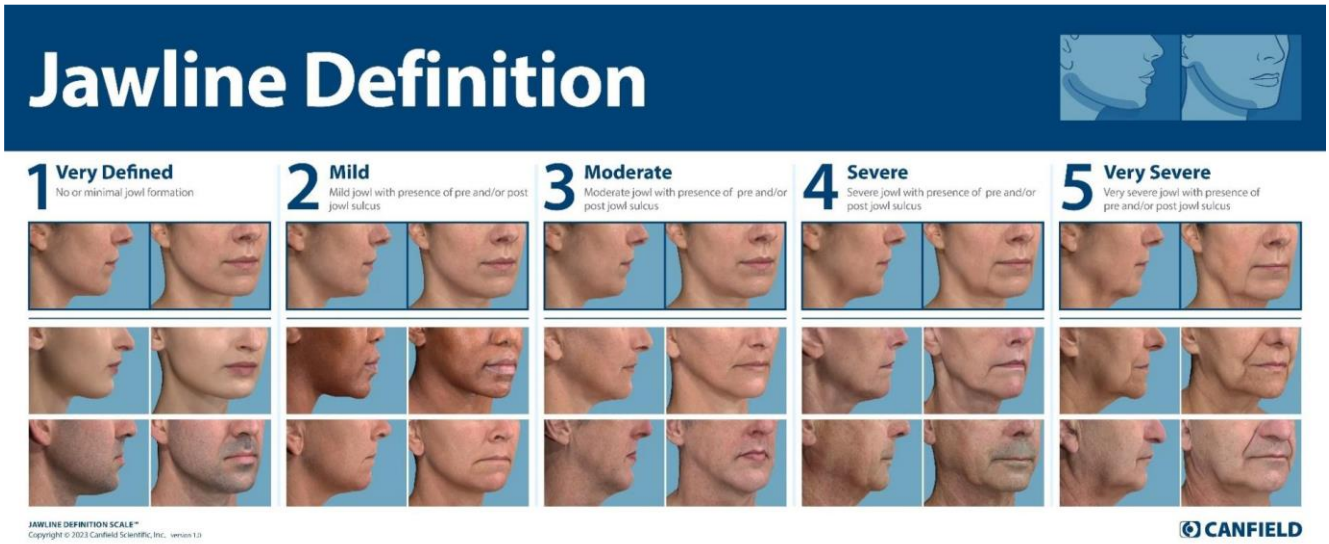
1 – Very Defined: No to minimal jowl formation

2 – Mild: Mild jowl with presence of pre and/or post jowl sulcus

3 – Moderate: Moderate jowl with presence of pre and/or post jowl sulcus

4 – Severe: Severe jowl with presence of pre and/or post jowl sulcus

5 – Very Severe: Very severe jowl with presence of pre and post jowl sulcus



19.3 Appendix C. Surgical Guide for APTOS Threads Absorbable Surgical Sutures

APTOS	Surgical Guide	
	Document Number	Surgical Guide – ECELLENCE-001
	Version number / Date	Version 1.0/ 15-APR-2024

SURGICAL GUIDE FOR APTOS THREADS ABSORBABLE SURGICAL SUTURES EXCELLENCE PRODUCT LINE MODELS

Excellence Product Line Devices models:
Visage Excellence Method
Visage Excellence Soft Method
Nano Excellence Method
Visage Excellence Method HA
Visage Excellence Soft Method HA
Nano Excellence Method HA

SURGICAL GUIDE:
(Safety Instructions)

1. Ensure patient's face is make-up free.
2. Mark the entry location where the Visage Excellence Method threads are to be inserted. Draw a horizontal line from the lateral canthus (lateral palpebral commissure) of the eye till the hair line. Mark entry point before the hair line approximately 1 cm above the most prominent part of the zygomatic arch. Draw 5 lines from entry point to until nasolabial fold (nasolabial sulcus) and marionette (mentolabial sulcus) lines (Image 1 in Figure 1:).
3. Clean the treatment site with antiseptic from the center to the periphery (Image 2 in Figure 1:).
4. Disinfect hands, wear sterile gloves, and avoid contact with non-sterile objects.
5. Remove sutures from protective pouch and place in sterile field using aseptic procedures. Warning! Only the internal surface of the inner pouch is sterile.
6. Infiltrate the entry point with the anesthetic solution. Make the pre-incision hole with an18G needle (supplied) in the entry point marked for insertion (Image 3 in Figure 1:).
7. Infiltrate the marked lines with the anesthetic solution for each thread placement by using the 23G round tip needle (Image 4 in Figure 1: ;).

1

Overall steps of thread treatment procedure are demonstrated in the illustration below (Figure 1:).

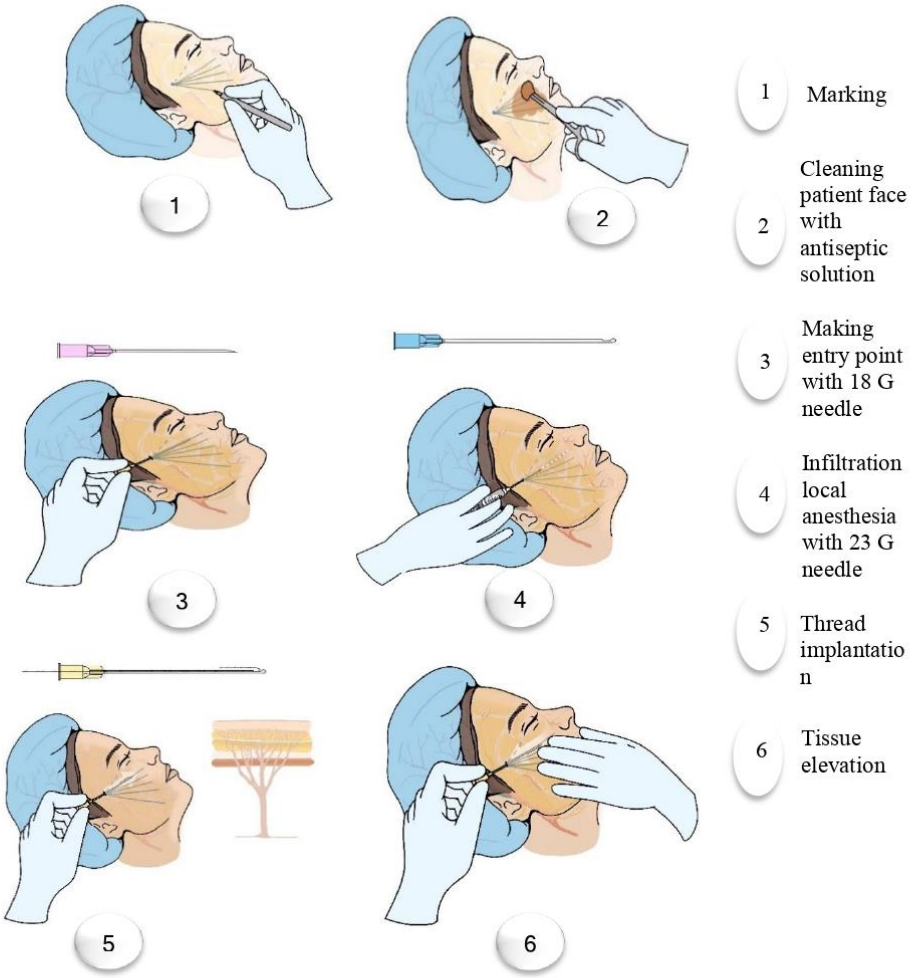


Figure 1: Overall Steps of Thread Treatment Procedure (Images 1 to 6).

3

	Surgical Guide	
APTOS	Document Number	Surgical Guide – ECELLENCE-001
	Version number / Date	Version 1.0/ 15-APR-2024



Figure 2:Thread Implantation Trajectory.



Figure 3:Compression Direction of Implanted Thread.

Post treatment recommendations:

•Patient should apply ice packs immediately after the procedure for next 24 hours intermittent (approx.. 5 minutes in each hour).

•Do not apply makeup for 48 hours.

•Sleep face up, in an elevated position on pillows for about 2-3 nights

•Do not wash face 2 days, clean treated areas with antiseptics solutions such as with Chlorhexidine, Miramistin or etc. Afterwards, wash face gently without rubbing or massaging for 3-5 days •No facial massage for 2 months.

•Avoid excessive face and neck movements for about 14 days

•No facial massage for 1 month

4

	Surgical Guide	
	Document Number	Surgical Guide – ECELLENCE-001
	Version number / Date	Version 1.0/ 15-APR-2024

•No thermal procedures (steam bath, bathtub, sauna) and avoid direct sunlight for 1 month.

•No sports activities for 2 weeks.

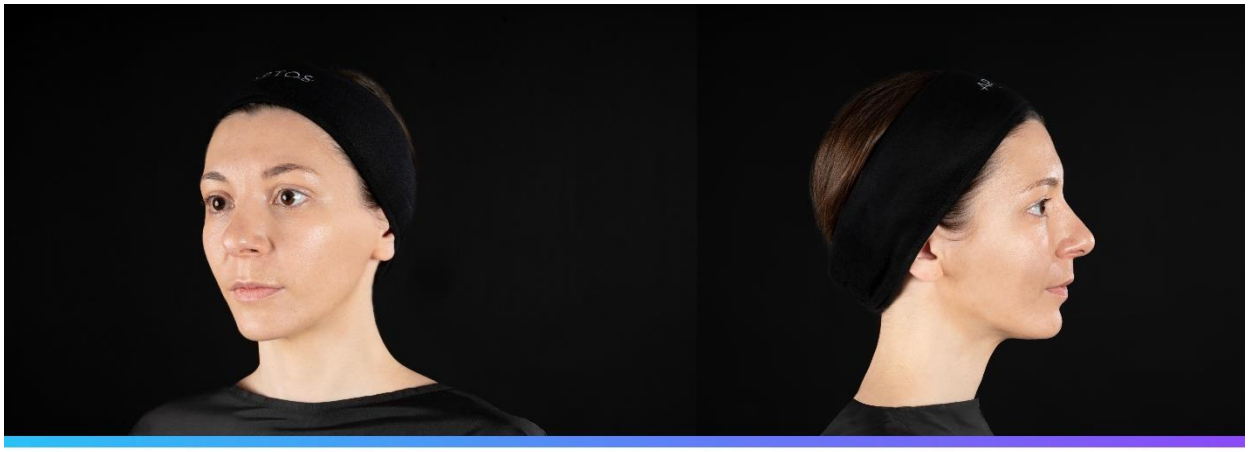
•Avoid dentist appointment for 3 weeks (except the emergency cases).

•In case of pain, prescribe any painkillers (for example, Paracetamol, Ibuprofen etc.).

•In case of a patient having high fever, increasing pain, redness and swelling at the area of intervention or other unpleasant and unnatural sensations, he/she should contact the doctor.

19.4 Appendix D. Aptos 2D Imaging Photo Guide



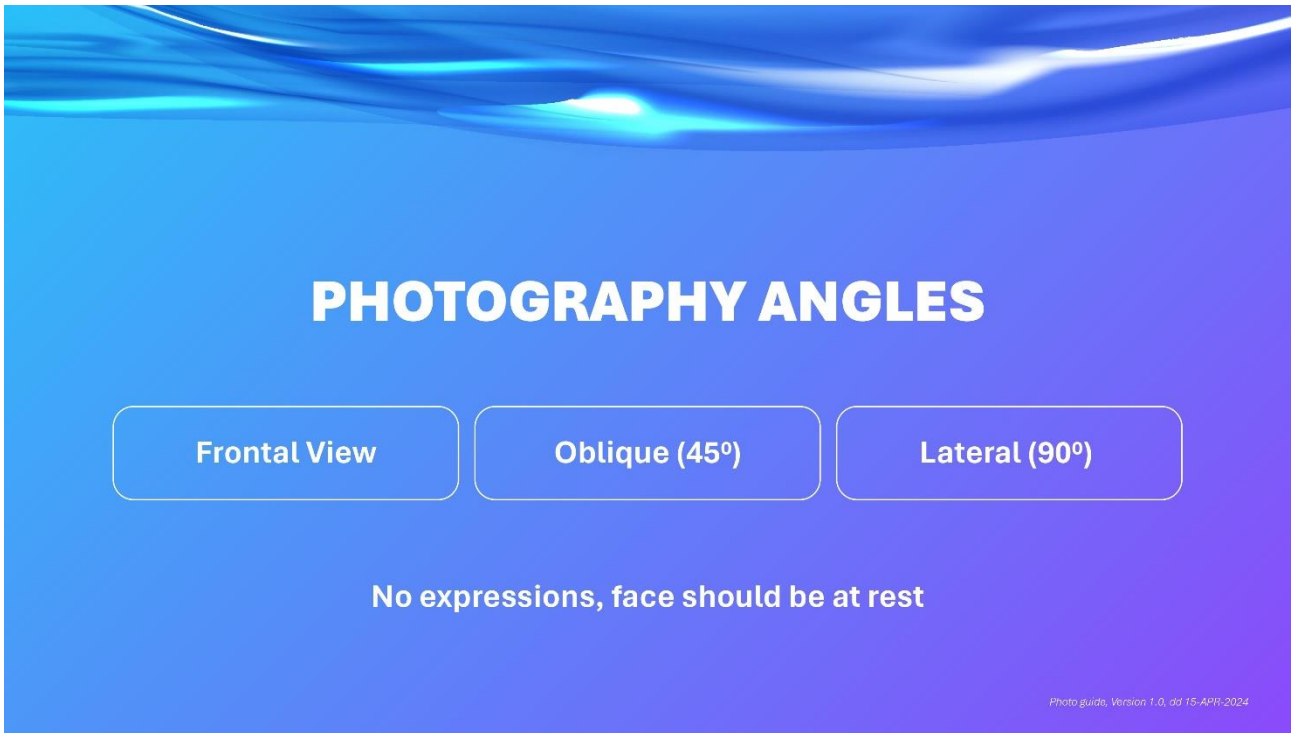


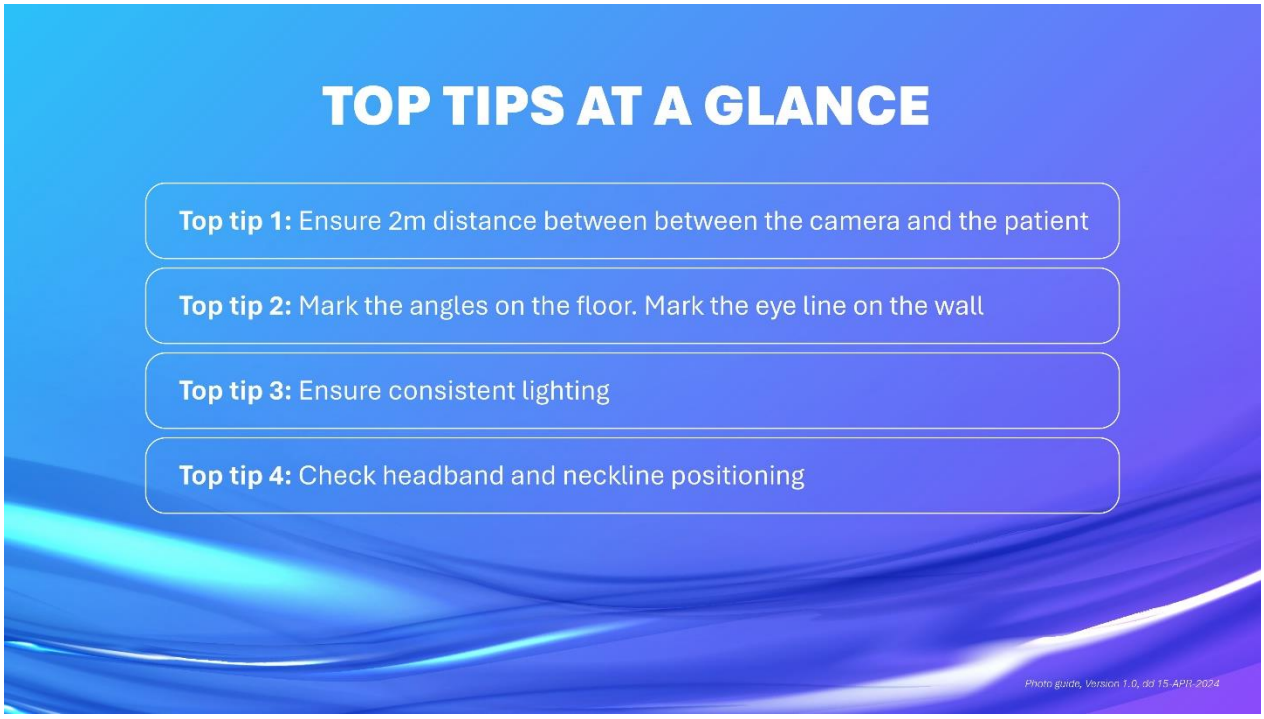
The success of our events depends on having high-quality, consistent clinical photos as they let us precisely depict and illustrate the results of therapy.

These images need to be of the highest quality because they will be used as case studies in instructional materials and upcoming training sessions.

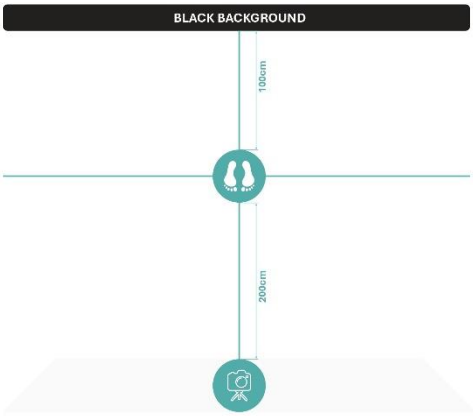
Here are some top guidelines to assist you meet Aptos Aesthetic requirements.

Photo guide, Version 1.0, dd 15-APR-2024


PHOTOGRAPHY ANGLES
Frontal View
Oblique (45º)
Lateral (90º)
No expressions, face should be at rest
Photo guide, Version 1.0, dd 15-APR-2024


TOP TIPS AT A GLANCE
Top tip 1: Ensure 2m distance between between the camera and the patient
Top tip 2: Mark the angles on the floor. Mark the eye line on the wall
Top tip 3: Ensure consistent lighting
Top tip 4: Check headband and neckline positioning
Photo guide, Version 1.0, dd 15-APR-2024

TOP TIP 1:MEASURE THE DISTANCE



Use 200 cm distance from the patient standardized position

Around 100cm distance from subject to the black background.

To ensure strictly the same distance from the background for each patient and each timepoint, mark the floor in 100cm distance from background

Photo guide, Version 1.0, dd 15-APR-2024

TOP TIP 2: MARK THE FLOOR



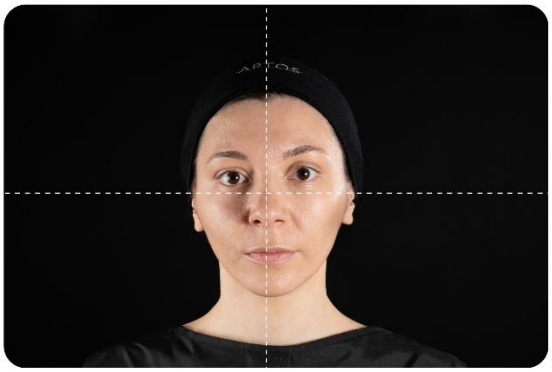
To help the patient understand where to stand at each angle, mark the floor.

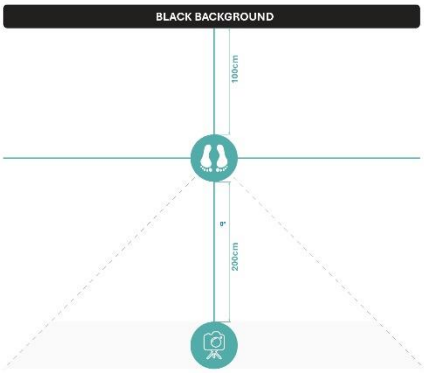
This will guarantee consistency between "before" and "after" photos.

Before the photo session, position the patient next to the tripod. Adjust the camera on the tripod to the patient's face height while standing, ensuring the portrait is centered on the face.

Photo guide, Version 1.0, dd 15-APR-2024

MARK THE FLOOR AT 0° FOR THE FRONTAL ANGLE



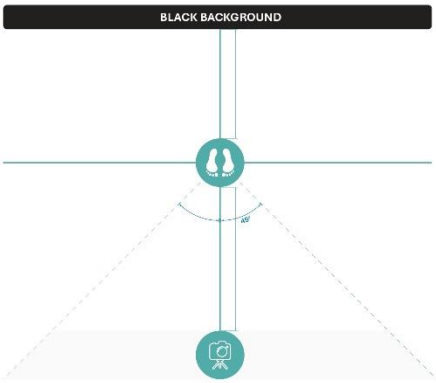


Straight gaze, nose in normal position, not tilted up

Photo guide, Version 1.0, dd 15-APR-2024

MARK THE FLOOR AT 45° ANGLE FOR OBLIQUE ANGLE





- Straight gaze
- You should do the marking on both sides of the floor

Make sure the subject's cheekbones are completely in sight.

Photo guide, Version 1.0, dd 15-APR-2024

MARK THE FLOOR AT 90⁰ FOR THE LATERAL ANGLE



Straight gaze

You should do the marking on both sides of the floor

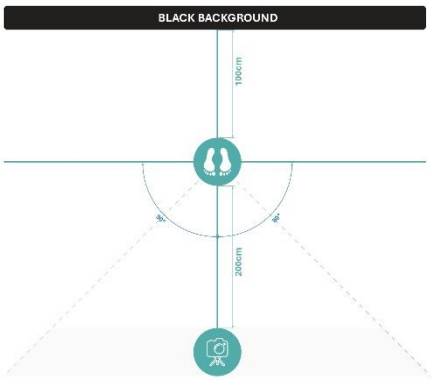


Photo guide, Version 1.0, dd 15-APR-2024

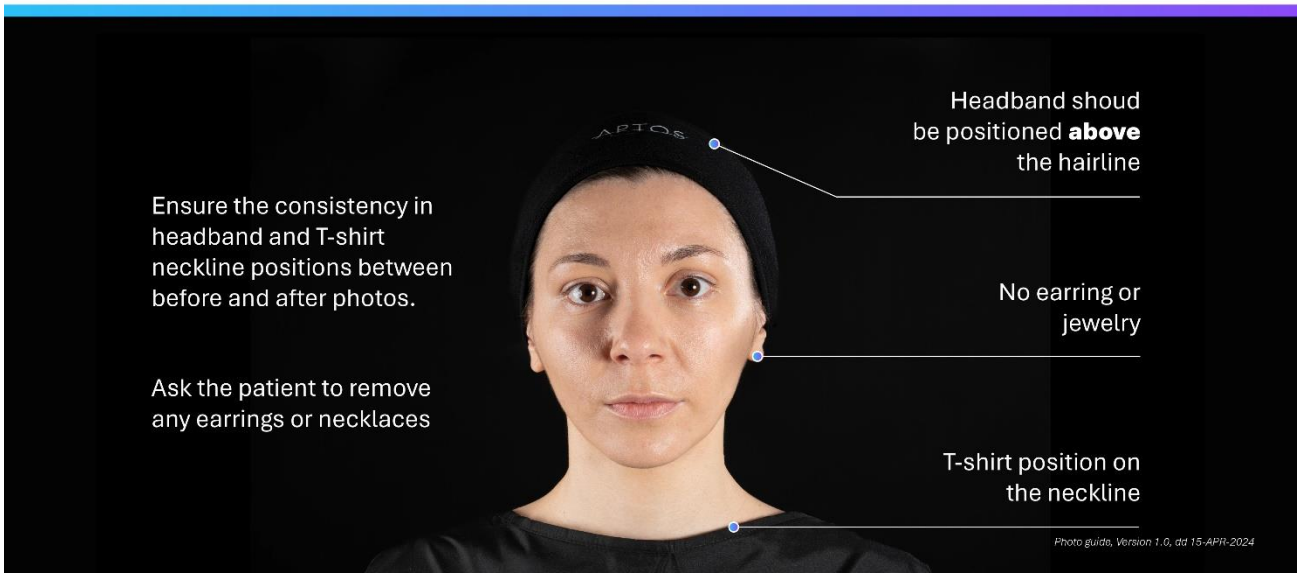
TOP TIP 3: ENSURE CONSISTENT LIGHTING

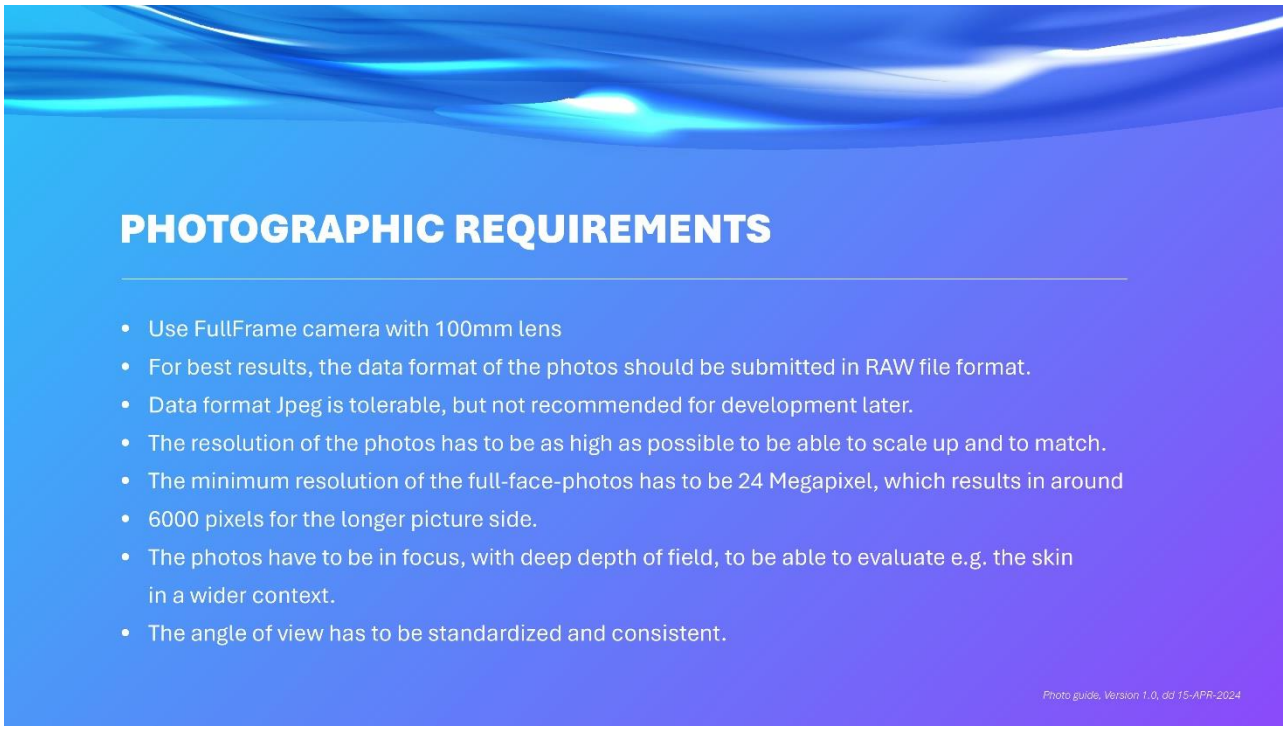
- Lightening must be consistent in all photographics and all angles
- Avoid shadows - Light should be evenly distributed on patient's full face
- The patient's distance from the camera, the angle, and the positioning remains constant
- Make sure there isn't any natural light present

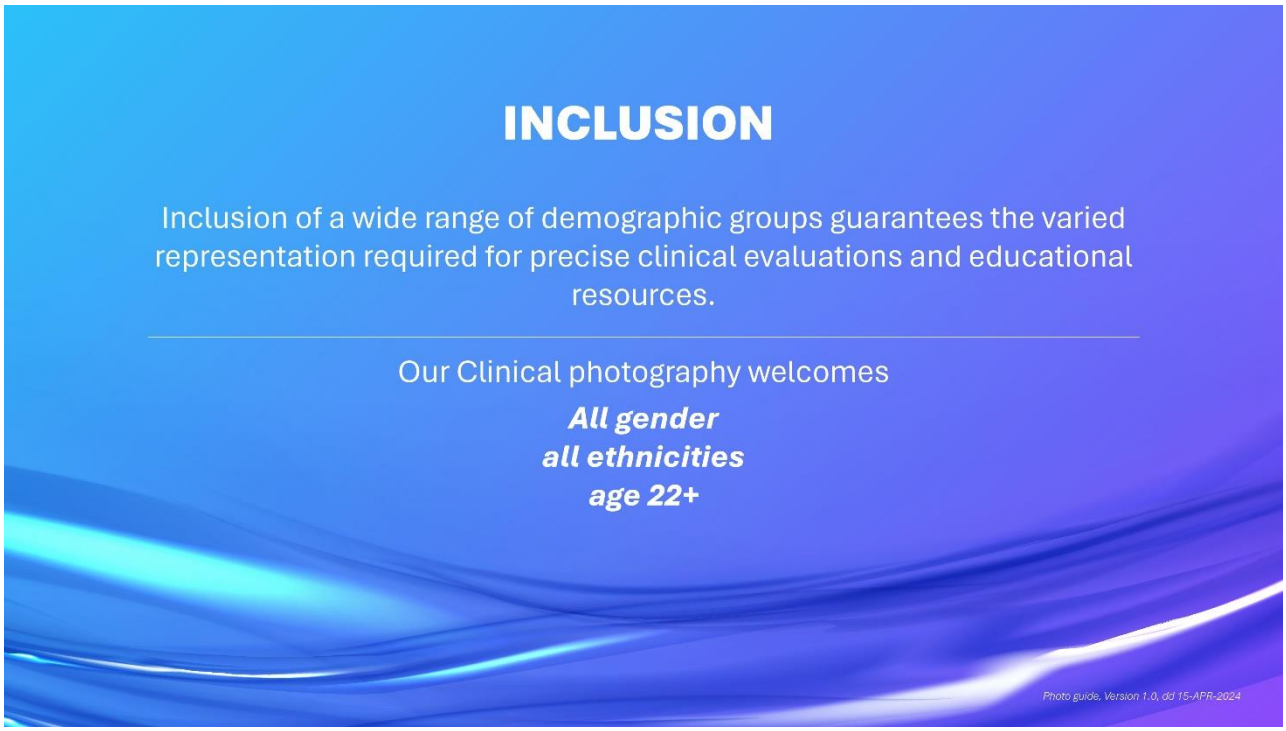


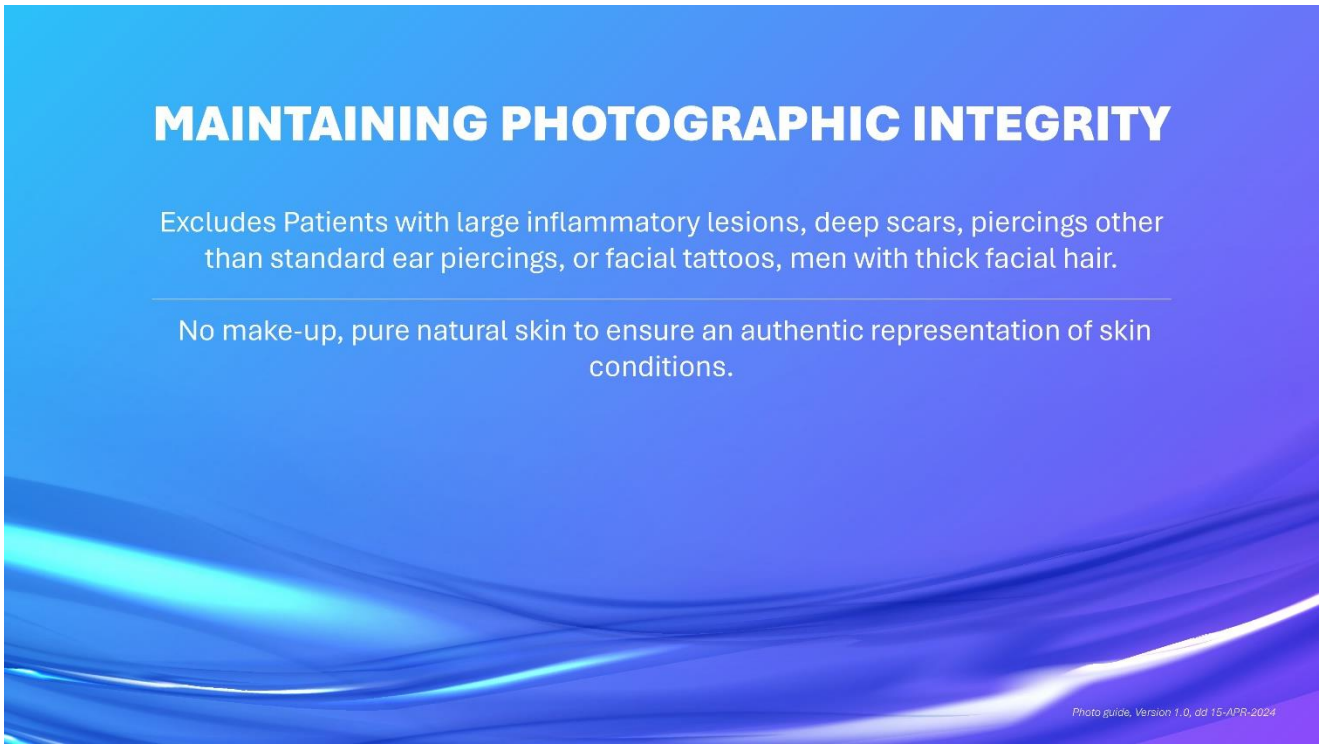
Photo guide, Version 1.0, dd 15-APR-2024

TOP TIP 4: CHECK HEADBAND AND NECKLINE






INCLUSION
Inclusion of a wide range of demographic groups guarantees the varied representation required for precise clinical evaluations and educational resources.
Our Clinical photography welcomes
All gender
all ethnicities
age 22+
Photo guide, Version 1.0, dd 15-APR-2024


MAINTAINING PHOTOGRAPHIC INTEGRITY
Excludes Patients with large inflammatory lesions, deep scars, piercings other than standard ear piercings, or facial tattoos, men with thick facial hair.
No make-up, pure natural skin to ensure an authentic representation of skin conditions.
Photo guide, Version 1.0, dd 15-APR-2024