Statistical Analysis Plan

Title: Prospective Clinical Stu**D**y of Tri-planar Tarsometatarsal (TMT) Arthro**D**esis with Early Weight-Bearing after Lapiplasty® Proce**D**ure through a **Mini**-Incision™ Approach (**Mini3D**)

NCT number: NCT05082012

Document Date: April 4, 2025

Document Name:	Statistical Analysis Plan for the Mini3D® Study
Protocol Number:	CP2021-1
Protocol Title:	Prospective Clinical Stu**D**y of Tri-planar Tarsometatarsal (TMT) Arthro**D**esis with Early Weight-Bearing after Lapiplasty® Proce**D**ure through a **Mini**-Incision Approach (**Mini3D®**)
Name of Finished Product(s):	Mini-Incision Precision Instrument Set Lapiplasty® Mini-Incision System
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Date Final:	04APR2025
Version:	V 2.0-04APR2025

Contents

Acronyms And Abbreviations

AE	Adverse Event
CAM	Controlled Ankle Motion
CRPS	Complex Regional Pain Syndrome
HV	Hallux Valgus
HVA	Hallux Valgus Angle
IMA	Intermetatarsal Angle
ITT	Intent-to-Treat
IRB	Institutional Review Board
MAA	Metatarsus Adductus
MOxFQ	The Manchester-Oxford Foot Questionnaire
MTP	Metatarsophalangeal
PI	Principal Investigator
POSAS	Patient and Observer Scar Assessment Scale
PP	Per-Protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
ROM	Range of Motion
RSD	Reflex Sympathetic Dystrophy
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
TSP	Tibial Sesamoid Position
VAS	Visual Analog Scale
WB	Weight-bearing

Introduction

Though the majority of hallux valgus (or "bunion") surgeries today are performed via a two-dimensional (2D) metatarsal osteotomy approach in which the metatarsal bone is cut and shifted over, this surgical approach has demonstrated unacceptably high variability with recurrence rates of up to 78%.[1,2,3] Recent research demonstrates that 87% of bunions[4] actually have three-dimensional (3D) deformities with abnormal frontal-plane rotation of the metatarsal bone, which cannot be addressed with a 2D metatarsal osteotomy. Correction of metatarsal rotation is critical for restoration of normal anatomic alignment, which left unaddressed, is associated with a 10.0-12.7 times likelihood of radiographic recurrence.[5,6] The Lapiplasty® Procedure (which was awarded a US patent on the surgical method) is a commercially available system that allows the surgeon to correct the bunion deformity at its apex and in all 3 anatomic planes (3D correction), including frontal-plane metatarsal rotation.

Correction at the 1st tarsometatarsal joint, also known as Lapidus fusion, provides the optimal surgical approach for true 3D anatomic restoration of the entire metatarsal bone, at the apex of the bunion deformity. However, the conventional Lapidus fusion technique has traditionally been a technically challenging procedure with high variability, requiring 6-10 weeks non-weightbearing, and furthermore does not directly address frontal-plane metatarsal rotation[7,8]. The patented Lapiplasty® Procedure is designed to allow the surgeon to perform a Lapidus fusion in a much more controlled and reproducible manner, while also correcting frontal-plane rotation of the metatarsal (i.e., 3D correction) and returning the patient to weight-bearing typically in less than 2 weeks.[9]

A recent multicenter, retrospective study demonstrated the benefits of the Lapiplasty® Procedure. In the study, 72 hallux valgus patients (61 feet meeting 1-year endpoint) were treated with the Lapiplasty® Procedure with an early return to weight-bearing (average 10.5 days post-op). At average follow-up of 13.5 months, the results demonstrated 96.7% of patients maintained their 3-plane correction (intermetatarsal angle, hallux valgus angle, and tibial sesamoid position), and only 1.6% experienced a symptomatic nonunion complication[7].

The purpose of this analysis is to evaluate key effectiveness, safety, health economic, and quality of life outcomes among subjects who undergo the Lapiplasty® Procedure using the Lapiplasty® Mini-Incision System. The Lapiplasty® Mini-Incision System is designed to deliver the same patented Lapiplasty® Procedure providing 3-plane correction through a 3.5cm dorsal incision.

Study Objectives and Endpoints

The objectives of this study are to evaluate outcomes of the Lapiplasty® Procedure using the Lapiplasty® Mini-Incision System for patients in need of hallux valgus surgery:

1.1 Objectives

1) To determine radiographic recurrence of hallux valgus and the timing of failure following hallux valgus correction with the Lapiplasty® Procedure.
2) To determine whether the Lapiplasty® Procedure effectively corrects anatomical alignment of the 1st metatarsal and sesamoids in all three planes.
3) To assess whether early weight-bearing (WB) after the Lapiplasty® Procedure affects the union rates or causes loss of 3-plane correction.
4) To evaluate the quality of life and pain scores following the Lapiplasty® Procedure.

1.2 Endpoints

1.2.1 Primary Endpoint

Proportion of subjects with radiographic recurrence of hallux valgus deformity (bunion recurrence) at 24 months, limited to subjects with successful correction at 6 weeks.

1.2.2 Secondary Endpoints

1) Change from baseline in radiographic angular/positional alignment at 6 weeks, 4 months, 6 months, 12 months, and 24 months post-Lapiplasty® Procedure.
2) Percentage of subjects with absence of clinical/radiographic healing, or non-union, at 12 months post-Lapiplasty® Procedure.
3) Clinical complications through 24-month follow-up visit due to the Lapiplasty® System Implants, the Lapiplasty® Procedure, the post-operative weight-bearing protocol or health conditions that could affect other outcome measures.
4) Time to start weight-bearing in boot, in days.
5) Time to start weight-bearing in shoes, in days.
6) Time to return to full unrestricted activity, in days.
7) Change from baseline in pain at the base of the big toe (bunion related) assessed via a Visual Analog Scale (VAS) at 0-14 days, 14-21 days, 6 weeks, 4 months, 6 months, 12 months, and 24 months.
8) Change from baseline in Quality of Life at 6 months, 12 months, and 24 months as measured by PROMIS-29 (for adult subjects), PROMIS-25 (for pediatric subjects), and MOxFQ (for all subjects.
9) Change from baseline in range of motion (ROM) of 1st MTP dorsiflexion and plantarflexion at 12 months and 24 months.
10) Change, if any, in incision length during the Lapiplasty® Procedure.
11) Change from baseline in radiographic foot length and width at 12 months post-Lapiplasty® Procedure.
12) Change in swelling at 6 weeks and 4 months post-Lapiplasty® Procedure as compared to 0-14 day visit.
13) Change in scar quality at 4 months, 6 months, and 12 months post-Lapiplasty® Procedure.
14) Correlation between amount of time external positioner is actively used during Lapiplasty® Procedure with necrosis, blistering, bruising, and tissue ulceration events.

1.2.3 Health Economic and Safety Endpoints

All health economic endpoints are exploratory in nature.

1) Complications below that are related to the Lapiplasty® Procedure or the Lapiplasty® System Implants requiring subsequent secondary surgical interventions, defined as the following:
    a) deviations/delay from normal operative plan
    b) readmission to hospital
    c) return to operating room
    d) unscheduled visits due to complications
    e) employment of home health services
    f) revisions
    g) hardware removals
    h) reoperations
    i) supplemental fixation
    j) wound healing
    k) infection at surgical site

2) Time to return to work (or normal household activities if non-working), in days, while noting work status and work classification (sedentary, light work, medium work, heavy work, very heavy work).
3) Time to return to full work (or normal household activities if non-working), in days, while noting work status and work classification (sedentary, light work, medium work, heavy work, very heavy work).
4) Percentage of subjects requiring post-operative physical therapy for recovery from the Lapiplasty ® Procedure.

1.2.4 Exploratory Endpoints

Additional endpoints may be pursued at the time of analysis and will be exploratory in nature.

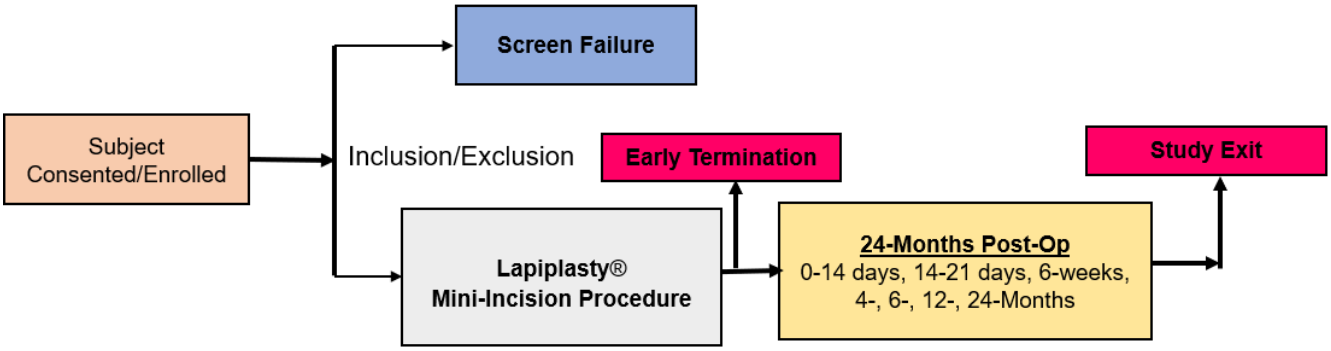
Study Methods

1.3 Overall Study and Design

This is a prospective, single-arm, multicenter, unblinded study. Subjects 14 years through 58 years with symptomatic hallux valgus are eligible to participate based on the inclusion and exclusion criteria defined below. The overall plan for all subjects consists of the following elements:

- Patients will be informed about the nature of the research, given the ICF to read, and if the patient understands and agrees to the procedure, they will be asked to provide written informed consent. Subjects are considered **enrolled** in the study when they have signed an informed consent;
    - Subjects will undergo screening procedures during the baseline visit to determine if inclusion and exclusion criteria are satisfied and the subject is eligible for the study procedure;
- Subjects must meet all inclusion/exclusion criteria before being **treated** in the study. If any eligibility criteria (including intra-operative criteria) are not satisfied, the subject will be considered a screen failure and will not be considered treated in the study;
- Subjects will undergo the Lapiplasty® Procedure, per protocol. Subjects are considered **treated** in the study when biplanar plating at the TMT joint is complete **and** the incision length is confirmed to meet criteria;
    - Subjects will be followed for up to 2 years post index procedure to evaluate outcomes and potential complications;
    - Subjects will be assessed for AEs and will be instructed to notify the PI of any AEs that occur during the entire course of the study. Data will be recorded into subject source medical records.

Subject Disposition Diagram



1.4 Inclusion-Exclusion Criteria

1.4.1 Inclusion Criteria

Subjects satisfying all the following inclusion criteria will be eligible for participation:

1) Male and females between the ages 14 and 58 years at the time of consent
2) Closed physeal plates at the time of consent
3) Intermetatarsal angle (IMA) between 10.0˚ - 22.0˚
4) Hallux valgus angle (HVA) between 16.0˚ - 40.0˚
5) Willing and able to adhere to early weight-bearing instructions post-operatively
6) Capable of completing self-administered questionnaires
7) Acceptable surgical candidate, including use of general anesthesia
8) Female subjects must be of non-childbearing potential or have a negative pregnancy test within 7 days prior to index procedure
9) Willing and able to schedule index procedure within 3 months of consent and able to return for scheduled follow-up visits
10) Willing and able to provide written informed consent

1.4.2 Exclusion Criteria

Subjects satisfying any one of the following exclusion criteria will not be eligible for participation:

1) Previous surgery for hallux valgus on operative side
2) Previous surgeries on operative foot involving fusion of foot or ankle joints (other than hammertoe or lesser toes/digits)
3) Additional concomitant procedures outside of the 1st ray
4) Moderate or Severe osteoarthritis of the MTP joint based on radiographic imaging (including lack of evident crista) or positive grind test
5) Symptomatic flatfoot or asymptomatic flatfoot (defined as calcaneal inclination <5˚and talonavicular subluxation/uncovering >50%)
6) BMI >40 kg/m²
7) Current nicotine user, including current use of nicotine patch

8) Current clinical diagnosis of diabetes with fasting plasma glucose >126 mg/dL and/or HbA1c ≥7.0
9) Current clinical diagnosis of peripheral neuropathy or by assessment on 4-point monofilament test
10) Current clinical diagnosis of fibromyalgia
11) Current clinical diagnosis of Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy (CRPS/RSD)
12) Current uncontrolled hypothyroidism
13) Previously sensitized to titanium
14) Currently taking oral steroids or rheumatoid biologics
15) Currently taking immunosuppressant drugs
16) Insufficient quantity or quality of bone to permit stabilization, conditions that retard healing (not including pathological fractures) and conditions causing poor blood supply such as peripheral vascular disease
17) Active, suspected or latent infection in the affected area
18) Use of synthetic or allogenic bone graft substitutes
19) Current diagnosis of metatarsus adductus (defined as MAA ≥ 23˚)
20) Known keloid and hypertrophic scar forming
21) Scheduled to undergo a same-day bilateral procedure. Subject agrees to refrain from the Lapiplasty® Procedure (or other hallux valgus procedures) on contralateral foot for minimum of 6 months post index procedure
22) Subject has previously been enrolled into this study for a contralateral procedure;
23) Scheduled for any concomitant procedure that would alter subject's ability to early weight-bear post-procedure
24) Subject requires an incision >4.0 com to complete the procedure (determined pre-operatively or intra-operatively)
25) Subject is actively involved with a workman's compensation case or is currently involved in litigation
26) Subject is currently or has participated in a clinical study in the last 30 days prior to signing informed consent or is considering participation in another research protocol during this study. Exceptions to this include survey clinical studies with no treatment or if subject is greater than 12 months post procedure in the Treace ALIGN3D™ study without ongoing protocol defined AE; these are not exclusionary
27) Subject has a condition or finding that, in the opinion of the Investigator, may jeopardize the subject's well-being, the soundness of this clinical study, or could interfere with provision of informed consent, completion of tests, therapy, or follow-up.

1.5 Schedule of Assessments

Study Activity	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Study Exit
	Baseline [1]	Index Lapiplasty® Procedure	0-14 Day follow-up	14-21 Day follow-up	6 Week follow-up	4 Month follow-up	6 Month follow-up	12 Month follow-up	24 Month follow-up	
Informed Consent	X									
Demographics	X									
Medical and Surgical History	X	X								
Targeted Physical Exam	X									

Study Activity	Visit 1 Baseline [1]	Visit 2 Index Lapiplasty® Procedure	Visit 3 0-14 Day follow-up	Visit 4 14-21 Day follow-up	Visit 5 6 Week follow-up	Visit 6 4 Month follow-up	Visit 7 6 Month follow-up	Visit 8 12 Month follow-up	Visit 9 24 Month follow-up	Study Exit
Height / Weight [2]	X									
Blood Collection, if required[3]	X									
4-Point Monofilament Test, if required [4]	X									
Radiographic Imaging[5]	X				X	X	X	X	X	
VAS Pain Scale	X		X		X	X	X	X	X	
QOL Measurements[6]	X						X	X	X	
Medications Review	X	X	X		X	X	X	X	X	
Digital Photos of Foot										
Clinical Exam of Foot	X		X		X	X	X	X	X	
Foot Measurements	X	X	X	X	X	X	X	X		
Pregnancy Test (if applicable) [7]	X									
Inclusion/Exclusion Criteria	X[8]	X[9, 10]								
Index Procedure		X								
Wound check/surgical site healing			X		X	X				
Return to Weight-Bearing Activities[11]			X		X	X	X			
Range of Motion[12]	X					X	X	X	X	
Secondary Surgical Interventions[13]			X		X	X	X	X	X	
Adverse Events Assessment[14]		X	X		X	X	X	X	X	
Radiographic Measurements[15]	X				X	X	X	X	X	
Healthcare Economic Outcomes[16]			X		X	X	X	X	X	
General Satisfaction Questionnaire										
Study Exit										X

[1] Baseline visit study activities must occur within 90 days of the Index Procedure unless otherwise noted.
[2] BMI should be calculated from height and weight measurement to determine subject eligibility.
[3] Blood collection is required only if subject has diagnosis of diabetes to determine fasting plasma glucose levels or HbA1c.
[4] 4-point monofilament test is required only if subject has diagnosis of diabetes or if warranted by PI to assess for peripheral neuropathy.
[5] Three radiographic views of the operative foot should be obtained per visit (weight-bearing AP, lateral and axial views of operative foot). The axial view should be collected using the study provided axial positioner.
[6] QOL assessment tools – MoxFQ and PROMIS-29 (PROMIS-25 for ages 14-17) and Sports Questionnaire
[7] Pregnancy test, if applicable, completed within 7 days of Index Procedure. May be completed on day of Index Procedure.
[8] For the purposes of determining IMA, HVA and MMA for subject eligibility, measurements will be made according to institutional SOC. For the purposes of all data analysis, measurements made by the Central Radiologist will be utilized. If there are minor differences in baseline IMA, HVA and MMA measurements made by the central radiologist, the measurements of the PI/site will remain acceptable for determining subject eligibility.
[9] Confirm exclusion criterion "subject is not a current nicotine user" prior to start of anesthesia. If subject indicates current use of nicotine, subject should be considered a screen failure.
[10] If subject requires an incision >4.0 cm ot complete the Lapiplasty® Procedure, the subject should be considered a screen failure.
[11] Documentation for return to weight bearing activities include time to start weight-bearing in boot, time to start weight-bearing in shoe, and time to full unrestricted activity.
[12] ROM - dorsiflexion and plantarflexion should be measured while subject is passive and non-weightbearing with the study provided goniometer.
[13] Secondary surgical interventions, Wound healing requiring intervention, infection requiring intervention, hardware removal, revision procedure of 1st ray, other complication requiring surgical intervention.
[14] Only AEs related to the Lapiplasty® Index Procedure or the Lapiplasty® System Implants will be recorded on the eCRF.
[15] Radiographic Measurements are completed by the Central Radiologist only.
[16] Healthcare Economic Outcomes, see Secondary Endpoints for data to be recorded on eCRF.

Sample Size

There is no formal sample size calculation as this is a single arm study and is descriptive in nature. A sample size of 200 patients is chosen, ensuring the feasibility of the study as clinical findings suggest that the bunion recurrence rate after the Lapiplasty® Procedure is low.

6 General Analysis Considerations

All analyses will be performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

6.1 Baseline

Baseline values are those which were collected at the Baseline visit (Visit 1). If a baseline value is missing, then the most recent value collected within 90 days prior to the Index Procedure will be used.

6.2 Analysis Populations

6.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all enrolled subjects who met inclusion/exclusion criteria and were treated with the Lapiplasty® Procedure using the Mini-Incision System.

6.2.2 Per-Protocol Population

The Per-Protocol (PP) population is defined as the ITT population who did not experience a major protocol violation. Major protocol violations include, but are not limited to, subjects who:

- Entered the study although they did not satisfy the eligibility criteria
- Completed incorrect version of PROMIS based on age of subject
- Did not return to protective weight-bearing activities by 3 weeks (+3 days)
- Received Lapiplasty® Procedure (or other hallux valgus procedures) on contralateral foot less than 6 months after initial index procedure
- Developed withdrawal criteria during the study, but were not removed from study participation

All effectiveness, safety, and health economic outcomes analyses will utilize the ITT population. If the PP population and ITT population differ considerably, sensitivity analyses will be performed using the PP population.

6.3 Missing Data

Effectiveness and health economic analyses will be based on available data, without imputation for missing values. For Quality of Life outcomes (MOxFQ and PROMIS-29/PROMIS-25), missing data will be handled as specified in the Derived Variables section. For safety analyses, missing event dates will be imputed as follows:

- If only month and year are reported, then day is assigned as the 15th of the month
- If only year is reported, then month and day is assigned as July 1st

6.4 Derived Variables

6.4.1 “Time To” variables

“Time to” variables such as time to follow-up, time to weight-bearing, and time to return to work will be computed in days as (date of interest - date of index procedure). “Time to” will be computed in weeks as (date of interest - date of index procedure)/7. “Time to” will be computed in months as (date of interest - date of index procedure)/30. “Time to” will be computed in years as (date of interest - date of index procedure)/365.25.

6.4.2 Change from Baseline

Change from baseline will be determined for ROM, VAS, PROMIS, MOxFQ, and radiographic measurements (IMA, HVA, tibial sesamoid position (TSP), sagittal plane). It will be calculated as value at timepoint of interest minus value at baseline.

6.4.3 Radiographic reads

For data analysis purposes, radiographic reads will be performed by a fellowship trained musculoskeletal radiologist. The following adjustment will be made to metatarsal length measurement data prior to analysis: if metatarsal length is recorded as a positive number, it will be converted to a negative number. If metatarsal length is recorded as a negative number, it will be converted to a positive number.

6.4.4 MOxFQ

The Manchester Oxford Foot Questionnaire (MOxFQ)[7] is a 16 item, subject-reported outcome measure designed for use with individuals who are undergoing foot or ankle surgery. Each of the 16 questions on the MOxFQ is scored in the same direction with the score increasing as the reported health status becomes worse. Scores for each domain of the MOXFQ are calculated as the sum of each individual item score. In each case, this is expressed on a metric of 0 – 100 (where a higher score represents greater severity) and will be calculated as (actual score/maximum possible domain score)*100. If a single item within any domain is unanswered, the mean value from the respondent's other item responses (series mean) within that domain will be used for the missing response. If more than one item within any domain is unanswered, then all item responses for that domain will be set to missing.

6.4.5 PROMIS-29/PROMIS-25

The PROMIS profile instruments[6] are a collection of short forms containing a fixed number of items. The PROMIS-29 is intended for adults (aged 18+ years) and assesses seven PROMIS domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities). The PROMIS-25 is intended for children (aged less than 18 years) and assesses six PROMIS domains (Depressive Symptoms, Anxiety, Physical Function-Mobility, Pain Interference, Fatigue, and Peer Relationships). Each domain has 4 items, with each item having five response options ranging in value from 1 to 5. A separate pain intensity item is also assessed and has eleven response options ranging in value from 0 to 10. All domains are assessed over the past seven days except for Physical Function (PROMIS-29) which has no timeframe specified.

A raw score is created from each short form that makes up the profile. To find the total raw score for a short form with all questions answered, sum the values of the response to each question within each domain. To translate the total raw score into a T-score for each short form for each participant, a PROMIS score conversion table is used. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. The standardized T-score is reported as the final score for each participant.

If an item in a short form is unanswered, then the total raw score and T-score for that short form will not be calculated.

6.4.6 POSAS

The Patient and Observer Scar Assessment Scale (POSAS) measures scar quality from the perspectives of both the patient and the clinician. It consists of two parts, the Patient Scale and the Observer Scale, each with 6 components that are scored on a scale of 1 – 10 where 1 indicates normal skin and 10 indicates largest difference from normal skin. Total score can range from 6 to 60 and is calculated by summing the 6 component scores.

6.4.7 Correction

Successful correction is defined as any two of the following 3 criteria being met at 6 weeks post-procedure: IMA <9.0°, HVA<15.0°, TSP as ≤3. In other words, if none or one of the measurements is out of range at 6 weeks, the foot is considered "corrected". If two or more measurements are out of range at 6 weeks, the foot is considered "not corrected".

6.4.8 Recurrence

Recurrence (loss of correction) is considered to have occurred at 24-months post-procedure if any two of the following 3 criteria are met: IMA of ≥12°, HVA ≥20°, TSP ≥4. An alternative definition of recurrence will also be applied: HVA ≥15°.

6.4.9 Non-union

Non-union is defined as pain at the TMT joint plus one or more of the following: lucency, hardware failure, or recurrence.

7 Statistical Analysis

All continuous variables will be summarized using the following descriptive statistics: n, mean, standard deviation, median, minimum, maximum, and where appropriate 95% confidence intervals (CIs). The frequency and percentages of observed levels will be reported for all categorical measures. In general, all summary tables will be annotated with the total population size relevant to that table, including any missing observations. Data listings will be sorted by site, subject, and when appropriate by visit type within subject.

Two-sided T-tests will be generated for change from baseline analyses. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". P-values less than 0.05 will be considered statistically significant. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

7.1 Study Subjects

7.1.1 Subject Disposition

All subjects who signed informed consent will be included in the subject disposition table. The number and percentage of subjects enrolled, screened, screen failed, treated, anesthetized but not treated, completed, and discontinued (including reason for discontinuation) will be summarized. Subjects are considered enrolled in the study when they have signed an informed consent. Subjects will undergo screening procedures during the baseline visit to determine if inclusion and exclusion criteria are satisfied and the subject is eligible for the study procedure. If any eligibility criteria (including intra-operative criteria) are not satisfied, the subject will be considered a screen failure and will not be considered treated in the study. Subjects are considered treated in the study when biplanar plating at the TMT joint is complete and the incision length is confirmed to meet criteria.

7.1.2 Protocol Deviations

Protocol deviations are events occurring during the conduct of the study which are not in compliance with the protocol and for which an amendment has not been granted. Protocol deviations affecting the scientific soundness of the study or the rights, safety, or welfare of the subjects, will be reported by the principal investigator (PI), as required by the Institutional Review Board (IRB). Protocol deviations will be summarized and grouped into relevant categories for analysis and may include, but not be limited to, subjects who:

- Entered the study although they did not satisfy the eligibility criteria
- Completed incorrect version of PROMIS based on age of subject
- Did not return to protective weight-bearing activities by 3 weeks (+3 days)
- Received Lapiplasty® Procedure (or other hallux valgus procedures) on contralateral foot less than 6 months after initial Index Procedure
- Developed withdrawal criteria during the study, but were not removed from study participation

A subject for whom at least one of the aforementioned deviations is reported may be excluded from the PP population.

Minor protocol deviations will be listed by site, subject, and visit within subject.

7.1.3 Demographic, Baseline, and Intra-Operative Characteristics

The following demographic and baseline variables will be summarized in accordance with Section 7:

- Date of birth (Age)
- Sex
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body Mass Index (BMI)
- Operative foot (Right, left)
- Diabetes (Yes, no)
- Labor class (Sedentary, light work, medium work, heavy work, very heavy work)
- Incision length (cm)
- Incision extended (yes/no)

7.2 Effectiveness Analysis

The ITT population will be used for all effectiveness analyses. Summary statistics will be produced in accordance with section 7.

7.2.1 Primary Effectiveness Analysis

The primary effectiveness analysis will determine the proportion of subjects with radiographic recurrence of hallux valgus deformity (bunion recurrence) at 24 months, limited to subjects with successful correction at 6 weeks. Successful correction is defined as meeting 2 of the following 3 criteria: IMA <9.0°, HVA<15.0° and TSP as ≤3 at 6 weeks post-index procedure. Recurrence is defined as meeting 2 of the following 3 criteria at 24 months post procedure: IMA of ≥12°, HVA ≥20° and TSP ≥4.

A sensitivity analysis of the primary effectiveness endpoint will be performed using the PP population if the PP and ITT populations differ considerably.

7.2.2 Secondary Effectiveness Analysis

Effectiveness analyses will be performed on the following secondary endpoints:

1) Percentage of subjects with recurrence at 12 months where recurrence is defined as meeting 2 of the following 3 criteria: IMA of ≥12°, HVA ≥20° and TSP ≥4.

2) Percentage of subjects with recurrence at 12 months and 24 months where recurrence is defined as HVA >15°.
3) Percentage of subjects with recurrence at 12 months and 24 months where recurrence is defined as HVA >20°.
4) Percentage of subjects with successful correction at 6 weeks.
5) Change from baseline in radiographic angular/positional alignment for HVA, IMA, TSP, and sagittal plane at 6 weeks, 4 months, 6 months, 12 months, and 24 months.
6) Percentage of subjects with non-union (absence of clinical/radiographic healing) at 12 months.
7) Time to weight-bearing in a controlled ankle motion (CAM) boot, in days.
8) Time to weight-bearing in shoes, in weeks.
9) Time to return to full unrestricted activity, in months.
10) Change from baseline in pain at the base of the big toe (bunion related) assessed via VAS at 0-14 days, 14-21 days, 6 weeks, 4 months, 6 months, 12 months, and 24 months.
11) Change from baseline in Quality of Life at 6 months, 12 months, and 24 months as measured by PROMIS-29 (for adult subjects), PROMIS-25 (for pediatric subjects), and MOxFQ (for all subjects).
12) Change from baseline in range of motion of the 1st MTP dorsiflexion, plantarflexion, and dorsiflexion plus plantarflexion at 4 months, 6 months, 12months, and 24 months.
13) Change from baseline in foot swelling measurements at 0-14 days, 14-21 days, 6 weeks, 4 months, 6 months, and 12 months.
14) Summary of POSAS responses over time at 4 months, 6 months, 12 months, and 24 months.

Statistical summaries will be produced in accordance with section 7, and listings will be generated by site, subject, and visit (where applicable) within subject.

7.3 Safety and Health Economic Outcomes Analysis

The ITT population will be used for all safety and health economic analyses. Statistical summaries will be produced in accordance with section 7, and listings will be generated by site, subject, and visit within subject. For the purposes of this analysis, coding dictionaries will not be utilized.

7.3.1 Adverse Events

Adverse events (AEs) related to the Lapiplasty® Procedure and the Lapiplasty® devices that are captured at the time of the index procedure and up until the time of the last study visit will be included in the analysis. Number and proportion of subjects with at least one AE, total number of AEs, and number of subjects with at least one AE by AE type will be summarized using the reported AE term, and the following summaries will be generated:

- All AEs
- Serious AEs (SAEs)
- AEs leading to death
- AEs leading to device removal/surgical intervention
- AEs leading to study discontinuation

Subject level listings will also be produced and will include subject ID, age, sex, AE term, AE description, AE start and end dates, action taken, outcome, primary relationship, secondary relationship, and SAE (y/n).

7.3.2 Clinical and Hardware Complications

The health economic outcomes analysis will determine the following endpoints:

Percentage of subjects experiencing clinical complications through 24 months requiring one or more subsequent interventions: a deviation or delay from the normal operative plan, readmission to hospital, return to operating room, unscheduled visits due to complications (revisions, hardware removals, reoperations, supplemental fixations, wound healing requiring surgical intervention, infection at surgical site requiring surgical intervention), employment of home health services, time (in days) to return to work and to full work, and percentage of subjects requiring post-operative physical therapy.

7.3.3 Return to Work

Time to return to work and time to return to full work (or normal household activities if non-working), in days, will be summarized.

7.3.4 Physical Therapy

Number and proportion of subjects requiring post-operative physical therapy will be summarized.

7.3.5 Concomitant Procedures

Number and proportion of subjects with at least one concomitant procedure, total number of concomitant procedures, and number of subjects by concomitant procedure type will be summarized using recorded procedure name.

7.4 Device and Product Experience

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. A product complaint may or may not be associated with an AE/SAE. A listing of all reported device observations, malfunctions or failures for the Lapiplasty® System products will be generated.

7.5 Exploratory Analysis

Additional endpoints may be pursued at the time of analysis and will be exploratory in nature.

Quality Assurance of Statistical Programming

Clinical operations will independently validate the safety analyses (adverse events and clinical complications). A second statistician will independently reproduce the primary, secondary, health economic, and summary statistics.

To provide high quality code that is understandable and allows for reproduction of the analysis, the following points will be followed:

- The population to be used in a table or listing will be explicitly set at the start of a block of code that computes the output.
- All outputs will include the date and time that the output was generated, and the name of the code file that produced the analysis.
- At the start of any code file, there will be a set of comments that provide the following information: author, date, references to inputs and outputs, reference to any parent code file that runs the child code file.

Summary of Changes to the SAP

N/A

References

[1] Ranging from 3.6%-78% recurrence at an average of 2.4-14 years post-surgery.

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[5] Okuda R, et al. The Shape of the Lateral Edge of the First Metatarsal Head as a Risk Factor for Recurrence of Hallux Valgus. J Bone Joint Surg Am. 2007; 89:2163-72.

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[7] Catanzariti AR, et al. J Foot Ankle Surg. 1999. 38:325-332.

[8] Galli SH, et al. Foot & Ankle Orthopaedics. 2020. 5(2) 1-2.

[9] Ray JJ, et al., Multicenter Early Radiographic Outcomes of Triplanar Tarsometatarsal Arthrodesis with Early Weightbearing. Foot Ankle Int. 2019; 40(8):955-960.

Table of Contents of Statisticial Outputs

Listing 5	Radiographic Measurements, ITT Population
Listing 6	Concomitant Procedures, ITT Population
Listing 7	Device and Product Experience, ITT Population