SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Total Talus Replacement

Device Trade Name: restor3d Total Talus Replacement

Device Procodes: QNN; QYQ

Applicant's Name and Address: restor3d
311 W Corporation St, Durham, NC 27701

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H230003

Humanitarian Use Device (HUD) Designation Number: HUD # 21-0464

Date of HUD Designation: March 9, 2022

Date of Notice of Approval to Applicant: November 17, 2023

II. INDICATIONS FOR USE

The restor3d Total Talus Replacement Implant is indicated for:

- avascular necrosis of the talus
- avascular necrosis of the talus in addition to talar collapse, cysts or non-union
- large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments
- non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments

The implant is patient specific and is designed from computed tomography (CT) scan. The anatomical landmarks necessary for the design and creation of the restor3d TTR Implant must be present and identifiable on CT scan.

Modifications from the HUD Designation

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "treatment of talus dysfunction requiring total talus replacement". It was modified for the HDE approval because specific pathologies of talus dysfunction requiring total talus replacement need to be specified in the indications for use statement, and patient-specific devices in orthopedics need to include image modality in the indications. Specifically, the image modality influences the device design and is crucial to the patient-specific process. The indications reflect the approved use of the specific image modality that has been validated for safe use of the subject device and the primary pathologies of the subjects in the clinical data.

III. CONTRAINDICATIONS

- Surgical procedures other than those listed in the indications for use.
- Use of implant greater than 6 months from date of patient's preoperative CT scan.
- Degenerative changes in the tibiotalar, subtalar or talonavicular joints.
- Gross deformity in sagittal or coronal planes. More than 15 degrees of varus or valgus deformity in the coronal plane, or more than 50% subluxation anteriorly or posteriorly of the talus in the sagittal plane.
- Patients with an active local or systemic infection.
- Osteonecrosis of the calcaneus, distal tibia or navicular.
- Known history of existing malignancy, or any systemic infection, local infection, or skin compromise at the surgical site.
- Blood supply limitations and previous infections that may prevent healing.
- Physical conditions that would eliminate adequate implant support or prevent healing, including inadequate soft tissue coverage.
- Conditions which may limit the patient's ability or willingness to restrict activities or follow directions postoperatively during the healing period.
- Presence of neurological deficit which would prevent patient postoperative compliance.
- Patients with foreign body sensitivity, suspected or documented material allergy or intolerance. Where material sensitivity is suspected, appropriate tests should be conducted, and sensitivity ruled out prior to implantation.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the restor3d Total Talus Replacement (TTR) Implant labeling.

V. DEVICE DESCRIPTION

The restor3d patient-specific TTR Implant and Instrumentation System is designed to replace a native talus bone that has been affected by a disease state or injury. Figure 1 shows the restor3d TTR Implant. The implant is an additively manufactured Cobalt Chromium alloy (ASTM F3213) construct produced by laser powder bed fusion. The data driven design of the implant enables the patient to maintain ankle range of motion, reduce pain and improve physical function.

The implant is patient-specific and made available in multiple sizes to facilitate intraoperative flexibility. Non-sterile single-use disposable instrumentation including size trials and impactors are provided to assist in the surgical placement of the implant. It is important that the provided trials and impactors are used to ensure accurate implantation of the device.

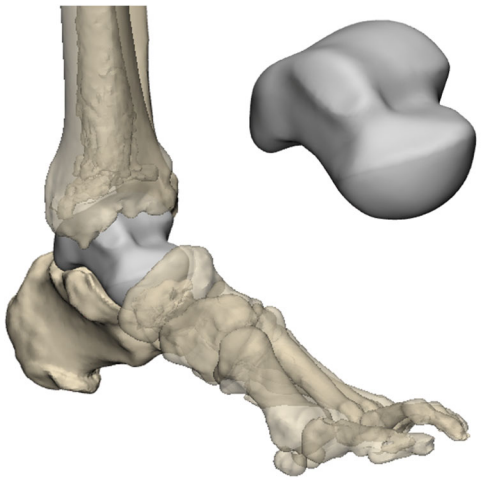

Figure 1. restor3d Total Talus Replacement Implant.

A. Patient-Specific Design Process

Physician Facing Process:

1. Patient CT imaging is obtained using restor3d CT scan protocol.
2. The scans are received from the prescribing physician either on a compact disc (CD) or directly uploaded on the r3id Application, a restor3d proprietary physician facing portal.
3. After receipt of case related information, restor3d begins the patient-specific design process which includes online discussion (emails, video calls, etc.) with the physician to confirm design inputs and create a planning record.
4. restor3d completes the implant and instrument design and a proposed surgical plan is supplied to the physician for approval on r3id. The proposed surgical plan includes, but not limited to, the preoperative anatomy, repositioned and resected anatomy, images of implant drawings and sizing information, images of soft tissue attachment sites (if applicable), and details about accessory instrumentation (trials and impactors) provided.
5. Once the surgical plan is approved, the patient- specific TTR Implant and Instruments are manufactured. Up to three sizes may be provided (small, nominal, and large). A trial instrument matching each implant size and two impactors (flat and contoured) are always provided.
6. The implant and instruments are provided clean, but non-sterile for terminal steam sterilization at the hospital. A copy of the approved surgical plan is sent to the physician.

restor3d Facing Digital Design Process:

1. restor3d receives patient CT imaging directly on r3id or on a physical CD via mail which is then uploaded into r3id internally.
2. Upon receipt, the CT scan undergoes deidentification, and is then reviewed by restor3d staff for accuracy and confirmation that the restor3d CT scan requirements have been met.

3. Preoperative and contralateral (if available) bone is then segmented and reconstructed using off-the-shelf cleared software. The segmented model files are reviewed, and final files are provided for design.

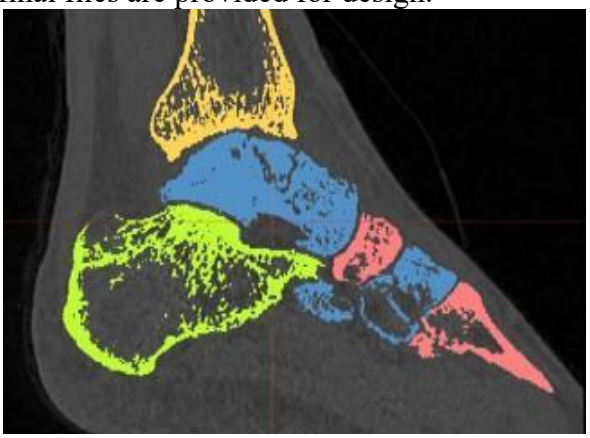

Figure 2. Representative Digital Imaging and Communications in Medicine (DICOM) segmentation of a foot and ankle CT scan.

4. Talus morphology is assessed, and requirements are gathered from the physician, including the input talus (preoperative or contralateral talus) to be used for implant construction. A planning record is created to capture requirements.

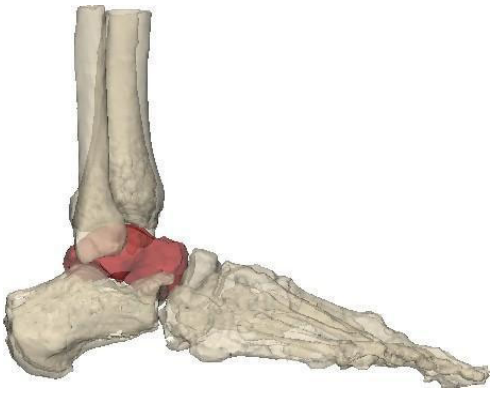

Figure 3. 3D reconstruction of the anatomy used for presurgical planning, showing diseased talus to be replaced in red.

5. The implant and instruments are designed based on the input talus using off-the-shelf design software. Design engineers can optionally utilize the Initial Body Algorithm to semi-automate part of the implant design process.

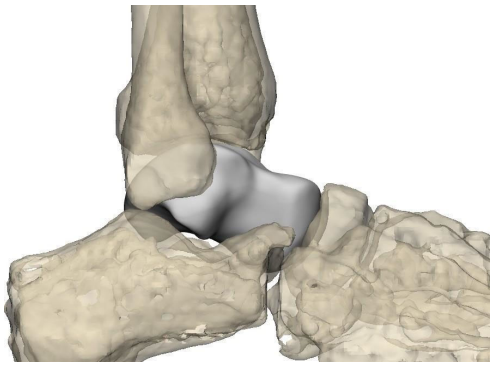

Figure 4. Representative realigned and reconstructed anatomy with restor3d Total Talus Replacement Implant.

6. All design deliverables including but not limited to planning record, surgical plan and manufacturing drawings undergo a formal design review. Internally reviewed surgical plan is shared with the physician for approval via signature.
7. After approval is received, the implant moves to manufacturing.
8. The implant and instruments are manufactured, inspected, cleaned, and provided to the physician non-sterile along with the approved surgical plan.

B. Additive Manufacturing Process

The restor3d TTR Implant is additively manufactured in Co-28Cr-6Mo (ASTM F3213) using laser powder bed fusion. Up to three sizes are provided to the surgeon, one being nominal to the patient's preoperative anatomy, and the others up to 10% larger or smaller based on the surgeon's preference. After printing, the device is polished to create an articulating surface.

C. Device Operation and Principles of Operation

The restor3d TTR Implant is a near-replica of the patient's native talus designed from CT scan images and generated using CAD software, including off-the-shelf software and proprietary algorithms. The implant mimics the native anatomy and is polished to an articulating surface to replace the native talus and articulate with the surrounding bones. The implant allows for maintenance of motion at the ankle and surrounding joints. The device also has optional soft tissue attachment sites that allow the physician to reattach the ligaments to the talus to restore soft tissue balancing. The implant is provided with size trials that can be used to estimate the size (nominal, larger than nominal, smaller than nominal) prior to implantation of the TTR Implant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of talar dysfunction (including avascular necrosis of the talus; avascular necrosis of the talus in addition to talar

collapse, cysts or non-union; large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments; union following talar fracture or talar extrusion, unresponsive to more conservative treatments) are total joint fusion or below-knee amputation (BKA). Total joint fusion for patients with ankle defects such as talar avascular necrosis is a unique clinical challenge as the necrotic or collapsed bone typically must be removed. Attempting to restore length with bulk femoral head allograft and to achieve union has historically shown poor results with union rates at 50%, among other risks.[1] The current commercially available Patient Specific Talus Spacer (H200001)does not have suture attachments sites as provided in the restor3d TTR Implant for optional soft tissue reconstruction.

VII. MARKETING HISTORY

The restor3d TTR Implant has not been marketed in the United States or any foreign country.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Infection, deep and superficial
- Loosening or migration of the implant
- Nerve damage due to surgical trauma
- Inadequate healing
- Increased pain, soft tissue discomfort or abnormal sensation due to the presence of the device
- Allergies or other reactions to implant materials
- Loss of anatomic position with rotation or angulation
- Bone resorption or over-production
- Untoward histological responses possibly involving macrophages and/or fibroblasts
- Migration of particle wear debris possibly resulting in a bodily response
- Embolism

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Objectives

The objectives of the laboratory studies were to test the mechanical strength of the restor3d TTR implant and the suture attachment sites, to confirm the adequacy of the software developed workflow for patient matching, to validate

the cleaning (including removal of residual particulate) and sterilization of the device and to ensure the device is biocompatible.

Dynamic Fatigue
Dynamic fatigue testing was conducted utilizing a modified cantilever bend set up from ASTM F1800-19e1: *Standard Practice for Cyclic Fatigue Testing of Metal Tibial Tray Components of Total Knee Joint Replacements* on a worst-case TTR Implant test coupon. Three devices were tested to runout of 10,000,000 cycles at 4,500N proving the TTR Implant can support physiologically relevant loads.

Suture Pull Out
Suture pull out testing was conducted utilizing FDA Guidance, *Bone Anchors – Premarket notification 510(k) submission guidance document*. Five samples were tested to failure at the suture site compared to a bone anchor assisted Brostrom procedure where a bone anchor is used on the native talus. The bone anchor failed before the device in all samples.

Porous Surface Characterization Testing
Testing was conducted to verify the mechanical properties of the surface porous region used at the suture attachment sites. The surface porosity was characterized utilizing the tests for metallic coatings outlined in the FDA Guidance Document, *Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement.* The testing performed included static shear (ASTM F1044-05, *Standard Test Method for Shear Testing of Calcium Phosphate Coatings and Metallic Coatings*), dynamic shear (ASTM F1160-14, *Standard Test Method for Shear and Bending Fatigue Testing of Calcium Phosphate and Metallic Medical and Composite Calcium Phosphate/Metallic Coatings*), tension (ASTM F1147-05, *Standard Test Method for Tension Testing of Calcium Phosphate and Metallic Coatings*) and taber abrasion (ASTM F1978-18, *Standard Test Method for Measuring Abrasion Resistance of Metallic Thermal Spray Coatings by Using the Taber Abraser*). The acceptance criteria from the ASTM and FDA Guidance Document were met for all tests.

Software Verification and Validation
Software verification and validation activities were executed for the Off-the-shelf software utilized in the digital design process, Mimics Medical (Materialise K183105) and 3Matic (Materialise K060950), and the proprietary Talus Initial Body Algorithm that may optionally be used. Software verification and validation activities were established based on FDA Guidance, *Content of Premarket Submissions for Software Contained in Medical Devices*. Off-the-shelf software and proprietary software have been validated for use in the patient-specific workflow.

Cleaning and Sterilization
The restor3d TTR is provided clean, but not sterile, and to be terminally sterilized at the hospital. restor3d has validated the cleaning process according to ASTM F3127-16, *Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices* and ISO 19227:2018, *Implants for surgery — Cleanliness of orthopedic implants — General requirements*, utilizing worst-case conditions. The validation samples were subject to the entire production process through cleaning to account for all potential contact materials and processes to validate the cleaning process' ability to remove residual manufacturing materials. The samples met the established visual and acceptance criteria.

The steam sterilization process parameters specified in the Instructions for Use have been validated to a sterility assurance level (SAL) of 1×10^{-6} for parts manufactured from the same materials and manufacturing, and worst-case features compared to the TTR Implant and Instrument using the biological indicator (BI) overkill method, with *Geobacillus stearothermophilus* as the indicator organism, with the partial cycle validation approach outlined in ANSI/AAMI/ISO 17665-1:2006/(R)2013, *Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*, Annex D and the validation approach outlined in ANSI/AAMI/ISO 14937:2009/(R)2013, *Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*, Annex D (Approach 3).

Residual Powder Particulate Analysis
Particle characterization testing was verified per ISO 17853:2011, *Wear of implant materials - Polymer and metal wear particles - Isolation and characterization,* ASTM F561-13, *Standard Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids,* and ASTM F1877-16, *Standard Practice for Characterization of Particles*. restor3d TTR Implant was compared to restor3d MTP Implant (K201393), a well performing and relevant legally marketed device made from a similar additively manufactured CoCr device with similar features to demonstrate safety regarding the particle size distribution, particle morphology and amount of residual additive manufacturing particulates.

Biocompatibility
The restor3d TTR Implant is additively manufactured from CoCr alloy conforming to ASTM F3213, with starting powder meeting ASTM F75. After the implants are manufactured and polished, and prior to cleaning, devices are passivated per ASTM F86, to passivate the surface of the implant. CoCr has a long history of use in medical implants with no significant biocompatibility safety issues. restor3d has a previously FDA cleared CoCr implant with the

same manufacturing and materials (MTP Implant, K201393) and another patient-specific total talus replacement device (H200001) on the market is additively manufactured from CoCr powder meeting ASTM F75.

Biocompatibility of the device was verified following ISO 10993-1:2018, *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process,* and the FDA Guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process."* The TTR Implant is characterized by a permanent contact duration (>30 days) with tissue/bone.

X. SUMMARY OF CLINICAL INFORMATION

This was a retrospective chart review study which examined the clinical and radiographic outcomes of patients who received a patient-specific TTR Implant manufactured by restor3d, for treatment of talar dysfunction under the Custom Device Exception per Section 520(b). All adult (≥22 years of age) patients who underwent a foot or ankle deformity correction with this product between January 1, 2019 and January 6, 2023 and met the eligibility criteria at the participating sites were included in this analysis. Patients who did not have any primary endpoint postoperative data available were considered screen failures and not enrolled.[1] During the study period, 27 patients were treated at one of the four study sites with a patient-specific, 3D-printed TTR Implant device manufactured by restor3d and were analyzed for safety and probable benefit endpoints per the protocol. The data collection was approved by two local Institutional Review Boards (IRBs), and a centralized IRB (WCG IRB).

The study enrolled patients from a diverse group of sites and surgeons. Each site enrolled between 4 to 12 patients who met the inclusion criteria, and each site had between 1 and 5 participating surgeons. These real-world data contribute to the development of an accurate safety profile and understanding of the probable benefits of the TTR device. The heterogeneous data types presented reflect the outcomes the study team would expect to see across the varying clinical settings. As such, given the retrospective approach, data for each endpoint and at each time point are not available for all patients, and instead, the data presented reflect the type and frequency of data collected in a real-world setting.

[1] Specifically, in two (2) cases, patients were out of state residents and elected to continue postoperative care with a local medical provider, and, in one (1) case, the patient had a postoperative visit but did not have radiographic or clinical data collected during the visit.

Safety Endpoints

The co-primary safety endpoints were: 1) the rate of adverse events (AEs), device- or procedure-related AEs, and serious AEs, 2) the rate of subsequent surgical intervention (SSI), defined as any surgical procedure or service required after the initial implant of the TTR device, and 3) the rate of implant survivorship.

Probable Benefit Endpoints

The primary probable benefit endpoint was improvement in pain, as measured by the Pain Numerical Rating Scale (NRS) and PROMIS 1.0 – Pain Interference scale, at last follow-up from baseline. The secondary probable benefit endpoints included physical function, as measured by the PROMIS 1.0 – Physical Function scale, and ankle range of motion (ROM).

Patient Demographics

A summary of the patient demographics is provided below in Table 1. Twenty-seven (27) patients were treated with 27 implants. None of the enrolled patients had bilateral procedures (i.e., a TTR Implanted in both the left and right ankles).

Table 1. Patient Demographics.

Age at Surgery (in years) (n=27)	
Mean ± SD	49.9 ± 15.0
Range	22-69
Race (n=27)	
Black/African American, n (%)	1 (3.70%)
White/Caucasian, n (%)	25 (92.6%)
Other, n (%)	1 (3.70%)
Ethnicity (n=27)	
Hispanic or Latino, n (%)	1 (3.70%)
Not Hispanic or Latino, n (%)	22 (81.5%)
Unknown, n (%)	4 (14.8%)
Education Level (n=27)	
12th grade or less, n (%)	1 (3.70%)
Graduated high school or equivalent, n (%)	6 (22.2%)
Some college, no degree, n (%)	1 (3.70%)
Bachelor's Degree, n (%)	2 (7.41%)
Unknown/Not Reported, n (%)	17 (44.4%)
BMI (n=27)	
Mean ± SD	32.6 ± 6.80
Range	21.2-51.2
Smoking Status (n=27)	
Current, n (%)	6 (22.2%)
Former, n (%)	10 (37.0%)
Never, n (%)	11 (40.7%)
Alcohol Use Status (n=27)	
Current, n (%)	15 (55.6%)
Former, n (%)	7 (25.9%)
Never Used, n (%)	5 (18.5%)
Laterality (n=27)	
Left, n (%)	12 (44.4%)
Right, n (%)	15 (55.6%)
Comorbid Conditions (n=27)[1]	
Yes, n (%)	13 (48.1%)
No, n (%)	14 (51.9%)
Surgical History (n=27)[2]	
Yes, n (%)	20 (74.1%)
No, n (%)	7 (25.9%)

[1]Comorbid conditions included: 5 (18.5%) patients with a history of anxiety, 4 (14.8%) with depression, 1 (3.70%) with non-atrial arrhythmia, 1 (3.70%) with peripheral vascular disease, 1 (3.70%) with a history of stroke or CVA, 1 (3.70%) with diabetes mellitus, 1 (3.70%) with moderate to severe chronic kidney disease, 1 (3.70%) with leukemia, 1 (3.70%) with a history of drug abuse, and 1 (3.70%) patient with HIV or AIDS.
[2]Surgical history was not limited to the affected limb.

Patient Accountability

Table 2 shows the overall number of patients by last follow-up data available at less than 1 year, 1 to 2 years, 2 to 3 years, or more than 3 years, and then provides a more granular view of patient accountability by primary safety endpoints (SSIs and AEs). The table also includes a summary of patients who contributed a minimum of one year of postoperative follow-up data in a ">1 Yr" column. Postoperative SSI and AE reporting data were available for all 27 patients. Implant survivorship was evaluated based on the SSIs and AEs reported for each patient and assessed qualitatively through review of follow-up notes written by the medical provider.

Table 2. Patient Accountability.

	Total Patients[1]	Follow-up Duration				
				>1 Yr in Yearly Increments		
		<1 Yr	>1 Yr[2]	1 - 2 Yrs	2 - 3 Yrs	3+ Yrs
Last Follow-Up (Overall)	27	12	**15**	7	7	1
Last Follow-Up Visit (by Measure)						
Co-Primary Safety						
SAE/SSI	27	14	**13**	6	6	1
AE	27	12	**15**	7	7	1

[1] Includes patients who reported primary safety outcomes at any time point (e.g., <1 year, 1-2 years, 2-3 years or 3+ years).
[2] Sum of patients who reported primary safety outcomes for 1-2 years, 2-3 years and 3+ years.

Safety Results

There was a total of ten (10) safety events reported in five (n=5, 18.5%) patients. The safety events include nine (9) SSIs across four (n=4, 14.8%) patients and one AE in one (n=1, 3.7%) patient that did not have an SSI. The nine (9) SSIs included one patient (RECLAIM-1-019) who had four (4) SSIs, one patient (RECLAIM-1-020) who had three (3) SSIs, and two patients (RECLAIM-1-014 and RECLAIM-1-016) who had one (1) SSI following the index surgery (additional details provided below). The initial safety event for each patient (e.g., four (4) initial SSIs to address wound dehiscence, osteochondral defect and tibial AVN, contracture of the flexor hallucis longus and plantar fasciitis, and one AE where the patient developed compartment syndrome) were categorized for their relatedness to the device (see Table 3 below). The initial safety events for three (3, 11.1%) patients were determined to be unrelated to the subject device, and for two (2, 7.4%) patients were determined to be possibly procedure-related. None (0, 0%) were determined to be device-related. The one (1) AE without an SSI was also

determined to be unrelated to the device. Importantly, to date, the study team has not received any reports of BKA, and all patients (27/27, 100%) were successfully able to salvage their limbs with the TTR device. See Table 3 for an overview of initial reported safety events.

Table 3. Categorization of Initial Reported Safety Events.

	Possibly Device-Related	Possibly Procedure-Related	Unrelated
Serious Adverse Events[1] (n=4)	0	2	2
Subsequent Surgical Interventions	0	2	2
Adverse Events (n=1)	0	0	1
Total[2] (n=5)	**0**	**2**	**3**

[1] Serious adverse event totals are inclusive of subsequent surgical interventions.
[2] Sum of SAEs and AEs.

Only one (1/27, 3.70%) AE was reported and was determined by the surgeon to not be related to the subject device. This patient developed chronic compartment syndrome of the lower extremity approximately 1.5 years after TTR device implantation. The patient was offered a subsequent surgical intervention but opted not to have surgery.

At the request of the surgeon, eight implanted (8/27, 29.6%) devices had soft tissue attachment sites for optional intraoperative use. In two (2/8, 25%) of these implants, attachment sites were used to attach patients' ligaments during device implantation and were not associated with any SAEs, SSIs or AEs. For the six implanted devices where the attachment sites were not used, one patient (RECLAIM-1-019) reported four (4) SSIs. This rate of patients with SSIs (1/8, 12.5%) for devices with attachment sites is equivalent to the rate of patients reporting SSIs across the entire study population (4/27, 14.8%), thereby not only demonstrating safety but also confirming that the inclusion of soft tissue attachment sites on the TTR Implant does not place the patient at additional risk for SAEs, SSIs or other AEs.

Implants remained in place for 26/27 (96.3%) patients, demonstrating a high rate of implant survivorship. To date, no additional implants have been removed in the study population.

Probable Benefit Analysis

Twenty-two (22/27, 81.5%) patients were available for the evaluation of probable benefit.[2] Probable benefit outcomes (e.g., pain, physical function, ROM) are measured in relation to date of surgery, and receiving additional surgical interventions after the initial TTR surgery is a confounding factor. Table 4 shows patient accountability for the analysis-eligible population by length of time to last follow-up (overall), and then by length of time to last follow-up for primary (pain) and secondary (physical function and ROM) probable benefit endpoints. The table also includes a summary of patients who contributed a minimum of one year of postoperative follow-up data in a ">1 Yr" column.

As previously noted, given the retrospective nature of this study utilizing real-world data, data for all endpoints are not available for all probable benefit endpoints at all timepoints; however, this study enrolled a heterogenous population implanted by multiple surgeons at multiple sites, broadening the generalizability of the findings.

Table 4. Patient accountability for the analysis-eligible population.

	Total Patients[1]	Follow-up Duration (Analysis Eligible Population)					
		<1 Yr	>1 Yr[2]	>1 Yr in Yearly Increments			No Postop Scores[3]
				1 - 2 Yrs	2 - 3 Yrs	3+ Yrs	
Last Follow-up with Patient Reported Measures	22	12	**10**	4	5	1	0
Last Follow-Up Visit (by Measure)							
Primary Probable Benefit							
Pain Overall[4]	22	14	**6**	4	2	0	2
Pain NRS and Patient Reported	22	14	**5**	4	1	0	3
PROMIS-Pain Interference	11	7	**4**	2	2	0	0
Co-Secondary Probable Benefit							
PROMIS-Physical Function	13	7	**4**	2	2	0	2
Range of Motion	13	7	**3**	2	1	0	3

[1] Includes patients who had any score (e.g., preoperative or postoperative score) at any time point.
[2] Sum of patients who reported primary safety outcomes for 1-2 years, 2-3 years and 3+ years.
[3] Patients who did not have postoperative scores on patient-reported outcome measures were excluded from analysis for lack of sufficient longitudinal data.
[4] Eleven (11) patients had pain scores on multiple measurement tools.

Probable Benefit Results

i. Perceived Pain – Patient-Reported Pain Measures

[2] Four (4) patients who received subsequent surgical interventions and the one (1) patient who reported an adverse event were excluded from analyses.

Pain scores were collected through retrospective chart review and included scores on the following measures: Pain Numerical Rating Scale (NRS), and PROMIS-Pain Interference Scale. Scores on the Pain NRS range from 0-10, and higher scores indicate more severe perceived pain. Of the 22 patients meeting the inclusion criteria for the analysis-eligible population, five (5) patients were excluded because of insufficient baseline and/or follow-up data. An additional five (5) patients were excluded because of the absence of a preoperative pain score. Pain NRS scores were reported for 54.5% (12/22) of the analysis-eligible population.

Pain scores were assessed preoperatively, and then at the most recent follow-up time point, grouped by the duration of time to last follow-up (e.g., <1 year, or >1 year). At baseline, the mean pain score was 4.50 ± 2.39; and at last follow-up, the mean pain score was 2.75 ± 2.38, indicating a 1.75-point mean improvement in scores on the Pain NRS (see Figure 5 and Table 5). Of note, the improvement in pain scores was sustained over time.

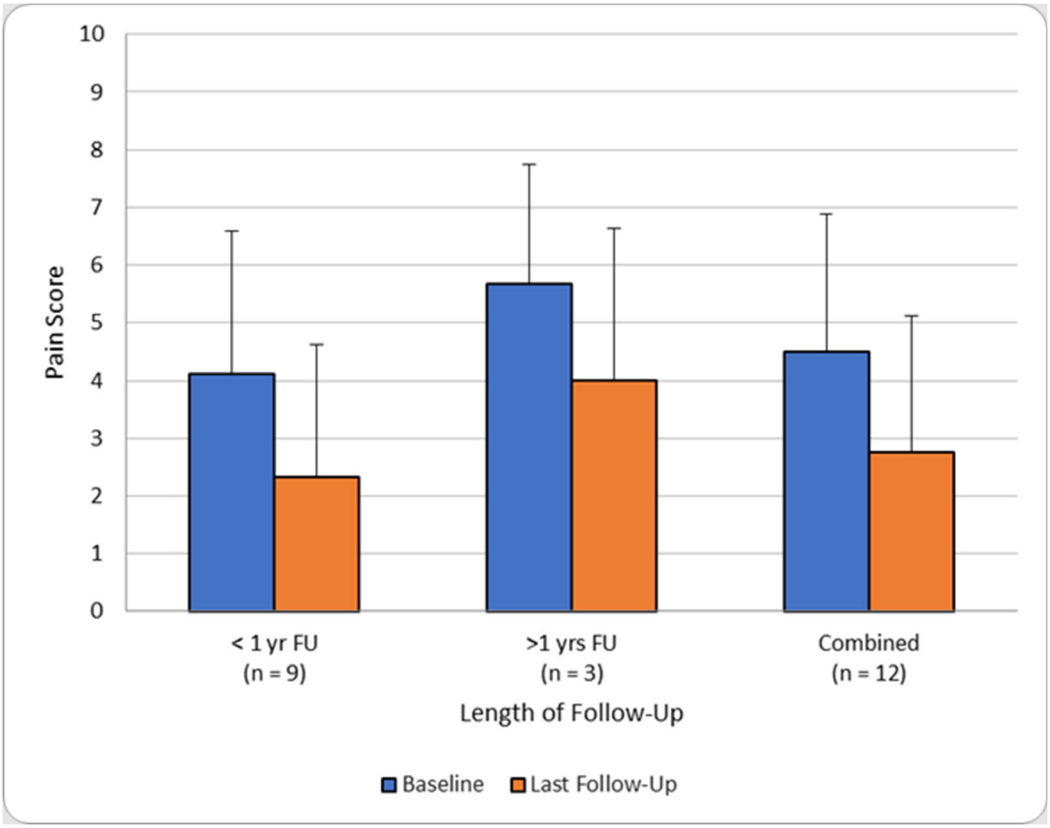

Figure 5. Pain NRS – mean baseline and last follow-up by duration of follow-up. Bars represent standard deviations.

Table 5. Pain NRS –baseline, last follow-up, and change from baseline scores by duration of follow-up.

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year (n=9)	Baseline	4.11	2.47	1 - 8	2.49, 5.73
	Last Follow-up	2.33	2.29	1 - 8	0.83, 3.83
	Change from Baseline	1.78	3.31	-3 - 7	-0.38, 3.94
>1 Year (n=3)	Baseline	5.67	2.08	4 - 8	3.31, 8.03
	Last Follow-up	4.00	2.65	1 - 6	1.01, 6.99
	Change from Baseline	1.67	1.53	0 - 3	-0.06, 3.40
Combined (n=12)	Baseline	4.50	2.39	1 - 8	3.15, 5.85
	Last Follow-up	2.75	2.38	1 - 8	1.40, 4.10
	Change from Baseline	1.75	2.90	-3 - 7	0.11, 3.39

ii. Perceived Pain – PROMIS-Pain Interference

PROMIS-Pain Interference is a measure utilizing computerized adaptive testing to better assess the impact of an individual's pain on physical, mental, and social functioning.[3] A T-score of 50 points represents the United States general population mean with a standard deviation of 10 points.[4] Higher T-scores indicate pain having a larger impact on an individual's life. T-scores less than 55 points are within normal limits; approximately 80% of the general population falls within this range. Scores between 55 and 60 points indicate mild pain, 60 and 70 points indicate moderate pain, and over 70 points indicate severe pain. Chen et al. (2018) reported that the "minimally important difference (MID), defined as the smallest difference in score in the domain of interest perceived as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management" is 2-3 T-score points in the pain population. Therefore, the study team defined a MID in pain as a 2.5-point reduction in T-scores from baseline to last follow-up on the PROMIS-Pain Interference scale.

PROMIS-Pain Interference scores were reported for 40.9% (9/22) of the analysis-eligible population. In each follow-up group, PROMIS-Pain Interference T-scores improved from baseline to last follow-up (see Figure 6 and Table 6). Across all cohorts, the mean baseline T-score was 63.8 ± 6.51 points, and at last follow-up, the mean T-score was 58.8 ± 5.91 points, indicating a 5.00-point mean improvement in T-scores, and well exceeding the MID noted in the literature. Importantly, last follow-up pain T-scores continued to improve as the follow-up period increased past the 1-year post operation time point (T-score = 56 points). Given that a T-score of 55 points is within normal limits, these patients returned to pain levels similar to the general U.S. population.

[3] Chen CX, Kroenke K, Stump TE, et al. Estimating minimally important differences for the PROMIS pain interference scales: results from 3 randomized clinical trials. Pain. 2018;159(4):775-782.
[4] Interpret Scores: PROMIS®. HealthMeasures. Accessed May 17, 2023. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis

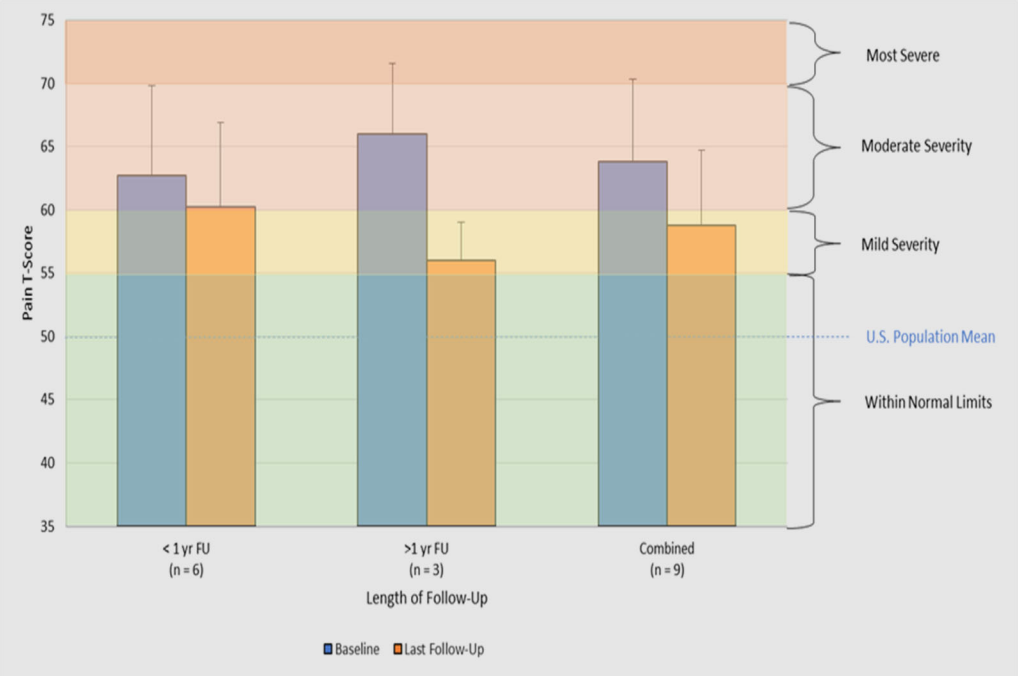

Figure 6. PROMIS-Pain Interference – mean baseline and last follow-up scores by duration of follow-up. Bars represent standard deviations.

Table 6. PROMIS-Pain Interference – baseline, last follow-up, and change from baseline scores by duration of follow-up.

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year (n=6)	Baseline	62.7	7.15	50 - 70	57.0, 68.4
	Last Follow-up	60.2	6.74	50 - 67	54.8, 65.6
	Change from Baseline	2.50	10.5	-17 - 12	-5.89, 10.9
>1 Year (n=3)	Baseline	66.0	5.57	60 – 71	59.7, 72.3
	Last Follow-up	56.0	3.00	53 – 59	52.6, 59.4
	Change from Baseline	10.0	2.65	7 – 12	7.01, 13.0
Combined (n=9)	Baseline	63.8	6.51	50 - 71	59.5, 68.1
	Last Follow-up	58.8	5.91	50 - 67	54.9, 62.7
	Change from Baseline	5.00	9.19	-17 - 12	-1.01, 11.0

iii. Exploratory Analysis of Potential Risk Factors Impacting Perceived Pain

Next, using baseline and last follow-up scores on the Pain NRS, the study team evaluated the impact of age, smoking status, alcohol use, and Body Mass Index (BMI) on perceived pain. The study team chose to use scores on the Pain NRS because pain was the primary probable benefit endpoint and more participants had scores available on this pain scale in comparison to the PROMIS-Pain Interference measure.

Age: To evaluate the impact of age on the Pain NRS, patients were grouped into two categories, less than 55 years and greater than 55 years of age. See Figure 7 and Table 7 for perceived pain data by age group. Of note, the mean improvement in scores on the Pain NRS was nearly identical across groups.

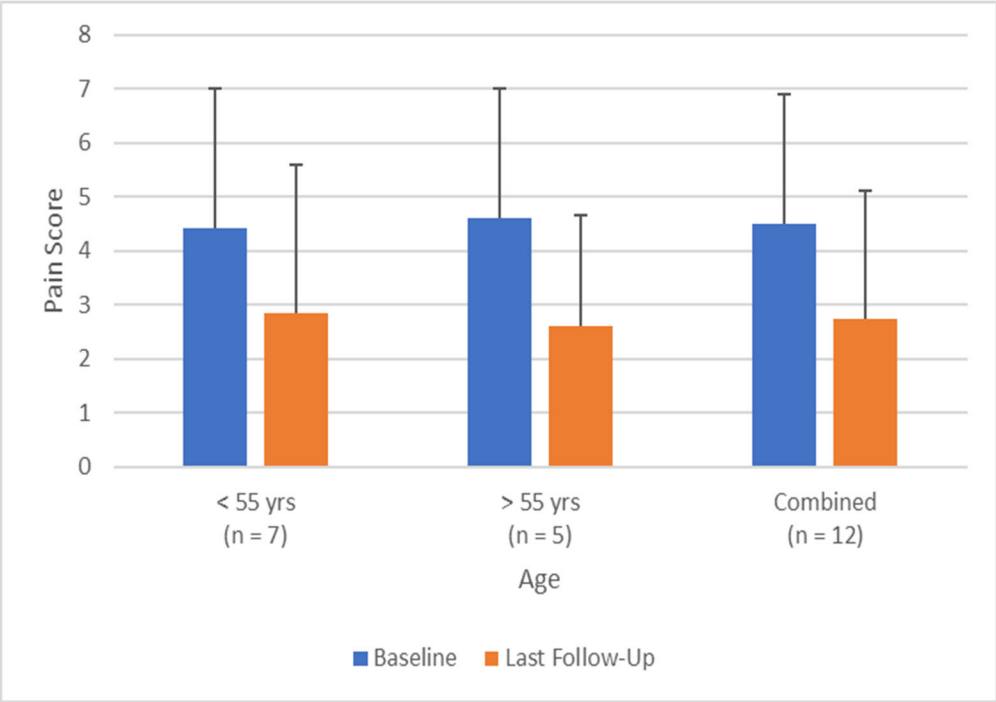

Figure 7. Mean change in perceived pain on the Pain NRS by age. Bars represent standard deviations.

Table 7. Pain NRS – baseline, last follow-up, and change from baseline scores by age group.

Cohort	Assessment	Mean	SD	Range	95% CI
<55 years (n=7)	Baseline	4.43	2.57	1 – 8	2.52, 6.34
	Last Follow-up	2.86	2.73	1 – 8	0.83, 4.89
	Change from Baseline	1.57	3.78	-3 – 7	-1.23, 4.37
>55 years (n=5)	Baseline	4.60	2.41	2 – 8	2.49, 6.71
	Last Follow-up	2.60	2.07	1 – 6	0.78, 4.42
	Change from Baseline	2.00	1.22	0 – 3	0.93, 3.07
Combined (n=12)	Baseline	4.50	2.39	1 – 8	3.15, 5.85
	Last Follow-up	2.75	2.38	1 – 8	1.40, 4.10
	Change from Baseline	1.75	2.90	-3 – 7	0.11, 3.39

Smoking status: To evaluate the impact of smoking status on the Pain NRS, patients were grouped into three categories: current smoker, previous smoker, or never smoked. See Figure 8 and Table 8 for perceived pain by smoking status. The group of current smokers had the smallest mean change in perceived pain at last follow-up (M = 0.00, SD = 2.83,

95% CI = -3.92 to 3.92), whereas the group of previous smokers had the largest mean change in perceived pain at last follow-up (M = 3.67, SD = 1.53, 95% CI = 1.94 to 5.40).

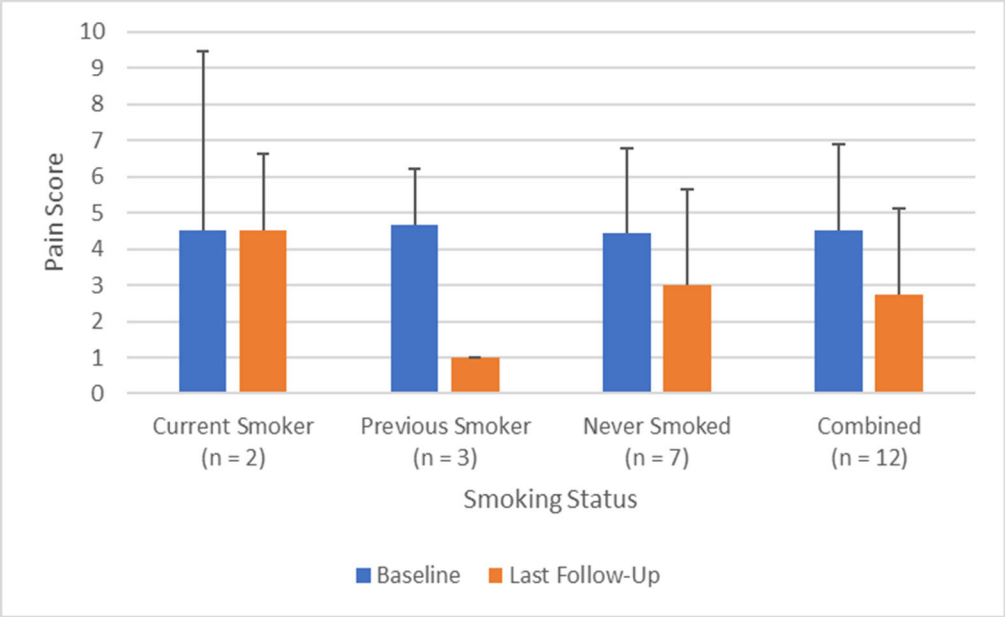

Figure 8. Mean change in perceived pain on Pain NRS by smoking status. Bars represent standard deviations.

Table 8. Pain NRS – baseline, last follow-up, and change from baseline scores by smoking status.

Cohort	Assessment	Mean	SD	Range	95% CI
Current Smoker (n=2)	Baseline	4.50	4.95	1 – 8	0.00, 10.0
	Last Follow-up	4.50	2.12	3 – 6	1.56, 7.44
	Change from Baseline	0.00	2.83	-2 – 2	-3.92, 3.92
Previous Smoker (n=3)	Baseline	4.67	1.53	3 – 6	2.94, 6.40
	Last Follow-up	1.00	0.00	1 – 1	*
	Change from Baseline	3.67	1.53	2 – 5	1.94, 5.40
Never Smoked (n=7)	Baseline	4.43	2.37	1 – 8	2.67, 6.19
	Last Follow-up	3.00	2.65	1 – 8	1.04, 4.96
	Change from Baseline	1.43	3.21	-3 – 7	-0.95, 3.81
Combined (n=12)	Baseline	4.50	2.39	1 – 8	3.15, 5.85
	Last Follow-up	2.75	2.38	1 – 8	1.40, 4.10
	Change from Baseline	1.75	2.90	-3 – 7	0.11, 3.39

*Standard deviation not available due to lack of variation in last follow-up pain scores.

Alcohol use: To evaluate the impact of alcohol use on the Pain NRS, patients were grouped into three categories: current alcohol use, previous alcohol use, and never used alcohol. See Figure 9 and Table 9 for perceived pain by alcohol use status. Interestingly, the group of patients who currently consume alcohol had the largest

mean improvement in perceived pain (M = 2.63, SD = 2.83, 95% CI = 0.67 to 4.59).

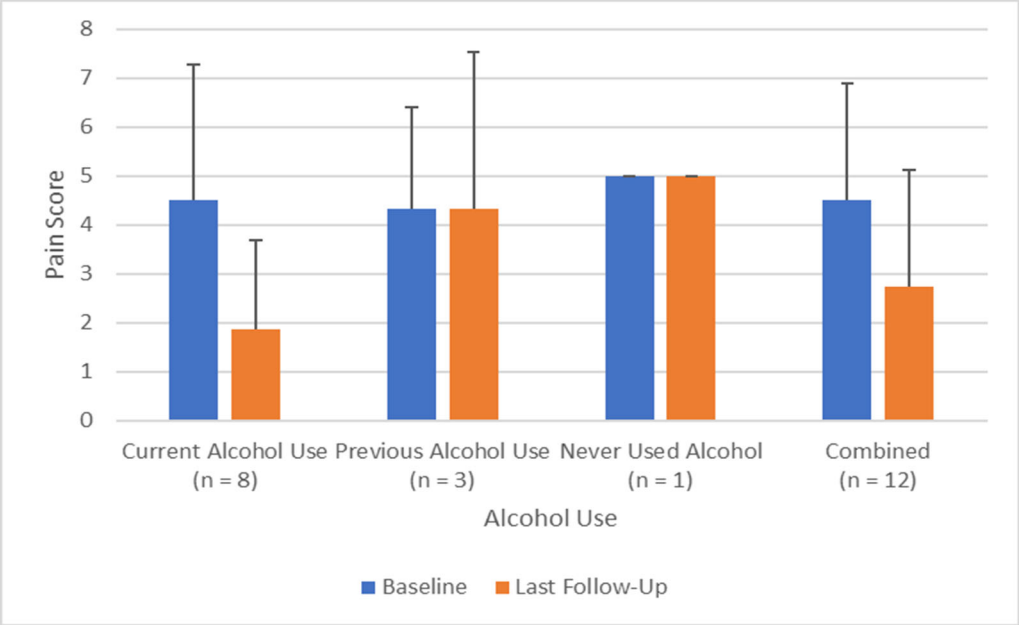

Figure 9. Mean change in Pain NRS by alcohol use status. Bars represent standard deviations.

Table 9. Pain NRS – baseline, last follow-up, and change from baseline scores by alcohol use status.

Cohort	Assessment	Mean	SD	Range	95% CI
Current Alcohol Use (n=8)	Baseline	4.50	2.78	1 – 8	2.58, 6.42
	Last Follow-up	1.88	1.81	1 – 6	0.63, 3.13
	Change from Baseline	2.63	2.83	-2 – 7	0.67, 4.59
Previous Alcohol Use (n=3)	Baseline	4.33	2.08	2 – 6	1.97, 6.69
	Last Follow-up	4.33	3.21	2 – 8	0.69, 7.97
	Change from Baseline	0.00	3.00	-3 – 3	-3.40, 3.40
Never Used Alcohol (n=1)	Baseline	5.00	*	*	*
	Last Follow-up	5.00	*	*	*
	Change from Baseline	0.00	*	*	*
Combined (n=12)	Baseline	4.50	2.39	1 – 8	3.15, 5.85
	Last Follow-up	2.75	2.38	1 – 8	1.40, 4.10
	Change from Baseline	1.75	2.90	-3 – 7	0.11, 3.39

*Standard deviation, range and 95% confidence interval not available due to limited sample size.

Body Mass Index (BMI): Lastly, to evaluate the impact of BMI on change in perceived pain, patients were grouped into three categories according to CDC (the Centers for Disease Control and Prevention) guidelines: healthy weight (e.g., <25

kg/m2), overweight (e.g., >25 kg/m2 and <30 kg/m2), or obese (e.g., >30 kg/m2).[5] See Figure 10 and Table 10 for change in perceived pain by BMI classification. Patients in the overweight category had the largest mean improvement in perceived pain (M = 5.00, SD = 2.83, 95% CI = 1.08 to 8.92).

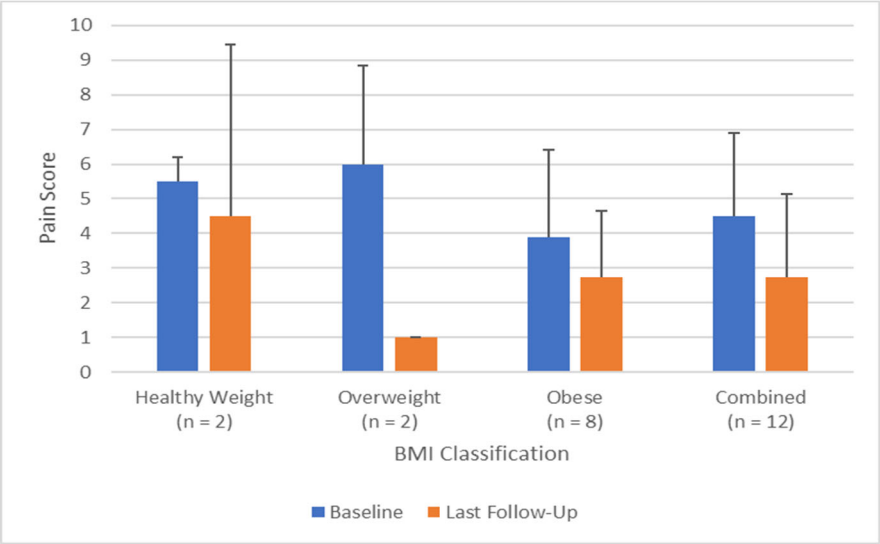

Figure 10. Mean change in Pain NRS by BMI classification. Bars represent standard deviations.

Table 10. Pain NRS – baseline, last follow-up, and change from baseline scores by BMI classification.

Cohort	Assessment	Mean	SD	Range	95% CI
Healthy Weight (n=2)	Baseline	5.50	0.71	5 – 6	4.52, 6.48
	Last Follow-up	4.50	4.95	1 – 8	0.00, 10.0
	Change from Baseline	1.00	5.66	-3 – 5	-6.84, 8.84
Overweight (n=2)	Baseline	6.00	2.83	4 – 8	2.08, 9.92
	Last Follow-up	1.00	0.00	1 – 1	*
	Change from Baseline	5.00	2.83	3 – 7	1.08, 8.92
Obese (n=8)	Baseline	4.17	2.53	1 – 8	2.13, 5.63
	Last Follow-up	2.67	1.91	1 – 6	1.43, 4.07
	Change from Baseline	1.50	1.96	-2 – 4	-0.23, 2.49
Combined (n=12)	Baseline	4.41	2.39	1 – 8	3.15, 5.85
	Last Follow-up	2.65	2.38	1 – 8	1.40, 4.10
	Change from Baseline	1.76	2.90	-3 – 7	0.11, 3.39

*Standard deviation not available due to lack of variation.

Based on these findings, the study team does not believe that patients should be ineligible for the subject device based on age, smoking status, alcohol use status,

[5] Defining Adult Overweight & Obesity. Centers for Disease Control and Prevention. Last Reviewed June 3, 2022. Accessed May 17, 2023. https://www.cdc.gov/obesity/basics/adult-defining.html#:~:text=If%20your%20BMI%20is%20less,falls%20within%20the%20obesity%20range

or BMI. While visually reviewing trends, the team hypothesized a potential interaction between smoking status and alcohol use but was unable to confirm because of the limited sample size. More data on smoking status and alcohol use should be collected in future, prospective, longitudinal studies to better understand the impact of these lifestyle choices on change in perceived pain.

Secondary Probable Benefit Endpoints Analysis

i. Physical Function

A subset of patients had PROMIS-Physical Function scores available in their medical record. PROMIS-Physical Function scores were reported for 45.5% (10/22) of the analysis-eligible population. Similar to the PROMIS-Pain Interference measure, the general population mean on the PROMIS-Physical Function measure is a T-score of 50 points (SD = 10). On the PROMIS-Physical Function measure, higher scores indicate that an individual has better physical function. Scores greater than 45 points are within normal limits, between 40 and 45 points indicate mild limitations, 30 and 40 points indicate moderate limitations, and less than 30 points suggest severe physical limitations.[6]

Across all patients, irrespective of follow-up duration, the mean baseline T-score was 35.9 ± 6.33 points, and at last follow-up was 38.9 ± 9.15 points, indicating a 3.00-point improvement in T-scores. When compared to the less than 1 year of follow-up, the patients who had more than 1 year of follow-up and consequently had more time elapse from surgery experienced greater improved physical functioning, and mean T-scores at last follow-up after 1 year were 43.7 ± 9.61 points. A T-score between 40 and 45 points represents mild physical limitations and the mean T-score of 43.7 points at last follow-up in the greater than 1 year cohort is within 1.5 points of normal (see Figure 11 and Table 11).

[6] PROMIS® Score Cut Points. HealthMeasures. Accessed May 17, 2023. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points.

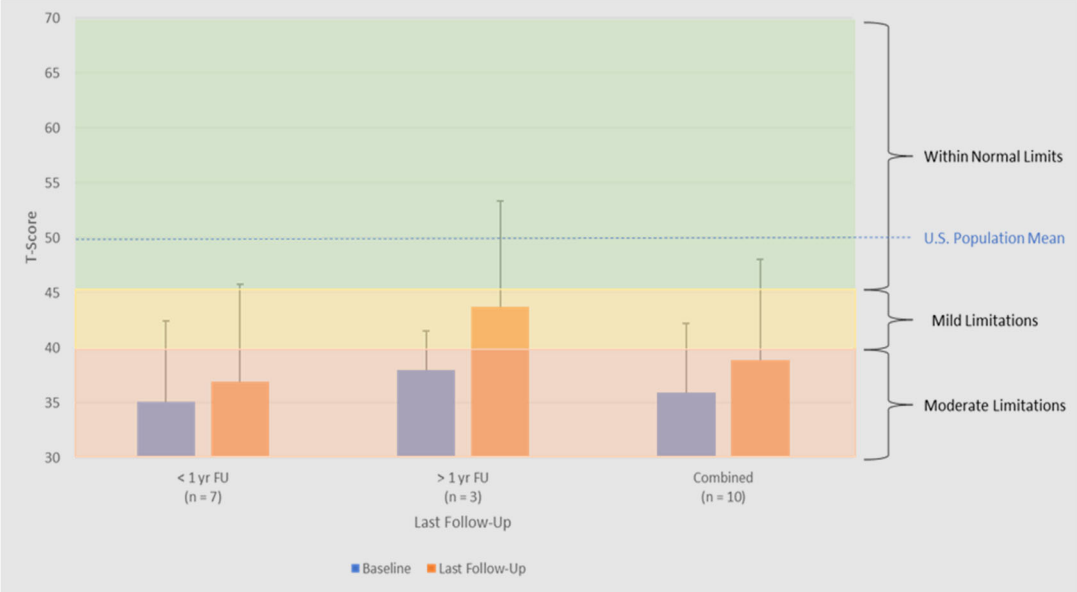

Figure 11. Mean PROMIS-Physical Function scores by follow-up duration. Bars represent standard deviations.

Table 11. PROMIS-Physical Function – baseline, last follow-up, and change from baseline scores by duration of follow-up.

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year (n=7)	Baseline	35.1	7.34	21 – 45	29.7, 40.5
	Last Follow-up	36.9	8.86	24 – 51	30.3, 43.5
	Change from Baseline	1.57	13.45	-11 – 30	-8.40, 11.5
>1 Year (n=3)	Baseline	38.0	3.51	34 – 41	34.0, 42.0
	Last Follow-up	43.7	9.61	35 – 54	32.8, 54.6
	Change from Baseline	6.00	8.66	1 – 16	-3.80, 15.8
Combined (n=10)	Baseline	35.9	6.33	21 – 45	32.0, 39.8
	Last Follow-up	38.9	9.15	24 – 54	33.2, 44.6
	Change from Baseline	3.00	11.9	-11 – 30	-4.38, 10.4

ii. Range of Motion

Finally, ankle plantarflexion and dorsiflexion were reviewed. The postoperative goal for ankle ROM in this study is return to preoperative ROM. Sagittal plane ROM was measured pre and postoperatively. See Figure 12 and Table 12 for plantarflexion scores, and Figure 13 and Table 13 for dorsiflexion scores. Eight (8/22, 36.4%) patients had preoperative and postoperative plantarflexion scores available. Similar to published reports, in the greater than 1-year postoperative cohort, there was no identified difference in pre and postoperative plantarflexion with a mean ROM of 30±10 degrees at last follow-up, signifying that these patients returned to their preoperative ROM after a year from surgery has elapsed. Patients in the less than 1 year follow-up cohort demonstrated an 11-degree

reduction in postoperative ROM, which likely contributed to the -6.9 ± 15.1-degree reduction in plantarflexion across all cohorts. One patient in the less than 1 year group had a 30-degree reduction (50 degrees to 20 degrees) in ROM from preoperative to postoperative timepoints, and because of the low sample size, these data points impacted the overall means in the <1 year and combined cohorts. When reviewing data summarized in the >1 year cohort, the results of this study demonstrate that ROM is restored to baseline over time.

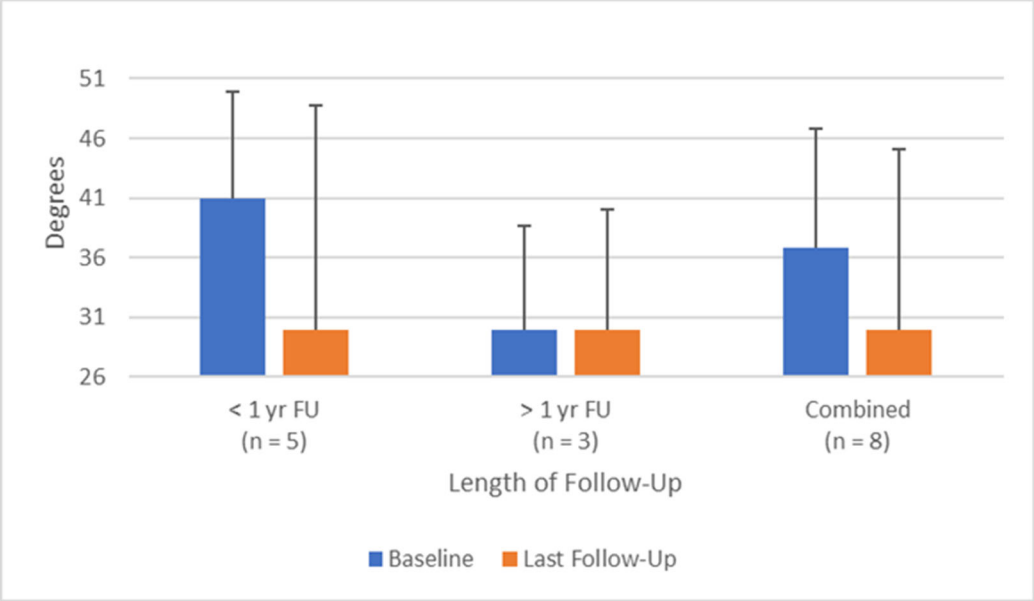

Figure 12. Mean degrees of plantarflexion by follow-up duration. Bars represent standard deviations.

Table 12. Plantarflexion – baseline, last follow-up, and change from baseline by duration of follow-up.

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year (n=5)	Baseline	41.0	8.94	30 – 50	33.2, 48.8
	Last Follow-up	30.0	18.7	10 – 50	13.6, 46.4
	Change from Baseline	-11.0	16.0	-30 – 10	-25.0, 3.00
>1 Year (n=3)	Baseline	30.0	8.66	20 – 35	20.2, 39.8
	Last Follow-up	30.0	10.0	20 – 40	18.7, 41.3
	Change from Baseline	0.00	13.2	-15 – 5	-15.0, 15.0
Combined (n=8)	Baseline	36.9	9.98	20 – 50	30.0, 43.8
	Last Follow-up	30.0	15.1	10 – 50	19.5, 40.5
	Change from Baseline	-6.90	15.1	-30 – 10	-17.4, 3.59

Seven (7/22, 31.8%) patients had preoperative and postoperative dorsiflexion measures available (see Figure 13 and Table 13). Similar to published reports and across all cohorts, there was no notable difference in degrees of dorsiflexion from preoperative to postoperative visits. Across all follow-up periods, mean dorsiflexion at last follow-up was 13.9 ± 6.12 degrees.

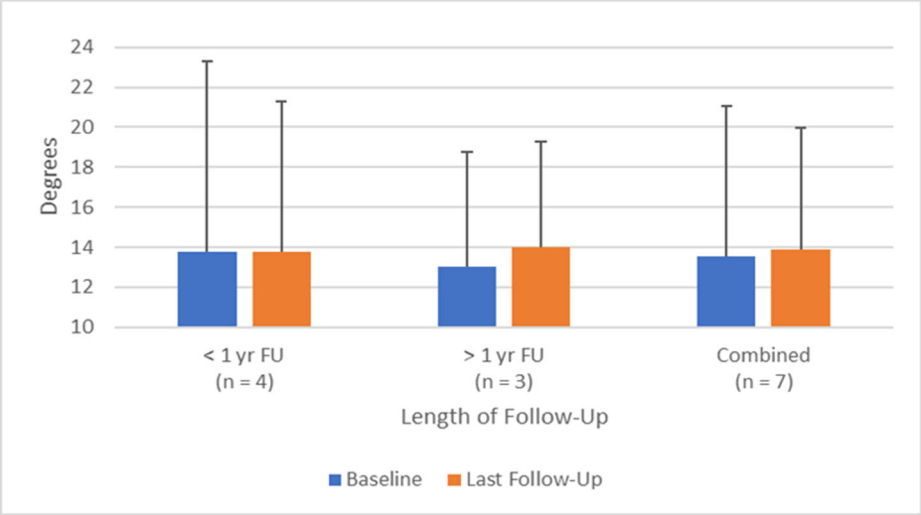

Figure 13. Mean degrees of dorsiflexion by follow-up duration. Bars represent standard deviations.

Table 13. Dorsiflexion – baseline, last follow-up, and change from baseline scores by duration of follow-up.

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year (n=4)	Baseline	13.8	9.46	0 – 20	4.52, 23.1
	Last Follow-up	13.8	7.50	5 – 20	6.48, 21.2
	Change from Baseline	0.00	10.8	-15 – 10	-10.8, 10.8
>1 Year (n=3)	Baseline	13.3	5.77	10 – 20	6.77, 19.8
	Last Follow-up	14.0	5.29	10 – 20	8.01, 20.0
	Change from Baseline	0.70	1.15	0 – 2	-0.64, 1.98
Combined (n=7)	Baseline	13.6	7.48	0 – 20	8.03, 19.1
	Last Follow-up	13.9	6.12	5 – 20	9.33, 18.4
	Change from Baseline	0.30	7.67	-15 – 10	-5.40, 5.98

Range of motion findings demonstrate the ability for the subject device to maintain sagittal plane ROM postoperatively. This finding is clinically meaningful given that most interventions aiming to reduce pain (e.g., ankle fusion), consequently result in a substantial decrease in ROM, ultimately impacting the patient's physical function and quality of life.[7,8]

[7] Valderrabano V, Hintermann B, Nigg BM, Stefanyshyn D, Stergiou P. Kinematic changes after fusion and total replacement of the ankle: part 1: Range of motion. Foot Ankle Int. 2003;24(12):881-887.
[8] Pedowitz DI, Kane JM, Smith GM, Saffel HL, Comer C, Raikin SM. Total ankle arthroplasty versus ankle arthrodesis: a comparative analysis of arc of movement and functional outcomes. Bone Joint J. 2016;98-B(5):634-640.

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support use of the subject device in pediatric patient populations.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

Surgeons implanted the TTR device as standard of care, prior to study initiation. The study included retrospective data collected by six investigators, of which none were full-time or part-time employees of the sponsor and all six had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Six investigators
- Significant payment of other sorts: Two investigators
- Proprietary interest in the product tested held by the investigator: None
- Significant equity[9] interest held by investigator in sponsor of covered study: Four investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

The restor3d TTR Implant is an innovative technology addressing a current gap in clinical treatment for patients with dysfunction of the talus due to avascular necrosis of the talus; avascular necrosis of the talus in addition to talar collapse, cysts or non-union; large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments; non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments. Except for the Patient Specific Talus Spacer (Paragon 28, Inc., H200001) there is no total talus replacement available in the United States. Alternative treatments for these patients are various non-surgical approaches, which may not be adequate due to

[9] Any equity interest at a private company is considered significant.

severity, or ankle fusion which sacrifices the mobility of the joint and has resulted in historically poor outcomes.

The clinical data and non-clinical testing of the restor3d TTR Implant demonstrate both safety and probable benefit of the device. Across the enrolled participants in the clinical study, it was demonstrated that the restor3d patient-specific TTR Implant provided a limb and joint sparing solution, as well as improvement in patient quality of life through reduction of pain, maintenance of range of motion and improved physical functioning. These positive impacts afford patients the ability to return to work, maintain a healthy lifestyle through physical activity, and engage with friends and family. More detailed assessment of the risks and probable benefit is below.

a. <u>Probable Benefit Conclusions</u>

The restor3d TTR device was able to restore motion to a degenerated joint that was plagued with risk of fusion or amputation.

- Patients reported an improvement in perceived pain from baseline to last follow-up on the Pain NRS and PROMIS-Pain Interference scales.
- Patients demonstrated improved physical function as more postoperative time elapsed. Importantly, patients who had more than 1 year of follow-up reported a 6.00-point improvement in PROMIS-Physical Function T-scores, nearly meeting the within normal limits cutoff value.
- By the 1-year postoperative time point, degrees of plantarflexion returned to baseline. Similarly, degrees of dorsiflexion returned to baseline, irrespective of follow-up duration.

The study team also evaluated the impact of potential risk factors (e.g., age, smoking status, alcohol use, and BMI) on change in perceived pain at last follow-up. The following observations were made:

- Age did not impact change in perceived pain at last follow-up and the <55 years and >55 years of age cohorts reported nearly identical improvements in perceived pain.
- Current smokers reported the smallest mean improvement in perceived pain at last follow-up in comparison to previous smokers and patients who never smoked.
- While alcohol use had minimal impact on perceived pain at last follow-up, patients who reported current alcohol use demonstrated the largest improvement in perceived pain at last follow-up.
- Similarly, while BMI had minimal impact on change in perceived pain, patients who were classified as overweight reported the largest improvement in perceived pain at last follow-up in comparison to those who were at a healthy weight or categorized as obese.

Based on these findings, the team does not recommend excluding eligible patients based on age, smoking status, alcohol use, or BMI.

b. Safety Conclusions

The risks of the device are based on non-clinical mechanical laboratory studies as well as data collected in a retrospective clinical study conducted to support HDE approval as described above.

In summary, non-clinical laboratory studies and clinical data support a favorable safety profile for the restor3d TTR device.

- The TTR device can withstand cyclic physiological loading of 4,500N out to 10,000,000 cycles.
- The device is biocompatible with no risks associated with residual particulates.
- No (0, 0%) surgical interventions were attributed to the subject device and only two patients (2/27, 7.41%) reported SSIs that were potentially attributed to the procedure, impacting less than 8% of the study population (2/27).
- No (0, 0%) AEs were attributed to the subject device.
- No (0, 0%) SAEs, SSIs or AEs were reported in patients where the soft tissue attachment sites were used, and the rate of patients with SSIs among the patients who had devices implanted with soft tissue attachment sites (1/8, 12.5%) was equivalent to the rate of patients with SSIs reported across the entire study population (4/27, 14.8%).
- More importantly, 26 (26/27, 96.3%) participants retained their devices, suggesting strong implant survivorship.
- No (0, 0%) patients reportedly received a BKA and all patients were successfully able to salvage their limbs.

c. Probable Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support HDE approval as described above. This retrospective, medical record review study enrolled patients from a diverse group of sites and surgeons. These real-world data contribute to the development of an accurate safety profile and understanding of the probable benefits of the TTR device. The heterogeneous data types presented reflect the outcomes the study team would expect to see across the varying clinical settings, rather than outcomes seen in a controlled environment. Given the retrospective nature of this study utilizing real-world data, data for all endpoints were not available for all probable benefit endpoints at all timepoints; however, this study enrolled a heterogenous population implanted by multiple surgeons at multiple sites, broadening the generalizability of the findings. As such, the risk of uncertainty is mitigated by the broad generalizability of these findings.

Additional factors to be considered in determining probable risks and benefits for the restor3d TTR Implant device include:

- It is important to note that all of the indications treated by a TTR Implant are irreversible, degenerating diseases and these disease states will not get better over time without surgical intervention. While alternative treatments exist (e.g., ankle fusion or amputation), treatment with a TTR Implant is the only treatment option that affords the patient the ability to salvage their limb and retain their mobility. While there were nine (9) SSIs across four (4) patients, and one (1) AE, 26 (26/27, 96.3%) participants retained their devices, suggesting strong implant survivorship. No patients progressed to below knee amputation, therefore proving the TTR Implant is a limb and joint device.
- The restor3d TTR Implant offers an innovative technology to address ankle deformity including avascular necrosis of the talus; avascular necrosis of the talus in addition to talar collapse, cysts or non-union; large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments; non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments. While there is another Humanitarian Use Device total talus replacement device approved (H200001), it is only indicated for talar avascular necrosis, leaving a subset of the population ineligible for the device. The restor3d team studied the use of the TTR Implant in additional patient populations and the data collected support clinical success in these populations. Additionally, the restor3d TTR Implant offers soft tissue reconstruction via soft tissue attachment sites that serve as bone anchors for sutures to reattach the ligaments during the total talus replacement. These soft tissue attachment features when utilized did not introduce additional risks.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the HDE for this device.

In conclusion, given the available information above, the data support that for avascular necrosis of the talus; avascular necrosis of the talus in addition to talar collapse, cysts or non-union; large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments; non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments the probable benefits outweigh the probable risks.

d. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. Across the enrolled participants, not only did the restor3d patient-specific TTR Implant provide a limb and joint sparing solution, but it also improved the quality of life for many patients through reduction of pain, maintenance of ROM and improved physical functioning. These positive impacts afford patients the ability to return to work, maintain a healthy lifestyle through physical activity, and engage with friends and family.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee because the information in this HDE did not raise any unanticipated safety concerns.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the restor3d Total Talus Replacement will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on November 17, 2023. The final clinical conditions of approval cited in the approval order are described below.

The Total Talus Replacement (TTR) PAS is a multicenter, single-arm, 5-year prospective study for patients who received the restor3d TTR device to evaluate the continued safety and probable benefit of the restor3d TTR device in commercial use in adults (≥22 years of age) for treatment of:

- Avascular necrosis of the talus
- Avascular necrosis of the talus in addition to talar collapse, cysts or non-union
- Large, uncontained, unstable, or cystic talar osteochondral defects with risk of collapse or talar osteochondral defects not responsive to traditional treatments
- Non-union following talar fracture or talar extrusion, unresponsive to more conservative treatments

It is planned for full enrollment of the subjects within 24 months, for a total of 50 subjects. This study will include a minimum of 5 U.S. centers, with a maximum of 20 patients at any one site that meets the selection criteria. The sample size should be

adequate to allow for inclusion of a diverse patient population with respect to age, sex, ethnicity, and race. Depending on the population enrolled for the study, oversampling may be necessary to ensure that the population enrolled is sufficiently representative of the US population. Once enrolled, subjects will be followed through 60 months from the time of each patient's index surgery, with interim visits at 3 months, 6 months, 12 months and annually thereafter.

The primary endpoint for this PAS is a composite of safety and probable benefit, which is the proportion of participants who pass safety and probable benefit outcomes at 5 years post-implantation. The safety endpoint is defined by the absence of a device-related serious adverse event (SAE) and a subsequent secondary surgical intervention (SSSI) on the affected joints. The probable benefit endpoint is defined by joint salvage with the restor3d implant in place.

Secondary safety endpoints include assessment of procedure-related SAEs, and device- or procedure-related adverse events (AEs). Secondary probable benefit endpoints include assessment of pain using the 11-point Pain Numeric Rating Scale (NRS), ankle Range of Motion (ROM), Foot and Ankle Outcome Scores (FAOS) Composite score, and FAOS Subscales (Pain subscale, Symptoms subscale, Sports/Recreation subscale, Quality of Life [QOL] subscale, and Activities of Daily Living [ADL] subscale).

Exploratory endpoints include x-ray assessments to evaluate the presence of AEs, tibiotalar alignment, talar tilt angle, Boehler's angle, talar declination angle and Meary's angle, patient preference questions (e.g., if the patient would choose to undergo this procedure again if given the option), and use of soft tissue attachment sites and any relationship to AEs or SAEs.

The data will be collected at various timepoints:

Collected at Baseline Only:

- Age
- Sex
- Race/Ethnicity
- CT Scan
- Indication for Use
- Surgical History
- Laterality of Index Ankle
- Implant Volume
- Use of Soft Tissue Attachment Site

Collected Annually Starting at 12 months:

- Preference Questions

Collected at All Timepoints (Baseline, 3 months, 6 months, 12 months and annually thereafter):

- BMI

- Smoking Status
- Working Status
- Ambulatory Status
- Comorbid Conditions
- 11-point Pain NRS
- FAOS Composite Score, and FAOS Subscales (Pain subscale, Symptoms subscale, Sports/Recreation subscale, QOL subscale, and ADL subscale)
- Ankle ROM
- Safety Events: AEs, SAEs, SSSIs
- X-Ray (including intraoperative scan)

Descriptive statistics will be presented for all analyses. For continuous variables, means, standard deviations, range, proportions, and 95% confidence intervals will be shown. For categorical variables, frequencies and percentages will be presented.

From the date of study protocol approval, the applicant must meet the following timelines for the Total Talus Replacement (TTR) PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, the applicant must submit separate periodic reports on the progress of the Total Talus Replacement (TTR) PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the HDE approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, the applicant must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies the applicant otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facility has been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), via the supporting documentation provided in H230003, and through a risk-based assessment.

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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