SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Total Talus Replacement

Device Trade Name: Patient Specific Talus Spacer

Device Procode: QNN

Applicant's Name and Address: Additive Orthopaedics, LLC
44 Riverdale Avenue
Monmouth Beach, NJ 07750

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H200001

Humanitarian Use Device (HUD) Designation Number: HUD # 2018-405

Date of HUD Designation: June 28, 2018

Date of Notice of Approval to Applicant: February 17, 2021

II. INDICATIONS FOR USE

The Patient Specific Talus Spacer is indicated for avascular necrosis of the ankle joint. The anatomical landmarks necessary for the design and creation of the Additive Orthopaedics Patient Specific Talus Spacer must be present and identifiable on computed tomography scan.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "avascular necrosis of the ankle joint". It was modified for the HDE approval because 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.

III. CONTRAINDICATIONS

The Patient Specific Talus Spacer should not be implanted in patients meeting any of the following conditions:

- Use of implant greater than 6 months from date of patient's computed tomography (CT) scan.
- Degenerative changes in the tibiotalar, subtalar or talonavicular joints.
- Presence of an active infection.
- 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.
- 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 post-operatively during the healing period.
- Presence of neurological deficit which would prevent patient post-operative compliance.
- Sensitivity or allergy to the metal implant. Where material sensitivity is suspected, appropriate tests should be made, and sensitivity ruled out prior to implantation.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Patient Specific Talus Spacer labeling.

V. DEVICE DESCRIPTION

The Patient Specific Talus Spacer is a solid, polished replica of the patient's bone to allow the patient to regain motion and reduce pain without an amputation or fusion until the time a fusion potentially becomes necessary. The device is available in cobalt-chromium (CoCr) metal alloy conforming to ASTM F75 and produced by laser sintering. The device is available in cobalt-chromium (CoCr) metal alloy conforming to ASTM F75 and produced by laser sintering. All surfaces of the device are hand polished to a mirror finish. The implant is then cleaned and passivated per ASTM A967 and will be sterilized by the end user via steam sterilization.

An exemplary device is shown in Figure 1. Creation of a patient-specific device is achieved via computed tomography (CT) scanning and CAD/CAM generation.

No specific instruments are provided with the subject device.

Figure 1: Example of the Patient Specific Talus Spacer (left) and rendering in a CAD model after implantation (right)

A. Description of the Patient-Specific Design Process

Surgeon-Facing Process:

1. A CT scan of the patient is obtained using Additive Orthopaedics' CT Scanning Protocol.
2. Within one month from the time the scan is obtained, the scan is sent to Additive Orthopaedics. Additive Orthopaedics then begins the patient-specific design process, which requires an online discussion with the patient's surgeon. The design is completed by Additive Orthopaedics.
3. After initial review and approval by the patient's surgeon, a final design package is supplied to the surgeon for final approval. A final design package includes, but is not limited to, the Order Form, Anatomy Models, Landmarks, and Implant Drawings.
4. Once the final design package is approved, the patient-specific implant is manufactured. Three implants are simultaneously built on the printing platform, one the expected size, one 10% larger, and one 10% smaller, which are shipped to the surgeon.

Company-Facing Process:

1. Additive Orthopaedics receives a CT scan of a patient and the scan is uploaded into the company's system.
2. The patient data is reviewed using cleared software, at which point:
   a. CT data is reviewed for accuracy and confirmation that the Additive Orthopaedics CT Scanning Protocol has been followed. The bone is either

reconstructed by mirroring the unaffected side or reconstructed with the current anatomy.

b. The source code implant file is opened in CAD and is modified according to the measurements of the mirrored side or the current side to create the final dimensions of the patient-specific implant.
c. A surgeon pre-planning meeting is conducted.
d. A drawing/technique guide is created that is specific to the unique number and patient, showing anatomy, anatomic landmarks, measurements, and modified implant.
e. The drawing/technique guide is shared with the surgeon with a request for approval.
f. A final manufacturing level drawing is created and reviewed and signed internally.
g. The implant moves to manufacturing.
h. The drawing/technique guide is shared again with the surgeon prior to the surgery date, with a request for an optional online meeting to review the final design and anatomy prior to the surgery date.

B. Additive Manufacturing Process

As noted above, the implant is 3D printed in CoCr using a laser sintering platform. Three implants are simultaneously built on the printing platform, one the expected size, one 10% larger, and one 10% smaller. The implant is simultaneously built with test coupons on the worst-case platform locations. The coupons are tested for each lot prior to implant release.

C. Device Operation and Principles of Operation

Using CAD/CAM techniques, a patient-specific talus implant that mimics the original bone geometry is manufactured. The implant replaces the necrosed bone and articulates against the surrounding bones. This restores the ankle joint to its original geometry while preserving joint motion. The surgeon first implants the nominal sized implant and checks for fit and motion. If the implant appears too large, it can be removed and replaced with the smaller size. If it appears too small, it can be removed and replaced with the larger implant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of avascular necrosis of the ankle joint include amputation or total joint fusion. The latter is extremely difficult on the patient because there is no way to restore the leg length due to the missing talus bone. Surgeons have to attempt to rebuild the patient's ankle with allograft which present risks such as a 50% non-union rate, that may result in amputation.[1]

VII. MARKETING HISTORY

The Patient Specific Talus Spacer 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
- 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

Mechanical and Biomechanical Testing

The clinical study was leveraged to address static compression and fatigue testing. There is a lack of adverse events of fracture or failure of the Patient Specific Talus Spacer in the clinical study. As the material properties of CoCr is expected to be mechanically stronger than the surrounding bones in the ankle joint and the device would be under constant compression, the expectation is failure of those bones would occur prior to device failure.

Biocompatibility Testing

The Patient Specific Talus Spacer components are additively manufactured from cobalt chromium ("CoCr") alloy conforming to ASTM F75. After the implants are manufactured and polished prior to cleaning. Devices are passivated per ASTM F86, which is known to remove any remaining contaminants. CoCr has a long history of use in medical implants with no significant biocompatibility safety issues.

Biocompatibility assessments have been conducted on the subject device in compliance with applicable requirements in the Good Laboratory Practice (GLP) regulations in 21 CFR 58, applicable ISO 10993 standard, *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*."

With regard to the Patient Specific Talus Spacer, an implanted device with permanent

duration contact (> 30 days) with tissue/bone, a complete biocompatibility risk assessment was conducted. All patient contact materials are considered biocompatible. The CoCr Patient Specific Talus Spacer conforms to ASTM F3213 requirements and passivated per ASTM F86.

Biocompatbilbility Requirement: Biocompatibility testing performed for permanent implant as per ISO 10993-1 **or** manufacturing justification e.g. presence of passivation as per ASTM F86.

Acceptance Criteria: Passivation performed as per ASTM F86 in the final step in the manufacturing process.

Provided in this submission: Passivation performed as per ASTM F86 on the final finished CoCr Patient Specific Talus Spacer followed by no other manufacturing process or materials included before packaging.

Result: Pass

Cleaning and Sterilization

The Patient Specific Talus Spacer is provided in its finished, final, and clean form, non-sterile packaged to the hospital. The hospital is required to steam sterilize the implant in accordance with the validated steam sterilization instructions as stated in the IFU. The sterilization process was validated to achieve a sterility assurance level ("SAL") of 10^{-6} using steam sterilization per ANSI/AAMI/ISO 17665-1:2006/® 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* per the overkill method.

X. SUMMARY OF CLINICAL INFORMATION

Thirty-one (n=31) patients (32 cases) were treated at a single center with Patient Specific Talus Spacer devices manufactured by Additive Orthopaedics. The purpose of the clinical evaluation was to demonstrate the safety and probable benefit of the Patient Specific Talus Spacer when used in the indicated population. The data collection was approved by the Institution's Review Board. The condition is so rare, hence the HUD, and in that sense many patients seek out surgeons who are experienced with this diagnosis. The single site and surgeon in this submission had previous extensive experience with the condition and had enough patients to conduct an appropriate clinical study for the subject device.

Safety Endpoints

The primary safety endpoint was the proportion of patients who underwent a secondary subsequent surgical intervention ("SSSI"). Other safety endpoints assessed included adverse events ("AEs"), device or procedure related AEs, AEs by severity, and serious AEs ("SAEs").

Probable Benefit Endpoints

The probable benefit endpoint was the reduction in baseline level pain following surgery using the Visual Analog Scale ("VAS") for pain. The secondary probable benefit endpoints assessed included ankle range of motion ("ROM") and Foot and Ankle Outcome Scores ("FAOS"). FAOS subscales, pain, symptom (stiffness, swelling, etc.), activities of daily living ("ADL"), ability to perform sports and recreational activities ("Sport/Rec"); and foot/ankle-related quality of life ("QoL") were also assessed.

Patient Demographics

A summary of the patient demographics is provided below in Table 1. Thirty-one (31) patients were treated for a total of 32 operations; 1 patient had a Patient Specific Talus Spacer implanted in both the left and right ankles.

Table 1: Patient Demographics

Age (n=31)	
Mean±SD	43 ± 15.3
Range	20-69
Gender (n=31)	
Male, n (%)	8 (25.8%)
Female, n (%)	23 (74.2%)
BMI (n=31)	
Mean±SD	31 ± 6.96
Range	20-48
Smoking Status (n=31)	
Current, n (%)	4 (12.9%)
Former, n (%)	3 (9.7%)
Never a smoker, n (%)	24 (77.4%)
Laterality (n=32)	
Left, n (%)	17 (54.8%)
Right, n (%)	13 (41.9%)
Both, n (%)	1 (3.2%)
Prior Surgeries (n=31)	
0, n (%)	15 (48.4%)
1, n (%)	9 (29.0%)
2, n (%)	5 (16.1%)
≥ 3, n (%)	2 (6.5%)

The table below shows the number of patients with last follow-up VAS pain data (primary endpoint) available at < 1 year, 1 year, 2 years or 3 years.

Table 2: Patient Accountability

Visit	Baseline	< 1 Yr	1 Yr	2 Yrs	3 Yrs
Last Follow–up	32	5	18	6	3

Safety Results

No device-related side effects or symptoms were observed for patients who underwent the Patient Specific Talus Spacer implantation procedure. The adverse events reported were related to reoperations and additional surgeries. Three (3) patients had additional surgeries performed at a later date after implantation of the device.

One patient underwent the Patient Specific Talus Spacer procedure in 2016. Six (6) months after their surgery, the patient required superficial irrigation and debridement at the wound site to promote healing of the infected tissue and contracture with tibial anterior release. Ultimately a below the knee amputation (BKA) was performed approximately 3 years post-index procedure to treat an underlying neurological condition.

Another patient underwent surgical treatment of superficial peroneal neuroma ("SPN") after implantation of the device. Although neruomas are generally uncommon, they may occur after direct trauma or operation. The most common symptom of SPN is pain, specifically neuralgia.[2] Here, the SPN was excised.

The final patient experienced progression of talus AVN to tibial AVN, after implantation of the Patient Specific Talus Spacer. This patient presented pre-operatively with cancer with widespread AVN in lower right extremity. The patient ultimately underwent revision surgery with a total ankle replacement ("TAR"). Chronic pain, including prior to the Patient Specific Talus Spacer procedure, was a long-term problem for this patient.

Probable Benefit Results

VAS pain scores were assessed prior to treatment and at the most recent follow-up time point, as shown in Figure 2. The total study population, as as each cohort, experienced mean improvement on VAS pain; across cohorts the magnitude of the improvement was positively correlated with the duration of follow up.

At baseline, the mean VAS score for the study population was 6.9 cm ± 2.0 and scores ranged from 3 – 10 cm, with 10 representing maximum pain intensity. Mean change from baseline for the entire study population was -2.8 cm ± 3.1. For the cohort analysis, mean improvement from for the <1 year, 1 year, 2 years, and 3 years cohorts was -1.2 cm ± 2.7, -2.2 cm ± 2.8, -3.7 cm ± 2.3, and -7.7 cm ± 3.2. Thus, improvement on VAS pain was consistent across duration of follow up. As anticipated, due to the lengthy recovery period associated with this patient population, average VAS pain outcomes continued to improve the longer the follow-up period.

Figure 2: VAS Pain (cm) – Mean Baseline and Last Follow-Up by Duration of Follow-Up

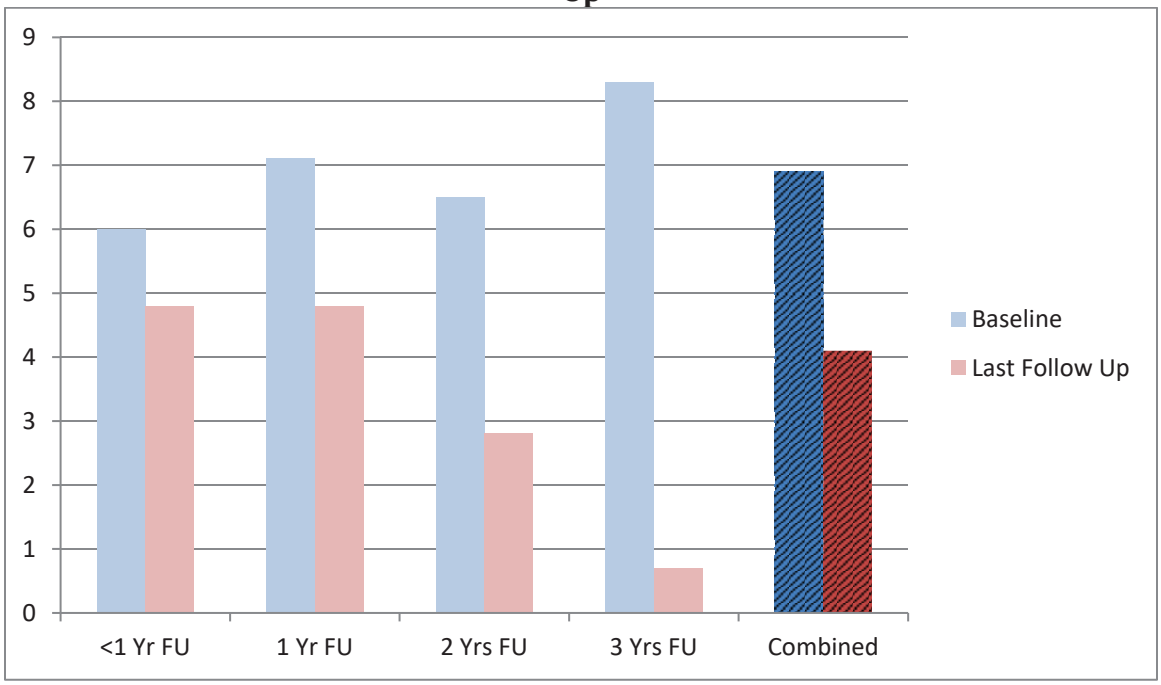


Table 3: VAS Pain (cm) Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Cohort	Assessment	Mean	SD	Median	Range	95% CI
	Baseline (n=5)	6.0	1.6	6.0	4 – 8	4.6, 7.4
< 1 Year	Last Follow Up (n=5)	4.8	1.5	5.0	3 – 7	3.5, 6.1
	Change from Baseline (n=5)	-1.2	2.7	-1.0	-4 - 3	-3.6, 1.2
	Baseline (n=18)	7.1	2.0	7.5	3 – 10	6.2, 8.0
1 Year	Last Follow Up (n=18)	4.8	2.9	5.5	0 - 8	3.5, 6.2
	Change from Baseline(n=18)	-2.2	2.8	-2.0	-7 - 5	-3.5, -0.9
2 Year	Baseline (n=6)	6.5	2.1	6.5	4 – 10	4.8, 8.2

Cohort	Assessment	Mean	SD	Median	Range	95% CI
	Last Follow Up (n=6)	2.8	1.6	3.0	1 - 5	1.6, 4.1
	Change from Baseline (n=6)	-3.7	2.3	-3.0	-7 - (-1)	-5.5, -1.8
	Baseline (n=3)	8.3	2.9	10.0	5 – 10	5.1, 11.6
3 Year	Last Follow Up (n=3)	0.7	0.6	1.0	0 - 1	0.0, 1.3
	Change from Baseline(n=3)	-7.7	3.2	-9.0	-10 - (-4)	-11.3, -4.0
	Baseline (n=32)	6.9	2.0	7.0	3 - 10	6.2, 7.6
Combined	Last Follow Up (n=32)	4.1	2.7	4.0	0 - 8	3.1, 5.0
	Change from Baseline (n=32)	-2.8	3.1	-3.0	-10 - 5	-3.9, -1.8

Clinical parameters were identified as a potentially confounding factor in device performance as detailed below. The worst-case scenario for each parameter was identified and used in the worst-case scenario assessment for each reported outcome:

- Age (Youngest; Oldest)
- BMI (Low; High)
- Device volume (Smallest; Largest)
- Follow-up Time (Shortest; Longest)
- Active Smoker
- Highest Baseline Pain (VAS)
- Smallest Baseline Ankle ROM
- Lowest Baseline Combined Average FAOS.

The average VAS score, average change from baseline, and average follow-up time for these worst case patients are described in Table 4. All worst-case categories showed post-operative improvement from baseline for VAS pain. Notably, of all 32 operations, only 3 cases reported deterioration in VAS pain, and 1 of those cases worsened by only 1 point compared to baseline. One patient, who showed worsening in VAS pain (+5), reported posterior tibial tendon pain. This tendon pain is not attributed to the device and explains the notable increase in VAS pain score. Additionally, the remaining patient who reported deterioration in VAS pain (+3) also reported ankle and subtalar arthritis, which may have contributed to their pain scores. Ultimately, almost all patients experience improvement in VAS pain demonstrating the probable benefit of the Patient Specific Talus Spacer.

Table 4: Worst Case Patients – VAS Pain

Characteristic	Mean at follow-up	Mean Change from baseline	Mean Follow-up (Yrs)
Age (Low)	5	-1	0.9
Age (High)	0	-10	3.6
BMI (Low)	2.5	-4	1.6
BMI (High)	0	-10	3.6
Device Volume (Low)	4	-3	1.9
Device Volume (High)	5	-3	0.8

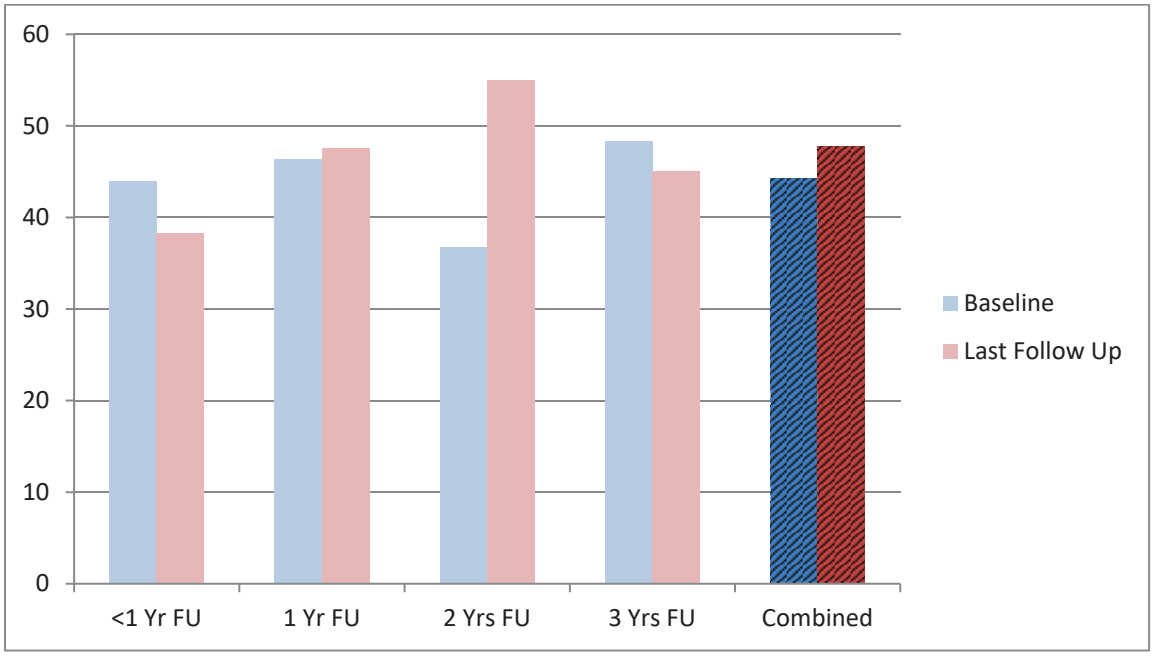
Characteristic	Mean at follow-up	Mean Change from baseline	Mean Follow-up (Yrs)
Active Smoker	5.3	-2	1.5
Follow-up Time (Low)	3	-4	0.02
Follow-up Time (High)	0	-10	3.6
Baseline VAS (High)	3	-7	2.8
Baseline Ankle ROM (Low)	4.7	-1	2.3
Baseline FAOS (Low)	8	-1	1.3

Secondary Probable Benefit Endpoints Analysis

Ankle ROM values were assessed for each patient, and reported based on the last follow-up data (Figure 3). The data summary presents outcomes for the entire study population, as well as by cohort based on duration of follow-up period (i.e., < 1 years, 1 year, 2 years, and 3 years).

As anticipated, patients still in active recovery from the device procedure (i.e., < 1 year of follow up) reported deterioration from baseline; the other cohorts either reported mean improvement or no change. When patients with < 1 year of follow-up are excluded from the study population the mean improvement for the remaining subjects is 5.9 degrees. Patients with 2-year follow-up data showed the greatest mean improvement in ankle ROM compared to baseline (25 degrees).

Figure 3: Ankle ROM – Mean Baseline and Last Follow-Up by Duration of Follow-Up



*In the 3 Yr Cohort, while mean ROM at last follow up is lower than baseline, the mean change from baseline to last follow up still showed imprmovement.

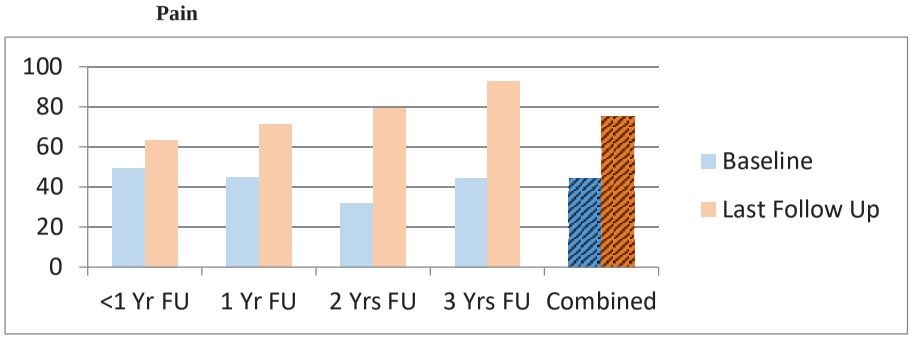
Table 5: Ankle ROM Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

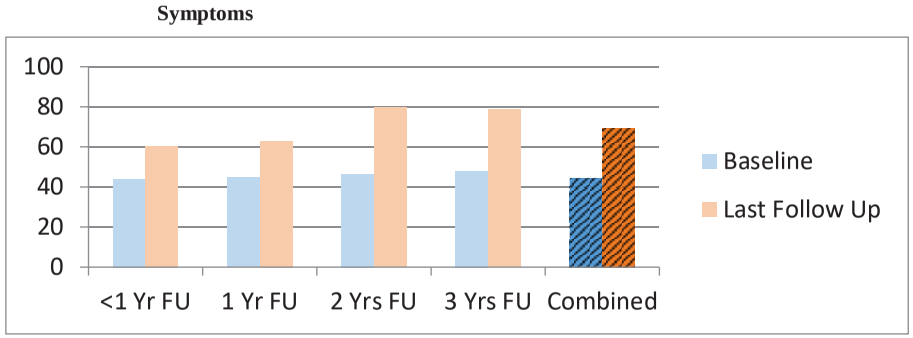
Cohort	Assessment	Mean	SD	Median	Range	95% CI
< 1 Year (n=3)	Baseline (n=5)	44.0	8.9	45.0	30-55	36.2, 51,8
	Last Follow Up (n=3)	38.3	24.7	50.0	10-55	10.4, 66.2
	Change from Baseline (n=3)	-10.0	22.9	-5.0	-35-19	-35.9, 15.9
1 Year (n=17)	Baseline (n=18)	46.3	18.5	49.0	0-70	37.7, 54.8
	Last Follow Up (n=17)	47.6	14.2	50.0	20-70	40.9, 54.4
	Change from Baseline (n=17)	1.0	24.2	0.0	-40-70	-10.5, 12.5
2 Year (n=5)	Baseline (n=6)	36.7	29.4	50.0	0-70	13.1, 60.2
	Last Follow Up (n=5)	55.0	20.6	60.0	20-70	36.9, 73.1
	Change from Baseline (n=5)	25.0	17.3	20	10-55	9.8, 40.2
3 Year (n=2)	Baseline (n=3)	48.3	5.8	45.0	45-55	41.8, 54.9
	Last Follow Up (n=2)	45.0	14.1	45.0	35-55	25.4, 64.6
	Change from Baseline (n=2)	0.0	14.1	0.0	-10-10	-19.6, 19.6
Combined	Baseline (n=32)	44.3	18.9	46.5	0-70	37.8, 50.8
	Last Follow Up (n=27)	47.8	16.3	50.0	10-70	41.6, 53.9
	Change from Baseline (n=27)	4.1	23.8	8.0	-40-70	-4.8, 13.1

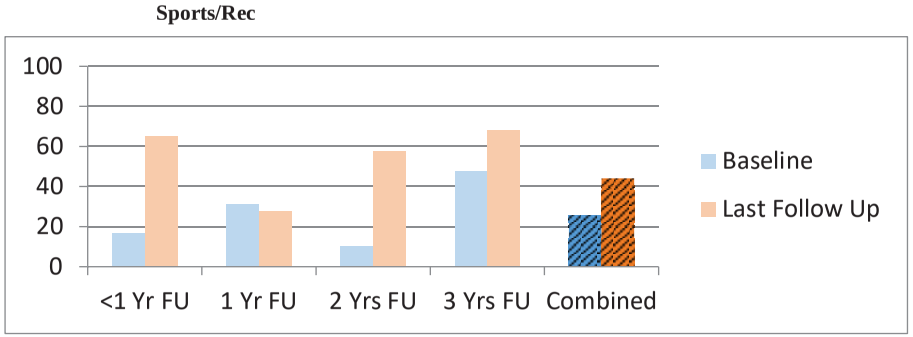
Average combined FAOS score, as well as each separate subscale (Pain, Symptoms, Sport/Rec, ADL, and QoL), were assessed pre-operatively and post-operatively. The mean change for FAOS average combined score and each subscale are reported with the last follow-up data combined (Figure 4). The data summary presents outcomes for the entire

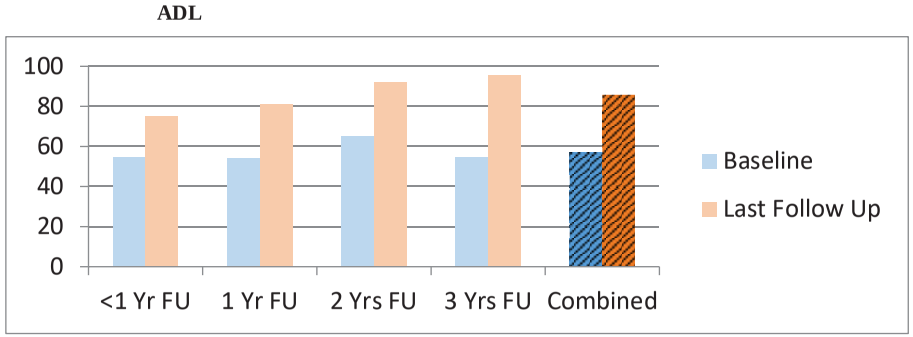
study population. As seen in Figure 4 below, patients showed an increase for each subscale at the last follow-up.

Figure 4: Mean FAOS Subscales Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up


Pain
100
80
60
40
20
0
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up


Symptoms
100
80
60
40
20
0
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up


Sports/Rec
100
80
60
40
20
0
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up


ADL
100
80
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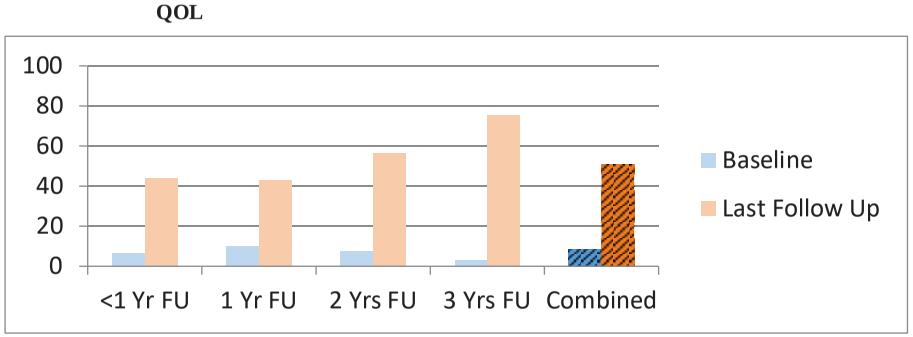
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up


QOL
100
80
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20
0
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up

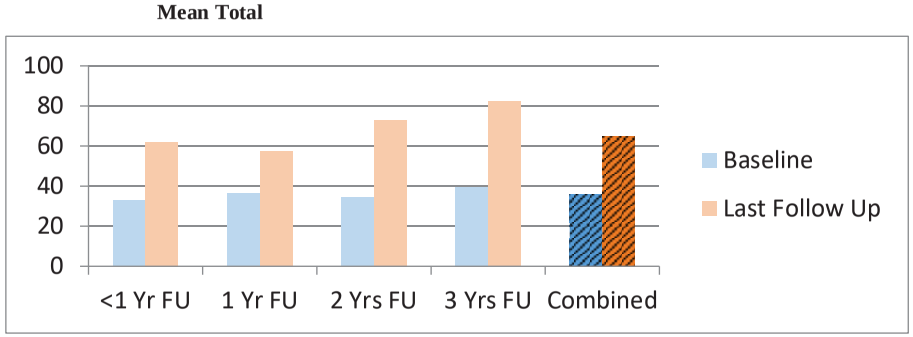
Mean Total
100
80
60
40
20
0
<1 Yr FU
1 Yr FU
2 Yrs FU
3 Yrs FU
Combined
Baseline
Last Follow Up

Table 6: Mean FAOS Subscales Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

	Assessment	Mean	SD	Median	Range	95% CI
FAOS PAIN						
< 1 Year	Baseline (n=3)	49.3	7.0	50.0	42 – 56	41.4, 57.3
	Last Follow Up (n=2)	63.4	27.6	63.5	44-83	25.3, 101.7
	Change from Baseline (n=1)	27.0	N/A	N/A	N/A	N/A
1 Year	Baseline (n=13)	44.8	25.1	44.0	6 - 86	31.1, 58.4
	Last Follow Up (n=12)	71.3	18.9	72.0	44-100	60.5, 82.0
	Change from Baseline (n=7)	20.9	27.3	22.0	-30-47	0.6, 41.1
2 Year	Baseline (n=6)	41.7	8.5	42.0	33-56	34.9, 48.5
	Last Follow Up (n=6)	79.2	11.4	77.5	67-92	70.1, 88.3
	Change from Baseline (n=6)	37.5	10.9	36.5	25-50	28.8, 46.2
3 Year	Baseline (n=2)	44.5	16.3	44.5	33 – 56	22.0, 67.0
	Last Follow Up (n=3)	92.7	10.2	97.0	81-100	81.1, 104.2
	Change from Baseline (n=2)	46.0	2.8	46.0	44-48	42.1, 49.9
Combined	Baseline (n=24)	44.5	19.1	43.0	6-86	36.9, 52.2
	Last Follow Up (n=23)	75.4	17.9	75.0	44-100	68.1, 82.7
	Change from Baseline (n=16)	30.6	20.9	36.5	-30-50	20.4, 40.8
FAOS SYMPTOM						
< 1 Year	Baseline (n=3)	44.0	20.7	50.0	21 – 61	20.6, 67.4
	Mean Score (n=2)	60.5	30.4	60.5	39-82	18.4, 102.6
	Mean Change from Baseline (n=1)	21.0	N/A	N/A	N/A	N/A
1 Year	Baseline (n=13)	44.8	14.4	39.0	14 – 61	35.3, 51.0
	Mean Score (n=12)	63.0	24.0	62.5	29-96	49.4, 76.6
	Mean Change from Baseline (n=7)	13.3	18.6	17.0	-22-32	-0.5, 27.1
2 Year	Baseline (n=6)	46.5	22.6	50.0	18 – 75	28.4, 64.6
	Mean Score (n=6)	79.7	14.5	84.0	57-96	68.1, 91.3
	Mean Change from Baseline (n=6)	33.2	20.4	30.0	7-61	16.9, 49.5
3 Year	Baseline (n=2)	48.0	12.7	48.0	39 – 57	30.4, 65.6
	Mean Score (n=3)	78.7	7.5	79.0	71-86	70.2, 87.2

	Assessment	Mean	SD	Median	Range	95% CI
	Mean Change from Baseline (n=2)	30.5	2.1	30.5	29-32	27.6, 33.4
Combined	Baseline (n=24)	44.5	16.3	44.5	14-75	38.0, 51.0
	Mean Score (n=23)	69.2	21.3	71.0	29-96	60.5, 77.9
	Mean Change from Baseline (n=16)	23.4	19.2	23.0	-22-61	13.9, 32.8
FAOS SPORT/REC						
< 1 Year	Baseline (n=3)	16.7	20.8	10.0	0 – 40	-6.9, 40.2
	Last Follow Up (n=2)	65.0	35.4	65.0	40-90	16.0, 114.0
	Change from Baseline (n=1)	80.0	N/A	N/A	N/A	N/A
1 Year	Baseline (n=14)	31.1	36.6	20.0	0 – 100	11.9, 50.2
	Last Follow Up (n=12)	27.8	27.7	22.5	0-90	12.1, 43.5
	Change from Baseline (n=8)	-5.1	35.7	7.0	-75-30	-29.9, 19.6
2 Year	Baseline (n=6)	10.0	9.5	10.0	0 – 25	2.4, 17.6
	Last Follow Up (n=6)	57.5	24.0	55.0	20-90	38.3, 76.7
	Change from Baseline (n=6)	47.5	19.4	47.5	20-80	32.0, 63.0
3 Year	Baseline (n=2)	47.5	3.5	47.5	45 – 50	42.6, 52.4
	Last Follow Up (n=3)	68.3	5.8	65.0	65-75	61.8, 74.9
	Change from Baseline (n=2)	17.5	3.5	17.5	15-20	12.6, 22.4
Combined	Baseline (n=25)	25.6	30.1	15.0	0-100	13.8, 37.4
	Last Follow Up (n=23)	44.1	29.8	45.0	0-90	31.9, 56.3
	Change from Baseline (n=17)	21.1	38.7	20.0	-75-80	2.7, 39.5
FAOS ADL						
< 1 Year	Baseline (n=2)	54.5	20.5	54.5	40 – 69	26.1, 82.9
	Last Follow Up (n=1)	75.0	N/A	N/A	N/A	N/A
	Change from Baseline (n=0)	N/A	N/A	N/A	N/A	N/A
1 Year	Baseline (n=14)	54.1	23.5	52.5	12 – 90	41.8, 66.5
	Last Follow Up (n=12)	81.2	13.1	83.0	57-100	73.7, 88.6
	Change from Baseline (n=8)	27.9	18.9	28.5	-2-60	14.8, 41.0
2 Year	Baseline (n=6)	65.3	19.9	57.0	49 – 100	49.4, 81.2
	Last Follow Up (n=6)	92.0	10.6	98.0	76-100	83.5, 100.5

	Assessment	Mean	SD	Median	Range	95% CI
	Change from Baseline (n=6)	26.7	17.8	25.5	-1-48	12.4, 40.9
3 Year	Baseline (n=2)	54.5	6.4	54.5	50 – 59	45.7, 63.3
	Last Follow Up (n=3)	95.7	1.5	96.0	94-97	93.9, 97.4
	Mean Change from Baseline (n=2)	42.0	7.1	42.0	37-47	32.2, 51.8
Combined	Baseline (n=24)	57.0	21.0	56.6	12-100	48.6, 65.4
	Last Follow Up (n=22)	85.8	12.7	87.5	57-100	80.5, 91.1
	Change from Baseline (n=16)	29.2	17.3	29.5	-2-60	20.7, 37.7
FAOS QoL						
< 1 Year	Baseline (n=3)	6.7	11.0	13.0	-6 – 13	-5.7, 19.1
	Last Follow Up (n=2)	44.0	26.9	44.0	25-63	6.8, 81.2
	Change from Baseline (n=1)	50.0	N/A	N/A	N/A	N/A
1 Year	Baseline (n=14)	9.9	16.3	0	0 – 50	1.3, 18.4
	Last Follow Up (n=12)	42.9	25.3	44.0	0-88	28.6, 57.2
	Change from Baseline (n=9)	32.9	27.2	25.0	-7-88	15.1, 50.6
2 Year	Baseline (n=6)	7.3	7.5	6.0	0 – 19	1.4, 13.3
	Last Follow Up (n=6)	56.3	22.1	56.0	31-94	38.7, 74.0
	Change from Baseline (n=6)	49.0	26.7	50.0	19-94	27.7, 70.3
3 Year	Baseline (n=2)	3.0	4.2	3.0	0 – 6	-2.9, 8.9
	Last Follow Up (n=3)	75.3	27.3	88.0	44-94	44.4, 106.2
	Change from Baseline (n=2)	63.0	26.9	63.0	44-82	25.8, 100.2
Combined	Baseline (n=25)	8.3	13.1	6.0	-6-50	3.2, 13.4
	Last Follow Up (n=23)	50.7	25.7	50.0	0-94	40.2, 61.2
	Mean Change from Baseline (n=18)	42.6	26.7	41.0	7-94	30.2, 54.9
FAOS COMBINED AVERAGE						
< 1 Year	Baseline (n=3)	32.9	7.3	35.0	24.8 – 39.0	24.6, 41.2
	Last Follow Up (n=2)	62.1	24.7	62.1	44.6-79.5	27.8, 96.3
	Change from Baseline (n=1)	44.5	N/A	N/A	N/A	N/A
1 Year	Baseline (n=14)	36.2	14.4	35.1	11.8 – 60.2	28.7, 43.7
	Last Follow Up (n=12)	57.2	19.4	53.9	28.4-94.2	46.2, 68.2

	Assessment	Mean	SD	Median	Range	95% CI
	Change from Baseline (n=9)	24.5	26.5	18.4	0-88	7.2, 41.9
2 Year	Baseline (n=6)	34.2	8.3	32.4	23.2 – 48.0	27.5, 40.8
	Last Follow Up (n=6)	72.9	11.2	75.6	59.0-83.8	64.0, 81.9
	Change from Baseline (n=6)	38.8	14.2	38.2	22.0-60.6	27.4, 50.2
3 Year	Baseline (n=2)	39.5	7.2	39.5	34.4 – 44.6	29.5, 49.5
	Last Follow Up (n=3)	82.1	9.1	87.0	71.6-87.8	71.8, 92.5
	Change from Baseline (n=2)	39.8	3.7	39.8	37.2-42.4	34.7, 44.9
Combined	Baseline (n=25)	35.6	11.7	34.6	11.8-60.2	31.0, 40.2
	Last Follow Up (n=23)	65.0	18.5	67.2	28.4-94.2	57.4, 72.6
	Mean Change from Baseline (n=18)	32.1	21.3	31.2	0-88	22.2, 41.9

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.s

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. The pivotal clinical study included one (1) investigator, who served as a consultant for the sponsor and had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). The investigator received compensation for conducting the study where the value could be influenced by the outcome of the study.

The applicant has adequately disclosed the financial interest/arrangements with the clinical investigator as well as the steps taken to minimize any potential bias of the clinical study results. The information provided does not raise any questions about the reliability of the data.The clinical study was performed under the supervision and following the ethics rules set forth by the Institutional Review Board. In addition, the clinical study endpoints included both objective and patient-assessed outcomes.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

For patients with AVN of the talus who have experienced collapse, the incongruity between the ankle and subtalar joint will lead to pain, stiffness, and disability. In the short-term, these patients lose the ability to walk unassisted, and in the long-term they often completely lose the ability walk and endure high levels of pain. Once collapse

occurs, treatment options are also limited, typically including only bracing for temporary relief, tibio-talar-calcaneal fusion, or amputation if fusion cannot be achieved. Joint fusion may provide some pain relief to patients, but many patients also experience loss of ankle and hindfoot motion and continued difficulties in walking and stress at the surrounding joints. Reported non-union rates for this type of fusion are as high as 50%.[3] Additionally, fusion often leads to significant leg length discrepancies, with the average leg length discrepancy postoperatively reported as 1.4 cm.[4] Finally, amputation has been reported to provide acceptable functional outcomes with short rehabilitation times, but many patients find this treatment option unacceptable and seek a treatment option that can replace the talus bone and delay the need for fusion or amputation.

A. Probable Benefit Conclusions

The primary probable benefit endpoint of the clinical study was the reduction in baseline level pain following surgery using the Visual Analog Scale ("VAS") for pain. The secondary probable benefit endpoints assessed included ankle range of motion ("ROM") and Foot and Ankle Outcome Scores ("FAOS"). FAOS subscales, pain, symptom (stiffness, swelling, etc.), activities of daily living ("ADL"), ability to perform sports and recreational activities ("Sport/Rec"): and foot/ankle-related quality of life ("QoL").

Use of the Patient Specific Talus Spacer is supported by clinical data from 32 cases in 31 US patients. The study population reported clinically meaningful improvement for the primary outcome, VAS pain, reducing from 6.9 cm (moderate to severe pain) at baseline to 4.1 cm post-operatively, reflecting mild pain (mean change -2.8 cm). As anticipated, due to the lengthy recovery period associated with this patient population, average VAS pain outcomes continued to improve the longer the follow-up period with the most pronounced improvement among patients with 3 years of follow-up data (mean change – 7.7 cm). Mean ROM at baseline was 44.3 degrees, and among patients with post-operative ROM data the mean value was 47.8 degrees (mean change 2.4 degrees). The mean post-operative ROM for the study population was influenced by patients with <1 year of follow-up (i.e., the beginning stage of surgical recovery) who reported a mean change in ROM from baseline of – 10 degrees. Patients with 2 years of follow up reported the most significant magnitude of change with mean improvement of 25 degrees from baseline. For FAOS, the overall study population improved at last follow up compared to baseline in the average combined FAOS assessment as well in each subscale, with a mean change of 32.1 points (average combined), 30.6 points (Pain), 23.4 points (Symptom), 21.1 points (Sports/Rec), 29.2 points (ADL), and 42.6 points (QoL). The improvement observed on all subscales except Sports/Rec met the Minimally Important Change (MIC) threshold identified by Sierevelt et al.[5] Of note, the improvement observed on Symptom was 3 times greater than the MIC threshold, Pain was 2 times greater than the MIC, and QoL was nearly 2 times greater than the MIC. Results were similar in the cohort analysis, with each cohort reporting improvement on each assessment.

A worst-case analysis was performed for each endpoint to assess the patients most likely to achieve poor results. Across the three efficacy endpoints (VAS pain, ankle ROM, and

FAOS score), no discernable pattern was observed. Moreover, most worst-case categories showed post-operative improvement compared to baseline.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support HDE approval as described above. Few safety events were observed during the study follow-up period. These included 2 pain events related to the treatment and 1 scar tissue formation event related to the treatment. In addition, there were 3 reoperations reported in 32 cases (9.4%). Two (2) of the reoperations were unrelated to the Patient Specific Talus Spacer. One (1) reoperation was possibly related to the surgical procedure and was associated with the scar tissue event. The 3 related adverse events and 3 reoperations occurred in 5 patients (15.6%). Both the proportion of patients experiencing a reoperation or related adverse event (15.6%) are very favorable, especially given the severity of the condition and limited treatment options available.

The most significant risk associated with the Patient Specific Talus Spacer is reoperation. One patient required superficial irrigation and debridement as well as tibial anterior contracture release approximately 6 months post index procedure. The infection was associated with a prior surgery for a vascularized pedicle graft. Ultimately, a below the knee amputation (BKA) was performed approximately 3 years post-index procedure to treat an underlying neurological condition. A second patient reported nerve pain where the index incision was located approximately 1 year and 9 months post index procedure and a procedure to release the nerve was performed approximately 2 years and 8 months post index procedure. The patient had resolution of symptoms after this reoperation and returned to work as a fireman. A third patient presented with cancer with widespread AVN in lower right extremity. The patient was implanted with the Patient Specific Talus Spacer and then underwent a revision surgery with a TAR. Chronic pain, including prior to the Patient Specific Talus Spacer procedure, was a long-term problem for this patient. Thus, 2 of the reoperations are likely unrelated to the Patient Specific Talus Spacer or the associated procedure and are most likely due to pre-existing comorbidities. One case is possibly procedure related, but is not related to the Patient Specific Talus Spacer. Overall, a reoperation rate of 9.4% is favorable given the severity of the condition and compared to fusion procedures, which require reoperation in instances of non-fusion as well as for other complications (e.g., ineffective results, infection, negative tissue reaction, etc.).

C. Probable Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in the clinical study conducted to support HDE approval as described above. The patients who were implanted with the Patient Specific Talus Spacer received a clinically meaningful probable benefit from the device. As discussed above, baseline VAS pain score were reduced by -2.8 cm postoperatively, from 6.9 cm (moderate to severe pain) to 4.1 cm (mild pain). ROM also improved on average, especially when limiting the analysis to

those patients who had at least 1 year of follow-up and thus had adequate time to rehabilitate. Functional outcomes based on FAOS subscales also improved, with average improvement on all subscales exceeding the associated MIC threshold except Sport/Rec.

The probable risks of the device are also based on data collected in the clinical study conducted to support HDE approval as described above. Few safety events were observed during the study follow-up period, including 2 pain events related to treatment and 1 scar tissue formation event related to treatment. In addition, there were 3 reoperations reported in 32 cases (9.4%). Two (2) of the reoperations were unrelated to the Patient Specific Talus Spacer. One (1) reoperation was possibly related to the surgical procedure and is associated with the scar tissue event. The 3 related adverse events and 3 reoperations occurred in 5 patients (15.6%). Both the proportion of subjects experiencing a reoperation (9.4%) and the proportion of patients experiencing a reoperation or related adverse event (15.6%) are favorable, especially given the severity of the condition and limited treatment options available.

In the clinical study of the Patient Specific Talus Spacer, all patients had trouble walking and the mean VAS pain score at baseline was 6.9 cm, indicating the study population ranged from moderate to severe pain. In addition, 50% of patients had undergone a prior surgery on the index ankle. Data from 32 cases where the Patient Specific Talus Spacer was used to treat AVN supports the probable benefits and safety of the device. This was the only treatment option available to these patients as an alternative to ankle fusion or amputation. Although there are limited long-term data available for the Patient Specific Talus Spacer, the shorter time points are able to demonstrate probable benefits consistent with the long-term data that is available. Improvement in pain and function measures, accompanied by a low rate of reoperation, is particularly meaningful to AVN talus patients who have limited options and high risk of needing to undergo fusion or amputation. The favorable probable benefit to risk profile of the device is further demonstrated by the activity levels reported for some patients post-operatively, which includes returning or continuing in their career, engaging in recreational activities, and returning to walking.

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 ankle joint, 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 the Patient Specific Talus Spacer when used in accordance with the indications for use. The patients who were implanted with the Patient Specific Talus Spacer received a clinically meaningful probable benefit from the device. Moreover, the rate of reoperation was low, with 9.4% of cases resulting in reoperation. Improvement in pain and function measures, accompanied by a low rate of reoperation, is particularly meaningful to AVN talus patients who have limited options and high risk of needing to undergo fusion or amputation.

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 Patient Specific Talus Spacer will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the Patient Specific Talus Spacer outweighs the risks of illness or injury. CDRH issued an approval order on February 17, 2021.The final clinical conditions of approval cited in the approval order are described below.

Based on the protocol summary received on February 2, 2021, the Patient Specific Talus Spacer Registry Post-Approval Study (PAS) is a prospective post-approval US registry study to provide ongoing safety and probable benefit assessment of the Patient Specific Talus Spacer in treatment of avascular necrosis of the ankle. It is planned for full enrollment of the subjects within 24 months, for a total of 50 subjects. Once enrolled, the subjects will be followed through 60-months from the time of each patient's index surgery, with interim visits at immediate post-operative up to 6-months, 12-months and annually thereafter.

The primary safety endpoint is proportion of patients who undergo a secondary subsequent surgical intervention (SSSI). Secondary safety endpoints include assessment of adverse events (AEs), device- or procedure related AEs, and serious AEs.

The primary probable benefit endpoint is improvement in VAS pain at 5 years compared to baseline. Additional analyses will be performed to observe improvement at 5-years post-procedure compared to baseline on ankle range of motion (ROM) and foot and ankle outcome scores (FAOS – includes Pain, Symptom, Sport/Rec, Activities of Daily Living [ADL], and Quality of Life [QoL]).

The data will be collected at various timepoints:

Collected at Baseline Only

- Age
- Gender
- Body Mass Index
- Smoking Status
- Laterality of Index Ankle
- Prior Index Ankle Surgeries
- American Society of Anesthesiologists Class
- Implant Volume
- Implant Material

Collected at All Timepoints

- VAS Pain
- FAOS
- Ankle ROM
- SSSI
- Adverse Events

Collected at Pre-Op, 6 months, 12 months, and annually thereafter

- X-ray of index ankle

Descriptive statistics will be presented for all analyses. For continuous variables, means and standard deviations will be shown. For categorical variables, frequencies and percentages will be presented.

From the time of study protocol approval, the applicant must meet the following timelines for:

- 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
- Submission of Final study report: 3 months from study completion (i.e. last subject, last follow-up date)

The applicant's manufacturing facilities have been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), via the supporting documentation provided in H200001, 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

1. Jeng CL, Campbell JT, Tang EY, Cerrato RA & Myerson MS, *Tibitalocalcaneal Arthrodesis with Bulk Femoral Head Allograft for Salvage of Large Defects in the Ankle*. Foot Ankle Int. 2013 Sep; 34(9): 1256-66. Doi. 10.1177/1071100713488765.

2. Kang J et al., *Traumatic neuroma of the superficial peroneal nerve in a patient: a case report and review of the literature*, World Journal of Surgical Oncology (2016) 14:242 (https://wjso.biomedcentral.com/track/pdf/10:1186/s12957-016-0990-6).

3. Jeng CL et al. *Tibiotalocalcaneal arthrodesis with bulk femoral head allograft for salvage of large defects in the ankle.* Foot Ankle Int. 2013 Sep;34(9):1256-66. doi: 10.1177/1071100713488765. Epub 2013 May 6. PMID: 23650649.

4. Chou LB et al., *Tibiotalocalcaneal arthrodesis*. Foot Ankle Int. 2000 Oct;21(10):804-8. doi: 10.1177/107110070002101002. PMID: 11128009.

5. Sierevelt et al., *Evaluation of the Dutch version of the Foot and Ankle Outcome Score (FAOS): Responsiveness and Minimally Important Change*, Knee Surg Sports Traumatol Arthrosc (2016) 24:1339-1347.