SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Total Ankle Replacement

Device Trade Name: Hintermann Series H3™ Total Ankle Replacement System

Device Procode: NTG

Applicant's Name and Address: DT MedTech, LLC
110 West Road
Towson, MD 21204

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160036

Date of FDA Notice of Approval: June 4, 2019

II. INDICATIONS FOR USE

The Hintermann Series H3™ Total Ankle Replacement System is indicated for use as a non-cemented implant to replace a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease.

The device system is for prescription use.

III. CONTRAINDICATIONS

The Hintermann Series H3™ Total Ankle Replacement prosthesis should not be implanted in patients with the following conditions:

- Skeletal immaturity
- Bone stock inadequate to support the device including:
  - Severe osteoporotic or osteopenic condition or other conditions resulting in poor bone quality
  - Avascular necrosis of the talus
- Active or prior deep infection in the ankle joint or adjacent bones
- Malalignment or severe deformity of involved or adjacent anatomic structures including:
  - Hindfoot or forefoot malalignment precluding plantigrade foot
  - Significant malalignment of the knee joint
  - Insufficient ligament support that cannot be repaired with soft tissue stabilization

- Charcot joint or peripheral neuropathy that may lead to Charcot joint of the affected ankle.
- Neuromuscular disease resulting in lack of normal muscle function about the affected ankle
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Poor skin and soft tissue quality about the surgical site
- Immunosuppressive therapy
- Prior ankle fusion or revision of total ankle replacement
- High demand sport activities (e.g. contact sports, jumping)
- Suspected or documented metal allergy or intolerance

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Hintermann Series H3™ Total Ankle Replacement System labeling.

V. DEVICE DESCRIPTION

General Device Description

The Hintermann Series H3™ Total Ankle Replacement System, also referred to as the H3, (Figure 1) are intended to replace the ankle joint in primary surgeries. The Hintermann Total Ankle is a three-component configuration that permits four degrees of freedom, providing an unconstrained tibial articulating surface and an semi-constrained talar articulating surface for anteroposterior translation, mediolateral translation, tibial rotation and dorsi/plantar flexion movement.

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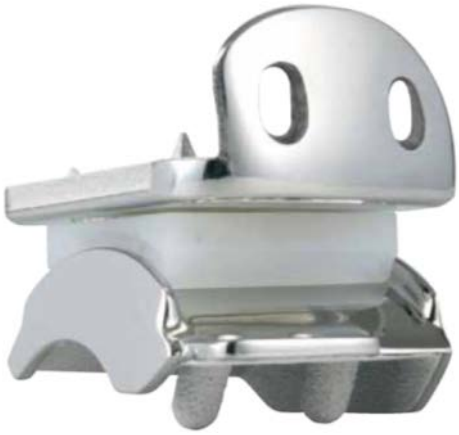

Figure 1 Hintermann Series H3™ Total Ankle Replacement System

Table 1 describes the system components and size offerings.

Table 1 Description of Hintermann Series H3™ Total Ankle System components

Component	Sizes	Material	Standard
Tibial Component	Sizes: 1 to 6	Cobalt Chromium alloy Titanium Plasma spray Hydroxyapatite	ISO 5832-4; ASTM F75 ASTM F1580 ISO 13779-2 (HAP coating) ISO 13779-6 (HAP powder)
Polyethylene Inlay (PE Inlay)	Sizes: 1 to 6 Thicknesses: 5, 6, 7, and 9 mm	UHMWPE Titanium alloy markers	ISO 5834-1, 2; ASTM F648 ISO 5832-3; ASTM F136
Talar Component	Sizes: 1 to 6	Cobalt Chromium alloy Titanium Plasma spray Hydroxyapatite	ISO 5832-4; ASTM F75 ASTM F1580 ISO 13779-2 (HAP coating) ISO 13779-6 (HAP powder)
Flat Cut Talar Component	Sizes: 1-5		

Additional information regarding the device is provided in the sections below and in the Hintermann Series H3™ Total Ankle System Instructions for Use and Surgical Technique.

Principles of Operation

The Hintermann Series H3™ Total Ankle Replacement System is a three component, mobile bearing ankle incorporating an unconstrained tibial articulating surface and an semi-constrained talar articulating surface, that was designed in 2000 by Dr. B. Hintermann, Dr. G. Dereymaeker, Dr. R. Viladot, and Dr. P. Diebold. The Hintermann Series H3™ Total Ankle Replacement System is a bone-sparing device designed for maximum contact area, minimal bone resection, optimal bone coverage, and optimal force distribution.

Device Components

H3 Tibial Component

The H3 Tibial Component is available in 6 sizes (1 to 6), in right and left versions, and manufactured from cobalt chromium. It is designed as a bone-sparing device and resurfaces the tibia with a large flat surface to provide a physiological load transfer and minimal contact stress to the bone. There are pyramidal peaks for anchoring in bone thus increasing stability in translation and rotation. The bone contacting surface of the tibial component is double coated (titanium plasma spray coated with hydroxyapatite) for optimal bone fixation. The articular surface is highly polished.

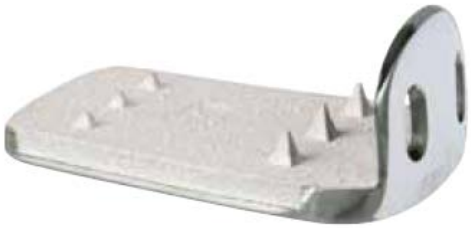

Figure 2 Hintermann Series H3 Tibial Component

H3 Polyethylene Inlay

The H3 Polyethylene (PE) Inlay is manufactured from ultra-high molecular weight polyethylene with a high congruency with the metal surfaces of both tibial and talar

components. The PE inlay is available in 6 sizes (1-6) in 4 thicknesses (5, 6, 7 and 9 mm). The PE inlay allows unconstrained rotatory gliding (sagittal and frontal plane) on the flat tibial surface with a semi-constrained free sagittal plane motion on the anatomical shaped conically talar surface. The PE inlay is designed to have a large contact area with both tibial and talar components to minimize contact stresses and wear, and to provide intrinsic stability against eversion-inversion forces. The PE inlay also includes titanium x-ray markers.

Figure 3 Hintermann Series H3 PE Inlay

Talar Component

The H3 Talar Component is available in 6 sizes (1 to 6), in right and left versions, and manufactured from cobalt chromium. It has an anatomical shape (furstro-conical surface) with a wide contact area to allow physiological talar motion and to minimize medial ligament stress. It has 2.5-mm high rims on each side that ensure stable positioning, guide the anteroposterior translation of the mobile bearing, and provide flexion stability to the construct. The talar component has anterior pegs to improve sagittal stability and positioning, and medial and lateral rims to guide movement of the PE inlay. The anterior shield is designed to prevent ingrowth of osteophytes. The articulating side of the component includes a highly polished articular surface. The bone contacting surface of the talar component is double coated (titanium plasma spray coated with hydroxyapatite coating) for optimal bone fixation.

Figure 4 Hintermann Series Talar Component

Flat Cut Talar Component
The Flat Cut Talar Component is available in 5 sizes (1 to 5), in right and left versions, and manufactured from cobalt chromium. It has the same design features of the Talar Component described in the previous section; however, the thickness has been increased to compensate for the additional bone resection, if needed based on patient anatomy.

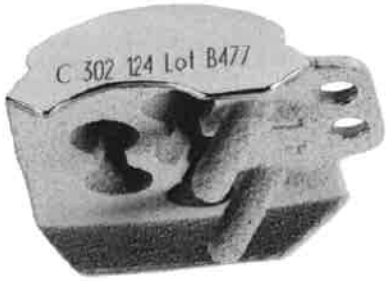

Figure 5 H3 Flat Cut Talar Component

Surface Treatment
The bone contacting surfaces of the tibial and talar components are double coated (titanium plasma spray coated with hydroxyapatite) for optimal bone fixation. There are no other specific surface treatments for the Hintermann Series H3™ Total Ankle Replacement System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several options for the surgical correction of a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease (e.g. rheumatoid arthritis, hemochromatosis). Each alternative treatment has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Conservative treatments for a painful arthritic ankle include heat, electrotherapy, physical therapy, bracing, and pain medication. When conservative therapy fails to relieve symptoms, surgical intervention may be recommended. Some surgeons recommend ankle fusion surgery (arthrodesis), in which the lower leg bone is fused to the foot. Some surgeons recommend total ankle replacement (TAR), in which the ankle joint is replaced by a prosthetic device which attempts to mimic the movement of the ankle. Total ankle replacement devices legally marketed in the United States include semi-constrained fixed bearing systems and mobile bearing systems. There are several semi-constrained fixed bearing systems that are legally marketed in the U.S. The Hintermann Series H3™ Total Ankle Replacement System is a mobile bearing system, and there is one other mobile bearing total ankle replacement legally marketed in the U.S.

VII. MARKETING HISTORY

The present version (third generation) of the Hintermann Series H3™ Total Ankle Replacement System is commercially available in the following countries outside the USA:

- Germany
- South Korea
- Denmark
- Czech Republic
- Finland
- Lithuania
- Italy
- Luxembourg
- Malaysia
- Hong Kong
- Switzerland
- Ireland
- United Kingdom
- Chile
- Canada
- Australia
- Costa Rica
- South Africa
- Belgium
- Netherlands

The Hintermann Series H3™ Total Ankle Replacement System has been implanted in over 20,000 procedures in OUS markets since May 2000. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL 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. This listing was derived from results of the Hintermann clinical study and published clinical literature for the same patient population.

Intraoperative events:
Fractures of bones adjacent to the implant site (medial or lateral malleolus, distal tibia, talus)
Soft tissue injuries at or adjacent to the surgical site (nerves, tendons, or blood vessels)
Malalignment of the tibia or talus

Postoperative events:
Infection (superficial or periprosthetic)
Aseptic loosening of the tibial or talar device components
Osteolysis of the tibia, talus or fibula
Subsidence of the tibial or talar device components
Problems with the polyethylene device component (fracture, instability, wear)
Fractures of bones adjacent to the implant site (medial or lateral malleolus, distal tibia, talus)
Adjacent joint arthritis
Arthrofibrosis/impingement
Avascular necrosis of the talus

Chronic pain
Complex regional pain syndrome (CRPS)
Edema
Equinus contracture
Heterotopic ossification
Hindfoot malalignment
Ligamentous instability
Metal component issues
Syndesmosis nonunion
Tarsal tunnel syndrome
Thromboembolism
Wound healing problems

Adverse effects may necessitate a non-operative treatment, reoperation, revision, or non-revision surgery.

For the specific adverse events that occurred in the clinical study, please see Section X.D.1., below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The technical and performance test plan was developed based on ASTM F2665-09, Standard Specification for Total Ankle Replacement Prosthesis. Testing for the Hintermann Series H3™ Total Ankle System components included the following:

- range of motion evaluation,
- tibial component stress analysis
- talar component stress analysis
- PE Inlay stress analysis
- contact area and contact pressure evaluations,
- constraint evaluations,
- wear simulator testing and particulate analysis.

A summary of each test is provided in the sections below.

Range of Motion Evaluation

Range of motion evaluations were conducted according to ASTM F2665-09 using CAD-Based 3D Models. The standard specifies that the range of motion in dorsiflexion and plantarflexion shall be greater than or equal to 15° (each direction) which is required for walking. A size 1 prosthesis was used for the evaluation as this represented a worst case because it has the least area of loading between the polyethylene and talar component which causes the least angle of travel in flexion. Based on the range of motion evaluation, the Hintermann Series H3™ Total Ankle System meets the specified minimum range of motion requirements.

Tibial Component Stress Analysis
As outlined in ASTM F2665-09, the tibial component was fatigue tested similar to the test method for knees in ASTM F1800. The worst case size selection was determined to be the largest tibial component (size 6) as it would have the largest bending moment. The maximum load value was defined by a preliminary dynamic test by progressive loading (ramp-test). One tibial component was tested by progressive loading starting at 1,500 N (337 lbf.) for 1 million cycles. Subsequently, the maximum load was increased by 100 N (22 lbf.) at every 1 million cycles. Six (6) tibial components were tested according to the protocol. The results confirm that the Hintermann Series H3™ Tibial Component is capable of withstanding expected *in vivo* loading of over 3.3 times bodyweight (2300 N).

Talar Component & PE Inlay Stress Analysis
A review was conducted to analyze the components (Tibial, PE Inlay, Talar) included in the Hintermann Series H3™ Total Ankle System, to determine the worst case component and the projected *in vivo* performance. The review confirmed the following:

- The Tibial Component is the weakest device in the system with the higher potential for failure. Fatigue testing confirmed that the Tibial Component is capable of withstanding expected *in vivo* loading.
- Contact area testing confirmed that the worst case size (5 mm) for the PE Inlay is capable of withstanding expected *in vivo* loading.
- Design comparisons and Talar Component testing confirmed that the worst case size for the Talar Component is capable of withstanding expected *in vivo* loading as it is a structurally stronger design than the Tibial Component.

Contact Area and Contact Pressure Evaluations
Testing to evaluate the pressure distribution and total contact area of the Hintermann Series H3™ Total Ankle System was conducted as outlined in ASTM F2665-09. The smallest size talar component (size 1) and the PE inlay (5 mm) were used as these are considered worst case as they have the potential to experience the highest stress. Testing was conducted using two-sheet type FUJI pressure sensitive films placed between the PE Inlay and the talar component.

All specimens were subjected to a specific loading regime where they were loaded to the maximum value within 10 sec., held at maximum load for 10 sec., and unloaded to zero load within 10 sec. The load was set at 3650 N (820 lbf.) and was applied at seven positions as follows:

- 0°
- 10°, 15° and 20° plantarflexion
- 10°, 15° and 18° dorsiflexion

A mean total contact area of 386.56 mm^2 was determined for all flexion angles tested. A review of the data including the results from the wear simulator testing confirmed that the Hintermann Series H3™ PE Inlay is capable withstanding expected in vivo loading.

Constraint Evaluations

As outlined in ASTM F2665-09, constraint data for internal-external rotation, anterior-posterior displacement and medial-lateral displacement was determined for the Hintermann Series H3™ Total Ankle System. The smallest size talar component (size 1) and the PE Inlay (5 mm) were used as these are considered worst case as they have the potential for the highest stress over the smallest area. The components were evaluated in a manner similar to the test methods outlined for knees in ASTM F1223-14, Standard Test Method for Determination of Total Knee Replacement Constraint. The constraint test series was performed at 18°, 10°, 0°, -10° and -20°. The results demonstrate that the Hintermann Series H3™ Total Ankle System exhibits minimal constraint in the anterior/posterior, medial/lateral, and rotational modes.

Wear Simulator Testing and Particulate Analysis

Wear testing was performed on the thinnest PE Inlay, smallest tibial component and smallest talar component to determine the worst case wear performance. The following angular displacements were simulated: dorsiflexion/plantarflexion and internal/external rotation (position controlled). Dorsiflexion/plantarflexion was applied to the talar component whereas internal/external rotation was applied to the tibial component. A maximum joint reaction force of 3.3 x bodyweight was applied.

For a 70 kg patient, this will result in a maximum load (joint reaction force) of approximately 2300 N. The joint reaction force data was derived from reference literature. The test was conducted at a frequency of 1.0 Hz in a test fluid maintained at 37°±2°C for 5 million cycles.

The Hintermann Series H3™ PE Inlays demonstrated a mean wear rate of 2.58 (SD 0.21) mg per million cycles. This wear rate was determined between 0.0 and 5.0 million cycles. This wear rate is below the acceptance criteria defined as 20 mg per million cycles.

Subsequent to the wear simulator testing, particulate analysis was conducted according to ASTM F1877-16, Standard Practice for Characterization of Particles. Acceptance criterion was based on reference literature and the analysis confirmed that the equivalent circle diameter and the aspect ratio met the acceptance criteria.

Coating Characterization

Characterization of the plasma spray and bilayer coating was performed according to FDA *Guidance for Industry on the Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements* (February 2, 2000). A summary of the mechanical testing that was conducted is provided in the table below.

Table 2 Mechanical testing of coatings

Characterization/ Test	Coating tested	Method	Results
Tibial Component mean coating thickness	Ti+HA	ASTM F1854	Ti: 94.88 µm HA: 76.68 µm
Talar Component mean coating thickness	Ti+HA	ASTM F1854	Ti: 131.00 µm HA: 83.49 µm
Tibial Component coupon mean porosity	Ti+HA	ASTM F1854	Ti: 23.42% HA: 4.69%
Talar Component coupon mean porosity	Ti+HA	ASTM F1854	Ti: 23.7% HA: 5.5%
Tibial Component coupon mean pore size	Ti+HA	ASTM F1854	Ti: 14.83 µm HA: 7.1 µm
Talar Component coupon mean pore size	Ti+HA	ASTM F1854	Ti: 12.45 µm HA: 6.62 µm
Shear fatigue strength	Ti+HA	ASTM F1160	10 MPa
Static shear strength	Ti+HA	ASTM F1044	32.74 MPa
Static tensile strength	Ti+HA	ASTM F1147	21.87 MPa
Abrasion testing	Ti	ASTM F1978	Mass loss was less 65 mg (by weight) when abraded for 100 cycles

In addition, the hydroxyapatite coating was characterized according to FDA guidance *510(K) Information Needed for Hydroxyapatite Coated Orthopedic Implants* (February 20, 1997). The hydroxyapatite coating met all applicable characterization requirements.

Biocompatibility

The implants are manufactured using implant grade materials and the instruments are manufactured using standard instrumentation materials. The biocompatibility was based on a review of the materials, manufacturing vendors, manufacturing validation testing (cytotoxicity, systemic toxicity, pyrogen testing, intracutaneous irritation), and manufacturing reagents. The risk assessment confirmed that there are no risks associated with the biocompatibility of the Hintermann Series H3™ Total Ankle Replacement System.

B. Animal Studies

Animal studies were not necessary to support the safety and effectiveness of the Hintermann Series H3™ Total Ankle System.

C. Additional Studies

Additional testing was performed as outlined in the table below.

Table 3 Additional testing summary

Test	Acceptance Criteria	Results	Analysis Type
Sterilization	Gamma irradiation sterilization process is used. It is considered an overkill sterilization cycle and is performed in accordance with accepted standards ANSI/AAMI/ISO 11137-1, 11137-2, and 11137-3. Devices must have a sterility assurance of at least 10^{-6}. Sterilization validation was performed by comparison to "worst case" devices.	Passed	Validation was performed on the thickest PE Inlay and the largest size Flat Cut Talar Component which were determined to create the worst case conditions for the poly and metal components, respectively.
Endotoxin	Total endotoxin should be less than 20 endotoxin units (EU)/Device.	Passed	Gel clot method testing was conducted on the Tibial Component, PE Inlay, and Talar Component.
Package performance	Visual Examination should be acceptable per ASTMF1886. All seals must pass integrity test. All seals must be greater than 1.2 Newtons/15mm which was the minimum peel strength achieved during the OQ testing. Labels must be legible and barcodes must scan. No delamination, tearing, or fracturing of the Tyvek upon opening that could prevent aseptic delivery. Tyvek may not split more than 10mm in length from the edge of the seal.	Passed	Samples processed under normal conditions at the minimum sealing parameters were evaluated via visual inspection, seal integrity (ASTM F-1886), bubble leak testing (ASTM F-2096), aseptic presentation (ISO 11607), peel strength (ASTM F-88), and label legibility.
Package stability testing	Seal strength must be greater than 1.2N/15mm.	Passed	Seal strength testing was conducted on the packaging configurations used for the subject device.
Cleaning validation	No visual soil should remain on the test articles. Protein level should be <6.4 $\mu g/cm^2$ for the processed test articles. Hemoglobin level should be < 2.2 $\mu g/cm^2$ for the processed test articles. MEM should have a reactivity grade of 2 or less. Samples deemed sterile after steam sterilization.	Passed	Cleaning validation was conducted on the instrument based on greatest risk.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of total ankle arthroplasty with the Hintermann Series H3™ Total Ankle Replacement System for primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease. The study was a retrospective, non-randomized, single-arm study in which clinical data for the Hintermann Series H3™ Total Ankle Replacement System was compared to Performance Goals (PGs). Data from this clinical

study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The data on Hintermann Series H3™ Total Ankle Replacement System were abstracted from data collected prospectively in the Foot and Ankle Registry currently maintained at Kantonsspital Baselland (H3 Registry). Kantonsspital Baselland (Canton Hospital, Basel, Switzerland) is a teaching hospital affiliated with the University of Basel. The version of the H3 that is the subject of this PMA has been commercially available in Europe since 2003 and therefore H3 clinical data supporting this PMA represent commercial, or real-world, use of the device.

The PGs used in this study are based on a prospectively defined, systematic meta-analysis of available published literature and registry data (Total Ankle Replacement for Ankle Arthritis study at Duke University) for a control mobile bearing total ankle system legally marketed in the United States at the time of the study. The meta-analysis was conducted following a prospectively defined protocol for data abstraction, and the screening and selection of studies used in the development of the PGs were completed by independent reviewers who were blinded to the H3 registry data and any prior data analyses. The other steps in the process of the development of the PGs, including the literature search and meta-analysis methods, were prospectively specified prior to the literature selection in order to avoid bias during the meta-analysis phase.

Data for the investigational subjects included in the Primary Safety and Effectiveness (PSE) Cohort have been audited to verify their accuracy and completeness. Subject selection for the PSE Cohort was performed programmatically without regard to outcomes, and a listing of subjects not selected for the PSE Cohort with the reason(s) was generated. Additionally, the subject selection criteria were finalized prior to the completion of data abstraction.

In addition to the comparison of the H3 registry data to PGs, the adverse event data from the H3 registry was compared to published adverse event data for the H3 and published literature and registry adverse event data available for the control. The adverse event data classifications were reviewed and confirmed by a Clinical Events Committee (CEC), and adjudicated for severity and device relatedness.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PSE Cohort was limited to patients who met the following inclusion criteria:

   - Skeletally mature
   - Primary diagnosis of osteoarthritis, post-traumatic arthritis or rheumatoid arthritis
   - Primary total ankle replacement

- Unilateral or the first ankle implanted if bilateral and the surgery dates for both sides are at least 6 months apart
- Implanted with the correct device without screws (for investigational arm, a 3rd generation Hintermann Series H3 Total Ankle Replacement; for control arm,the only legally marketedmobile bearing total ankle system device in the U.S. at the time of the study)
- Poor pre-operative American Orthopaedic Foot and Ankle Society Hindfoot Score (< 60 points)
- Eligible for at least 2 years of follow-up (implanted in 2013 or earlier). Note that all subjects implanted in 2013 or earlier were included regardless of whether they were revised prior to the 2 year endpoint.
- Gave informed consent (unless IRB/Ethics Committee waived this requirement)

Patients were <u>not</u> permitted to enroll in the H3 PSE Cohort study if they met the following exclusion criterion:

- Prior TAR or arthrodesis at the involved ankle joint

2. <u>Follow-up Schedule</u>
   All subjects were eligible for a minimum of 2 years follow up. At the time of database closure, the maximum follow-up was 10 years for the Hintermann subjects enrolled in the Kantonsspital Baselland registry.

   The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. <u>Clinical Endpoints</u>
   The primary endpoints in this study consisted of three individual co-primary endpoints:
   1. American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score at 2 years or later.
   2. Survivorship (absence of revision/removal) within 5 years
   3. Occurrence of a Serious Device-Related Adverse Event (SADE), as determined by the independent Clinical Events Committee) other than a removal/revision within 2 years

   These endpoints were treated as co-primary endpoints, in which statistical significance must be shown on all three endpoints individually in order for the study to be successful.

   The primary safety assessment for this study is based on a comparison of the serious device related adverse event rates recorded for the H3 study population to the serious device related adverse event rates from the studies that were selected for the meta-analysis which served as the basis for the PGs.

B. <u>Accountability of PMA Cohort</u>

As of August 20, 2018, there were 1,316 ankles with H3 implants maintained in the H3 registry, of which 428 met all inclusion/exclusion criteria and were included in the Primary Safety and Effectiveness (PSE) cohort. Of these 428 ankles, 298 have H3 devices that were implanted without the use of optional fixation screws, and therefore, these 298 ankles are the subjects included in the PSE Cohort referenced throughout this report.

Table 4: PSE Cohort

Criterion	Excluded Ankles	Included Ankles
Original Database	-	1316
Criterion #1: Surgery Group (Primary TAR only)	276	1040
Criterion #2: Surgery Date <=2014	0	1040
Criterion #3: Generation 3 (H3) device	167	873
Criterion #4: Enrolled at Kantonsspital Baselland	192	681
Criterion #5: Preoperative AOFAS Total Score < 60	196	485
Criterion #6: No use of revision or sensitive components	7	478
Criterion #7: Unilateral Total Ankle Replacement or if qualifying Bilateral*, earliest qualifying ankle is included.	50	428
Criterion #8: H3 device implanted without the use of screws	130	298

*Bilateral where surgical dates for both sides are at least 6 months apart

The first H3 subject was enrolled in the Foot and Ankle Registry at Kantonsspital Baselland on 08/17/2006 and the last follow-up visit prior to database closure was conducted on 8/20/2018.

At the Month 3-6 follow-up interval, any data were available on 122 of the 298 subjects (40.9%). At the Year 1 follow-up, any data were available for 217 of the 298 subjects (Actual Follow-up rate 73.9%). At the Year 2 follow-up, any data were available for 255 of the 298 subjects (Actual Follow-up rate 88.9%). At the Year 2+ follow-up interval, any data were available for 273 of the 298 subjects (Actual Follow-up rate 95.5%). Finally, at the Year 5+ follow-up interval, the actual follow-up rate was 61.9%.

Table 5. Subject Accountability by Visit, PSE Cohorts

	3-6 MONTH	1 YEAR	2 YEAR	2+ YEAR	5+ YEAR
Theoretical	298	298	298	298	298
Deaths(cumulative)	0	1	11	12	20[c]
Expected[a]	298	297	287	286	278
Revision (cumulative)[b]	14	19	22	24[d]	27[e]
Actual: Any Follow-Up Data	122	217	255	273	172
% Follow-Up	40.9%	73.1%	88.9%	95.5%	61.9%
Actual: All Primary Endpoint Data Available	.	.	.	253	.

[a] Expected = Theoretical – Deaths
[b] Revisions are considered as "any data", as they are part of the co-primary endpoints. Thus, they are included in the Actual: Any Follow-up Data row and also included in the "Expected" row.
[c] There are 21 total deaths. One subject had a 5+-year follow-up visit but then a subsequent death. Thus, the subject is considered to be "expected" at this visit.
[d] There are 24 revisions at or prior to the 5 year visit, and 3 additional revisions occurring after the 5-year upper window limit.
[e] Total 27 revisions; 24 at or prior to 5 years and 25 at or prior to 7 years.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical study of subjects undergoing total ankle arthroplasty in the US.

Demographic data collected at baseline for the PSE Cohort are presented in the table below. There are 298 subjects in this cohort, 43.6% female and 56.4% male. The mean age is 63.2 years, and mean body mass index (BMI) is 27.7.

Table 6: Demographic Data, PSE Cohort

Demographic Data (PSE Cohort)		
Characteristic	**Statistic/Category**	**H3 (N=298)**
Age	N	298
	Mean±SD	63.2 ± 12.38
	Range	21.0 to 88.0
	Median	64.5
Gender	Female	130 (43.6%)
	Male	168 (56.4%)
BMI	N	298
	Mean±SD	27.7 ± 4.78
	Range	16.5 to 48.4
	Median	26.9
Height (cm)	N	298
	Mean±SD	171.4 ± 9.56
	Range	147.0 to 204.0
	Median	171.0
Weight (kg)	N	298
	Mean±SD	81.3 ± 15.81
	Range	45.0 to 140.0
	Median	82.0

Table 7: Baseline Characteristics: Primary Diagnosis, PSE Cohorts

Characteristic	**Statistic/Category**	**H3 (N=298)**
Primary Diagnosis	Posttraumatic Arthritis	215 (72.1 %)
	Primary Arthritis	48 (16.1 %)
	Rheumatoid Arthritis	19 (6.4 %)
	Other	16 (5.4 %)

Table 8: Baseline Characteristics: Smoking Status, PSE Cohort

Characteristic	**Statistic/Category**	**H3 (N=298)**
Smoking Status	Current Smoker	36 (12.1 %)
	Never Smoked	237 (79.5 %)
	Previous Smoker	23 (7.7 %)
	Unknown	2 (0.7 %)

Table 9: Baseline Characteristics: AOFAS Scores, PSE Cohort

Characteristic	Statistic/Category	H3 (N=298)
AOFAS Score	N	298
	Mean±SD	39.2 ± 12.40
	Range	7.0 to 59.0
	Median	41.0
AOFAS Alignment	Poor	90 (30.2 %)
	Fair	116 (38.9 %)
	Good	92 (30.9 %)

Table 10: Baseline Characteristics: Device Sizes and Side, PSE Cohort

Characteristic	Statistic/Category	Investigational (N=298)
Tibial Size	Large (Sizes 4-6)	138 (46.3 %)
	Small (Sizes 1-3)	160 (53.7 %)
Talar Size	Large (Sizes 4-5)	38 (12.8 %)
	Small (Sizes 1-3)	260 (87.2 %)
Side	Left	130 (43.6 %)
	Right	168 (56.4 %)

D. Safety and Effectiveness Results

The primary objective this study was to determine the safety and effectiveness of the H3 based on the comparison to three separate Performance Goals (PG).

(1) American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score at 2 years or later.
(2) Survivorship (absence of revision/removal) within 5 years
(3) Occurrence of a SADE, (as determined by the independent CEC) other than a removal/revision within 2 years

These endpoints were treated as co-primary endpoints and therefore statistical significance was required to be shown on all three endpoints individually in order for the study to be successful. Each endpoint is tested independently using alpha = 0.05. The results of the analyses of each co-primary endpoint is presented and discussed below.

The PGs were developed by an independent statistician according to a pre-specified protocol and were based on all available and applicable data for the control device, which is the only currently approved mobile bearing TAR device in the US.

1. Safety Results

The primary safety assessment for this study is based on a comparison of the serious device related adverse event rates recorded for the H3 PSE Cohort, compared to published adverse event data for the H3 and published and

unpublished adverse event data available for the control device. A comprehensive search of the published literature was conducted according to a prospective protocol, and adverse event data were recorded and classified according to the method described by Mercer et al[1]. Adverse event data from national joint registries (NJR) were also recorded and classified, and the adverse event data recorded in the H3 registry were also classified according to the Mercer method. The adverse event data classifications were reviewed and confirmed by CEC, and adjudicated for severity and device relatedness.

The analysis of the primary safety endpoint showed that the percent of patients with SADEs associated with the H3 device was significantly lower than the percent of patients with SADEs associated with the control device. The percent of patients in the H3 PSE Cohort with serious device related adverse events was consistent with the percent of patients in the H3 literature.

Table 11 Primary Safety Assessment: Serious Device Related Adverse Events (SADE)

Percent of Patients with Serious Device-Related Adverse Events Hintermann Registry, H3 and Control Literature and National Joint Registries (NJR)			
SADE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	5.9% (16/ 273)	6.0% (146/2437)	10.5% (316/3020)

Adverse effects that occurred in the PMA clinical study:

Table 112: Serious Device Related Adverse Events - Listing

Hintermann Series H3™ Total Ankle Replacement System Serious Device Related Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
-	Chronic Pain	0.4% (1/ 273)		
-	Chronic Pain, Stiffness			0.2% (5/3020)
Aseptic Loosening	-	0.7% (2/ 273)	2.5% (60/2437)	3.5% (105/3020)
Aseptic Loosening	Talus		0.2% (6/2437)	0.4% (12/3020)
Aseptic Loosening	Tibia	0.4% (1/ 273)	0.2% (5/2437)	0.4% (11/3020)
Aseptic Loosening	Tibia, Talus			0.1% (4/3020)
Aseptic Loosening, Infection, Fracture	Tibia, Talus		0.6% (14/2437)	

Hintermann Series H3™ Total Ankle Replacement System Serious Device Related Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Aseptic Loosening, Metal Component Fracture, Malalignment	-			0.2% (6/3020)
Aseptic Loosening, Osteolysis, Infection, Fracture	Impingement		0.5% (12/2437)	
Fracture, Other	-			0.4% (11/3020)
Loosening	-		0.4% (10/2437)	
Loosening	Talus			0.1% (2/3020)
Loosening	Tibia			0.2% (5/3020)
Loosening	Tibia, Ossification			0.1% (3/3020)
Loosening	Tibia, Talus			0.1% (3/3020)
Lysis	-		0.1% (2/2437)	
Malalignment	Tibia Or Talus			0.3% (9/3020)
Osteolysis	-		0.5% (13/2437)	0.4% (13/3020)
Osteolysis	Talus	0.4% (1/ 273)		
Osteolysis	Tibia	0.4% (1/ 273)		0.5% (15/3020)
Other	-		0.0% (1/2437)	0.7% (20/3020)
Other, Polyethylene Problems	-		0.2% (5/2437)	
Polyethylene Problems	-		0.1% (2/2437)	0.7% (21/3020)
Polyethylene Problems	Fracture	0.7% (2/ 273)	0.3% (7/2437)	1.6% (49/3020)
Polyethylene Problems	Instability		0.1% (3/2437)	
Polyethylene Problems	Ossification			0.0% (1/3020)
Polyethylene Problems	Wear	0.7% (2/ 273)	0.1% (2/2437)	
Polyethylene Problems, Other	Fracture			0.0% (1/3020)
Subsidence	-		0.2% (4/2437)	0.7% (20/3020)
Subsidence	Talus	1.5% (4/ 273)		0.0% (1/3020)
Subsidence	Talus & Tibia	0.4% (1/ 273)		

Hintermann Series H3™ Total Ankle Replacement System Serious Device Related Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Subsidence	Tibia	0.4% (1/ 273)		0.0% (1/3020)

[1]Mercer et al. Provides a classification system for adverse events in TAR. Classification 1 is the proposed adverse event category. Each category is then subclassified further by type of adverse event, or specific anatomic location (Classification 2). (Mercer J., Penner M. et al. Inconsistency in the Reporting of Adverse Events in Total Ankle Arthroplasty: A Systemic Review of the Literature. Foot & Ankle International 2016, Vol. 37(2) 127-136).

Device Related Adverse Events

In the PSE Cohort, a device related adverse event was associated with the H3 device in 18/273 subjects (6.6%). Based on data extracted from the published literature and from national joint registries, the device related adverse event rate for the H3 device was 6.0%, and was 14.0% for the control device. The DRAE rate for the H3 PSE Cohort was the same as the DRAE rate for the H3 device reported in the published literature.

Table 123: Device Related Adverse Events - Summary

Hintermann Series H3™ Total Ankle Replacement System: Percent of Patients with Device-Related Adverse Events Hintermann Registry, H3 and ControlLiterature and National Joint Registries (NJR)			
DRAE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	6.6% (18/ 273)	6.0% (147/2437)	14.0% (424/3020)

The following table lists the device related adverse events organized by Mercer classifications as reviewed and adjudicated by the CEC.

Table 14: Device Related Adverse Events - Listing

Hintermann Series H3™ Total Ankle Replacement System Device Related Adverse Events: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
-	Chronic Pain	0.4% (1/ 273)		
-	Chronic Pain, Stiffness			0.2% (5/3020)
-	Ossification			0.0% (1/3020)
Aseptic Loosening, Subsidence	-			0.2% (5/3020)

Hintermann Series H3™ Total Ankle Replacement System Device Related Adverse Events: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Aseptic Loosening	-	0.7% (2/ 273)	2.5% (60/2437)	3.7% (112/3020)
Aseptic Loosening	Talus		0.2% (6/2437)	0.4% (12/3020)
Aseptic Loosening	Tibia	0.4% (1/ 273)	0.2% (5/2437)	0.4% (11/3020)
Aseptic Loosening	Tibia, Talus			0.2% (5/3020)
Aseptic Loosening, Infection, Fracture	Tibia, Talus		0.6% (14/2437)	
Aseptic Loosening, Metal Component Fracture, Malalignment	-			0.2% (6/3020)
Aseptic Loosening, Osteolysis, Infection, Fracture	Impingement		0.5% (12/2437)	
Fracture, Other	-			0.4% (11/3020)
Loosening	-		0.4% (10/2437)	
Loosening	Talus			0.1% (2/3020)
Loosening	Tibia			0.2% (5/3020)
Loosening	Tibia, Ossification			0.1% (3/3020)
Loosening	Tibia, Talus			0.1% (3/3020)
Lysis	-		0.1% (2/2437)	
Malalignment	Talus			0.0% (1/3020)
Malalignment	Tibia Or Talus			0.3% (9/3020)
Osteolysis	-	0.4% (1/ 273)	0.5% (13/2437)	0.8% (25/3020)
Osteolysis	Talus	0.4% (1/ 273)		
Osteolysis	Tibia	0.7% (2/ 273)		0.8% (24/3020)
Other	-		0.0% (1/2437)	0.7% (21/3020)
Other, Polyethylene Problems	-		0.2% (5/2437)	
Polyethylene Problems	-		0.1% (2/2437)	1.6% (47/3020)
Polyethylene Problems	Fracture	0.7% (2/ 273)	0.3% (7/2437)	1.6% (49/3020)

Hintermann Series H3™ Total Ankle Replacement System Device Related Adverse Events: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Polyethylene Problems	Instability		0.1% (3/2437)	
Polyethylene Problems	Ossification			0.0% (1/3020)
Polyethylene Problems	Wear	0.7% (2/ 273)	0.1% (2/2437)	0.1% (2/3020)
Polyethylene Problems, Other	Fracture			0.0% (1/3020)
Subsidence	-		0.2% (5/2437)	0.7% (21/3020)
Subsidence	Talus	1.5% (4/ 273)		0.9% (27/3020)
Subsidence	Talus & Tibia	0.4% (1/ 273)		
Subsidence	Tibia	0.4% (1/ 273)		0.6% (17/3020)

[1]Mercer et al. Provides a classification system for adverse events in TAR. Classification 1 is the proposed adverse event category. Each category is then subclassified further by type of adverse event, or specific anatomic location (Classification 2). (Mercer J., Penner M. et al. Inconsistency in the Reporting of Adverse Events in Total Ankle Arthroplasty: A Systemic Review of the Literature. Foot & Ankle International 2016, Vol. 37(2) 127-136).

Serious Adverse Events

In the PSE Cohort, a serious adverse event was associated with the H3 device in 92/273 subjects (33.7%). Based on data extracted from the published literature and from national joint registries, the serious adverse event rate for the H3 device was 9.8% and was 21.9% for the control device.

Table 15: Serious Adverse Events (SAE)

Hintermann Series H3™ Total Ankle Replacement System Percent of Patients with Serious Adverse Events Hintermann Registry, H3 and Control Literature and National Joint Registries (NJR)			
SAE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	33.7% (92/ 273)	9.8% (238/2437)	21.9% (660/3020)

The reason for increased SAEs in the H3 PSE cohort is unknown.

Table 13: Serious Adverse Events / Serious Device Related Adverse Events

Comparison of Serious Adverse Events to Serious Device Related Adverse Events: H3 PSE Cohort, H3 Literature, Control			
SAE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**

Comparison of Serious Adverse Events to Serious Device Related Adverse Events: H3 PSE Cohort, H3 Literature, Control			
SAE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	33.7% (92/ 273)	9.8% (238/2437)	21.9% (660/3020)
SADE-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	5.9% (16/ 273)	6.0% (146/2437)	10.5% (316/3020)

The following table lists the serious adverse events organized by Mercer classifications as reviewed and adjudicated by the CEC.

Table 17: Serious Adverse Events - Listing

Hintermann Series H3™ Total Ankle Replacement System Serious Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
-	Arthritis			0.0% (1/3020)
-	Arthritis, Pain			0.0% (1/3020)
-	Arthrofibrosis	0.4% (1/ 273)	0.0% (1/2437)	
-	Pain, Arthrofibrosis		0.2% (5/2437)	
-	Avascular Necrosis Of Talus	0.4% (1/ 273)		0.0% (1/3020)
-	Chronic Pain	0.4% (1/ 273)	0.1% (2/2437)	0.7% (22/3020)
-	Chronic Pain, Hindfoot Malalignment	0.4% (1/ 273)		
-	Chronic Pain, Stiffness			0.4% (12/3020)
-	Edema	0.4% (1/ 273)		
-	Equinus Contracture	0.4% (1/ 273)		
-	Heterotopic Ossification, Chronic Pain			0.2% (6/3020)
-	Hindfoot Malalignment	0.4% (1/ 273)		0.2% (7/3020)
-	Hindfoot Malalignment, Ligamentous Instability	0.8% (2/273)		
-	Hindfoot Malalignment			0.0% (1/3020)
-	Impingement	0.4% (1/ 273)	0.0% (1/2437)	
-	Lateral Instability			0.0% (1/3020)
-	Ligamentous Instability	4.0% (11/273)	0.1% (2/2437)	0.2% (6/3020)

Hintermann Series H3™ Total Ankle Replacement System Serious Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
-	Lateral Malleolus			0.2% (6/3020)
-	Ossification			0.0% (1/3020)
-	Tarsal Tunnel Syndrome	0.8% (2/273)	0.1% (2/2437)	
-	Tarsal Tunnel Syndrome, Arthrofibrosis	0.4% (1/ 273)		
-	Thromboembolism			0.1% (2/3020)
-	Wound Healing Problem		0.1% (2/2437)	0.1% (3/3020)
-	Wound Healing Problems			0.6% (19/3020)
Aseptic Loosening	-	0.8% (2/273)	2.5% (61/2437)	3.5% (105/3020)
Aseptic Loosening	Talus		0.2% (6/2437)	0.4% (12/3020)
Aseptic Loosening	Tibia	0.4% (1/ 273)	0.2% (5/2437)	0.4% (11/3020)
Aseptic Loosening	Tibia, Talus			0.1% (4/3020)
Aseptic Loosening, Infection, Fracture	Tibia, Talus		0.6% (14/2437)	
Aseptic Loosening, Metal Component Fracture, Malalignment	-			0.2% (6/3020)
Aseptic Loosening, Osteolysis, Infection, Fracture	Impingement		0.5% (12/2437)	
Fracture	-	0.4% (1/ 273)	0.1% (2/2437)	0.5% (14/3020)
Fracture	Arthritis			0.0% (1/3020)
Fracture	Fibula	0.8% (2/273)		
Fracture	Lateral Malleolus		0.0% (1/2437)	0.3% (9/3020)
Fracture	Malleolus		0.3% (8/2437)	1.1% (33/3020)
Fracture	Medial Malleolus	10.3% (28/273)		0.8% (25/3020)
Fracture	Talus	0.8% (2/273)		
Fracture	Tibia	1.5% (4/273)		
Fracture, Other	-			0.4% (11/3020)
Infection	-	2.6% (7/273)	0.7% (16/2437)	1.1% (34/3020)

Hintermann Series H3™ Total Ankle Replacement System Serious Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
Infection	Periprosthetic	2.6% (7/273)	0.2% (4/2437)	0.8% (24/3020)
Infection	Superficial	0.4% (1/ 273)		
Infection	Wound Healing Problems		0.4% (9/2437)	1.5% (44/3020)
Loosening	-		0.4% (10/2437)	
Loosening	Talus			0.1% (2/3020)
Loosening	Tibia			0.2% (5/3020)
Loosening	Tibia, Ossification			0.1% (3/3020)
Loosening	Tibia, Talus			0.1% (3/3020)
Lysis	-		0.1% (2/2437)	
Malalignment	-			0.3% (8/3020)
Malalignment	Talus	0.4% (1/ 273)		
Malalignment	Tibia	1.1% (3/273)		0.4% (11/3020)
Malalignment	Tibia Or Talus	0.8% (2/273)		0.9% (27/3020)
Malalignment Tibia	-		0.1% (3/2437)	
Malalignment Tibia	Tibia Or Talus		0.1% (2/2437)	
Malalignment Tibia And Talus	-			0.0% (1/3020)
Malalignment Tibia/Talus	Tibia Talus	0.4% (1/ 273)		
Osteolysis	-		0.5% (13/2437)	0.4% (13/3020)
Osteolysis	Talus	0.4% (1/ 273)		
Osteolysis	Tibia	0.4% (1/ 273)		0.5% (15/3020)
Other	-	1.1% (3/273)	0.9% (22/2437)	2.1% (62/3020)
Other	Wound Healing Problems			0.1% (3/3020)
Other, Polyethylene Problems	-		0.2% (5/2437)	
Polyethylene Problems	-		0.1% (2/2437)	0.7% (21/3020)
Polyethylene Problems	Fracture	0.8% (2/273)	0.3% (7/2437)	1.6% (49/3020)

Hintermann Series H3™ Total Ankle Replacement System Serious Adverse Events H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
Polyethylene Problems	Instability	2.2% (6/273)	0.2% (4/2437)	
Polyethylene Problems	Ossification			0.0% (1/3020)
Polyethylene Problems	Wear	0.8% (2/273)	0.1% (2/2437)	
Polyethylene Problems, Other	Fracture			0.0% (1/3020)
Soft Tissue	Nerve		0.1% (2/2437)	
Soft Tissue	Nerve Injury	0.4% (1/ 273)		
Soft Tissue	Tarsal Tunnel Syndrome, Nerve		0.3% (7/2437)	
Soft Tissue	Tendon Injury	0.4% (1/ 273)		
Subsidence	-		0.2% (4/2437)	0.7% (20/3020)
Subsidence	Talus	1.5% (4/273)		0.0% (1/3020)
Subsidence	Talus & Tibia	0.4% (1/ 273)		
Subsidence	Tibia	0.4% (1/ 273)		0.0% (1/3020)

[1]Mercer et al. Provides a classification system for adverse events in TAR. Classification 1 is the proposed adverse event category. Each category is then subclassified further by type of adverse event, or specific anatomic location (Classification 2). (Mercer J., Penner M. et al. Inconsistency in the Reporting of Adverse Events in Total Ankle Arthroplasty: A Systemic Review of the Literature. Foot & Ankle International 2016, Vol. 37(2) 127-136).

Revisions

A revision of the TAR device as defined by the Mercer classifications was asssociated with the H3 in 27/273 subjects (9.9%). Based on data extracted from the published literature and from national joint registries, the revision rate for the H3 was 5.5%, but was 12.9% for the control device.

Table 18: Revisions - Summary

Hintermann Series H3™ Total Ankle Replacement System: Percent of Patients with Revisions Hintermann Registry, H3 and Control Literature and NJR			
Revisions-Percent of Patients	**H3 - PSE Cohort**	**H3 Literature**	**Control-All**
	9.9% (27/273)	5.5% (134/2437)	12.9% (391/3020)

Table 19: Revisions - Listing

Hintermann Series H3™ Total Ankle Replacement System Revision Intervention: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
-	Arthritis, Pain			0.0% (1/3020)
-	Arthrofibrosis		0.0% (1/2437)	
-	Avascular Necrosis Of Talus	0.4% (1/ 273)		
-	Avascular Necrosis Talus			0.0% (1/3020)
-	Chronic Pain	0.4% (1/ 273)	0.1% (2/2437)	0.7% (22/3020)
-	Equinus Contracture	0.4% (1/ 273)		0.0% (1/3020)
-	Hindfoot Malalignment	0.4% (1/ 273)		
-	Impingement	0.4% (1/ 273)	0.0% (1/2437)	
-	Lateral Malleolus			0.2% (6/3020)
-	Ligamentous Instability	0.4% (1/ 273)	0.0% (1/2437)	0.2% (6/3020)
-	Pain, Arthrofibrosis		0.2% (5/2437)	
-	Wound Healing Problems			0.3% (10/3020)
Aseptic Loosening	-	0.4% (1/ 273)	2.3% (56/2437)	3.5% (105/3020)
Aseptic Loosening	Talus		0.2% (6/2437)	0.4% (12/3020)
Aseptic Loosening	Tibia	0.4% (1/ 273)	0.2% (5/2437)	0.4% (11/3020)
Aseptic Loosening	Tibia, Talus			0.1% (4/3020)
Aseptic Loosening, Infection, Fracture	Tibia, Talus		0.6% (14/2437)	
Aseptic Loosening, Metal Component Fracture, Malalignment	-			0.2% (6/3020)
Fracture	-			0.4% (13/3020)
Fracture	Arthritis			0.0% (1/3020)

Hintermann Series H3™ Total Ankle Replacement System Revision Intervention: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Fracture	Malleolus			0.6% (19/3020)
Fracture	Tibia	0.4% (1/ 273)		
Fracture, Other	-			0.4% (11/3020)
Infection	-	0.4% (1/ 273)	0.4% (10/2437)	0.7% (21/3020)
Infection	Periprosthetic	1.8% (5/ 273)	0.2% (4/2437)	0.2% (6/3020)
Loosening	Talus			0.1% (2/3020)
Loosening	Tibia			0.1% (4/3020)
Loosening	Tibia, Ossification			0.1% (2/3020)
Loosening	Tibia, Talus			0.1% (3/3020)
Malalignment	-			0.1% (4/3020)
Malalignment	Talus	0.4% (1/ 273)		
Malalignment	Tibia	0.4% (1/ 273)		0.2% (5/3020)
Malalignment	Tibia Or Talus	0.4% (1/ 273)		0.7% (20/3020)
Malalignment Tibia	Tibia Or Talus		0.1% (2/2437)	
Malalignment Tibia And Talus	-			0.0% (1/3020)
Malalignment Tibia/Talus	Tibia Talus	0.4% (1/ 273)		
Osteolysis	-			0.4% (11/3020)
Osteolysis	Talus	0.4% (1/ 273)		
Other	-	0.4% (1/ 273)	1.0% (24/2437)	1.7% (52/3020)
Polyethylene Problems	Fracture	0.4% (1/ 273)		0.3% (8/3020)
Polyethylene Problems	Instability		0.1% (3/2437)	
Polyethylene Problems	Ossification			0.0% (1/3020)

Hintermann Series H3™ Total Ankle Replacement System Revision Intervention: H3 and Control Literature and National Joint Registries (NJR)				
Mercer Classification 1[1]	**Mercer Classification 2**	**H3 - Updated PSE cohort**	**H3 Literature**	**Control-All**
Polyethylene Problems	Wear	0.4% (1/ 273)		
Soft Tissue	Tendon Injury	0.4% (1/ 273)		
Subsidence	-			0.7% (20/3020)
Subsidence	Talus	0.7% (2/ 273)		0.0% (1/3020)
Subsidence	Tibia	0.4% (1/ 273)		0.0% (1/3020)

[1]Mercer et al. Provides a classification system for adverse events in TAR. Classification 1 is the proposed adverse event category. Each category is then subclassified further by type of adverse event, or specific anatomic location (Classification 2). (Mercer J., Penner M. et al. Inconsistency in the Reporting of Adverse Events in Total Ankle Arthroplasty: A Systemic Review of the Literature. Foot & Ankle International 2016, Vol. 37(2) 127-136).

2. Effectiveness Results

Primary Endpoints

The primary objective of this analysis is to determine the safety and effectiveness of the Hintermann Series H3 Total Ankle Replacement System compared to three separate Performance Goals (PGs). The PGs were developed by an independent statistician according to a pre-specified protocol and were based on all available and applicable data for the control device, which is the only currently approved mobile bearing TAR device in the US. PGs were developed for the three co-primary endpoints for this study:

(1) American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score at 2 years or more,
(2) the survivorship (absence of removal/revision) within 5 years, and
(3) the percentage of subjects with a serious device-related adverse event (SADE) other than a revision or removal within 2 years.

These endpoints are treated as co-primary endpoints and therefore statistical significance must be shown on all three endpoints individually in order for the study to be successful. Each endpoint is tested independently using alpha = 0.05. The results of the analyses of each co-primary endpoint is presented and discussed below.

American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score: One of the three co-primary endpoints in this study is the American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score at 2 years or later. For this endpoint, the AOFAS score at 2 years was used if possible; if it was not available then the AOFAS at the next available time point was used. The Performance Goal for this endpoint

was 71 points. Thus, the null and alternative hypothesis for each of the co-primary endpoints are as follows:

H_0: $\mu_{H3} \leq 71$ points
H_A: $\mu_{H3} > 71$ points
Where:
μ_{H3} = The mean AOFAS score at 2+ years for the PSE Cohort

The AOFAS study hypotheses was evaluated using a one-sided, 95% confidence interval for the mean AOFAS score at 2 years or greater, displayed in the table below.

Table 20 AOFAS at 2+ Years – PSE Cohort

N	Mean	Std Dev	Min	Max	Lower 95% Confidence Limit for Mean
253	78.0	18.08	13.0	100	76.12

The lower limit of this confidence interval is 76.12 points, which is greater than the fixed PG of 71 points for this endpoint.

Absence of Revision at 5 Years: Another of the three co-primary endpoints in this study is the Absence of Revision at the 5 year time point. The occurrence of a revision intervention was defined as specified in the methods developed by Mercer, et al. and was adjudicated by an independent CEC.
The Performance Goal for this endpoint was 0.83. Thus, the null and alternative hypothesis for each of the co-primary endpoints are as follows:

H_0: $p_{H3} \leq 0.83$
H_A: $p_{H3} > 0.83$
Where:
p_{H3} = The proportion of subjects in the PSE Cohort without a Revision at 5 years

The Absence of Revision/Removal study hypotheses was evaluated using a one-sided, 95% Exact Clopper-Pearson confidence interval for the proportion of subjects that have not had a revision/removal within 5 years.

Table 21: Absence of Revision at 5 Years - Updated PSE

Proportion Unrevised	CI Type	Lower 95% Confidence Limit
0.912 (248/272)	Clopper-Pearson (Exact)	0.878

The lower limit of this confidence interval is 0.878, which is greater than the fixed PG of 0.83 for this endpoint.

Absence of Serious Device-Related Adverse Events at 2 Years: Another of the three co-primary endpoints in this study is the Absence of SADE (as adjudicated by the independent CEC) at the 2 year time point.

The Performance Goal for this endpoint was 0.937. Thus, the null and alternative hypothesis for each of the co-primary endpoints are as follows:
H_0: $p_{H3} \leq 0.937$
H_A: $p_{H3} > 0.937$
Where:
p_{H3} = The proportion of subjects in the PSE Cohort without a SADE at 2 years

The Absence of SADE study hypothesis was evaluated using a one-sided, 95% Exact Clopper-Pearson confidence interval for the proportion of subjects that have not had a SADE within 2 years.

Table 22 Absence of SADE at 2 Years - Updated PSE

Proportion Without SADE	CI Type	Lower 95% Confidence Limit
0.963 (263/273)	Clopper-Pearson (Exact)	0.939

The lower limit of this confidence interval is 0.939 points, which meets the fixed PG of 0.937 for this endpoint.

Survivorship: Kaplan Meier Analysis

Kaplan Meier survivorship for the PSE Cohort from 0 to 7 years is shown in the table below. Device failure is defined as an adverse event requiring a revision intervention as adjudicated by the CEC. At 2 years, the survival estimate is 0.93 (95% CI: 0.900-0.959). At 5 years, the survival estimate for the investigational group is 0.92 (95% CI: 0.887-0.952) and at 7 years is 0.88 (95% CI: 0.824-0.936).

Table 23 Kaplan Meier Survivorship – Metal Components, PSE Cohort

Year	Survival	N*Revised (Cumulative)	N*Remaining at Risk	95% Confidence Interval
0	1.00	0	298	NA*
1	0.94	18	259	0.909, 0.965
2	0.93	20	226	0.900, 0.959
3	0.93	21	172	0.894, 0.956
4	0.92	22	153	0.887, 0.952
5	0.92	22	129	0.887, 0.952
6	0.90	24	63	0.856, 0.942
7	0.88	25	31	0.824, 0.936

Patient Satisfaction: Subjects in the H3 PSE Cohort were asked to rate their satisfaction with the TAR procedure according to the modified Coughlin scale[1]. At each long term follow up interval, the majority of subjects reported being very to moderately satisfied with the H3 TAR; at 2+ years, 94.4% of subjects were very to moderately satisfied with the procedure, and at 5+ years this number was 95.9%.

Table 24: Patient Satisfaction

Visit	Statistic/Category	H3
Year 1 (n = 189)	Very Good - Very Satisfied	78 (41.3)
	Good - Satisfied	71 (37.6)
	Moderate – Moderately Satisfied	28 (14.8)
	Bad - Not Satisfied	12 (6.3)
	Unknown/Missing	109
Year 2 (n=145)	Very Good - Very Satisfied	71 (49.0)
	Good - Satisfied	41 (28.3)
	Moderate – Moderately Satisfied	24 (16.6)
	Bad - Not Satisfied	9 (6.2)
	Unknown/Missing	153
Year 2+ (n=253)	Very Good - Very Satisfied	123 (48.6)
	Good - Satisfied	78 (30.8)
	Moderate – Moderately Satisfied	38 (15.0)
	Bad - Not Satisfied	14 (5.5)
	Unknown/Missing	45
Year 5+ (n=145)	Very Good - Very Satisfied	80 (55.2)
	Good - Satisfied	42 (29.0)
	Moderate – Moderately Satisfied	17 (11.7)
	Bad - Not Satisfied	6 (4.1)
	Unknown/Missing	153

3. Subgroup Analyses

   There appeared to be a trend for lower effectiveness in the smaller tibial sizes. A subgroup analysis of effectiveness by tibial size showed that the trend was driven by the AOFAS scores.

Table 25: Tibial size vs. Composite Primary Endpoint of the primary endpoint

	Size 1	2	3	4	5	6
Overall Success	0% (0/1)	59% (20/34)	69% (66/95)	76% (65/86)	88% (30/34)	66% (2/3)
Female	0% (0/1)	58% (19/33)	73% (43/59)	80% (12/15)	100% (1/1)	--
Male	--	100% (1/1)	64% (23/26)	75% (23/71)	88% (29/33)	66% (2/3)

1 Coughlin MJ. Arthrodesis of the first metatarsophalangeal joint with mini-fragment plate fixation. Orthopedics. 1990;13(9):1037–44.

Table 26: Tibial size vs. Components of the primary endpoint

	Size 1	2	3	4	5	6
AOFAS Success	0% (0/1)	59% (20/34)	72% (68/95)	78% (67/86)	91% (31/34)	66% (2/3)
Absence of SADE	100% (1/1)	100% (39/39)	92% (96/104)	98% (91/93)	100% (33/33)	100% (3/3)
Absence of Revision	100% (1/1)	90% (35/39)	85% (88/103)	96% (89/93)	97% (32/33)	100% (3/3)

Although the mean AOFAS at 2+ Years showed a trend for lower effectiveness in the smaller sizes, it was also true that the mean AOFAS at baseline for the H3 PSE cohort shows that subjects with smaller tibial sizes tended to have lower baseline scores than those with larger tibial sizes subjects. Thus, at 2+ years the mean changes from baseline still showed an minimial clinically important difference (MCID).

Table 27: Tibial size vs. AOFAS score

Tibial Size	N	Mean Score At Baseline	Mean Score at 2+ Years	AOFAS Change from Baseline
1	1	36.0	60.0	24
2	34	35.9 ± 14.8	68.4 ± 23	32.4 ± 24.2
3	95	40.6 ± 12.3	76.6 ± 19.5	36.1 ± 21.5
4	86	40.5 ± 10.8	80.6 ± 14.6	40.1 ± 16.9
5	34	39.9 ± 12.1	86.0 ± 10.5	46.2 ± 14.3
6	3	39.3 ± 3.5	71.7 ± 20.3	32.3 ±23.7

4. Pediatric Extrapolation

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

E. 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 registry study included 32 investigators. At the creation of the registry, none of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). Since that time, the primary investigator has been hired part-time by the company as Chief Medical Officer. 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.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The co-primary endpoints consisted of the mean AOFAS score at 2+ years, the proportion of subjects without a revision within 5 years, and the proportion of subjects without a serious adverse device effect within 2 years.

- The 95% lower confidence limit for the mean AOFAS score at 2+ years was 76.12 points for the PSE cohort, which is greater than the fixed PG of 71 points for this endpoint.

- The 95% lower confidence limit for the proportion of subjects without a metal component revision at 5 years was 0.878, which is greater than the fixed PG of 0.83 for this endpoint.

- The 95% lower confidence limit for the proportion of subjects without a SADE at 2 years was 0.939, which is greater than the fixed PG of 0.937 for this endpoint.

Thus, the primary effectiveness evaluation demonstrates that the PSE cohort has exceeded the Performance Goals to show that the Hintermann Series H3™ Total Ankle Replacement System has a reasonable assurance of effective to replace a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The analyses of safety data showed that the Hintermann Series H3™ Total Ankle Replacement System has a reasonable assurance of safety.

The primary safety assessment for this study compares the serious device related adverse event rates recorded for the H3 study population to those from the studies that were selected for the meta-analysis of PGs.

Among the three groups compared, the H3 PSE cohort had the lowest percentage of SADE, although the SADE percentage for the H3 literature was similar. The SADE percentage for the control group was 10.5%, higher than that for the H3 PSE Cohort or the rate calculated for the published reports and national joint registry reports for the H3. Please note that the SADE rates are not based on a specific time point and some devices may have been implanted longer than others.

Table 28: Primary Safety Assessment

Percent of Patients with Serious Device-Related Adverse Events Hintermann Registry, H3 and Control Literature and NJR			
SADE-Percent of Patients	**H3 - PSE cohort**	**H3 Literature**	**Control-All**
	5.9% (16/273)	6.0% (146/2437)	10.5% (316/3020)

There were no unanticipated adverse events, and all adverse event information reported in this study is consistent with the types, incidences and occurrences of adverse events reported in the literature to be associated with total ankle replacement.

A revision of the TAR device as defined by the Mercer classifications was associated with the H3 in 27/273 subjects (9.9%). Based on data extracted from the published literature and from national joint registries, the revision rate for the H3 was 5.5%, but was 12.9% for the control device.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. There are probable benefits, including pain reduction and restoration of function, associated with total ankle replacement with the Hintermann Series H3 system, and the clinical study demonstrated that for each of the 3 co-primary study endpoints, the H3 Updated PSE Cohort exceeded the fixed PG. Further, the KM Survivorship at 7 years is 0.88 (95% CI: 0.824-0.936).

The PGs used in this study are based on a prospectively defined systematic meta-analysis of available published literature and registry data on the control device.

The screening and selection of studies used to develop PGs were completed by independent reviewers, and the literature search and meta-analysis methods were prospectively specified. The statistical analysis plan was submitted to FDA for review and comment before the analysis was undertaken.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The risks of TAR with the H3 system do not differ significantly from the risks associated with the control TAR

system, and no new or additional risks were identified in this study compared to the risks of TAR reported in the literature.

The types of device-related serious adverse events in H3 Updated PSE Cohort did not differ from the complications reported in the literature for the H3 device or for the control device, although rates differed. The SADE rate for the H3 study population was 5.9% and was 10.5% for the control device. The types and rates of device related adverse events, comparing the H3 Cohort, reports of the H3 device in national joint registries and in the literature, and reports of the control device in national joint registries and in the literature, were organized by Mercer classifications and reviewed and adjudicated by a CEC.

1. Patient Perspectives

   Patients choose to undergo total ankle replacement to reduce pain and improve function. The AOFAS Score, which measures improvement in pain, function and ankle alignment, showed that improvement in AOFAS for the H3 PSE Cohort was greater than the fixed PG for this endpoint.

   Subjects in the Updated H3 PSE Cohort were asked to rate their satisfaction with the TAR procedure according to the modified Coughlin scale. At each long term follow up interval, the majority of subjects reported being very to moderately satisfied with the H3 TAR; at 2+ years, 94.4% of subjects were very to moderately satisfied with the procedure, and at 5+ years this number was 95.9%.

In conclusion, given the available information above, the data support that for the Hintermann Series H3™ Total Ankle Replacement System, for use as a non-cemented implant to replace a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Hintermann Series H3™ Total Ankle Replacement System when used in accordance with the indications for use.

This study demonstrated that the Hintermann Series H3™ Total Ankle Replacement System exceeded the Performance Goals established for this study, had the same safety profile as published reports and national joint registry data for the H3 system, and had a more favorable safety profile compared to published reports for the control system. The Kaplan Meier survivorship estimate is 0.88 at 7 years.

The pre-clinical and clinical data in this PMA application support the reasonable assurance of safety and effectiveness of the Hintermann Series H3 total ankle replacement system for use in patients undergoing primary total ankle arthroplasty to

replace a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease.

XIII. CDRH DECISION

CDRH issued an approval order on June 4, 2019. The final conditions of approval cited in the approval order are described below.

1. The first post-approval study is designed to evaluate the long-term safety and effectiveness of the Hintermann Series H3™ TAR System among patients included in the Primary Safety and Effectiveness (PSE) Cohort. A prospective, single-center, single arm study design with hypothesis testing will be used to determine the 10-year survivorship and effectiveness of arthroplasty using the Hintermann Series H3™ TAR System in comparison to historical literature controls for a legally marketed mobile bearing ankle. If possible, Performance Goals (PGs) similar to the original study, should be constructed for the 10-year endpoint. The PGs used in the PMA study are based on a prospectively defined, systematic meta-analysis of available published literature and registry data for the control (a legally marketed mobile bearing ankle). The study population will consist of all living subjects who participated in the PSE cohort, regardless of whether or not the patient has had a revision/removal followed through the 10-year post-operation visit. A follow-up rate of 85% is expected at each timepoint. Specific attention will be given to patients with the smaller sized tibial implants (i.e. 1, 2, and 3), as the results appear to show a lower overall effectiveness for patients with the smaller sized implants. Patients will undergo clinical and radiographic evaluation postoperatively at 5 and 10 years. The 5 and 10-year data will be collected as in the PSE cohort during the PMA study. You have agreed to take reasonable measures to avoid loss to follow-up and statistically analyze impact of any missing data.

   You have agreed to collect information about any reoperation, revisions or removals of the Hintermann Ankle device components, and effectiveness endpoints, including the American Orthopaedic Foot and Ankle Society, the survivorship (absence of removal/revisions to include polyethylene revision), and the percentage of subjects with a serious device-related adverse event other than a revision or removal. Again, special attention should be paid to the patients receiving the smaller sized (Size 1, 2 and 3) tibial implants in case the trend of lower effectiveness results still continues. You have also agreed to collect information about all adverse events reported for these patients, including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome. Additionally, you have agreed to provide a detailed explant analysis of any explanted devices during the PAS.

   Every six months for the first two years and then annually until the study is completed you are to submit a progress report to the FDA that includes, but is not limited to, the status of site enrollment, the status of patient enrollment, the status of patient follow-up, and other milestones as it compares to the stated goals in the protocol. Please provide all safety and effectiveness data collected during the reporting period and provide an explanation for any delay in meeting the stated goals in the protocol.

You must also update your patient and physician labeling (via a PMA supplement) to reflect the 10-year findings, as soon as these data are available, as well as any other timepoint deemed necessary by FDA if significant new information from this study becomes available.

Be advised that failure to comply with any post-approval requirement, including the requirements to meet the enrollment, treatment and completion dates outlined above, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c).

2. You have agreed to perform a second post-approval study to evaluate the trend in performance between each implant size and assess the outcomes of the primary surgeon of the study (accounting for approximately 80% of the registry) compared to other surgeons that are less familiar with the device. You agree to use a prospective, multicenter, single arm study design, and hypothesis testing to evaluate the performance of the different implant sizes of the Hintermann Series H3™ TAR System compared to the Hintermann Series H3™ TAR System performance in the PSE cohort. Multiple investigators should be recruited so that one surgeon does not conduct the majority of the cases. At the time of this approval, there are minimal data for several tibial sizes (Sizes 1, 2, 5, and 6), with size 1 and 6 having n =1 and n =3, respectively. Therefore, additional patients in each size are needed to demonstrate that the trend for overall lower success scores in smaller sizes is not an artifact due to the low sample size. Furthermore, approximately 80% of the clinical data in the primary safety and effectiveness cohort was conducted by one surgeon. Additional surgeons unfamiliar with the device should be recruited to evaluate the impact of experience on overall outcomes.

You have agreed to enroll 220 new study subjects and follow these subjects for 5 years. We strongly encourage that the majority of these subjects be enrolled in the United States. Enough subjects should be enrolled in each tibial size to be able to evaluate the trend in performance between each size. Study subjects will undergo clinical and radiographic evaluation postoperatively at 6 weeks, 6 months, and yearly afterwards. You have agreed to take reasonable measures to avoid loss to follow-up. A follow-up rate of 85% is expected at each timepoint.

You have agreed to collect information about safety, including any reoperation, revisions or removals of the Hintermann Ankle device, and effectiveness endpoints, including the American Orthopaedic Foot and Ankle Society at 2 years or more, the survivorship (absence of removal/revisions to include polyethylene revision), the percentage of patients subjects with a serious device-related adverse event other than a revision or removal within 2 years, VAS score, patient satisfaction, and either SF-36 or PROMIS for general well-being. You will also collect information about all adverse events reported for these patients, including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome. Additionally, you have agreed to provide a detailed explant analysis of any explanted devices during the PAS. Failure to obtain adequate study subject numbers for each size could potentially

result in requirements to update labeling with advisory statements regarding the affected sizes, or the Agency taking action to remove approval of the affected sizes.

Be advised that failure to comply with any post-approval requirement, including the requirements to meet the enrollment, treatment and completion dates outlined above, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

Mercer J., Penner M. et al. Inconsistency in the Reporting of Adverse Events in Total Ankle Arthroplasty: A Systemic Review of the Literature. Foot & Ankle International 2016, Vol. 37(2) 127-136.