

SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name: Mobile Bearing Total Ankle Prosthesis

Device Trade Name: Scandinavian Total Ankle Replacement System (STAR Ankle)

Applicant's Name and Address: Small Bone Innovations, Inc.
1380 South Pennsylvania Avenue
Morrisville, Pennsylvania 19067

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Premarket Approval Application (PMA) Number: P050050

Date of FDA Notice of Approval: May 27, 2009

Expedited: Expedited review granted on September 5, 2003

II. INDICATIONS FOR USE

The STAR Ankle is indicated for use as a non-cemented implant to replace a painful arthritic ankle joint due to osteoarthritis, post-traumatic arthritis or rheumatoid arthritis.

III. CONTRAINDICATIONS

- Active or prior deep infection in the ankle joint or adjacent bones
- 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
 - Prior surgery and/or injury that has adversely affected ankle bone quality
- 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
- Neuromuscular disease resulting in lack of normal muscle function about the affected ankle
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Charcot joint or peripheral neuropathy that may lead to Charcot joint of the affected ankle
- Prior arthrodesis at the ankle joint
- Poor skin and soft tissue quality about the surgical site

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the STAR Ankle labeling.

V. **DEVICE DESCRIPTION**

General Overview

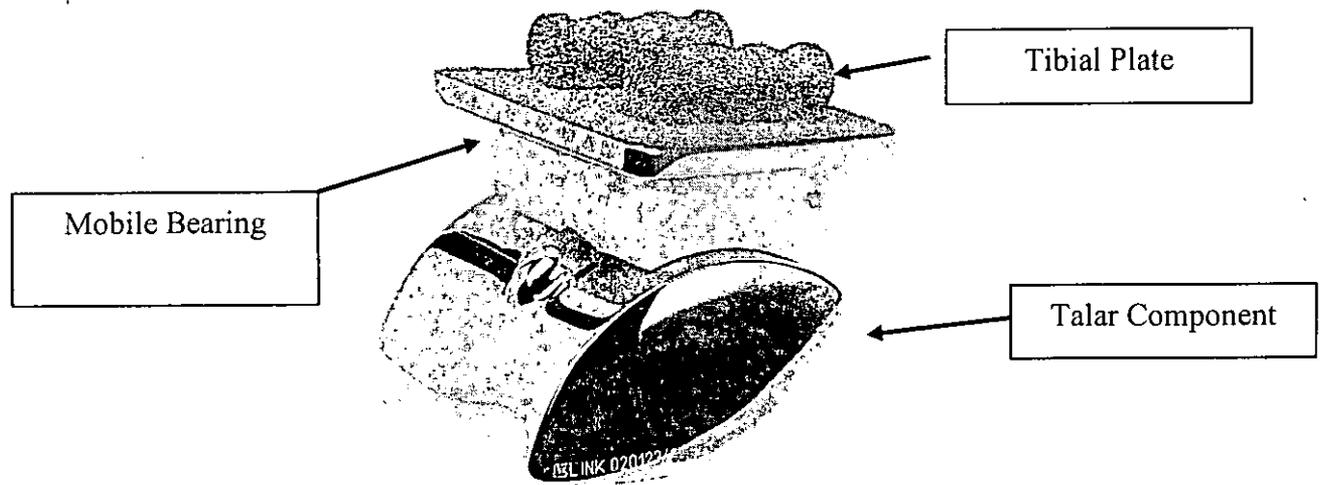
The Scandinavian Total Ankle Replacement System (STAR Ankle) is comprised of a Tibial Plate, Mobile Bearing, and Talar Component. See **Table 1** for a description of the components.

Table 1: Description of Components

Component	Sizes	Material	Standard
Tibial Plate	Extra Small (30mm x 30mm)	Cobalt-Chromium-Molybdenum Alloy with Titanium Plasma Spray Coating	Co-Cr-Mo (ASTM F75 ¹) Coating (ASTM F67 ²)
	Small (32mm x 30mm)		
	Medium (32.5mm x 35mm)		
	Large (33mm x 40mm)		
	Extra Large (33.5mm x 45mm)		
Mobile Bearing	Thicknesses of 6, 7, 8, 9, 10 mm Revision bearings in thicknesses of 11, 12, 13, and 14mm	Ultra-High Molecular Weight Polyethylene (UHMWPe) with stainless steel radiographic marker wires	UHMWPe (ASTM F648 ³) Stainless Steel (ASTM F138 ⁴)
Talar Component	Extra-extra Small (28mm x 29mm)	Cobalt-Chromium-Molybdenum Alloy with Titanium Plasma Spray Coating	Co-Cr-Mo (ASTM F75) Coating (ASTM F67)
	Extra Small (30mm x 31mm)		
	Small (34mm x 35mm)		
	Medium (36mm x 35mm)		
	Large (38mm x 35mm)		

The STAR Ankle is designed to replace a portion of the distal tibial and proximal talar bones of the natural ankle joint. The mobile bearing articulates with both the Tibial Plate and Talar Component as shown in the photograph of the three components of the STAR Ankle system below:

Figure 1. STAR Ankle



Tibial Plate

When viewed from the top, the Tibial Plate has a trapezoidal shape with rounded corners. This component is shaped to conform to the existing anatomy thereby reducing the need to remove excess bone around the joint. On the proximal surface of the Tibial Plate, two parallel cylindrical barrels are positioned equidistant from the center of the plate running anterior to posterior for bone fixation.

When viewed from the side, the plate is 2.5mm thick. The distal surface of the plate on which the mobile bearing articulates is flat and polished.

The Tibial Plate is coated on the bone-opposing surfaces with a titanium plasma spray coating. The Tibial Plate is intended to be press-fit without the use of cement, and should rest on anterior and posterior cortical bone.

Mobile Bearing

The proximal surface of the Mobile Bearing is flat. The distal (talar) surface is concave and has a central radial groove running from anterior to posterior. The walls of the bearing component are straight. A 0.5mm stainless steel x-ray marker wire is placed 2mm from the proximal surface.

Talar Component

The Talar Component is designed as an anatomical prosthesis to cover the talar dome, anterior, posterior, and medial and lateral facets. The Talar Component is designed to minimize the amount of bone that must be removed. From the apex of the dome, the walls slope outwards to conform to the normal bone anatomy.

Viewed from the side, the proximal surface of the Talar Component is dome-shaped to conform to the talar dome of the natural ankle. A small, raised half-cylindrical ridge runs from anterior to posterior in the medial-lateral center of the dome. The purpose of this ridge is to constrain the medial/lateral motion of the mobile bearing.

- As with the Tibial Plate, the Talar Component is also provided with a titanium plasma spray coating.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Treatments for degenerative ankle disease range from conservative methods, such as rest, heat, electrotherapy, physical therapy, bracing, and pain medication to surgery. When conservative therapy fails to relieve patient 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, in which the ankle joint is replaced by a prosthetic device which attempts to mimic the movement of the ankle. Currently, there are several semi-constrained ankle prostheses available in the United States.

Each alternative 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.

VII. MARKETING HISTORY

The STAR Ankle has been marketed in Europe since 1990. It has been distributed in the countries listed in **Table 2**. The STAR Ankle has not been withdrawn from the market in any country for reasons related to its safety or effectiveness.

Table 2: Worldwide Marketing History

Australia	Hong Kong	Poland
Austria	Hungary	Portugal
Belarus	India	Russia
Belgium/Lux	Ireland	Slovakia
Brazil	Israel	Slovenia
Canada	Italy	South Africa
China	Japan	Spain
Czech Rep	Korea	Sweden
Denmark	Lithuania	Switzerland
Finland	Malaysia	Taiwan
France	Netherlands	Thailand
Germany	Norway	UK

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with ankle replacement surgery, including surgery using the STAR Ankle:

1. Device failure
2. Dislocation
3. Loosening of any of the components
4. Fatigue fracture of the implants

5. Peripheral neuropathies, nerve damage, circulatory compromise
6. Heterotopic bone formation
7. Surgical complications including, but not limited to: vascular disorders, thrombophlebitis, hematoma or damage to blood vessels resulting in blood loss, or death
8. Delayed wound healing
9. Superficial or deep infection at any point in time postoperatively
10. Adverse effects may necessitate reoperation, revision, arthrodesis of the involved ankle, and/or amputation of the ankle
11. Intraoperative or postoperative bone fracture
12. Wear deformation of the articular surface
13. Damage to ligamentous, tendinous, and surrounding soft tissues
14. Osteolysis and/or other periprosthetic bone loss
15. Metal sensitivity reactions or allergic reactions or metallosis
16. Limb length discrepancy
17. Increased ankle pain and/or reduced ankle function

Any of these adverse effects may require medical or surgical intervention.

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

IX. SUMMARY OF PRECLINICAL STUDIES

The following studies were carried out on the Scandinavian Total Ankle Replacement System (STAR Ankle): intrinsic stability, wear, surface coating characterization and oxidative age testing. In addition, a retrieval study to evaluate UHMWPE wear was also performed. There are currently no guidance documents or recognized standards for total ankle replacements.

A. Laboratory Studies

Intrinsic Stability Testing:

This test measured the degree of constraint imposed by the STAR Ankle prosthesis in rotation, anterior/posterior, and medial/lateral directions. Testing was performed using an Instron dynamic testing machine capable of applying biaxial loads. The degree of constraint was determined under compressive loading conditions intended to replicate loads seen in normal walking (i.e., 3,650 N, which is five times the body weight of a 165 lb person). The compressive load was applied at 10° flexion to represent conditions of maximum shear. These conditions were designed to model the range of loads encountered in a single-leg stance in the normal *in vivo* gait cycle. Three 7mm polyethylene components were tested.

The anterior/posterior testing mode applied shearing displacements at 12.5 cm/minute until implant failure or subluxation occurred and measured the maximum shear at failure. Similar procedures were followed for the medial/lateral testing modes. For rotation, the same compressive load was applied at 10° flexion in addition to 8.5 Nm horizontal torque. The internal and external angular displacements were recorded as a measure of rotational constraint.

The results demonstrate that the STAR Ankle exhibits minimal constraint in the anterior/posterior, medial/lateral, and rotational modes.

Wear Testing:

Wear testing was performed on the thinnest Mobile Bearing (i.e., 6mm), and the smallest sizing combination for the Tibial Plate and Talar Component to explore the potential worst case scenario with respect to wear.

The wear characteristics of the STAR Ankle were measured under simulated functional use. Each specimen was aligned in 5 degrees of plantar flexion and loaded statically at $3,000 \pm 62$ N of joint compression through a center of rotation of the STAR Ankle via a compression spring. Under displacement control, the prosthesis was articulated through 2.0 ± 0.5 degrees of fully reversing axial rotation about the geometric center of the prosthesis. In addition, the prosthesis was articulated through 15.0 ± 0.5 degrees of fully reversing flexion about a center 9.7mm anterior of the designed center of rotation of the prosthesis. This shift in rotational centers resulted in 2.5 mm of fully reversing anterior translation coupled to flexion. All motions were sinusoidal and at a rate of 1 Hz. All testing was conducted in $37^\circ\text{C} \pm 3^\circ\text{C}$. Wear was evaluated through gravimetric weight loss following the guidelines from ASTM F1714⁵ and articular surface examination.

Weight loss, total wear, and wear rate were reported for each specimen after correcting for fluid absorption in the soak controls. All specimens completed 10 million cycles of motion without gross failure. The Mobile Bearings showed a mean volumetric wear rate of 56.9 mm^3 after 10 million cycles, which represents $5.6 \text{ mm}^3/\text{million cycles}$. This value is lower than values reported in the literature for Co-Cr / UHMWPe hip replacements ($7\text{-}25 \text{ mm}^3/\text{million cycles}$) and knee replacements ($>70 \text{ mm}^3/\text{million cycles}$)^{6,7,8}. Volumetric wear rates of ankle replacements in literature have not been reported by the applicant. A correlation between ankle wear rates reported in this study and wear rates reported in hip and knee replacement cannot be made due to differences in loading, bearing surface characteristics and surface area.

Contact Stress:

In this test, medium and low pressure films (Pressurex Film, Sensor Products, Inc., East Hanover, NJ) with readable pressure ranges of 10 to 50 MPa and 2.5 to 10MPa, respectively, were used to assess the distribution of contact stresses across the Mobile Bearing component of the implant when loaded. Axial loads of 3,650 N were applied, representing five times the body weight of an average adult male weighing 164lbs. The effect of varying thicknesses of the Mobile Bearing (i.e., 6, 7, 8, 9, and 10mm), and of different flexion angles of the insert (25° , 0° , -25°), were also evaluated. Testing was repeated 3 times for each of the 3 test specimens.

The test demonstrated that the entire surface area for Tibial Plate / Mobile Bearing contact, experienced as least 1 MPa of contact pressure. Two areas of concentration were observed at the center over the two Talar Component contact surfaces, with pressures of approximately 10 MPa.

Surface Coating Characterization:

The Tibial Plate and Talar Component are coated with a plasma sprayed unalloyed titanium coating.

The static shear strength of the surface coating/substrate interface should exceed 20 MPa for porous surface coatings as tested per ASTM F1044⁹ Standard Test Method for Shear Testing of Calcium Phosphate Coatings and Metallic Coatings. The static tensile strength of the surface/substrate shall exceed 20 MPa for porous surface coatings.

The static shear strength of the surface coating/substrate interface was tested per ASTM F1044. The static tensile strength of the surface coating/substrate interface was evaluated per ASTM F1147¹⁰. **Table 3** summarizes the results of the plasma spray coating characterization. The coating met all acceptance criteria.

Table 3. Plasma Spray Coating¹ Characterization

	Bond Coat	Top Coat
Particle Size	90 μm	180 μ
Coating Thickness	50 \pm 10 μm	225 \pm 50 μm
Porosity	Dense	30 \pm 5%
Pore Size		90 μm
Roughness		90 μm
Tensile Strength		63.09 \pm 5.72 MPa ²
Shear Strength		30.35 \pm 15.57 MPa ²

¹Coating includes a bond coat and a top coat. The tensile and shear testing were conducted on the coating system (i.e., substrate, bond coat, and top coat)

B. Animal Studies

Animal studies were not necessary to support the safety and effectiveness of the STAR Ankle.

The materials used in the STAR Ankle have a long established history of clinical use in orthopedics. The applicant provided appropriate biocompatibility information according to ISO 10993.

C. Additional Studies

Retrieval Study

Thirty-five (35) retrieved UHMWPE components from the STAR Ankle were analyzed for wear damage. Each specimen was examined under a stereomicroscope for damage. Damage was divided into seven modes: burnishing, abrasion, pitting, surface deformation, delamination, scratching and debris capture. After analysis of the 35 retrieved specimens, burnishing was determined to be the most common mode of wear followed by scratching, pitting and abrasion. Three of thirty-five specimens presented with fractures that precluded reasonable function. Nine of thirty-five specimens demonstrated significant damage to the

keel-trough. Nine of thirty-five specimens demonstrated significant loss of material on the edges of the component due presumably to bone contact.

Sterilization, Validation, Packaging, Shelf-Life and Oxidative Aging

Device components are sterilized via gamma irradiation at a dosage of 25 – 29 kGy. Contract sterilizers use gamma irradiation at a dosage of 25-29 kGy to irradiate all STAR Ankle components. Sterilization was validated using the method described in ANSI/AAMI/ISO 11137-1995. The sterility assurance level (SAL) is 10^{-6} . The UHMWPE mobile bearing has a shelf-life of 5 years.

Components are double-pouched in PA/PE-laminated foil peel-pouches. The inner pouch is subject to vacuum prior to heat sealing. The inner pouch is placed in an outer pouch that is also heat-sealed. Each component is packaged in a box separately. The functionality of the peel-pouch has demonstrated a long history of use (more than 15 years with no complaints of packaging malfunction).

An investigation was performed to evaluate oxidative aging of the mobile bearings during a shelf life of up to 5.6 years. Testing was conducted to characterize the oxygen level present in the packaging as well as oxidation in the mobile bearing of the STAR Ankle. All oxidation testing of the STAR components was conducted in accordance with ASTM F2102-06¹¹ (this standard is not recognized by FDA). The evaluation tested 5 specimens of 10mm meniscal bearing components of the STAR Ankle with real-time aging of 20 days, 1.3 years, 2.2 years, 4.6 years and 5.6 years. Each component had been packaged, sterilized, and stored in accordance with the standard procedure used for the final product. The oxidation index was calculated for each sample of the bearing component using Fourier transform infrared spectrometry (FTIR) according to ASTM F2102-06.

Loss of mechanical properties to below ASTM minima (1.5) occurs when critical oxidation is reached. No mobile bearings reached the ASTM minima within the shelf life of 5.6 years as tested. All oxidation levels were below 1.5. Therefore, the acceptance criteria were met by all samples. See **Table 4** below for a summary of the oxidative aging analysis.

Table 4. Oxidation Index at 5.6 years Self-Storage

Sample Information	UHMWPE Mobile Bearings
Thickness at sample position for oxidation index measurement	10 mm
Gamma sterilization date	2002-04
Real time shelf-storage	5.6 years
Number of samples analyzed	5
Maximal oxidation (mean ± s.d.)	1.39 ± 0.07

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of total ankle arthroplasty with the STAR Ankle for the treatment of a painful arthritic ankle joint due to osteoarthritis, post-traumatic arthrosis or rheumatoid arthritis in the US under IDE #G000140. Data from this clinical study were the basis for the PMA approval decision. The study had three cohorts: pivotal, bilateral and continued access. The bilateral and continued access cohorts will be described in more detail under section XI. **Table 5** summarizes the US clinical studies performed under G000140.

Table 5: US Clinical Studies for the STAR Ankle

Cohort	Definition	Number of Centers	Enrolled Patients
Pivotal	Non-randomized, concurrent, multi-center study to evaluate the safety and effectiveness of the STAR Ankle compared to ankle arthrodesis at 2 years	10 STAR Ankle; 5 arthrodesis	158 STAR Ankle patients; 66 arthrodesis control patients
Bilateral	Single-arm multi-center cohort to evaluate the safety of bilateral STAR Ankle implantation	6	21 bilateral STAR Ankle patients
Continued Access	Single-arm, multi-center cohort to confirm the findings of the pivotal study	10	448 STAR Ankle patients

A. Study Design

Pivotal STAR study patients were treated between September 15, 2000 and December 10, 2001 and pivotal arthrodesis study patients were treated between October 26, 2000 and April 27, 2005. The database for this PMA reflected data collected through August 30, 2007 and included 224 pivotal patients. There were 15 investigational sites.

The study was a prospective, multi-center, non-randomized, non-blinded; concurrently controlled clinical study. The study was designed as a non-inferiority study comparing the safety and effectiveness of the STAR Ankle to the arthrodesis control. Study duration was out to 2 years. There was a 2:1 ratio of STAR Ankle patients to arthrodesis patients in the pivotal study. The patient sample size was based on the individual patient safety endpoint. The applicant stated that the study hypothesis was that treatment effectiveness, safety, and overall patient success at one year, with further confirmation at two years, of the STAR Ankle group would not be inferior to the arthrodesis group. Patient outcomes at two years were ultimately used to evaluate device safety and efficacy. The non-inferiority margin deltas were 10 points in Buechel-Pappas score for effectiveness and 15% for the safety and overall patient success.

The control group received fusion of the tibio-talar joint in the ankle (i.e. arthrodesis). Several legally marketed devices (e.g. screws) with similar indications for use can create an ankle arthrodesis and were compared to the STAR Ankle.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the STAR Ankle study was limited to patients who met the following inclusion criteria:

- Moderate or severe pain, loss of mobility and function of the ankle (Buechel-Pappas Scale total score of less than 50 and Buechel-Pappas pain score of 20 or less)
- Primary arthrosis, post traumatic arthrosis or rheumatoid arthrosis
- At least six months of conservative treatment for severe ankle conditions, confirmed by the patient medical history, radiograph studies and medication record
- Willing and able to give informed consent

Patients were not permitted to enroll in the STAR Ankle study if they met any of the following exclusion criteria:

- Patients who have not reached skeletal maturity
- Active or prior deep infection in the ankle joint or adjacent bones
- Prior arthrodesis at the involved site
- History of prior mental illness or patient demonstrates that their mental capacity may interfere with their ability to follow the study protocol
- Obesity (weight greater than 250 lbs)
- History of current or prior drug abuse or alcoholism
- Any physical condition precluding major surgery
- Hindfoot malpositioned by more than 35 degrees or forefoot malalignment which would preclude a plantigrade foot
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Avascular necrosis of the talus
- Inadequate skin coverage about the ankle joint
- Patients under the age of 35 who are unwilling or unable to accept the physical limitations imposed by ankle arthroplasty, including limitations on certain vigorous physical activities (e.g. basketball, football, etc) and on manual labor
- Juvenile onset type I diabetes
- Adult onset Type II diabetes when accompanied by neuropathic changes or a history of foot infection in either foot
- Pregnancy
- Avascular necrosis of the tibia
- Significant bone tumor of the foot or ankle
- Severe deformity that would not normally be eligible for ankle surgery
- Prior surgery and/or injury that has adversely affected the ankle bone stock
- Severe osteoporotic or osteopenic condition or other conditions that may lead to inadequate implant fixation in the bone
- Insufficient ligament support
- Motor dysfunction due to neuromuscular impairment

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 2 weeks (2-3 weeks), 6 weeks (± 1 week), 3 months (± 2 weeks), 6 months (± 2 weeks), 12 months (± 4 weeks), and 24 months (± 4 weeks) postoperatively.

Table 6 displays all pre- and post-operative evaluation assessments and time points. Adverse events and complications were recorded at all visits.

Table 6: Follow-up Schedule

Assessment	Baseline	Follow-up					
		2-3 Weeks	6 Weeks	3 Month	6 Month	12 Month	24 Month
Eligibility	X						
Medical History	X						
Physical Exam	X	X	X	X	X	X	X
Medication History	X	X	X	X	X	X	X
Complication Report		X	X	X	X	X	X
Radiographic Evaluation	X	X	X	X	X	X	X
Buechel-Pappas Scale	X			X	X	X	X
Pain VAS	X			X	X	X	X
Coughlin Score				X	X	X	X
SF-36	X			X	X	X	X

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

3. Clinical Endpoints

Table 7 summarizes the success criteria for the STAR Ankle study:

Table 7: Success Criteria for the STAR Ankle

	STAR	Control (Arthrodesis)
Effectiveness Success	≥ 40 point improvement in Buechel Pappas Score	≥ 40 point improvement in Buechel Pappas Score
Safety Success	Clinical Safety Success: Absence of major complications, device failure, removal/revision	Clinical Safety Success: Absence of major complications, revision
	Radiographic Safety Success: Absence of radiolucencies, tilting or migration > 4 mm	Radiographic Safety Success: Absence of non-union, mal-union, delayed union
Overall Patient Success	Patients meeting each of the above STAR efficacy and success criteria are considered to be an overall patient success	Patients meeting each of the above control efficacy and success criteria are considered to be an overall patient success

The primary safety endpoint for the STAR Ankle cohort as defined in the IDE study (G000140) was comprised of clinical success (absence of major complications, device failure or removal/revision) and radiographic success (no radiolucency, tilting or migration > 4mm). The primary safety endpoint for the arthrodesis cohort was also comprised of clinical success (absence of major complications and revisions) and radiographic success (absence of non-union, mal-union or delay union).

The primary effectiveness endpoint was based on improvement in mean Buechel Pappas (BP) score¹². The BP score is based on a 100-point scale consisting of subscales for pain (40 points), function (40 points), range of motion (15 points) and deformity (5 points). Efficacy success was defined as a minimum 40 point increase from baseline.

Secondary effectiveness endpoints consisted of the following:

- BP score subscales of function and range of motion,
- % of patients with improvement in total BP score of 40 points or more,
- Pain visual analog scale (VAS, 100 mm scale),
- Patient satisfaction (Coughlin rating four category scale: excellent, good, fair, poor),
- Quality of life (SF-36), and
- Medication usage

With regard to success/failure criteria, overall patient success was defined as a patient meeting both efficacy and safety endpoints as described above. The study hypothesis was that treatment effectiveness, safety, and overall patient success at one year, with further confirmation at two years, of the STAR Ankle group would not be inferior to those of the arthrodesis group. FDA used two year data to make the final determination of safety and effectiveness. The non-inferiority margin deltas were 10 points in BP score for effectiveness and 15% for the safety and overall patient success.

The primary effectiveness endpoint of mean total Buechel-Pappas score was compared between the two treatment groups using the method of Blackwelder¹³ to determine if the overall outcome in the STAR Ankle group was not inferior to that of the arthrodesis group. In addition, based on the methodology proposed by Dunnett and Gent¹⁴ and Morikawa & Yoshida¹⁵, a two-sample t-test was performed, without adjustment for multiple comparisons, to determine if the STAR outcome was also superior to arthrodesis. The secondary endpoints of function and range of motion subscale scores were compared between treatment groups using a two-sample t-test to determine if function and range of motion with the STAR Ankle were superior to function and range of motion with arthrodesis. The percentage of patients with a 40-point increase in total Buechel-Pappas score was compared between treatment groups using a Chi-square test. Pain visual analog scale (VAS) score, patient satisfaction, and quality of life were compared between the groups using a two-sample t-test to determine whether these parameters were similar between the two groups.

B. Accountability of PMA Cohort

At the time of database lock, of 224 pivotal study subjects enrolled in the PMA study, 96.7% (145/150) of the STAR Ankle subjects and 73.8% (48/65) of the arthrodesis patients were available for analysis at the completion of the study, the 24 month post-operative visit.

A total of 224 patients were enrolled in the pivotal study. Of these patients, 158 subjects were enrolled and treated in the arthroplasty group (or the STAR Ankle group) and the remaining 66 patients were enrolled and treated in the Arthrodesis group. Each patient underwent a baseline evaluation to determine eligibility and establish preoperative pain and functional status. Patients were asked to return to postoperative evaluations at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 24 months. The number of patients with data available, at the time of database closure, for each of these study follow-up evaluations is summarized in **Table 8**. As shown below, follow-up evaluations for STAR patients were completed for 96.7% of expected patients at 12 months and 24 months. Follow-up evaluations in the arthrodesis group were completed for 80.3% and 73.8% of expected patients at 12 months and 24 months, respectively.

Analyses were based on an intent-to-treat (ITT) patient population where that analysis population included all patients who enrolled in the study, where data were available. Additional analyses of the effectiveness, safety and patient success rates were based on the Per Protocol population and the ITT patient population to ensure that results were consistent using these analysis populations.

Table 8: STAR Ankle Pivotal Study Accountability Summary Table

	Pre-op		2 Weeks		6 Weeks		3 Months		6 Months		12 Months		24 Months	
	C	S	C	S	C	S	C	S	C	S	C	S	C	S
Theoretical	66	158	66	158	66	158	66	158	66	158	66	158	66	158
Deaths - cumulative	0	0	0	1	0	1	0	1	0	2	0	3	1	4
Failures ¹ - cumulative	0	0	0	0	0	0	0	1	0	1	0	1	0	2
Transferred to Bilateral Arm - cumulative	0	0	0	0	0	0	0	0	0	0	0	2	0	2
Not Yet Overdue	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Expected	66	158	66	157	66	157	66	156	66	155	66	152	65	150
Actual ²	66	158	66	155	66	157	65	154	63	151	53	147	48	145
% Follow-up (based on Actual)	100%	100%	100%	98.7%	100%	100%	98.5%	98.7%	95.5%	97.4%	80.3%	96.7%	73.8%	96.7%

Notes: C=Control; S=STAR Ankle

¹ Patients were considered failures if the investigational device was completely removed and they underwent an arthrodesis.

² Patients with any follow-up data reviewed or evaluated by investigator.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an orthopedic device study performed in the US. Baseline demographics for both the STAR and Arthrodesis groups are outlined in **Table 9**. The average age of patients in the study was approximately 60 years, >90% were Caucasian, the average body mass index (“BMI”) was approximately 28, and males and females were nearly equally represented. There was no significant difference ($p>0.05$) between study groups in the distribution of gender, smoking status, height, weight or BMI. There was a statistically significant difference between groups in age, with the Arthrodesis patients being an average of 5 years younger than the STAR patients.

Table 9: Study Baseline Demographics

	Control (N=66)	STAR Pivotal (N=158)	P-value for Comparison between STAR Pivotal and Arthrodesis Control
Age			0.004
Mean (SD)	57.1 (12.3)	62.7 (12.6)	
Gender			0.593
Male	30 (45.5%)	78 (49.4%)	
Female	36 (54.5%)	80 (50.6%)	
Race			0.205
Caucasian	60 (90.0%)	152 (96.2%)	
Hispanic	3 (4.5%)	1 (0.6%)	
African American	2 (3%)	4 (2.5%)	
Other	1 (1.5%)	1 (0.6%)	
Current Smoker			0.433
Yes	5 (13.9%)	15 (20%)	
No	31 (86.1%)	60 (80%)	
History of Smoking			0.946
Yes	31 (47%)	75 (47.5%)	
No	35 (53%)	83 (52.9%)	
Height (SD)	67.0 (4.5)	67.3 (3.7)	0.612
Weight (SD)	185.6 (38.6)	180.9 (34.9)	0.378
BMI (SD)	29.1 (5.8)	28 (4.8)	0.409
Primary Diagnosis			0.054
Primary Arthrosis	19 (28.8%)	62 (39.2%)	
Posttraumatic Arthrosis	43 (65.2%)	76 (48.1%)	
Rheumatoid Arthrosis	4 (6.1%)	20 (12.7%)	
Metabolic disorder			
Baseline Total BP Scores			0.058
Mean (SD)	43.0 (8.8)	40.8 (7.4)	
Baseline Pain VAS Scores			0.073
Mean (SD)	65.8 (19)	71.1 (17)	

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety for the pivotal cohort was based on 194 patients (142 STAR patients, 52 arthrodesis patients) available for the 24 month evaluation. The primary safety endpoint success rates for the pivotal study are presented below in **Table 10**. The population used to calculate these rates included patients for whom the necessary follow-up data required to determine safety at the 24 month time point was available at the time of database closure. Adverse effects are reported in **Tables 11 to 14**. Note that 24+ Month data are presented in **Tables 11 and 12** below, while **Tables 13 and 14** display 24 Month data. Additional safety information from the CA cohort is presented in Section XI of this document.

Table 10: Pivotal Safety Success Rates at 24 Months Rate

24 Month Success Rates	Control			STAR		
	n	N	%	n	N	%
Safety Success Rates	43	52	82.7%	108	142	76.1%

As shown in **Table 10**, the safety success rates at 24 months were 82.7% and 76.1% for the control and STAR arms, respectively. Safety success was based on clinical success and radiographic success as defined more specifically in **Table 7** above. Several patients were clinically successful in spite of not meeting the prespecified radiographic success criteria; per the definition of safety success, these patients were not included in the safety success rate calculation.

Adverse effects that occurred in the PMA clinical study:

The most common adverse events in the pivotal study were related to the specific approaches and procedures (arthrodesis vs. STAR Ankle) and specific to the operative site, which included the following 24+ month events:

- a. ankle instability (none in control vs. 6 in STAR)
- b. bone fracture (2 in control vs. 29 in STAR)
- c. bony changes such as osteolysis, exostosis or osteophytes (none in control vs. 16 in STAR)
- d. device failure, instability, device migration, device removal and subsidence (1 in control vs. 19 in STAR)
- e. infection rates were similar for the control and the STAR cohorts
- f. nerve injury (5 in controls vs. 35 in STAR)
- g. pain (33 in control vs. 74 in STAR)
- h. soft tissue edema (4 in controls vs. 28 in STAR)
- i. wound problems (4 in controls vs. 33 in STAR)

A summary of all operative site adverse events out to 24+ months for the pivotal study are listed in **Table 11**. Post-operative ankle pain was noted in more STAR patients than the controls. Surgically-related nerve injury was more pronounced in the STAR population than the controls at 24+ months (22% [35/158] for STAR vs. 7.6% [5/66] for control).

Wound problems were more common with the STAR Ankle than arthrodesis controls (20.8% [33/158] for STAR vs. 6.1% [4/66] for control). These problems included skin necrosis, wound dehiscence and delayed healing but in the majority of cases no additional surgical intervention was needed. Bony fracture and bony changes also occurred at higher rates in the STAR group. In all, major complications were more common with STAR patients than the controls.

Table 11: Operative Site Adverse Events - Patient Basis (24+ Months)

Operative Site Events, in alphabetical order (with definitions)	Control	STAR
# Patients evaluated	66	158
Anesthesia	.	1
ankle deformity (progression of varus or valgus deformity after treatment)	1	2
ankle instability (ligamentous laxity that leads to instability)	.	6
ankle slippage (feeling of 'giving away' with walking without evidence of reason for the instability)	.	1
bone fracture	2	29
bony changes (e.g. osteolysis, exostosis or osteophyte formation)	.	16
decreased ROM	.	11
device failure (designated when an individual component of the device failed as observed by radiograph or intraoperatively at the time of removal)	.	4
device instability (instability at the ankle due to the interaction of the individual device components)	.	4
device migration	1	3
device removal (does not include all device removals)	.	1
device subsidence	.	7
embolism (pulmonary or deep vein thrombosis)	.	4
foot deformity (development of a foot deformity after initial treatment)	.	1
fusion problems (i.e. pseudarthrosis or mal-union that required additional treatment)	2	.
gait problems	1	5
Hematoma	1	.
incision (e.g. burning or blisters at incision site)	.	1
infection (e.g. superficial or deep)	7	8
motor deficit	.	2
muscle problems (e.g. muscle cramps or muscle spasms)	1	3
nerve injury (e.g. numbness, decreased sensation, known sacrificed nerve)	5	35
pain (pain at treated ankle, heel, or associated tendons)	33	74
soft tissue edema	4	28
symptomatic hardware	2	1
tendon problem (e.g. tendonitis, tendon rupture)	5	5
wound problem (e.g. wound dehiscence, delayed wound healing, skin necrosis)	4	33

Table 12 compares the more common adverse events seen in the pivotal study at specific points in time out to 24+ months. Bone fractures were noted primarily in the STAR patients. Intra-operative fractures were recognized at the time of surgery and in the majority of cases treated with internal fixation. 9.5% (15/158) of STAR patients had an intraoperative fracture compared to 1.5% (1/66) for arthrodesis patients. Post-operative fractures occurred either relatively early (within the first six months) and in many cases required additional surgical intervention such as surgical reduction and fixation. The applicant indicated that fractures that were noted late (greater than one year after surgery) were

considered to be stress fractures and in the majority of cases were treated non-surgically, with immobilization; however, it is unclear how these are not device-related.

Table 12: Time Course of Adverse Events in the Pivotal Study

Operative Site Events	OP		DC-6WKS		6WKS-3MO		3MO-6MO		6MO-12MO		12MO-24MO		24MO+	
	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR
	N=66	N=158	N=66	N=158	N=66	N=157	N=64	N=154	N=63	N=151	N=53	N=147	N=48	N=146
	n	n	n	n	n	n	n	n	n	n	n	n	n	n
anesthesia		1												
ankle deformity							1		1				1	
ankle instability						1		2						3
ankle slippage						1								
bone fracture	1	15		6		2		6		1	1	2		1
bony changes		1						1		3		9		6
decreased ROM		3		3		3		1		1				2
device failure										1				3
device instability						1		1		1		1		1
device migration				1	1							2		1
device removal														1
device subsidence				1		1		1		1				3
embolism		1		3						1				
foot deformity														1
fusion problems							2							
gait problems	1	1				1		2				1		
hematoma									1					
incision				2										
infection		1	2	6	1		3	1	1				2	1
motor deficit				2										
muscle problems				2		1		1					1	
nerve injury		9	1	9	1	1	2	9	1	4		3		4
pain	4	12	4	14	1	16	15	20	14	19	10	20	3	17
soft tissue edema		3	1	8	1	9	2	6				3		3
symptomatic hardware						1	1				1			
tendon problem					1		3		1	1	1	1	2	3
wound problem		2	4	31	1	5		1			1	1		5
Total Events	6	49	12	88	7	43	28	53	18	34	14	43	9	55

Table 13 provides a more detailed breakdown of adverse events occurring up to 24 months at the operative site for the pivotal study. Note the higher rates of bone fracture, bony changes, wound problems, surgical interventions and major complications for the STAR patients.

Table 13: Adverse Events and Surgical Interventions in the Pivotal Study up to 24 Months*

Adverse Events	Control (N=66)	STAR Pivotal (N=158)
Bone fracture	2 (3.0%)	28 (17.7%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)
<i>Medial Malleolus</i>	1 (1.5%)	8 (5.1%)
<i>Fibula</i>	0 (0.0%)	6 (3.8%)
<i>Tibia</i>	0 (0.0%)	1 (0.63%)
Post-operative fracture	1 (1.5%)	14 (8.9%)
<i>Medial Malleolus</i>	0 (0.0%)	7 (4.4%)
<i>Fibula</i>	0 (0.0%)	2 (1.3%)
<i>Tibia</i>	0 (0.0%)	3 (1.9%)
<i>Other*</i>	1 (1.5%)	2 (1.3%)
Bony changes	0 (0%)	12 (7.6%)
Pain	32 (48.5%)	69 (43.7%)
Nerve injury	5 (7.6%)	32 (20.3%)
<i>Deep Peroneal Nerve</i>	0 (0%)	9 (5.7%)
<i>Medial Branch of the Superficial Peroneal Nerve</i>	1 (1.5%)	6 (3.8%)
<i>Posterior Tibial Nerve</i>	0 (0%)	1 (0.6%)
<i>Saphenous Nerve</i>	0 (0%)	1 (0.6%)
<i>Superficial Peroneal Nerve</i>	3 (4.5%)	9 (5.7%)
<i>Numbness</i>	1 (1.5%)	6 (3.8%)
Wound problem	4 (6.1%)	32 (20.3%)
Surgical intervention	7 (10.6%)	26 (16.5%)
Revision or removal	6 (9.1%)	12 (7.6%)
Other intervention	1 (1.5%)	18 (11.4%)
Major complication	1 (1.5%)	14 (8.9%)
Infection	1 (1.5%)	2 (1.3%)
Bone problem	0 (0%)	8 (5.1%)
Wound problem	1 (1.5%)	5 (3.2%)
Wound problems and infection	0 (0%)	1 (0.6%)

* The control (arthrodesis) subjects experienced one post-operative navicular fracture (1). The pivotal STAR subjects experienced post-operative lateral/posterior malleolus fracture (1) and an unknown fracture (1).

As indicated in the table above, some adverse events required additional surgical interventions; these are listed in **Table 14**. In the pivotal study, STAR patients had a higher overall rate of additional surgical interventions (STAR 16.5% [26/158] vs. 10.6% [7/66] for control). Surgical revision was more common in STAR patients (7.0% [11/158] for STAR vs. 4.5% [3/66] for control) with major operative site procedures also more common in STAR patients (STAR 12.0% [19/158] vs. control 4.5% [3/66]).

Table 14. Summary of Surgical Interventions for Pivotal Study out to 24 Months

	Control (N=66)	STAR Pivotal (N=158)
Surgical Interventions	9	33
Patients with Surgical Interventions	7 (10.6%)	26 (16.5%)
Intervention Type		
Revision	3 (4.5%)	11 (7.0%)
Removal	4 (6.1%)	2 (1.3%)
Reoperation	0	8 (5.1%)
Other Intervention	1 (1.5%)	10 (6.3%)
Intervention Class by Subgroup		
Minor Operative Site Procedures	4 (6.1%)	9 (5.7%)
Hardware Removal	4 (6.1%)	1 (0.6%)
Excision Exostosis	0	5 (3.2%)
Minor wound problem	0	3 (1.9%)
Major Operative Site Procedures	3 (4.5%)	19 (12.0%)
Component removal	0	10 (6.3%)
Infection	1 (1.5%)	1 (0.6%)
Fracture fixation (ORIF)	0	2 (1.3%)
Repair nonunion	2 (3%)	0
Fusion, adjacent joint	0	3 (1.9%)
Osteotomy for malalignment	0	3 (1.9%)
Major Procedure Not Device-Related	2 (3.0%)	3 (1.9%)
Hardware removal	1 (1.5%)	0
Fusion, adjacent joint	1 (1.5%)	0
Other	0	3 (1.9%)

In summary, the information provided in the **Tables 11 – 14** above showed a higher incidence of adverse events associated with the STAR Ankle device throughout the duration of the pivotal study in comparison to the standard of care, which is arthrodesis.

2. Effectiveness Results

The analysis of effectiveness was based on the 189 patients evaluable at the 24-month timepoint. Key effectiveness outcomes are presented in **Tables 15 to 17**.

Effectiveness success rates for the pivotal study based on all data available at 24 months are shown in **Table 15** below. The population used to calculate these rates included patients for whom the necessary follow-up data required to determine effectiveness at the 24 month time point was available at the time of database closure. As demonstrated in the table, statistically significantly higher efficacy success rates were shown for the STAR Ankle patients at 24 months as compared with the arthrodesis patients ($p < 0.001$).

Table 15: Effectiveness Success Rates at 24 Months

Effectiveness Success Rate	Pivotal					
	Control			STAR		
	N	Mean	%	N	Mean	%
	7	47	14.9	83	142	58.5

Table 16 below shows the primary effectiveness endpoint results based on the mean Buechel-Pappas score at 24 months and the change in Buechel-Pappas score at 24 months from baseline. Comparisons between groups were made using the Wilcoxon Test, due to the non-normality of the Buechel-Pappas score distribution. All comparisons showed a statistically significantly higher score in the STAR Ankle group when compared with the arthrodesis group with $p < 0.001$. The Buechel-Pappas score at 24 months remained significantly higher in the STAR Ankle group when using various imputation methods to account for missing data including a multiple imputation method and a last observation carried forward method.

Table 16: Mean Buechel-Pappas Score at 24 Months

Buechel-Pappas Score	Pivotal					
	Control			STAR		
	N	Mean	Std Dev	N	Mean	Std Dev
24 Month	47	69.7	16.8	142	81.6	14.0
Improvement at 24 Months	47	26.3	17.1	142	40.5	15.1

Prior to surgery, STAR Ankle patients had a higher level of pain than did arthrodesis patients. At all follow-up evaluations, pain levels in both groups dropped substantially. There was a larger improvement in mean STAR Ankle patient pain VAS scores over the course of the study as opposed to arthrodesis patients (51.8 versus 44.6 at 24 months).

As described previously, range of motion (ROM) is a 15 point component of the Buechel-Pappas score. The STAR Ankle, which is designed to preserve motion, has a natural advantage over the arthrodesis control in this regard. Consequently, the applicant was asked to conduct post-hoc analyses using a modified Buechel-Pappas score which excluded ROM. When ROM is removed, the Buechel-Pappas score at 24 months decreases to 69.2 and 66.4 for the STAR Ankle and arthrodesis control, respectively. The non-inferiority delta for effectiveness success is still met under this revised analysis.

3. Overall Patient Success

Overall patient success rates based on all data available at 24 months are shown in **Table 17** below. Patients meeting both effectiveness and success criteria are considered to be an overall patient success.

Table 17: Overall Patient Success Rates at 24 Months

24 Month Success Rates	Pivotal					
	Control			STAR		
	n	N	%	n	N	%
Patient Success Rate	7	51	13.7%	68	142	47.9%

As noted in **Table 18**, higher overall patient success rates were determined for the STAR Ankle patients at 24 months as compared with arthrodesis patients. Higher patient success rates were primarily based on the higher BP component of the composite evaluation formula.

Table 18: Components of Composite Patient Success Rates at 24 Months

	Controls			STAR		
	n	Evaluated	%	n	Evaluated	%
Overall Patient Success*	7	51	13.7%	68	142	47.9%
Success on B-P (≥ 40 pt Improvement)	7	47	14.9%	83	142	58.5%
Success on Safety Component	43	52	82.7%	101	142	71.1%
No Surgical Interventions	47	52	90.4%	122	142	81.0%
No Major Complications	51	52	98.1%	128	142	90.1%
Fusion (union)	46	52	88.5%	NA	NA	NA
Success on X-Ray	NA	NA	NA	117	138 ⁺	84.8%

*Please refer to Table 7 for the definition of patient success.

+ Missing one or more X-ray measures to determine X-ray success/failure for 5 patients at 12 months and 4 patients at 24 months.

4. Subgroup Analyses

The preoperative characteristics presented in **Table 19** were evaluated for potential association with outcomes.

Table 19: Success Rates by Subgroups at 24 Months

Success Rates by Subgroups	Patient Success 24 Months		Efficacy Success 24 Months		Safety Success 24 Months	
	Control	STAR	Control	STAR	Control	STAR
Age Category						
< 50	4 (30.8%)	8 (33.3%)	4 (33.3%)	11 (47.8%)	12 (85.7%)	19 (79.2%)
50 - 70	1 (3.6%)	33 (44%)	1 (3.8%)	44 (57.1%)	24 (85.7%)	53 (71.6%)
> 70	2 (20.0%)	23 (53.5%)	2 (22.2%)	28 (66.7%)	7 (70.0%)	29 (65.9%)
BMI Category						
Normal (BMI < 25)	3 (21.4%)	20 (52.6%)	3 (25.0%)	25 (65.8%)	11 (78.6%)	29 (78.4%)
Overweight (BMI 25 - 29)	3 (15.0%)	24 (40%)	3 (15.0%)	32 (53.3%)	17 (85.0%)	39 (67.2%)
Obese (BMI > 30)	1 (5.9%)	20 (45.5%)	1 (6.7%)	26 (59.1%)	15 (83.3%)	33 (70.2%)
Primary Diagnosis						
Primary Arthrosis	2 (14.3%)	32 (56.1%)	2 (15.4%)	37 (64.9%)	12 (85.7%)	39 (69.6%)
Posttraumatic Arthrosis	4 (13.8%)	25 (37.3%)	4 (13.3%)	35 (51.5%)	28 (82.4%)	49 (73.1%)
Rheumatoid Arthrosis	1 (25%)	7 (38.9%)	1 (25%)	11 (64.7%)	3 (75%)	13 (68.4%)
Race						
Caucasian	7 (15.2%)	63 (46%)	7 (16.3%)	81 (59.1%)	40 (85.1%)	97 (70.8%)
Hispanic		1 (100%)		1 (100%)	2 (66.7%)	1 (100%)
African American				1 (33.3%)		3 (75%)
Other					1 (100%)	
Gender						
Male	3 (12.5%)	36 (50.7%)	3 (13.6%)	41 (58.6%)	19 (79.2%)	50 (72.5%)
Female	4 (14.8%)	28 (39.4%)	4 (16.0%)	42 (58.3%)	24 (85.7%)	51 (69.9%)
History of Smoking						
Yes	7 (25.9%)	28 (44.4%)	7 (28%)	39 (60.9%)	23 (85.2%)	45 (70.3%)
No	0	36 (46.2%)	0	44 (57.1%)	20 (80.0%)	56 (72.7%)
Missing						

At the 24-month evaluation, older (> 70), lighter, STAR patients with a primary diagnosis of primary or rheumatoid arthrosis seem to have higher overall patient success rates than other patients.

For arthrodesis patients, at 24 months, the younger, lighter, female patients seem to have the highest patient success rates. Older female patients (50-70 years of age) did equally well as the patients < 50 years of age.

Please note that the success rates presented in **Table 19** are not statistically powered and are the results of post-hoc analyses. Thus, any conclusions drawn from these results may have limited utility.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental Cohort Designs – Continued Access and Bilateral

The applicant provided data from an additional series of patients in a continued access (CA) cohort to supplement the results of the pivotal study. The database for this PMA reflected data collected through August 30, 2007. The CA cohort enrolled 448 STAR Ankle patients in 10 centers. CA patients were enrolled between March 19, 2002 and

October 4, 2006. A bilateral cohort composed of patients previously enrolled in the unilateral pivotal or continued access cohort who later developed disease in the contralateral ankle or patients diagnosed with bilateral disease (and excluded from enrollment into the pivotal cohort) also provided supplemental information in support of safety. The bilateral cohort included 21 patients in 6 centers. At the time of database closure, data were available on 435 CA patients and 16 bilateral patients.

The inclusion and exclusion criteria for the CA cohort were similar to those for the pivotal cohort except for inclusion of metabolic disorders (e.g., hemochromatosis). The exclusion criteria were also the same, with the exception that "motor dysfunction due to neuromuscular impairment" was expanded to include "motor dysfunction due to neuromuscular impairment, insulin dependent diabetes, peripheral neuropathy, or Charcot changes."

Eligible patients for inclusion into the bilateral cohort were patients with bilateral disease requiring surgical intervention (and excluded from enrollment into the pivotal cohort) or patients who had either been previously enrolled in the unilateral pivotal or continued access cohorts but who had or later developed disease in the contralateral ankle. Other eligibility criteria were the same as for the pivotal study.

Follow-up Schedule and Success Criteria

The follow-up examination schedule for the CA and bilateral cohorts was identical to that of the pivotal study (see **Table 7**), as was the success criteria (see **Table 8**).

Patient Demographics

Patient demographics and baseline disease history for the CA cohort were comparable to those of STAR Ankle patients in the pivotal study. Some differences in primary diagnoses were noted with a higher percentage of posttraumatic arthritis in the continued access cohort as compared to the pivotal study (62.1% versus 48.1%) and a lower percentage of primary arthritis (21.5% versus 39.2%). Patients with a primary diagnosis of a metabolic disorder (9.2%) were also treated in the continued access cohort. There were no notable differences in baseline evaluations or operative procedures for the CA patients as compared to the pivotal study.

Patient Accounting

In the CA cohort, patient follow-up was approximately 92% (408/444) through 12 months and approximately 79% (328/416) through 24 months. There were 5 patient withdrawals from the study. Three (3) patients received a second STAR device in their contralateral ankle and were transferred to the bilateral cohort. Four patients expired during the course of the study, though none of these deaths were considered device-related. **Table 20** below summarizes the patient accountability for the CA cohort out to 24 months.

Table 20: CA Patient Accountability for 24 Month Visit as of August 30, 2007

	24 month
Theoretical	429
Deaths (cumulative)	4
Failures (cumulative)	0
Transferred to Bilateral Arm	3
Not Yet Overdue	6
Expected (N)	416
Actual Data Collection (n/N)	
Overall	328 (79%)
Efficacy Success	314 (75%)
Safety Success*	273 (66%)
Patient Success*	276 (66%)

* Includes patients with radiographic data. Radiographic success is a component of safety success

Data were available on a total of 16 patients in the bilateral cohort of the STAR Ankle and a total of 27 ankles. Four (4) of the 16 patients reported in this section were originally enrolled in the pivotal study but were transferred to the bilateral cohort upon placement of a second STAR Ankle. Two (2) patient deaths occurred by 24 months. Neither of these deaths was believed to be device-related.

Safety Results

A total of 448 patients received the STAR ankle in the CA cohort. **Table 21** shows the time course of surgically related adverse events in the CA cohort. A common event continued to be bone fracture; 21 fractures occurred intra-operatively and 30 occurred post-operatively. Also particularly common were nerve injury, pain, soft tissue edema and wound problems.

Table 21: Continued Access Cohort – STAR Operative Site Adverse Events Over Time at 24+ Months (Patient Basis)

Operative Site Events	Intra-operative	Discharge-6wk	6wk-3mo	3mo-6mo	6mo-12mo	12mo-24mo	24mo+	Total [^]
	N*=435	N=435	N=432	N [†] =432	N=420	N=408	N=328	-
	n	n	n	n	n	n	n	n
Ankle deformity	1 (0.3)	1
Bone fracture	21 (4.8)	9 (2.1)	8 (1.8)	6 (1.4)	5 (1.2)	1 (0.2)	1 (0.3)	49
Bony changes	.	1 (0.2)	.	1 (0.2)	5 (1.2)	10 (2.4)	12 (3.7)	28
Decreased ROM	.	3 (0.7)	3
Device failure	1 (0.2)	.	1 (0.3)	2
Device instability	2 (0.6)	2
Device migration	1 (0.2)	1 (0.2)	3 (0.9)	4
Device subsidence	.	.	.	3 (0.7)	3 (0.7)	2 (0.5)	2 (0.6)	10
Embolism	.	3 (0.7)	.	.	.	2 (0.5)	.	4
Foot deformity	1 (0.2)	2 (0.5)	.	3
Gait problems	.	.	1 (0.2)	.	.	2 (0.5)	.	3
Infection	.	5 (1.1)	8 (1.8)	.	1 (0.2)	1 (0.2)	2 (0.6)	17
Muscle problems	.	1 (0.2)	1 (0.2)	.	1 (0.2)	.	.	3
Nerve injury	33 (7.6)	29 (6.7)	16 (3.7)	12 (2.8)	9 (2.1)	10 (2.4)	1 (0.3)	104
Pain	11 (2.5)	14 (3.2)	19 (4.4)	48 (11)	43 (10.2)	26 (6.4)	16 (4.9)	146
Soft tissue edema	2 (0.5)	1 (0.2)	12 (2.8)	7 (1.6)	4 (0.9)	7 (1.7)	.	30
Tendon problem	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.9)	5 (1.2)	2 (0.5)	3 (0.9)	14
Wound problem	.	72 (16.5)	13 (3.0)	2 (0.5)	1	2 (0.5)	.	86

*N is the number of patients with clinical visit data available at the beginning of the interval.

[†]No visit was scheduled at 3 months post-op in the continued access cohort; the number of patients with data available for the 6 week visit was used.

[^]Total column contains the number of unique patients experiencing each specific event during the study.

Because a patient may be reporting the same type of adverse event at different time points over the course of the study, the row total may or may not add up to the number reported in the Total column.

As noted in **Table 22** below, the frequency of many adverse events decreased in the CA cohort when compared to the pivotal study. The rates of intraoperative fractures, surgical interventions and major complications were all lower in the CA cohort. The applicant believes that refinements and modifications to the STAR surgical technique and instrumentation helped reduce the occurrence of some of these adverse events.

Table 22: Adverse Events and Surgical Interventions up to 24 Months¹ – CA Cohort Comparison

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	STAR Continued Access Cohort (N=416)
Bone fracture	2 (3.0%)	28 (17.7%)	46 (11.1%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)	21 (4.8%)
<i>Medial Malleolus</i>	1 (1.5%)	8 (5.1%)	11 (2.6%)
<i>Fibula</i>	0 (0.0%)	6 (3.8%)	1 (0.02%)
<i>Tibia</i>	0 (0.0%)	1 (0.63%)	5 (1.2%)
<i>Other²</i>	0 (0.0%)	0 (0.0%)	4 (1.0%)
Post-operative fracture	1 (1.5%)	14 (8.9%)	26 (6.3%)
<i>Medial Malleolus</i>	0 (0.0%)	7 (4.4%)	14 (3.4%)
<i>Fibula</i>	0 (0.0%)	2 (1.3%)	4 (1.0%)
<i>Tibia</i>	0 (0.0%)	3 (1.9%)	6 (1.4%)
<i>Other³</i>	1 (1.5%)	2 (1.3%)	5 (1.2%)
Bony changes	0 (0%)	12 (7.6%)	17 (4.1%)
Pain	32 (48.5%)	69 (43.7%)	139 (33.4%)
Nerve injury	5 (7.6%)	32 (20.3%)	99 (23.8%)
<i>Deep Peroneal Nerve</i>	0 (0%)	9 (5.7%)	22 (5.3%)
<i>Dorsomedial Cutaneous Nerve</i>	0 (0%)	0 (0%)	1 (0.2%)
<i>Medial Branch of the Superficial Peroneal Nerve</i>	1 (1.5%)	6 (3.8%)	3 (0.7%)
<i>Posterior Tibial Nerve</i>	0 (0%)	1 (0.6%)	1 (0.2%)
<i>Saphenous Nerve</i>	0 (0%)	1 (0.6%)	3 (0.7%)
<i>Sciatic Nerve</i>	0 (0%)	0 (0%)	2 (0.5%)
<i>Superficial Peroneal Nerve</i>	3 (4.5%)	9 (5.7%)	36 (8.6%)
<i>Medial Plantar Nerve</i>	0 (0%)	0 (0%)	1 (0.2%)
Numbness	1 (1.5%)	6 (3.8%)	27 (6.5%)
Wound problem	4 (6.1%)	32 (20.3%)	81 (19.5%)
Surgical intervention	7 (10.6%)	26 (16.5%)	33 (7.9%)
Revision or removal	6 (9.1%)	12 (7.6%)	14 (3.4%)
Other intervention	1 (1.5%)	18 (11.4%)	21 (5.0%)
Major complication	1 (1.5%)	14 (8.9%)	22 (5.3%)
Infection	1 (1.5%)	2 (1.3%)	4 (1.0%)
Bone problem	0 (0%)	8 (5.1%)	13 (3.1%)
Wound problem	1 (1.5%)	5 (3.2%)	7 (1.7%)
Wound problems and infection	0 (0%)	1 (0.6%)	0 (0%)

¹ Not all 435 CA patients had reached their 24-month follow-up as of the time of database closure. To permit a reasonable comparison to the pivotal study data, with the exception of intra-operative fracture, the adverse event rate for the CA cohort has been calculated using data from the 416 patients who have reached 24 months post-procedure only. For the comparison of intra-operative fracture rate, all 435 CA patients were analyzed.

² The CA STAR subjects experienced other intra-operative bone fractures as follows: medial tibia (1); posterior malleolus (1); talus (1); lateral malleolus (1).

³ The control (arthrodesis) subjects experienced one post-operative navicular fracture (1). The pivotal STAR subjects experienced post-operative lateral/posterior malleolus fracture (1) and an unknown fracture (1). The CA STAR subjects experienced other post-operative bone fractures as follows:

posterior distal tibia (1); posterior malleolus (1); talus (1); anterior tibia (1); and an unknown fracture (1).

Table 23 below summarizes the experience of events requiring surgical intervention for the CA cohort and pivotal study.

Table 23: Surgical Interventions – Summary of Interventions - CA Cohort Comparison at 24 Months

	Control (N=66)	STAR Pivotal (N=158)	STAR Continued Access Cohort (N=416)
Surgical Interventions	9	33	43
Patients with Surgical Interventions	7 (10.6%)	26 (16.5%)	35 (8.4%)
Intervention Type			
Revision	3 (4.5%)	11 (7.0%)	10 (2.4%)
Removal	4 (6.1%)	2 (1.3%)	6 (1.4%)
Reoperation	0	8 (5.1%)	7 (1.7%)
Other Intervention	1 (1.5%)	10 (6.3%)	15 (3.6%)
Intervention Class by Subgroup			
Minor Operative Site Procedures	4 (6.1%)	9 (5.7%)	13 (3.1%)
Hardware Removal	4 (6.1%)	1 (0.6%)	3 (0.7%)
Excision Exostosis	0	5 (3.2%)	4 (1.0%)
Minor wound problem	0	3 (1.9%)	4 (1.0%)
Ligament reconstruction	0	0	3 (0.7%)
Major Operative Site Procedures	3 (4.5%)	19 (12.0%)	14 (3.4%)
Component removal	0	10 (6.3%)	8 (1.9%)
Infection	1 (1.5%)	1 (0.6%)	2 (0.5%)
Fracture fixation (ORIF)	0	2 (1.3%)	4 (1.0%)
Repair nonunion	2 (3%)	0	1 (0.2%)
Fusion, adjacent joint	0	3 (1.9%)	0
Osteotomy for malalignment	0	3 (1.9%)	0
Major Procedure Not Device-Related	2 (3.0%)	3 (1.9%)	10 (2.4%)
Hardware removal	1 (1.5%)	0	0
Fusion, adjacent joint	1 (1.5%)	0	9 (2.2%)
Other	0	3 (1.9%)	1 (0.2%)

Note: Numbers and events are patient-based.

At the 24 months endpoint, surgical interventions were performed in 35 patients (8.4% of the 416 patients with data available) throughout the course of the CA cohort. The surgical interventions consisted of 10 patients with revisions, 6 patients with removals, 7 patients with re-operation and 15 patients with other interventions. The rate of surgical interventions decreased in the CA cohort when compared to the pivotal study.

The analysis of safety for the CA cohort was based on 273 patients (all STAR patients) available for the 24 month evaluation.

The same types of adverse events as seen in the pivotal study and CA cohort were observed among the 16 bilateral patients for whom data were available at the time of database closure. A total of 3 surgical interventions occurred within the bilateral cohort. These surgical interventions (component removal, fusion of an adjacent joint, and excision of an exostosis) were among the most frequently encountered interventions seen

in the pivotal study. No major complications occurred in the bilateral cohort. The most frequently seen adverse events in the bilateral cohort, such as pain, bone fracture, nerve injury, and wound problems, were similar to those adverse events seen in the pivotal study. No new types of adverse events were observed in the bilateral cohort.

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

A. Panel Meeting Recommendation

At an advisory meeting held on April 24, 2007, the Orthopedics and Rehabilitation Devices Panel recommended that the Link America, Inc. PMA for the STAR Ankle be conditionally approved. This decision was based on the results of the pivotal study and CA cohort. The following link contains the panel transcript for the STAR Ankle: <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4299t1-01.pdf>. The panel recommended the following conditions of approval:

- There should be a post approval clinical study with independent radiographic assessment to evaluate the long-term safety and performance of the STAR ankle prosthesis.
- There should be an update to the surgical manual to reflect modifications not yet implemented but described by the applicant.
- There should be pre-clinical studies to validate the applicant's proposed weight limit.
- There should be patient education to describe the warnings contained in the package insert in layperson terminology.
- "Severely deformed" terminology should be removed from the indications for use, and primary arthrosis should be replaced with degenerative arthritis in the indications for use.

B. FDA's Post-Panel Action

FDA chose to accept most of the panel's recommendations. The applicant will perform a post approval study which has been agreed to by the Agency, the surgical technique was appropriately modified, patient education materials have been provided, and the appropriate modifications have been made to the indications for use. With regard to preclinical testing validating the applicant's proposed weight limit, in lieu of preclinical testing, FDA analyzed additional clinical data from patients who were studied out to 3 and 4 years. A warning was added to the Prescriber's Information Labeling stating that the safety and effectiveness of the STAR Ankle has not been studied in patients weighing greater than 250 lbs.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the STAR Ankle are based on data collected in a clinical study conducted to support PMA approval as described above. In the pivotal study, surgical interventions and major complications were more common with STAR Ankle patients than arthrodesis patients. There was a decreased rate of surgical interventions and

major complications in the larger, CA cohort. Improvements with regard to the surgical technique and instrumentation may have contributed to the decreased adverse event rates when comparing the CA cohort results to those in the pivotal study. It should also be noted that the control procedure, ankle arthrodesis, is the standard of care for ankle arthritis. The results of both the pivotal study and CA cohort helped provide a reasonable assurance of safety for the STAR Ankle.

B. Effectiveness Conclusions

In the majority of effectiveness parameters measured (including overall patient success, total Buechel-Pappas score, 40 point or greater improvement in Buechel-Pappas score), the STAR Ankle showed favorable results when compared to ankle arthrodesis. The primary effectiveness parameter of mean total Buechel-Pappas Score for the STAR ankle was shown to be superior to arthrodesis for the pivotal study.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. CDRH believes that it is reasonable to conclude that the benefits of the use of the STAR Ankle for the target population outweigh the risk of injury when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on May 27, 2009. 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 STAR Ankle among patients who participated in the continued access cohort (CAC) under the investigational device exemption (IDE) study. A prospective, multi-center, single arm study design with hypothesis testing will be used to determine the 8-year survivorship and effectiveness of arthroplasty using the STAR Ankle in comparison to ankle arthrodesis from historical literature controls. The study population will consist of all living subjects who participated in the continued access cohort, regardless of whether or not the patient has had a revision/removal with at least 250 STAR Ankle patients followed through the 4-year visit and a minimum of 100 STAR Ankle patients followed through the 8-year post-operation visit. Patients will undergo clinical and radiographic evaluation postoperatively at 4, 6 and 8 years. The baseline, 6-week, 1-year and 2-year data will be used as collected in the continued access cohort during the IDE study. Data on ankle arthrodesis controls identified by a systematic review of the literature will be summarized. You have agreed to take reasonable measures to avoid loss to follow-up.

You have agreed to collect information about any reoperation, revisions or removals of the STAR Ankle device, and effectiveness endpoints, including total Buechel-Pappas Scale score, Pain Visual Analog Scale (VAS), Quality of Life (SF-36) and AOFAS, and radiographic endpoints (radiolucency and migration). 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.

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 and an explanation for a delay, if any in meeting these goals, and the safety and effectiveness data collected during that reporting period.

You must also update your patient and physician labeling (via a PMA supplement) to reflect the 4, 6 and 8 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.

2. You have agreed to perform a second post-approval study that uses a prospective, multi-center, single arm study design and hypothesis testing to examine the performance of the STAR Ankle under actual conditions of use, compared to the STAR Ankle performance in the continued access cohort. You will recruit 5 new investigational sites and investigators. You will enroll 125 new study subjects and follow them for 2 years, with a minimum of 100 study subjects followed through the 2- year follow-up visit. Study subjects will undergo clinical and radiographic evaluation postoperatively at 6 weeks, 6 months, 12 months, and 24 months. You have agreed to take reasonable measures to avoid loss to follow-up.

You have agreed to collect information about safety, including 1) revisions, removals or reoperations; 2) wound problems requiring surgical intervention; 3) infections requiring surgical intervention; and 4) peri-operative fractures of the talus that require surgical reduction and fixation. You have also agreed to collect information about effectiveness endpoints, including total Buechel-Pappas Scale score, Pain Visual Analog Scale (VAS), Quality of Life (SF-36) and AOFAS, and radiographic endpoints (radiolucency and migration). 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.

Every six months for the first two years and then annually until the studies are 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, other milestones as it compares to the stated goals in the protocol and an explanation for a delay, if any in meeting these goals and the safety and effectiveness data collected during that reporting period.

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

3. FDA would like to remind you that you must submit a full post-approval study protocol for each of the required studies in a PMA Supplement and reach agreement with OSB on the protocol within 30 days after the approval order is issued to address the remaining issues of the PAS identified in the FDA comments sent to you via email on May 13, 2009 . FDA intends to act on and respond to an applicant's protocol submission within 60 calendar days of receipt.

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

XV. 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.

XVI. REFERENCES

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2. ASTM F67 - 06 Standard Specification for Unalloyed Titanium, for Surgical Implant Applications.
3. ASTM F648 - 07e1 Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants.
4. ASTM F138 - 08 Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants.
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