# FDA EXECUTIVE SUMMARY

## Introduction

The subject of this Executive Summary is Link Orthopaedics' Scandinavian Total Ankle Replacement System (STAR Ankle), a mobile bearing ankle replacement consisting of three components – a cobalt chromium molybdenum (CoCrMo) tibial component with a commercially pure titanium (cpTi) plasma spray coating, an ultra high molecular weight polyethylene (UHMWPE) mobile bearing and a CoCrMo talar component with cpTi plasma spray coating. The device has been reviewed by the Orthopedic Joint Devices Branch of the Division of General, Restorative, and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

This summary includes eight sections:

The first section is an overview of the issues facing the FDA with respect to the interpretation of the clinical data and also presents our rationale for presenting this PMA to the advisory panel.

The second section describes the device and Indications for Use proposed by the applicant.

The third section summarizes the preclinical data and prior clinical investigations which were provided by the applicant to support the device's safety and effectiveness.

The fourth and fifth sections describe the clinical study protocol and patient outcomes respectively presented in the PMA submission by the applicant to support the safety and effectiveness of the device.

The sixth section contains any additional statistical issues, not covered in sections four and five.

The seventh section describes the applicant's proposed plan for conducting a post-approval study if the device is recommended for approval with conditions with one of those conditions being a post-approval study.

The eighth section summarizes FDA's overall issues related to this PMA submission which generated the questions to the advisory panel.

## TABLE OF CONTENTS

**Section** **Page Number**


Introduction ..... **1**
I. Rationale for Presentation to the Panel ..... **3**

II. Background Information ..... **6**
- **A. Indications for Use** ..... 7
- **B. Device Description** ..... 8

III. Pre-Clinical Data ..... **12**
- **A. Intrinsic Stability Testing** ..... 12
- **B. FEA and Contact Stress Testing** ..... 12
- **C. Wear in Simulated Functional Use** ..... 13
- **D. Explant Analyses** ..... 15
- **E. Sterilization** ..... 16
- **F. Biocompatibility** ..... 16
- **G. Summary** ..... 16

IV. Clinical Protocol ..... **18**
- **A. Study Description and Patient Populations** ..... 18
- **B. Inclusion/Exclusion Criteria** ..... 19
- **C. Study Endpoint Assessments** ..... 20
- **D. Evaluation Schedule** ..... 22
- **E. Changes in the Study Conduct and Analyses** ..... 22
- **F. Surgical Technique** ..... 24

V. Clinical Results ..... **25**
- **A. Patient Accounting** ..... 25
- **B. Protocol Deviations** ..... 25
- **C. Patient Demographics and Baseline Characteristics** ..... 25
- **D. Operative Data** ..... 26
- **E. Primary Efficacy Endpoint for the Pivotal Study** ..... 27
- **F. Results of the Safety Endpoints for the Pivotal Study** ..... 28
- **G. Continued Access (CA) Cohort Results** ..... 44
- **H. Bilateral Cohort Results** ..... 47
- **I. Learning Curve** ..... 47
- **J. Overview of Training Program** ..... 48

VI. Additional Statistical Considerations ..... **49**
- **A. Study Design and Analysis** ..... 49

VII. Post-Approval Study ..... **51**
- **A. Overview of Post-Approval Study Proposal** ..... 51

VIII. Summary ..... **53**

## I. Rationale for Presentation to the Panel

This section describes the rationale for presentation of this PMA to the Orthopedic and Rehabilitation Devices Advisory Panel. This PMA application for the Link Orthopaedics' Scandinavian Total Ankle Replacement System (STAR Ankle) is the first-of-a-kind non-constrained mobile bearing total ankle system the FDA has reviewed. Semi-constrained ankle replacements have been reviewed via the 510(k) process. However, the STAR Ankle limits minimally (less than normal anatomic constraints) translation in one or more planes. The device also has no linkage across the joint so is considered to be non-constrained. These characteristics are consistent with 21 CFR 888.3120, Ankle joint metal/polymer non-constrained cemented prosthesis with the exception of the means of fixation. Therefore, the STAR Ankle is a Class III device and requires a PMA. It should also be noted that the STAR Ankle is intended to be implanted without bone cement.

In general, the panel will be asked to provide input on the following issues:

1) **Clinical Issues:** Using the predefined safety evaluations of the originally approved IDE in the PMA for the evaluation of safety, the STAR Ankle did not meet the primary safety endpoint. The applicant has recently revised the criteria used to assess the radiographs, which influences the outcomes for the safety success and the overall patient success outcomes for the study. Using the applicant's revised criteria proposed in Amendments dated February 8 and March 5, 2007, the analyses of the STAR Ankle data appears to meet the primary safety endpoint. Based on the patient outcomes, intraoperative and post operative adverse event information, there are also potential questions regarding the STAR Ankle surgical technique, surgical learning curve and follow-up of continued access patients.

2) **Pre-Clinical Issue:** Various pre-clinical tests were performed to evaluate the safety of the STAR Ankle. One of these tests, functional wear testing, was performed at loads below what has been reported as being expected physiological loads. In addition, there were fractures noted in the implant in retrieval analysis. There are questions related to the adequacy of the retrieval analyses and whether or not there is a need for any further characterization and any further durability testing.

## A. Clinical Issues

1) There are risk/benefit questions associated with the STAR Ankle. The primary efficacy endpoint (mean total BP score) in the pivotal study was met; however, the primary safety endpoint (composite of no device failures, revisions or removals; radiographic evaluation parameters; and no major complications) using the approved original IDE protocol, as originally provided in the PMA, was not met. The original safety success rate for the STAR Ankle in comparison to the arthrodesis control was 71.1% versus 82.7%, respectively. The STAR Ankle rate did not meet the 15% non-inferiority delta margin for safety, since the lower bound of the two-sided 90% confidence interval for the difference in success rates between the control and STAR Ankle (Control – STAR) was greater than 15%.

   In a PMA amendment response from the applicant dated February 8, 2007, with additional information provided on March 5, 2007, the applicant performed a revised radiographic analysis, which differed from what was outlined in the original PMA, to include:

- Not Carrying Forward Radiographic Failures
  In the original analysis provided in the PMA, all STAR subjects who did not meet the radiographic success criteria at 6 or 12 months were not further evaluated clinically or radiographically for overall success at 24 months, even if they met the radiographic success criteria at 24 months. Consequently, in this additional post hoc analysis, using revised success criteria, the applicant identified 7 patients who were not previously considered to be a radiographic success at 24 months because the initial failure observation at 6 or 12 months was carried forward despite apparent radiographic success at 24 months. If these patients are classified as successes, the overall safety success rates for the STAR Ankle group is improved to 76.1% versus 82.7% for the control. The rate still did not meet the 15% delta for safety.

- Reassessment of Radiographic Success Criteria
  The applicant has provided several literature references in an attempt to support that the original definition of radiographic success was not clinically appropriate for the STAR Ankle. The applicant has reassessed the outcomes for 5 patients who did not meet the radiographic success criteria as proposed in the pivotal study. If these 5 additional patients are classified as successes (based not on radiographic findings, but on clinical outcomes only), the overall safety success rates for the STAR Ankle group is further improved to 79.6% versus 82.7% for the control. This new rate appears to meet the 15% delta for safety.

  Additionally, how the changes in radiographic analyses are directly related to the clinical outcomes are not clearly defined in the PMA amendment, and it is unclear whether radiographic findings in the post-hoc analysis were reevaluated by an independent radiologist. Further, it is unclear whether the applicant reassessed all radiographs for the entire patient population.

2) The continued access (CA) cohort of this study was designed to further address the safety of the STAR Ankle and consisted of 424 patients. Of the 424 patients enrolled, the applicant indicated that 320 patients are expected for 24 month follow-up. Data has been provided on 211 subjects (211/320; 66%).. It should be noted that the applicant has provided independent radiographic evaluation during the 24 month follow-up visit for 80 patients (80/320; 25%) in the CA cohort; however, the applicant also indicated that 215 patients actually had 24 month radiographs taken. It is uncertain how the applicant selected these 80 patients to have independent radiographic analyses and how the process potentially impacted the resulting reported outcomes.

   Further, the applicant has proposed numerous modifications to the surgical techniques and instrumentation, primarily after the conclusion of the pivotal study.

   The applicant has indicated that these modifications are adequate to address concerns with adverse events associated with implantation of the STAR Ankle and appear to have contributed to a decrease in the adverse events associated with the STAR Ankle observed from the pivotal cohort to the continued access cohort.

   The panel will be asked to comment on the impact of the limited continued access data to support the safety of the device and the adequacy of the modifications to the surgical techniques.

3) Based on the experiences of the investigators participating in the pivotal and continued access study, the applicant has determined that the learning curve is approximately 15 patients. Intra-operative fracture, surgical intervention and major complications (wound, infection or bony changes) of the pivotal patients were compared to the first 15 patients of the continued access and to the remaining patients of the continued access study. Many surgeons participating in the continued access study have also participated in the pivotal study and thus their first 15 patients in the continued study may not truly be "new" to these surgeons, i.e., some surgeons may have already completed their learning curve. They also evaluated outcomes for three of the investigators who only participated in the continued access portion of the study. Using the applicant's analysis of surgical complications rate from the pivotal to the continued access group, we will be asking the panel to provide recommendations related to training and assessment of the learning curve for this device.

## B. Pre-Clinical Issue

1) The applicant has performed a series of pre-clinical tests to support the safety of the STAR Ankle, which includes intrinsic stability testing, finite element analysis (FEA), contact stress testing, simulated wear testing, and an informal retrieval analysis of 35 star compone[redacted]ear analysis was perform[redacted]g a continuous [redacted] which represent[redacted]times body w[redacted] individual, for [redacted]s. All samples t[redacted]rvived out to[redacted]. However, fra[redacted]ure mode that has also been reported in the l[redacted] was reported in 4 mobile bearings, of implanted STAR Ankles. Despite generally low fracture rates reported in the literature and in the current PMA, we will be asking the panel to comment on whether the pre-clinical testing provided adequately reflects a surrogate endpoint for the potential long-term durability of the UHMWPE mobile bearing, particularly since the follow-up for the STAR Ankle US cohorts were only carried out to 2 years postoperatively.

## C. Summary

The Agency is requesting the Panel's input to determine whether the clinical data collected in the study and presented in this PMA demonstrates the safety and effectiveness of the Scandinavian Total Ankle Replacement System (STAR Ankle). The Panel questions in Section VIII of this Executive Summary reflect the issues in which FDA seeks your discussions and recommendations.

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[1] Anderson et al 2003, Uncemented Star total ankle prostheses, J. of Bone and Joint Surgery, Vol. 85-A, number 7, pgs 1321-1329.
[2] Christ RM, Hagena FW: Complications and revision surgery in total ankle arthroplasty. "Fuss & Sprunggelenk", Vol. 2:1-10, 2004, Published by Steinkopff Verlag, Darmstadt.
[3] Schill S, Thabe H: Ankle Arthroplasty: A Clinical Follow-Up. "Current Status of Ankle Arthroplasty", Chapter 19, pages 90-93, Published by Springer Verlag, 1998

## II. Background Information

Applicant and Address:
Link America, Inc.
DBA Link Orthopaedics
300 Roundhill Drive
Rockaway, NJ 07866

Manufacturer and Address:
Waldemar Link GmbH and Co.
Barkhausenweg 10
D-22339 Hamburg

## A. Indications for Use

The applicant has proposed the following Indications for Use:

The STAR Ankle is intended for use as a non-cemented implant to replace a painful arthritic and/or severely deformed ankle due to rheumatoid arthritis, primary arthrosis, or posttraumatic arthrosis. The device is designed as an alternative to an arthrodesis of the ankle, allowing the patient to regain and/or retain some of his/her normal ankle mobility and function.

Contraindications:

1. Active or prior deep infection in the ankle joint or adjacent bones
2. Prior arthrodesis at the ankle joint
3. Hindfoot or forefoot malalignment precluding plantigrade foot
4. Severe deformity that would not normally be eligible for ankle arthroplasty
5. Avascular necrosis of the talus
6. Charcot joint
7. Severe osteoporotic or osteopenic condition or other conditions resulting in poor bone quality that may result in inadequate bony fixation
8. Prior surgery and/or injury that has adversely affected ankle bone quality
9. Insufficient ligament support that cannot be repaired with soft tissue stabilization
10. Skeletal maturity not yet reached
11. Obesity (weight greater than 250 lbs)
12. Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
13. Poor skin and soft tissue quality about the surgical site
14. Neuromuscular disease resulting in lack of normal muscle function about the affected ankle
15. Psychiatric problems that hinder adequate cooperation during perioperative period
16. Significant malalignment of the knee joint
17. Peripheral neuropathy that may lead to Charcot joint of the affected ankle

## B. Device Description

The STAR Ankle system consists of three principal components: a tibial component, an UHMWPE mobile bearing, and a talar component (see picture below). The mobile bearing articulates with both the tibial and talar components. Such designs are considered to be non-constrained designs and are regulated under 21 CFR 888.3120, Ankle joint metal/polymer non-constrained cemented prosthesis. The system is intended to preserve the normal ankle joint's range of motion and surrounding bone as much as possible. The STAR Ankle is intended for implantation without bone cement.

*The STAR Ankle*

**Design Features of the STAR Ankle**

***Articulations***

The STAR Ankle employs two articulating surfaces:

- Tibial Component/Mobile bearing: The flat, polished distal surface of the Tibia Component articulates with the flat proximal surface of the mobile bearing.
- Mobile bearing/Talar Component: The convex distal surface of the mobile bearing articulates with the polished convex proximal surface of the talar component.

The mobile-bearing design is intended to reduce the shear and torque forces on the mobile bearing which can lead to loosening of the tibial and talar components, and decrease stress at the metal/bone interface.

***Range of Motion***

The STAR Ankle is intended to maintain the ranges of motion indicated in Table 1 below.

*Table 1: STAR Ankle Range of Motion*

| | STAR Ankle | Normal Ankle Joint |
|---|---|---|
| Congruency | 100% | 96% |
| Rotation | 12 - 15° talus rotation plus tibia-meniscal rotation | 12 - 15° talus rotation |
| Extension/Flexion | 7°/20° | 10°/30° |

Tibial Component

The tibial component is fabricated from a CoCrMo alloy that conforms to ASTM F75 "Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants". A commercially pure titanium (cpTi) plasma spray coating is applied to the superior (bone interfacing) surface and conforms to ISO5832-2 "Implants for Surgery - Metallic Materials - Part 2: Unalloyed Titanium". Table 2 outlines the characteristics of the plasma spray coating. The distal (articulating) surface of the tibial component has a surface roughness of Ra = 0.5.

*Table 2: Plasma Spray Coating Characteristics*

| | **Bond Coat** | **Top Coat** |
|---|---|---|
| Particle Size | 90 μm | 180 μm |
| Coating Thickness | 50 ± 10 μm | 225 ± 50 μm |
| Porosity | dense | 30 ± 5% |
| Pore Size | - | 75 - 200 μm |
| Roughness | - | 60 ± 10μm |
| Tensile Strength | >50 MPa (F1147) | >50 MPa (F1147) |
| Shear Strength | >20 MPa (F1044) | >20 MPa (F1044) |

When viewed superiorly, the tibial component has a trapezoidal cross-section with rounded corners where the smaller end of the trapezoid is on the posterior aspect of the ankle joint. The distal surface is flat for mating with the mobile bearing, whereas the proximal surface has two raised cylindrical projections oriented in the anterior/posterior direction. These cylindrical projections are to be inserted into hard, subchondral bone.

The tibial component is offered in 5 sizes (see Table 3 below). The cylinders for all sizes of the tibial component are 20.6mm long and have a diameter of 4.7mm with four sections along the length where the diameter is increased to 6.0mm. The cylinders have a 13.9 center-to-center distance.

*Table 3: Tibial component dimensions*

| | M/L Width (mm) | A/P Length (mm) |
|---|---|---|
| Extra Small | 30 | 30 |
| Small | 32 | 30 |
| Medium | 32.5 | 35 |
| Large | 33 | 40 |
| Extra Large | 33.5 | 45 |

*(Note: Excluding the cylinders, all sizes are 2.5 mm thick)*

Mobile Bearing

The mobile bearing is manufactured from UHMWPE and conforms to ASTM F648 "Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants". The properties of the polyethylene are characterized below in Table 4. Each core contains two radiographic marker wires placed at 90° to one another; one is placed 2mm from the proximal surface and the other wire is placed 3mm from the proximal surface.

*Table 4: Polyethylene Characterization*

| | |
|---|---|
| Ultimate Tensile Strength | ≥ 35 MPa |
| Yield Strength | ≥ 21 MPa |
| Young's Modulus (Modulus of Elasticity) | Approx. 720 MPa |
| Poisson's Ratio | 0.46 |
| % Elongation | ≥ 300 % |
| Molecular Weight | Approx. $5*10^6$ |
| Density | 927 – 944 $kg/m^3$ |
| Porosity | n.a. |
| Crystallinity | Approx. 45-55% |
| Glass Transition Temperature, $T_g$ | -90° C |
| Melting Temperature, $T_m$ | 130 – 135° C |

*(Note: The polyethylene is not cross-linked)*

The proximal surface of the mobile bearing is flat and interfaces with the tibial component. The distal surface is concave with a radius of curvature of 20.4 mm. The distal surface also contains a central radial groove (2.85 mm) running through its entire surface from anterior to posterior. The groove mates with a ridge on the talar component to constrain motion of the mobile bearing in the medial/lateral direction. The walls of the mobile bearing are straight. Thickness ranges are summarized below in Table 5.

*Table 5: Bearing Thicknesses*

| Nominal Bearing Thickness | Minimum Bearing Thickness |
|---|---|
| 6mm | 3.1mm |
| 7mm | 4.1mm |
| 8mm | 5.1mm |
| 9mm | 6.1mm |
| 10mm | 7.1mm |

The applicant proposes various sizes of a revision mobile bearing as summarized in Table 6. It should be noted that the revision mobile bearings were not used in the IDE study (although they have been used in Europe since 1999). The revision bearings have the same design as the mobile bearings included within the IDE study, except for thickness.

*Table 6: Proposed Revision Bearing Thicknesses*

| Nominal Bearing Thickness | Minimum Bearing Thickness |
|---|---|
| 11mm | 8.1mm |
| 12mm | 9.1mm |
| 13mm | 10.1mm |
| 14mm | 11.1mm |

<u>Talar Component</u>

The talar component is fabricated from a CoCrMo alloy that conforms to ASTM F75 "Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants". A cpTi plasma spray coating is applied to the inferior (bone interfacing) surface and conforms to ISO5832-2 "Implants for Surgery - Metallic Materials - Part 2: Unalloyed Titanium". The proximal (articulating) surface has a surface roughness of $R_a = 0.5$.

The component is designed to cover the talar dome and anterior, posterior, medial and lateral facets. The sloped sides are intended to serve two functions: (1) to minimize the amount of bone resection and (2) improve weight-bearing characteristics. The dome has a radius of curvature of 20.2 mm. A small, raised half-cylindrical ridge runs in the A/P direction in the M/L center of the talar dome. The ridge has a radius of 2.5 mm and is intended to constrain the M/L motion of the mobile bearing. The distal surface of the talar component has a fin extending inferiorly from the approximate center of the component.

The component is offered in 5 sizes and in both left- and right-sided configurations (see Table 7 below).

*Table 7: Talar Component Dimensions*

| | M/L Width (mm) | A/P Length (mm) |
|---|---|---|
| Extra Extra Small | 28 | 29 |
| Extra Small | 30 | 31 |
| Small | 34 | 35 |
| Medium | 36 | 35 |
| Large | 38 | 35 |

## III. Pre-Clinical Data

The following types of testing were performed on the STAR Ankle: Intrinsic Stability, Finite Element Analysis (FEA), Contact Stress, Wear in Simulated Functional Use and Retrieval Analysis of the STAR Ankle Prosthesis.

### A. Intrinsic Stability Testing

Testing was conducted to evaluate the stability [redacted] AR Ankle in rotation, A/P displacement, and M/L displacement. A comp[redacted]ssive load o[redacted]w[redacted]ed to represent worst cas[redacted]

The STAR Ankle exhibits minimal constraint in the A/P, M/L, and rotational modes. This is purported to promote load sharing through displacements between the tibial and talar components

### B. FEA and Contact Stress Testing

An FEA was conducted to assess the stresses within the polyethylene Mobile bearing, and to identify areas of any stress concentrations. A pressure sensitive film study was conducted to evaluate the pressure distribution on the contact surfaces of the polyethylene insert and to validate the FE model.

The total contact area available on the tibial and talar contact surfaces of the polyethylene insert is 644.6 $mm^2$ and 327.4 $mm^2$, respectively.

Simulations for the [redacted] the pressure sensitive film testing were performed under static loading conditions [redacted] using all t[redacted] polyethylene inserts (6, 7, 8, 9, and 10mm) and at different relative flexion angles ([redacted] of the insert. The special case of incomplete coverage ("overhang") of th[redacted] tibial component was examined.

For the inferior (talar) surface, the contact pressure appeared evenly distributed across these contact surfaces in the range o[redacted] except for the higher pressures observed at the interior, anterior, and posterior edges. [redacted]tress analysis did not reveal any areas of high stress concentration other than at the anterior and posterior edges where the high contact stresses were predicted and observed. Other than at the edges, stresses were highest at the A/P midline where the insert is at its thinnest.

Comparable results were obtained using the two independent methods, pressure sensitive film and FEM with one exception, the overhang scenario. The FEA predicted a 30 to 40% increase in contact stress while the pressure sensitive film showed no significant difference from the non-overhang conditions.

The results showed that bearing thickness had a visibly noticeable effect on the contact stress distributions seen on the pressure sensitive film (i.e., the thinner the bearing, the higher the stress).

## C. Wear in Simulated Functional Use

Methods

*1. Testing Protocol*

ed by the . A total of five (5) sterilized devices were evaluated by joint nal two (2) devices serving as controls. According to the applicant, worst case analysis resulted in the smallest sizing combination for the device (maximum contact stress and minimum contact area):

- Tibial Component: Size x-small (30 mm x 30 mm)
- Talar Component: Size xx-small (28 mm x 29 mm)
- Mobile Bearing: Size 6 mm height

Testing endpoints were set at cycles. All tests were conducted at 37 ± 3°C in filtered and sterilized, bovine calf ser nt diluted to a total protein concentration of 20 grams per liter with phosphate buffered saline. The lubricant contained 0.2% sodium azide and ethylene-diaminetetraacetic acid (EDTA) at a concentration of 20 mM. Distilled water was added daily to correct for evaporation.

The mechanical test onment is summarized be The compression loads used for testing were approximately times body weight for a individual.

- Dorsiflexion:
- Internal Rotation:
- Anterior-Posterior Tr d)
- **Axial Compress**
- Posterior S
- Frequency:

*2. Gravimetric Wear*

Wear was evaluated by the gravimetric weight loss following the guidelines from ASTM F1714, Standard Guide for Gravimetric Wear Assessment of Hip-Desi ulator Devices. Specimens were evaluated before testin ycles and cycles, and every 1 million cycles thereafter to test cessation . Evaluation i hotographic documentation of the articular surfaces. The weight loss, total wear, and wear rate were reported for each specimen at each interval after correcting for fluid absorption in soak controls.

*3. Articular Surface Examination*

Gross visual observation of the articular surface was made at every interval. Post-test specimens were evaluated by laser profilometry, and scanning white light interferometry. Failures were classified as "Functional" or "Mechanical". A functional failure denoted permanent deformation rendering the device ineffective or unable to resist load and/or maintain adequate attachment. A mechanical failure denoted the onset of a defect in the material (e.g., crack initiation or surface wear). The total number of cycles without failure was recorded for each specimen.

*4. Laser Profilometry*

Three-dimensional pro nalysis was completed on the mobile bearing for each STAR specimen that survived cycles of loading without "functional" failure.

5. *Surface Roughness*

Surface roughness was calculated on specimens that survived [redacted] cycles of loading without functional failure using a non-contacting imaging surf [redacted] re analyzer.

Results

All test specimens survived [redacted] cycles of wear simulation without functional failure. According to the report, no [redacted] deviations occurred during testing. Fracture of the radiographic marker wires occurred in 3 of the 5 mobile bearing components. Weight loss was corrected in these specimens for the loss of the wire.

Based on the report provided by the applicant, after [redacted] cycles of simulated ankle motion, the STAR prosthesis demonstrated:

1. A mean total volumetric wear for the mobile bearing component of 56.90 $mm^3$.

2. [redacted] olumetric wear rate for the mobile bearing component over [redacted] of [redacted] per million cycles

3. A mean total volumetric wear for the CoCrMo Talar component of 2.56 $mm^3$. This level is not substantiated from visual observations of the articular surface and is likely a byproduct of test mounting.

4. [redacted] olumetric wear rate for the CoCrMo Talar component over [redacted] cycles of [redacted] per million cycles. This level is not substantiated from visu [redacted] tions of [redacted] lar surface and is likely a byproduct of test mounting.

5. A mean total volumetric wear for the CoCrMo Tibial component of [redacted]

6. A mean volumetric wear rate for the CoCrMo Tibial component over [redacted] cycles of $mm^3$ per million cycles

7. Polishing and pitting of the mobile bearing talar articular surfaces in all specimens by visual and scanning white light interferometry.

8. Polishing of the mobile bearing tibial articular surfaces in all specimens by visual and scanning white light interferometry.

9. Minor scratching of the CoCrMo Talar and Tibial articulation surfaces in all specimens.

10. Average maximum wear of the mobile bearing component was 0.80 mm and located on the posterior medial talar articular surface.

11. Average loss of height in the mobile bearing component was 0.19 mm on the talar articular surface and 0.18 mm on the tibial articular surface.

**PANEL QUESTION: Because wear testing is often used as a surrogate to support the potential long-term durability of device components, please be advised that you will be asked to discuss the appropriateness of the loading regime and test methods used for wear testing for the STAR Ankle.**

## D. Explant Analyses

Background

Due to concerns about potential polyethylene wear leading to osteolysis and cyst formation, FDA requested detailed explant data on all implants that were removed and available for review from the pivotal, bilateral, and continued access arms. The investigational plan in the approved IDE did not require collection of explanted devices for evaluation. Accordingly, clinical sites were not instructed to explant components in a controlled manner. However, the applicant made an effort to collect explanted devices, particularly explanted mobile bearings.

In the pivotal study, there were 24 revisions or component removals in 20 patients (20/158, 12.7%). Among the continued access patients, there were 14 revisions or device removals in 11 patients (11/354, 3.1%). With regard to the accountability of explanted devices, the PMA database documented 31 explanted components in 26 patients. Of these 31 components, 23 were analyzed in a report provided by the applicant as part of the PMA (13 components/11 patients in the pivotal study; 9 components/7 patients in the continued access study; 1 component/1 patient in the bilateral study). There were an additional 12 explants in 12 patients analyzed for which there was no surgical intervention data in the PMA database (3 components/3 patients in the pivotal study; 7 components/7 patients in the continued access study; 1 component/1 patient in the bilateral study; 1 component/1 patient among additional cases. In total, 35 bearings were analyzed.

Methods

The applicant provided a brief summary of an analysis of thirty-five (35) retrieved mobile bearings from IDE patients, including pivotal, bilateral and continued access subjects. The length of time each bearing was implanted prior to retrieval and the reason for surgeries which led to the [redacted] ed by the [redacted]

In the absence of a formal explanation protocol, explanted devices were removed, handled, stored and shipped in an uncontrolled manner. Additionally, the applicant noted that devices were often forcibly removed during explantation, damaging the component and complicating subsequent analysis. Though these are important considerations when analyzing the retrieved data, it should also be noted the one cannot determine if mobile bearing fracture and/or damage occurred during explantation or while they were *in vivo*.

A classification scheme was used to describe mobile bearing damage and was divided into seven modes: burnishing, abrasion, pitting, surface deformation, delamination, scratching, and debris capture. In addition to the seven classic damage categories, the analysis included track scratching, biologic skiving, fracture, and explantation damage.

Results

Photographs and a summary of the thirty-five retrieved bearings were provided in the PMA. Burnishing, which is characterized by a highly polished surface, was the most common mode of wear followed by scratching, pitting and abrasion. The additional observations were also made*:

- Three of thirty-five (3/35) specimens presented with fracture. The fractures involved 7, 9 and 10 mm components.
    - Patient 1: Continued access arm, removed 9.63 months after a previous revision surgery (initial bearing implant was not a fracture).
    - Patient 2: Continued access arm, removed 42.17 months from original surgery.
    - Patient 3: Continued access arm, removed 33.60 months from original surgery.
- Nine of thirty-five (9/35) specimens demonstrated significant damage to the keel-trough.
- Nine of thirty-five (9/35) specimens demonstrated significant loss of material on the edges of the component due presumably to bone contact.

*Please note that there is some overlap in the three groups. Also note there was an additional mobile bearing fracture reported in the pivotal study that was not analyzed in the explant analysis.

## E. Sterilization

The implants are sterilized using gamma irradiation at a dosage of 25 – 29 kGy. The applicant has requested a shelf life of 5 years and has performed sterility validation in accordance with ANSI/AAMI ISO 11137-1995.

## F. Biocompatibility

The materials proposed for use in the STAR Ankle are standard materials used in permanently, implanted orthopaedic implants, including total hip and total knee replacements. There are no concerns related to biocompatibility of the STAR Ankle components.

## G. Summary

The applicant has performed Intrinsic Stability, Finite Element Analysis (FEA), Contact Stress, Wear in Simulated Functional Use and Explant Analyses on the STAR Ankle device.

From the retrieval analysis of 35 mobile bearings, 3 of the 35 specimens retrieved were fractured while 9 of the 35 specimens demonstrated significant damage to the keel-trough region of the meniscal component. In addition, 9 of the 35 specimens demonstrated significant loss of UHMWPE material on the edges of the component presumably due to bone contact. Fractures of the STAR Ankle mobile bearing have also been reported in the literature[1] .

Wear analysis was [redacted]med using a continuous load of [redacted], which represents [redacted] times [redacted] eight for a [redacted] individual, for [redacted] cycles. All samples tested survi [redacted] ut to [redacted] [redacted] cycles.

Several articles were cited by the applicant showing that ankle joint forces range from 2 to 5.5 times body weight during normal gait. As cited by the applicant, the maximum compressive force in the ankle during normal gait is 5.5 times body weight [2]. According to the exclusion criteria for the STAR ankle, the maximum weight for a patient receiving this device is 250 lbs. This generates a worst case compressive loading condition of 6,116 N, which was not utilized in wear testing.

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[1] Anderson et al 2003, Uncemented Star total ankle prostheses, J. of Bone and Joint Surgery, Vol. 85-A, number 7, pgs 1321-1329.
[2] Stauffer RN, Chao, EYS, Brewster, RC: Force and Motion Analysis of the Normal, Diseased, and Prosthetic Ankle Joint. Clinical Orthopaedics, 127:189,1977.

In light of the mobile bearing fractures reported in both the literature and this study's explant analysis, we will be asking the panel to discuss adequacy the analyses conducted and whether or not any additional functional fatigue testing is necessary to support long term survivorship of the STAR Ankle.

## IV. Clinical Protocol

### A. Study Description and Patient Populations

The applicant has presented data from a series of multi-center, non-randomized clinical studies used to evaluate the Link Scandinavian Total Ankle Replacement System (STAR Ankle) within the PMA submission (P050050).

Under US IDE (G000140), the applicant was granted approval to enroll a total of 624 patients (158 pivotal, 450 continued access and 16 compassionate use cases) using the STAR Ankle into the IDE studies. The study populations are identified as the following:

#### *1. Pivotal Study Cohort*

In G000140, the applicant received approval to enroll 237 patients (158 STAR Ankle and 79 arthrodesis controls) in a 2:1 ratio (STAR Ankle to arthrodesis control) at 16 institutions for the pivotal study cohort. The pivotal study was designed as a multi-center, non-randomized, concurrently controlled clinical study. The study was designed as a non-inferiority study comparing the safety and efficacy of the STAR Ankle to the arthrodesis control.

A total of 224 patients (158 STAR Ankle patients and 66 arthrodesis patients) were enrolled into the pivotal cohort. The study was designed by the applicant for specific sites to exclusively enroll STAR Ankle (10 sites) or arthrodesis patients (5 sites). Enrollment of all planned investigational patients in the pivotal study was considered completed by the applicant on December 10, 2001. These patients comprised the primary safety and effectiveness cohort for this PMA.

#### *2. Continued Access (CA) Cohort*

Between 2002 and 2004, the applicant conducted three phases of CA, each with approval to enroll up to 150 STAR Ankle patients (n = 450 patients). The CA patients were to utilize a similar follow-up schedule and evaluation parameters (e.g., radiographic evaluation) used for STAR Ankle patients enrolled in the pivotal study. The specific objectives were to: (i) determine whether changes to the surgical procedure can reduce the incidence of intraoperative fractures (refer to Section IV, Subgroup F for surgical changes); (ii) continue to obtain data to confirm the results obtained in the pivotal study; (iii) compare BP scores with AOFAS scores to compare the STAR outcomes with historical outcomes of arthrodesis; and (iv) further expand knowledge base regarding device performance.

At the time of PMA submission, the applicant had enrolled 448 patients at the same 10 IDE participating centers who enrolled STAR Ankle patients into the pivotal study. A total of 352 CA patients are considered evaluable in the PMA since they were eligible for 2-year follow-up at the time of PMA submission. The applicant has only provided 24 month follow-up information on 211/320 subjects so they only have follow-up rate of 66%. It should be noted that the applicant has provided independent radiographic evaluation during the 24 month follow-up visit for only 80 patients (80/320; 25%) in the CA cohort.

#### *3. Bilateral Patient Cohort*

The bilateral cohort was composed of patients previously enrolled in the unilateral pivotal or continued access cohort but who had or later developed disease in the contralateral ankle *or* patients diagnosed with bilateral disease (and excluded from enrollment into the pivotal cohort). Twenty-one (21) bilateral ankle patients were evaluated in 5 centers, which also participated in the STAR pivotal study. The purpose of the bilateral cohort was to further

evaluate safety of the STAR ankle for patients with bilateral disease who required bilateral STAR Ankle implantations. Bilateral patients were included only in the safety analysis of the STAR Ankle.

#### *4. Control Patients*

For the evaluation of efficacy for the pivotal study, the control group (for the pivotal study) consisted of 66 concurrently recruited open surgery ankle arthrodesis patients, which was performed through a lateral approach to the ankle joint.

To supplement the arthrodesis control group, the applicant also conducted a literature-based meta-analysis of historical arthrodesis cases to provide further comparative safety information for the STAR Ankle for the pivotal study. Forty-two (42) articles with 1,264 patients published after 1978 were reviewed by the applicant. From these articles, the applicant has only included 12 articles published between 1983 and 2003 with 413 patients in the meta-analysis. According to the applicant's analysis, the historical complication rates for arthrodesis were comparable to the rates observed for arthrodesis patients and STAR Ankle patients in the pivotal study. However, the post-hoc nature of this analysis and the large number of excluded articles and patients make it difficult to assess the extent of the selection bias.

The concurrently controlled patients in this study, even though not randomized, likely provide more comparable, contemporary data.

### B. Inclusion/Exclusion Criteria

#### *1. Pivotal Cohort*

Table 8 below summarizes the inclusion/exclusion criteria used for the pivotal study.

*Table 8: Patient Inclusion/Exclusion Criteria for Pivotal Study*

| **Inclusion: ALL of the following:** | |
|---|---|
| 1. Moderate or severe pain, loss of mobility and function of the ankle (B-P Scale total score of less than 50, B-P pain score of 20 or less).<br>2. Primary arthrosis, post traumatic arthrosis or rheumatoid arthrosis.<br>3. At least 3 months conservative treatment (e.g., foot and ankle orthosis, counseling on changing employment to non-manual labor job, planned pain, anti-inflammatory meds), confirmed by patient history, radiographs and medication record [Note: the duration was "at least 6 months" in the original IDE, but changed (at FDA's request) to "at least 3 months" and approved in an IDE/Supplement.]<br>4. Willing and able to give informed consent. | |
| **Exclusion: ANY of the following:** | |
| 1. Skeletally immature<br>2. Active or prior deep infection in ankle or adjacent bones<br>3. Prior arthrodesis at involved site<br>4. Mental illness that may interfere with ability to follow protocol<br>5. Heavier than 250lbs<br>6. Drug use or alcoholism<br>7. Any physical condition precluding major surgery | 15. Bilateral cases Note: On April 6, 2001 through an IDE/S, the applicant received conditional approval/approval to add a 20-patient "bilateral" arm consisting of:<br>a) Patients with bilateral disease not previously enrolled<br>b) Patients enrolled for treatment of a single ankle, but who subsequently undergo surgery on the contralateral ankle |

| | |
|---|---|
| 8. Hindfoot malpositioned by more than 35° or forefoot malalignment which would preclude a plantigrade foot<br>9. Lower extremity vascular insufficiency<br>10. Avascular necrosis of the talus<br>11. Inadequate skin coverage about the ankle joint<br>12. 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<br>13. Juvenile onset Type I diabetes<br>14. Adult-onset Type II diabetes when accompanied by neuropathic changes or a history of foot infection in either foot | If the contralateral ankle was operated on during the course of the study, the patient's data would only be used for safety reporting and not efficacy<br>16. Pregnancy<br>17. Avascular necrosis of the tibia<br>18. Significant bone tumor of the foot or ankle<br>19. Severe deformity not normally eligible for ankle arthroplasty<br>20. Prior surgery or injury that has adversely affected the ankle bone stock<br>21. Severe osteoporotic or osteopenic condition<br>22. Insufficient ligament support<br>23. Motor dysfunction due to neuromuscular impairment |

***2. Continued Access Cohort***

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., hemachromatosis) and exclusion of motor dysfunction due to neuromuscular impairment, insulin dependent diabetes, peripheral neuropathy, or Charcot changes.

***3. Bilateral Cohort***

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.

## C. Study Endpoint Assessments

***1. Pivotal Study***

For the pivotal study, the following endpoints were initially used:

*Endpoints:*

a. The ***primary efficacy endpoint*** was the mean total Buechel-Pappas Scale (BP) score measured at 12 months, with further confirmation at 24 months. The Agency advised the applicant that 24 month follow-up evaluations would be necessary to provide sufficient information on potential failure modes and all of the information provided in this summary reflects 24-month outcomes. 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 originally defined as a minimum 40 point increase in BP score from baseline.

***Note:*** In the comparison of function as defined by the BP score, the STAR Ankle patients should have a natural advantage over the arthrodesis control patients in the section assessing range of motion (ROM), which is a component of the overall BP score.

Consequently, the applicant was requested to conduct post-hoc analyses using a modified BP score which excluded points contributed by ROM (15 points) and determine whether the STAR Ankle met the non-inferiority efficacy margin.

b. The ***primary safety endpoint*** per the original IDE protocol was a composite endpoint derived from three criteria:
a) no device failures, revisions or removals,
b) radiographic evaluation parameters, and
c) no major complications
*NOTE: Refer to Section IV. E regarding more specifics as well as modifications to the original radiographic success criteria proposed by the applicant initially on February 8, 2007 (Amendment 11) with additional information provided on March 5, 2007 (Amendment 15). Modifications to the radiographic success criteria influence the outcomes for the safety analyses and the overall patient success.

c. ***Overall patient success*** for an individual patient was defined as success for both efficacy and safety. All of the following criteria needed to be met for the patient to be considered a success:
a) $\geq$ 40 point improvement in total BP score,
b) no device failures, revisions, or removals,
c) radiographic success, defined as no radiographic evidence of loosening or migration in the STAR ankle group and no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group; and
d) no major complications, defined as lack of significant infection, no delayed wound healing requiring surgical intervention, no significant post-operative fractures of adjacent bones and no significant bony changes of adjacent bones requiring surgical intervention.

Note: The non-inferiority margin of delta for supporting patient efficacy was prospectively specified at 10 points in BP score at the IDE stage. The non-inferiority margin of delta for patient safety success was originally specified at 15% at the IDE stage and the sample size was calculated using a 15% delta. However, FDA also considers whether orthopaedic devices can meet a more stringent, clinically meaningful, 10% non-inferiority margin of delta, when compared to the control. It should be noted that the study was underpowered to detect a 10% delta in patient safety success.

*Secondary Endpoints:*
The study ***secondary efficacy endpoints*** consisted of the following:
a) BP score subscales of function and range of motion,
b) improvement in total BP score of 40 points or more,
c) Pain Visual Analog Scale (VAS, 100 mm scale),
d) patient satisfaction (Coughlin rating four category scale: excellent, good, fair, poor),
e) quality of life (SF-36), and
f) medication usage.

***2. Continued Access Cohort***
For the CA cohorts, assessments were identical to those for the pivotal study patients, with addition of the American Orthopaedic Foot and Ankle Society (AOFAS) scale. The CA cohorts were to utilize similar follow-up schedule and evaluation parameters used for STAR Ankle patients enrolled in the pivotal study.

### *3. Bilateral Cohort*

Bilateral patients were only subject to a safety analysis.

## D. Evaluation Schedule

Study examinations were to be performed pre-operatively, perioperatively and post-operatively at 2 and 6 weeks and at 3, 6, 12, and 24 months. Physical examination, medication history, complications and radiographs were to be evaluated at all time points. BP scores, pain VAS, and SF-36 were to be evaluated pre-operatively and at all intervals after 6 weeks. Patients were followed biennially past 24 months until the last patient enrolled into the study reached their 2-year evaluation.

## E. Changes in the Study Conduct and Analyses

The applicant confirmed that no changes were made to the STAR Ankle device during the pivotal clinical study. It should be noted that the applicant made several protocol modifications during the conduct of the study. Some of these modifications were implemented during enrollment in the pivotal study whereas other modifications were made during enrollment in the CA phases.

### *1. Protocol changes*

Several ***protocol*** changes were made from July 2000 through September 2001. These changes included the following:

a. The eligibility criteria for the arthrodesis group was changed to be identical to the criteria for the arthroplasty group; and
b. The measurements for assessing range of motion (ROM) in the BP score were changed from radiographic means to clinical means using a goniometer.

From October 2001 through September 2002, the additional ***protocol*** change was made:

c. Inclusion of the American Orthopaedic Foot and Ankle Society (AOFAS) scale was added as an additional patient assessment for patients enrolled into the arthrodesis group of the pivotal trial after April 2002. [Note: Although enrollment into the STAR Ankle group of the pivotal study was completed by December 2001, the applicant was still enrolling patients into the control arm of the study during this time.]

### *2. Changes to postoperative Patient Instructions*

a. Increased emphasis on patient instructions to ensure patient compliance with post-operative recovery regimens.

### *3. Changes to Analyses - Radiographic Success*

On February 8, 2007 (Amendment 11), after the initial analysis of the data, the applicant proposed that the original IDE defined radiographic success criteria were overly conservative and biased against the STAR Ankle group. The applicant indicated that their safety outcomes would be significantly improved if more clinically-relevant radiographic success criteria were applied to the study. FDA requested further supportive information regarding this proposed change in radiographic success from the original study design,

Within Amendment 15, provided on March 5, 2007 to the PMA, the applicant proposed the following radiographic reanalysis, which differed from what was outlined in the original PMA submission:

- Not Carrying Forward Radiographic Failures

In the original analysis provided in the PMA, all STAR subjects who did not meet the radiographic success criteria at 6 or 12 months were not evaluated further for overall success at 24 months, even if they met the radiographic success criteria at 24 months.

In a post-hoc analysis, the applicant identified seven additionally radiographic and overall successful patients who were not previously considered to be successes at 24 months because of a prior observation that was carried forward as a failure from the 6 or 12 month evaluation, despite radiographic success at 24 months. This approach is adequate provided that patients in both arms who were failures at 6 and 12 months were similarly re- evaluated; however, it does not appear that the radiographs for any of the control patients were re-evaluated.

- Reassessment in Radiographic Success

In the original PMA submission, the criteria considered in the independent radiographic review of the pivotal study radiographs to assess for possible loosening or migration included any of the following findings at any aspect of the bone-prosthesis (tibia or talar components) interface to be a failure:
(1) a radiolucency of greater than 4 mm;
(2) tilting in any direction (varus-valgus or plantiflexion/dorsiflexion) of greater than 4 mm; or
(3) migration in any direction of greater than 4 mm.
The applicant has provided several literature references in the PMA to show that the original definition was not clinically appropriate for the STAR Ankle. The applicant has reassessed the outcomes for five patients who did not initially meet the radiographic success criteria as proposed in the pivotal study, who now meet the success criterion proposed by the applicant, which appears to be based not on radiographic findings but on clinical outcomes. Further, is it unclear whether all patients were reassessed in this manner to come up with a new resulting outcome. Additionally, radiographic criteria directly related to the clinical outcomes are not clearly defined at the present time, nor is it clear that the outcomes were reassessed globally by an independent radiologist.

While the applicant has proposed that a 4mm radiolucency be the benchmark for establishing progressive changes, the literature (Valaderrabano *et al.*[1] also utilized independent radiographic analysis of STAR Ankle patients) describes radiographic loosening as progressive radiolucency greater than 2mm either in AP or lateral view. Thus, it does appear that there is some uncertainty regarding what is the most appropriate definition for radiographic success for the evaluation of total ankle implants.

**PANEL QUESTION: You will be asked to comment on the appropriateness of the proposed changes in radiographic interpretation by the applicant and the potential impact of these changes on the interpretation of the safety outcomes and overall patient success for the STAR Ankle patients.**

[1] Valderrabano et al. 2004, Scandinavian Total Ankle Replacement, Clinical Orthopedics and Related Research, number 424, pp.47-56.

## F. Surgical Technique

The applicant has made a number of modifications to the recommended procedures for implantation of the STAR Ankle, as outlined below, to address issues identified during the pivotal study and attempt to reduce the risk of tissue damage.

1. ***Changes Made to Instruments for the STAR Ankle System***
   a. Modification of captured tibial saw alignment guides to decrease the possibility of bone nicking and notching, to reduce the risk of subsequent fractures (introduced between February and March 2003);
   b. Medial/lateral adjustable guide block modification to allow more precise device placement (introduced between February and March 2003); and
   c. Addition of talar trials and talar tamp to assist in proper device placement (introduced at the end of the pivotal study).

2. ***Surgical Technique Changes***
   a. The use of smaller STAR Ankle talar components, allowing resection of less bone from the malleoli when a patient's talar footprint was between component sizes, to decrease the bony stress that may result from use of a larger component [Note: The applicant indicated that prior to commencement of CA, the decision to use the smaller talar component was implemented];
   b. Use of thicker mobile bearings to potentially reduce component wear;
   c. Use of hand retractors instead of self-retaining retractors to minimize risk of tissue trauma;
   d. General lengthening of the anterior surgical incision to allow for retraction while trying to minimize the risk of tissue damage; and
   e. Use of a two-layer skin closure technique replaced the use of skin staples.
   f. To avoid intra-operative medial malleolar fractures, specifically, in instances where there was a high risk of malleolar fracture, it was recommended to investigating surgeons that two K-wires be inserted into the malleolus prior to the tibial cut and that these wires be removed prior to the end of the case.

The applicant has purported that these modifications have contributed to a decrease in the adverse events associated with implantation of the STAR Ankle. Comparisons of the adverse events identified in the pivotal cohort versus the continued access cohorts do show a decrease in the adverse events; however, there are still safety concerns associated with implantation of the STAR Ankle which could be mitigated with implementation of further modifications. The Surgical Technique Manual and the Implant and Instruments Manual, as provided by the applicant, may be found in Tabs 8 and 9, respectively, of this Panel Pack.

**PANEL QUESTION: We will be asking the panel to discuss whether or not the modifications currently proposed by the sponsor are sufficient to allow safe implantation of the device.**

## V. Clinical Results

There were 158 total patients enrolled at 10 sites and a total of 158 patients treated with a unilateral and 21 patients at 6 sites with bilateral STAR total ankle implantation. There were 66 control patients treated with arthrodesis at 5 sites concurrently.

### A. Patient Accounting

The applicant has used the following terminology to refer to different analysis populations used for evaluating the study endpoints, at 24 months as follows:

- Intent-to-Treat (ITT): includes all enrolled patients.
- Completers: includes all patients for whom the necessary follow-up data required to determine safety and effectiveness at the 24-month timepoint was available at the time of database closure.
- Per Protocol (PP): includes all 'completers' without major protocol deviations.

Taking into account expected patients with any follow-up testing available in the pivotal study at 12 months, there was 81.5 % (53/65) follow-up for arthrodesis controls and 96.7% (147/152) follow-up for STAR Ankle patients (cumulative total of 3 patient deaths, 1 device failure, and 2 patient transfers to the bilateral group). At 24 months, the follow-up for ITT patients was 77.4% (48/62) for controls and 96.7% (145/150) for the STAR group (cumulative total of 4 patient deaths, 2 device failures, and 2 transfers to the bilateral group). The applicant provided sensitivity analyses for multiple imputations and last observation carried forward.

For the purposes of panel presentation, 24 month efficacy and safety data provided by the applicant from the pivotal study were reviewed. The 24 month CA data were reviewed for evaluation of device safety.

### B. Protocol Deviations

A number of protocol deviations were noted in the pivotal study. These deviations included 23 patients (10 STAR and 13 arthrodesis) with pre-surgery BP scores of > 50. However, 18 of those patients (8 STAR and 10 arthrodesis) had BP scores $\leq$60 and were included in the data analysis. Four patients (1 STAR and 3 Arthrodesis) had weights in excess of 250 lbs. One of these patients, an arthrodesis patient weighing 283 lbs was excluded from the PP analysis. One STAR patient with a history of osteoporosis was also excluded from the PP analysis. Three arthrodesis patients were treated with bone growth stimulation following their surgery, yet were included in the PP analysis.

### C. Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the pivotal study cohort are summarized in Table 9.

#### *1. Pivotal Study*

For the ***pivotal*** study, in the STAR Ankle cohort the male/female ratio was evenly divided. The arthrodesis control had approximately 10% more females enrolled. The STAR Ankle population was slightly older (62.7 years vs. 57.1 years), had slightly more Caucasians [96.2% (152/158) vs. 90.9% (60/66)], and more smokers [20% (15/158) vs. 13.9% (5/66)] than the arthrodesis controls. The arthrodesis cohort consisted of slightly heavier patients (185.6 lb vs. 180.9 lb) with slightly higher body mass index (BMI of 29.1 vs. 28) than the

STAR cohort. No appreciable differences between the cohorts were noted in patient height. The STAR cohort had a higher percentage of subjects with primary arthrosis, lower baseline BP scores and higher baseline pain VAS scores in comparison to the arthrodesis control. The baseline BP scale revealed the STAR group to have a higher percentage of patients with severe pain than the control group (84.8% [134/158] vs. 71.2% [47/66]). In the range of motion portion of the BP scale, the STAR group had a greater percentage of patients with pre-operative ankle motion ranging from 15-34 degrees (57% [90/158] vs. 36.4% [24/66] for controls). Overall, the baseline BP score was < 55 and thus rated "poor" in 90.9% (60/66) of the controls and 97.5% (154/158) of the STAR patients.

Several of the baseline demographics were statistically different between groups. Since the study was not randomized, it is not unexpected that differences exist between the patient characteristics of the STAR Ankle and arthrodesis control groups.

*Table 9. Patient Demographics and Baseline Characteristics*

| | Control (N=66) | STAR Pivotal (N=158) | STAR Continued Access (N=424)[1] | P-value for Comparison between STAR Pivotal and Arthrodesis Control |
|---|---|---|---|---|
| Age | | | | 0.004 |
| Mean (SD) | 57.1 (12.3) | 62.7 (12.6) | 62.9 (11.6) | |
| | | | | |
| Primary Diagnosis | | | | 0.054[2] |
| Primary Arthrosis | 19 (28.8%) | 62 (39.2%) | 83 (21.0%) | |
| Posttraumatic Arthrosis | 43 (65.2%) | 76 (48.1%) | 246 (62.3%) | |
| Rheumatoid Arthrosis | 4 (6.1%) | 20 (12.7%) | 27 (6.8%) | |
| Metabolic disorder | | | 39 (9.9%) | |
| | | | | |
| Baseline Total BP Scores | | | | 0.058 |
| Mean (SD) | 43.0 (8.8) | 40.8 (7.4) | 37.5 (8.6) | |
| | | | | |
| Baseline Pain VAS Scores | | | | 0.073 |
| Mean (SD) | 65.8 (19) | 71.1 (17) | 76.6 (14) | |

[1]There were 29 patients missing primary diagnosis and 11 patients missing baseline VAS
[2] Please note that this p-value appears to have grouped the 4 specific diagnoses.

### *2. Continued Access Cohort*

While the general demographics of the ***CA cohort*** were comparable to those of the pivotal patient group, the CA cohort had a higher percentage of post-traumatic arthrosis as the primary diagnosis and lower percentage of primary arthrosis in comparison to the STAR Ankle population for the pivotal study.

## D. Operative Data

### *1. Pivotal Study*

Operative data for the ***pivotal*** study indicated similarity among the control and the STAR cohorts in tourniquet time, operative time, anesthesia time and length of hospital stay. Local anesthesia was predominantly used in the control group, 56.1% (37/66) vs. 28.7% (45/158), while the combination of local and general anesthesia was predominantly used for the STAR Ankle patients. The estimated blood loss was less in STAR patients (53.1 cc vs. 75.3 cc) than the controls.

### 2. *Continued Access Cohort*

In the ***continued access*** group, fewer patients were operated under general anesthesia (16.5% (69/417) for the CA vs. 37.6% (59/158) for the pivotal STAR Ankle group). No appreciable differences between the pivotal and the CA groups were noted in total blood loss. The length of hospital stay was slightly decreased in the CA group (2.8 days vs. 3.1 days for the pivotal STAR Ankle group).

## E. Primary Efficacy Endpoint for the Pivotal Study

### 1. *24-Month BP Scores*

Both the control and the STAR Ankle group have shown improvements in the total BP score over the baseline values (Table 10). The STAR Ankle cohort had a mean BP score of 81.6 vs. a mean BP score of 69.7 for the arthrodesis control. The STAR cohort demonstrated a mean improvement in BP score of 40.5 points compared to 26.3 points for the arthrodesis control group.

The patient outcomes related to pain and function as measured by the BP score demonstrated non inferiority for the STAR Ankle group in comparison to arthrodesis including an analysis which removed the ROM component from consideration (Table 10).

*Table 10. Primary Endpoint Analysis - BP Score With and Without ROM at 24 Months*

| | | Control | | STAR | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Population** | **BP Score** | **N** | **Mean** | **N** | **Mean** | **Difference (STAR - Control)** | **Lower Bound of 90% CI for Difference** | **10 point Delta met?** |
| **BP Score With ROM** | | | | | | | | |
| Completers | 24-month BP | 47 | 69.7 | 142 | 81.6 | 11.9 | 7.8 | Yes |
| | 24-month BP Change from Baseline | 47 | 26.3 | 142 | 40.5 | 14.2 | 9.9 | Yes |
| Per Protocol | 24-month BP | 36 | 70.1 | 127 | 81.7 | 11.6 | 7.1 | Yes |
| | 24-month BP Change from Baseline | 36 | 28.0 | 127 | 40.6 | 12.5 | 7.8 | Yes |
| **BP Score Without ROM** | | | | | | | | |
| Completers | 24-month BP | 47 | 66.4 | 142 | 69.2 | 2.8 | -1.2 | Yes |
| | 24-month BP Change from Baseline | 47 | 30 | 142 | 36.9 | 6.9 | 2.8 | Yes |
| Per Protocol | 24-month BP | 36 | 67.6 | 127 | 69.3 | 1.6 | -2.7 | Yes |
| | 24-month BP Change from Baseline | 36 | 32.4 | 127 | 36.8 | 4.4 | -0.1 | Yes |

### 2. *Additional Statistical Considerations*

Further, the applicant conducted covariate-adjusted and propensity score adjusted analyses on 24-month BP and BP change from baseline using the original BP score and the modified BP score excluding ROM. The STAR Ankle group showed non-inferiority (delta=10 point in BP score) to the arthrodesis control in both the 'completers' and PP population in these analyses.

Single imputation using Last-Observation-Carried-Forward (LOCF) and multiple imputations were conducted to impute the missing data on the Intent-to-treat (ITT) population. The results were similar to those on the Completers and Per Protocol population.

## F. Results of the Safety Endpoints for the Pivotal Study

### *1. Deaths*

Five patients died within 24 months after surgery, 4 in the STAR group and 1 in the control group. One of those was due to pulmonary embolism 7 days after surgery and the others died from causes not related to ankle surgery (1 stroke 94 weeks after surgery, 1 myocardial infarction 13 weeks after surgery, 1 from metastatic cancer 63 weeks after surgery, 1 from congestive heart failure 49 weeks after surgery). It does not appear that any deaths were related to the STAR Ankle.

### *2. Procedure Related Adverse Events*

The surgical issues primarily associated with the STAR Ankle included ligament release and/or reconstruction, and additional surgical procedures, complications and "operative difficulties", which included the following: a) bone fracture (8 patients), b) bone injury (1 patient), c) difficulty with ankle positioning (1 patient), d) difficulty with component placement (4 patients), and e) injury to superficial peroneal nerve. Operative difficulties were encountered more frequently with the STAR Ankle patients (10.1%; 16/158) in comparison to the control patients (0%).

In the ***pivotal*** study group, additional operative site events were noted prior to patient discharge. These events included the following (N = 158): a) bone fractures (15 patients or 9.5% in STAR cohort vs. 1 patient or 1.5% in the control cohort), b) nerve injury (9 patients or 5.7% in STAR vs. none in the control), c) pain (12 patients or 7.6% in STAR vs. 3 patients or 4.5% in the arthrodesis control). In all, 42 (26.6%) STAR patients had some operative site event compared to 4 (6.1%) control patients. No appreciable differences were noted between cohorts in non-operative site events (10.8% for controls vs. 12.7% for STAR patients).

### *3. Device Failures, Revisions or Removals*

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

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, all noted in the STAR group (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 are listed in Table 11.

*Table 11. Operative Site Adverse Events - Patient Basis*

| **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. Bone fractures, intraoperative and post operative were noted predominantly in the STAR patients (30 STAR patients (30/158) versus 2 control (2/66)). Intra-operative fractures were recognized at the time of surgery and in the majority of cases treated with internal fixation. 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 (> 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 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 |

Bony changes were noted on radiographs in 12 patients. These changes included bony cyst formation osteolysis or heterotropic bone formation. According to the applicant, osteolysis and cyst formation are often the result of wear debris, sub-optimal device placement or device loosening.

As noted in Table 12, 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 (20.3% for STAR vs. 7.6% for control).

Wound problems were more common with the STAR Ankle than arthrodesis controls (20.3% for STAR vs. 6.1% for controls). These problems included skin necrosis, wound dehiscence and delayed healing but in the majority of cases no additional surgical intervention was needed. In all, major complications were more common with STAR patients than the controls (8.9% for STAR vs. 1.5% for the control). The most significant of these complications involved the ankle bony structures (5.1% for STAR vs. 0.0% for controls).

In some cases, the above noted adverse events required additional surgical interventions. These are listed in Table 13. In the pivotal study, STAR patients had a higher overall rate of additional surgical interventions (STAR 21.5% [34/158] vs. 16.7% [11/66] for control). Surgical revision was more common in STAR patients (10.8% for STAR vs. 6.1% for controls) with major operative site procedures also more common in STAR patients (STAR 14.6% [23/158] vs. control 4.5% [3/66]). The arthrodesis group had a higher percent of hardware removal (1.5% [1/64] for control vs. 0.6% [1/158]) for the pivotal group.

*Table 13. Summary of Surgical Interventions for Pivotal Study*

| | Control | STAR |
|---|---|---|
| **Surgical Interventions** | **15** | **45** |
| **Patients with Surgical Interventions** | **11 (16.7%)** | **34 (21.5%)** |
| **Intervention Type** | | |
| Revision | 4 (6.1%) | 17 (10.8%) |
| Removal | 7 (10.6%) | 6 (3.8%) |
| Re-operation | 2 (3%) | 9 (5.7%) |
| Other Intervention | 1 (1.5%) | 10 (6.3%) |
| **Intervention Class by Subgroup** | | |
| Minor Operative Site Procedures | 7 (10.6%) | 10 (6.3%) |
| Hardware Removal | 7 (10.6%) | 1 (0.6%) |
| Excision Exostosis | | 5 (3.2%) |
| Minor wound problem | | 3 (1.9%) |
| Synovectomy | | 1 (0.6%) |
| Major Operative Site Procedures | 3 (4.5%) | 23 (14.6%) |
| Component removal | | 17 (10.8%) |
| Infection | 2 (3%) | 1 (0.6%) |
| Bone graft for osteolysis | | 1 (0.6%) |
| Fracture fixation (ORIF) | | 2 (1.3%) |
| Repaid nonunion | 2 (3%) | |
| Fusion, adjacent joint | | 3 (1.9%) |
| Osteotomy for malalignment | | 3 (1.9%) |
| Major Procedure Not Device-Related | 4 (6.1%) | 4 (2.5%) |
| None | | 3 (1.9%) |
| Hardware removal | 1 (1.5%) | 1 (0.6%) |
| Fusion, adjacent joint | 3 (4.5%) | |

As noted in Table 14, surgical interventions in the STAR ankle cohort included removal and replacement of various device components. The mobile bearings were the device component most frequently removed and/or replaced (17 procedures) followed by the talar and tibial components (7 each). This information is summarized in Tables 14 and 15.

*Table 14. STAR Surgical Interventions Pivotal Study*

| | STAR (n%) |
|---|---|
| Surgical Interventions | 45 |
| Patients with Surgical Interventions | 34 (21.5%) |
| Mobile bearing Removed | 17 (10.8%) |
| Mobile bearing Replaced | 15 (9.5%) |
| Talar Component Removed | 7 (4.4%) |
| Talar Component Replaced | 4 (2.5%) |
| Tibial Component Removed | 7 (4.4%) |
| Tibial Component Replaced | 3 (1.9%) |
| Visible Evidence of Loosening around Device | 2 (1.3%) |
| Specific component | |
| meniscal component | 1 |
| subsidence of talar component | 1 |

Table 15 provides more details with the number of patients who had one or more device components removed and or replaced. Twenty one patients underwent STAR component revisions, which consisted of removal/revisions of all three components (8 patients) or partial components (meniscal component alone in 8 patients, meniscal and talar components in 2, meniscal and tibial components in 2 and "other" in 3 patients).

*Table 15. STAR Surgical Interventions*

| **Patient Ankle Components Revised or Removed** | **Patients** |
|---|---|
| | **N** |
| All Three Components | 6 |
| Meniscal Component Only | 8 |
| Meniscal and Talar Components | 2 |
| Meniscal and Tibial Components | 2 |
| Other | 3 |
| Total Patients with Revision/Removal | 21 |

In summary, the information provided in the tables above showed a higher incidence of adverse events associated with the STAR Ankle device throughout the duration of the study in comparison to the standard of care, which is arthrodesis. Consequently, the risk of having an adverse event, which includes an additional surgical intervention, with implantation of the STAR Ankle is higher.

***4. Radiographic Findings***

Radiographic success was originally defined by the applicant as the lack of radiographic evidence for device loosening or migration in the STAR Ankle group and lack of radiographic evidence of non-union, delayed union or mal-union in the control arthrodesis group. Tables 16 and 16A show the radiographic findings at various time points using the originally-defined endpoints. Over the time course between 6 months and 24 months, there appeared to be moderate progression of talar component migration, increase in plantar flexion-dorsiflexion of tibial and talar components and radiolucencies around the talar component. At 6 months, the radiographic failure rate was 3.4% (5/147). At 12 months, the non-cumulative rate was 6.0% (8/133). At 24 months, the non-cumulative rate was 9.3% (13/140). The applicant has not provided cumulative failure rates in Tables 16 and 16A as some patients have not yet reached all follow-up visits or the patient's X-rays have not been evaluated.

*Table 16. Pivotal Study STAR Radiographic Data Summary – Original Radiographic Findings*

| Visit | Tibial Component Migration* | Talar Component Migration* | Varus-Valgus Tilt of Tibial Component* | Varus-Valgus Tilt of Talar Component* | Plantarflexion - Dorsiflexion of Tibial Component* | Plantarflexion - Dorsiflexion of Talar Component* |
|---|---|---|---|---|---|---|
| **6 Months** | | | | | | |
| None | 145 (98%) | 144 (97.3%) | 148 (100%) | 148 (100%) | 145 (98%) | 141 (95.3%) |
| 0-4 mm | 1 (0.7%) | 2 (1.4%) | | | 1 (0.7%) | 5 (3.4%) |
| > 4mm | 2 (1.4%) | 2 (1.4%) | | | 2 (1.4%) | 2 (1.4%) |
| **12 Months** | | | | | | |
| None | 132 (98.5%) | 123 (91.8%) | 134 (100%) | 134 (100%) | 132 (98.5%) | 123 (91.8%) |
| 0-4 mm | 1 (0.7%) | 8 (6%) | | | 1 (0.7%) | 9 (6.7%) |
| > 4mm | 1 (0.7%) | 3 (2.2%) | | | 1 (0.7%) | 2 (1.5%) |
| **24 Months** | | | | | | |
| None | 137 (97.9%) | 121 (86.4%) | 139 (99.3%) | 137 (99.3%) | 134 (95.7%) | 124 (88.6%) |
| 0-4 mm | 1 (0.7%) | 13 (9.3%) | | | 4 (2.9%) | 7 (5%) |
| > 4mm | 2 (1.4%) | 6 (4.3%) | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 9 (6.4%) |
| Missing | 1 | 1 | 1 | 3 | 1 | 1 |

*Patients were originally considered a failure on X-ray if any of these measurements are >4 mm. Failure rates are based on each visit and are not cumulative.

*Table 16A. Pivotal Study STAR X-Ray Data Summary- Original Radiographic Findings (Continued)*

| Visit | Radio-lucencies for Tibial Component* | Radio-lucencies for Talar Component* | Osteolysis by Tibial Component | Osteolysis by Talar Component | Sclerosis by Tibial Component | Sclerosis by Talar Component | Failure on X-Ray* | Cumulative Failures** |
|---|---|---|---|---|---|---|---|---|
| **6 Months** | | | | | | | | |
| None | 36 (24.5%) | 80 (54.8%) | 144 (98%) | 146 (100%) | 143 (97.3%) | 145 (98.6%) | 5 (3.4%) | 5 |
| 0-4 mm | 111 (75.5%) | 66 (45.2%) | 3 (2%) | | 4 (2.7%) | 2 (1.4%) | | |
| > 4mm | | | | | | | | |
| Missing | 1 | 2 | 1 | 2 | 1 | 1 | | |
| **12 Months** | | | | | | | | |
| None | 38 (28.6%) | 85 (64.4%) | 132 (99.2%) | 133 (100%) | 120 (90.2%) | 132 (99.2%) | 8 (6.0%) | 11 |
| 0-4 mm | 94 (70.7%) | 46 (34.8%) | 1 (0.8%) | | 13 (9.8%) | 1 (0.8%) | | |
| > 4mm | 1 (0.8%) | 1 (0.8%) | | | | | | |
| Missing | 1 | 2 | 1 | 1 | 1 | 1 | | |
| **24 Months** | | | | | | | | |
| None | 71 (50.4%) | 129 (91.5%) | 136 (96.5%) | 139 (98.6%) | 129 (91.5%) | 140 (100%) | 13 (9.3%) | 21 |
| 0-4 mm | 68 (48.2%) | 12 (8.5%) | 5 (3.5%) | 2 (1.4%) | 12 (8.5%) | | | |
| > 4mm | 2 (1.4%) | | | | | | | |
| Missing | | | | | | 1 | | |

*Patients were originally considered a failure on X-ray if any of these measurements are >4 mm. Failure rates are based on each visit and are not cumulative.
** Percents are not given for cumulative failures as some patients have not yet reached all follow-up visits or the patient's X-rays have not been evaluated.

For the arthrodesis group, as summarized in Table 17, the radiographic fusion rates increased with time, 90.5% at 6 and 12 months to 93.3% at 24 months, with non-union noted in 2.2 % of patients. The fusion status was not reported in 2 patients at 24 months.

*Table 17. Fusion Data Summary for Arthrodesis Patients*

| | 2 Weeks | 6 Weeks | 12 Weeks | 6 Months | 12 Months | 24 Months |
|---|---|---|---|---|---|---|
| **A/P & Lat Views Taken?** | | | | | | |
| No | 7 (10.6%) | | | | 1 (1.9%) | |
| Yes | 59 (89.4%) | 66 (100%) | 65 (100%) | 63 (100%) | 52 (98.1%) | 45 (100%) |
| **Are Views Weight-Bearing?** | | | | | | |
| No | 57 (89.1%) | 44 (66.7%) | 30 (46.9%) | 7 (11.1%) | 5 (9.6%) | 3 (6.7%) |
| Yes | 1 (1.6%) | 21 (31.8%) | 33 (51.6%) | 56 (88.9%) | 47 (90.4%) | 42 (93.3%) |
| N/A | 6 (9.4%) | 1 (1.5%) | 1 (1.6%) | | | |
| **Device Intact?** | | | | | | |
| No | 1 (1.5%) | 1 (1.5%) | 1 (1.5%) | | 1 (1.9%) | 1 (2.3%) |
| Yes | 54 (83.1%) | 61 (92.4%) | 60 (92.3%) | 55 (91.7%) | 45 (84.9%) | 41 (93.2%) |
| N/A | 10 (15.4%) | 4 (6.1%) | 4 (6.2%) | 5 (8.3%) | 7 (13.2%) | 2 (4.5%) |
| **Fusion** | | | | | | |
| Union | | 3 (4.5%) | 34 (52.3%) | 57 (90.5%) | 47 (90.4%) | 42 (93.3%) |
| Delayed Union | | | 1 (1.5%) | 3 (4.8%) | 2 (3.8%) | |
| Mal-union | | | | 1 (1.6%) | | |
| Non-union | | | | 2 (3.2%) | 2 (3.8%) | 1 (2.2%) |
| NA | 66 (100%) | 63 (95.5%) | 30 (46.2%) | | 1 (1.9%) | 2 (4.4%) |

Changing the radiographic success criteria as proposed by the applicant appears to affect the safety success and overall patient success rates for the study as further discussed in Section 3.

### *5. Safety Success*

Safety success was defined as: a) no device failures, revisions or removals; b) radiographic success (no radiographic evidence of loosening or migration in the STAR ankle and no radiographic evidence of non-union, delayed union, or mal-union in control arthrodesis group); and c) lack of major complications for the original PMA submission. This evaluation formula was used in Table 18 to compare overall safety rates for the STAR ankle and the control population. At 12 and 24 months, the control cohort has demonstrated a higher safety profile than the STAR per protocol patients. For the PP patients, the control success rate was 86% (43/50) vs. 79.5% (97/122) for the STAR Ankle at 12 months and 82.5% (33/40) vs. 71.1% (101/142) for the STAR Ankle at 24 months. Thus, the 15% delta was not met by the STAR patients at the 12 or the 24 month evaluation periods to support safety success.

*Table 18. Pivotal Cohort Safety Success Rates at 12 and 24 Months*

| | | Control | | | STAR | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Follow-up Visit** | **Patient Population** | **n** | **N** | **%** | **n** | **N** | **%** | **Difference in Success Rates (STAR - Control)** | **Lower bound of 90% CI for Difference** | **15%Delta Met?[1]** |
| Month 12 | Per Protocol | 43 | 50 | 86.0% | 97 | 122 | 79.5% | -6.5% | -16.6% | No |
| | Completers | 50 | 57 | 87.7% | 109 | 136 | 80.1% | -7.6% | -16.7% | No |
| | ITT - Single Imputation | 58 | 66 | 87.9% | 127 | 158 | 80.4% | -7.5% | -15.9% | No |
| | ITT - Worst Case Scenario | 59 | 66 | 89.4% | 109 | 158 | 69.0% | -20.4% | -29.1% | No |
| Month 24 | Per Protocol | 33 | 40 | 82.5% | 88 | 126 | 69.8% | -12.7% | -24.6% | No |
| | Completers | 43 | 52 | 82.7% | 101 | 142 | 71.1% | -11.6% | -22.2% | No |
| | ITT - Single Imputation | 55 | 66 | 83.3% | 112 | 158 | 70.9% | -12.5% | -22.1% | No |
| | ITT - Worst Case Scenario | 57 | 66 | 86.4% | 101 | 158 | 63.9% | -22.4% | -31.8% | No |

1. The 15% noninferiority margin delta is met if the lower bound of the 90% confidence interval for the difference in success rates (STAR – Control) is greater than -15%.

As further depicted in Table 19 below, STAR Ankle patients showed lower safety success rate at 24-months compared to the arthrodesis control patients and the 15% non-inferiority margin delta was not met in any of the unadjusted or adjusted analyses, including single and multiple imputations.

*Table 19. Pivotal Study Patient Safety Success at 24-months (With Original Radiographic Interpretations)*

| Unadjusted Analyses | | | | | |
|---|---|---|---|---|---|
| | **Control Success Rate** | **STAR Success Rate** | **Difference in Success Rates (STAR – Control)** | **Lower bound of 90% CI for Difference** | **15% Delta Met?[1]** |
| Per Protocol | 33/40 (83%) | 88/126 (70%) | -13% | -25% | No |
| "Completers" | 43/52 (83%) | 101/142 (71%) | -12% | -22% | No |
| ITT-Single Imputation | 55/66 (83%) | 112/158 (71%) | -12% | -22% | No |

| Adjusted Analyses | | | |
|---|---|---|---|
| | Adjusted Odds-Ratio for Success (STAR/Control) | Lower bound of 90% CI for Adjusted Odds-Ratio | 15% Delta Met?[2] |
| "Completers" – Covariate-adjusted | 0.54 | 0.27 | No |
| Per Protocol Covariate-adjusted | 0.51 | 0.24 | No |
| ITT Covariate-adjusted (LOCF) | 0.48 | 0.24 | No |
| ITT Covariate-adjusted (Multiple Imputations) | 0.57 | 0.28 | No |

1. The 15% noninferiority margin delta is met if the lower bound of the 90% confidence interval for the difference in success rates (STAR – Control) is greater than -15%.
2. A conservative way to detect whether the 15% non-inferiority margin delta is met is to compare the lower bound of the 90% CI for the odds-ratio with 0.55. The delta will be met for any value higher than 0.55.

Table 20 shows how not carrying the radiographic failures forward affects the patient safety success rates. It should be noted that the 15% delta is not met.

*Table 20. Pivotal Study Patient Safety Success at 24-months (Comparing Original & Modified Radiographic Interpretations)*

| Unadjusted Analyses on "Completers" | | | | | |
|---|---|---|---|---|---|
| | Control Success Rate | STAR Success Rate | Difference in Success Rates (STAR – Control) | Lower bound of 90% CI for Difference | 15% Delta Met? |
| Original Radiographic Interpretations[1] | 43/52 (82.7%) | 101/142 (71.1%) | -11.6% | -22.2% | No |
| Modified Radiographic Interpretations[2] | 43/52 (82.7%) | 108/142 (76.1%) | -6.6% | -17.1% | No |

1. Seven (7) STAR Ankle patients had early radiographic failures and were carried forward as failures under the original radiographic interpretations, even though their 24-month radiographs showed success.
2. Radiographic success was based only on the 24-month radiograph. No early radiographic failures were carried forward to 24 month.

The applicant has also proposed to change the stringency in their radiographic success criteria which the applicant identifies as affecting an additional five patients in the analysis. As shown in Table 21, it appears that the safety success is changed by removing radiographic findings or changing radiographic success criteria. However, the applicant has not clearly redefined the new radiographic criteria with new specific numerical measurements. It should be noted that taking into consideration these additional five patients identified by the applicant changes further improves the safety success rate for the STAR Ankle group in the pivotal study to 79.6%, which changes the safety analysis from a failure to a success so that the applicant meets the 15% delta margin in the pivotal study. It is not clear whether this reanalysis were applied to both the investigational and control groups.

*Table 21: Summary of 5 Patients Who Are Now Considered Successes by Applicant*

| Patient ID | Reason for Not Meeting Radiographic Success Criteria | Other Safety Information | 48 month Visit Comments |
|---|---|---|---|
| 2-081 | Talar Migration and Flexion Tilt | No major complications or surgical interventions | No change in clinical exam, satisfaction excellent with minimal pain, investigator reports excellent position with no evidence of subsidence on radiographs, no reported adverse events or surgical interventions |
| 2-088 | Tibial Migration and AP and Flexion Tilt | No major complications or surgical interventions but conservatively casted for stabilization of subsidence | Radiographically same observation with no progression; no change in clinical exam, BP=79 (10 point improvement from 24 month visit), no new adverse events or surgical interventions for this ankle |
| 2-101 | Talar Flexion Tilt | No major complications or surgical interventions | At 24 months new bone was formed in the region of the deltoid ligament. This bone was present at the 48 month visit and noted by the investigator. The patient had no complaints related to the ankle |
| 2-126 | Talar Flexion Tilt | No major complications or surgical interventions | Radiographically same observation with no progression |
| 2-168 | Talar Flexion Tilt | No major complications or surgical interventions | Investigator reports no radiographic findings, no change in clinical exam, satisfaction excellent and no pain, no adverse events or surgical interventions |

To demonstrate how changing the radiographic analysis has affected the safety success outcomes, Table 22 summarize the results.

*Table 22. Patient success rates for completers at 24 months, based on both initial PMA criteria and revised radiographic criteria*

| | **Pivotal** | |
|---|---|---|
| **Safety Success at 24 months** | **Control** | **STAR** |
| Original Criteria | 43/52 (82.7%) | 101/142 (71.1%) |
| Revised, without carrying forward prior X-ray failures | 43/52 (82.7%) | 108/142 (76.1%) |
| Revised, without carrying forward prior X-ray failures + reassessed radiographs | 43/52 (82.7%) | 113/142 (79.6%) |
| **Components of Safety Endpoint** | | |
| No surgical intervention | 47/52 (90.4%) | 122/142 (81.0%) |
| No major complication | 51/52 (98.1%) | 128/142 (90.1%) |
| Fusion (union) | 46/52 (88.5%) | N/A |
| **Success on X-ray** | | |
| Original Criteria | N/A | 117/138 (84.8%) |
| Revised, without carrying forward prior X-ray failures | N/A | 124/137* (90.5%) |
| Revised, without carrying forward prior X-ray failures + reassessed radiographs | N/A | 129/137* (94.2%) |

*One patient was not included in the denominator for the revised criteria for radiographic success because this patient did not have a 24 month X-ray but was considered as a failure for other reasons.

### *6. Overall Patient Success*

Overall (composite) patient success for an individual patient was defined as success for both efficacy and safety at 12 and 24 months. All of the following criteria needed to be met for the patient to be considered a success:

a) ≥ 40 point improvement in total BP score,
b) no device failures, revisions, or removals,
c) radiographic success, and
d) no major complications.

As noted in Tables 23 and 23A, the STAR patients seem to have an overall success edge over the controls at the 12- and 24- month evaluation periods primarily based on higher BP component of the composite evaluation formula. As summarized in Table 24, STAR Ankle patients did show an advantage to the controls in most analyses.

*Table 23. Components of Composite Patient Success Rates for Completers at 12 months*

| | **Control** | | | **STAR** | | |
|---|---|---|---|---|---|---|
| | **n** | **Evaluated** | **%** | **n** | **Evaluated** | **%** |
| Overall Patient Success | 6 | 53 | 11.3% | 63 | 137 | 46.0% |
| Success on B-P (≥ 40 pt Improvement) | 7 | 53 | 13.2% | 84 | 143 | 58.7% |
| Success on Safety Component | 50 | 57 | 87.7% | 109 | 136 | 80.1% |
| No Surgical Interventions | 54 | 57 | 94.7% | 125 | 136 | 91.9% |
| No Major Complications | 56 | 57 | 98.2% | 126 | 136 | 92.6% |
| Fusion (union) | 51 | 57 | 89.5% | NA | NA | NA |
| Success on X-Ray | NA | NA | NA | 120 | 131+ | 91.6% |

*Patients are considered a success on X-ray if all measurements are <4mm. + 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.

*Table23A. Components of Composite Patient Success Rates for Completers at 24 months*

| | **Controls** | | | **STAR** | | |
|---|---|---|---|---|---|---|
| | **n** | **Evaluated** | **%** | **n** | **Evaluated** | **%** |
| Overall Patient Success | 7 | 51 | 13.7% | 64 | 142 | 45.1% |
| 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% |

*Patients are considered a success on X-ray if all measurements are <4mm. + 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.

*Table 24. Overall Patient Success at 24-months*[1]

| Unadjusted Analyses | | | | |
|---|---|---|---|---|
| | Control Success Rate | STAR Success Rate | Difference in Success Rates (STAR – Control) | Lower Bound of 90% CI for Difference |
| "Completers" | 7/51 (14%) | 64/142 (45%) | 31% | 21% |
| Per Protocol | 6/40 (15%) | 59/128 (46%) | 31% | 19% |
| ITT-Single Imputation | 17/66 (26%) | 72/158 (46%) | 20% | 9% |
| ITT-Worst Case[2] | 22/66 (33%) | 64/158 (41%) | 7% | -4% |
| Adjusted Analyses | | | | |
| | Adjusted Odds-Ratio for Success (STAR/Control) | | Lower Bound of 90% CI for Adjusted Odds-Ratio | |
| "Completers" – Covariate-adjusted | 4.6 | | 2.1 | |
| Per Protocol Covariate-adjusted | 4.2 | | 1.9 | |

1. Overall patient success was defined as safety success and BP score improvement >= 40.
2. ITT – Worse Case was defined as all missing STAR patients imputed as failures and all missing control patients imputed as successes.

In Table 25, patient success rates are reported after removal of the ROM component of the BP scale as was requested by the Agency for the primary effectiveness endpoint. Once the ROM is removed from the patient success formula, the PP control group had a slightly lower overall success rate at 12 months [60.9% (28/46) for the control and 65.0% (80/123) for the STAR cohort]. However, at the 24-month evaluation period, the control group had a higher success score than the STAR group [67.5% (27/40) for the controls vs. 60.6% (77/127) for the STAR cohort]. The overall patient success appears to be sensitive to the cutoff point of BP score and whether range of motion is included.

*Table 25. Patient Success minus ROM at 12 and 24 Months*

| | | Control | | | STAR | | | |
|---|---|---|---|---|---|---|---|---|
| **Follow-up Visit** | **Patient Population** | **n** | **N** | **%** | **n** | **N** | **%** | **Differences in Success Rates* (STAR - Control)** |
| Month 12 | Per Protocol | 28 | 46 | 60.9% | 80 | 123 | 65.0% | 4.2% |
| | Completers | 33 | 53 | 62.3% | 90 | 136 | 66.2% | 3.9% |
| | ITT - Single Imputation | 39 | 66 | 59.1% | 104 | 158 | 65.8% | 6.7% |
| | ITT - Worst Case Scenario ** | 46 | 66 | 69.7% | 90 | 158 | 57.0% | -12.7% |
| Month 24 | Per Protocol | 27 | 40 | 67.5% | 77 | 127 | 60.6% | -6.9% |
| | Completers | 33 | 51 | 64.7% | 87 | 142 | 61.7% | -3.0% |
| | ITT - Single Imputation | 38 | 66 | 57.6% | 96 | 158 | 60.8% | 3.2% |
| | ITT - Worst Case Scenario ** | 48 | 66 | 72.7% | 87 | 158 | 55.1% | -17.7% |

*Overall patient success defined as safety success and at least a 25 point improvement in BP score.
** ITT-Worst Case defined as all missing STAR patients imputed as failures and all missing control patients imputed as successes.

Tables 26 and 26A present the success rates by subgroups. Please note that the success rates presented in these tables were not powered and are the results of post-hoc analyses.

*Table 26. Success Rates by Subgroups at 12 Months*

| **Success Rates by Subgroups** | **Patient Success 12 Months** | | **Efficacy Success 12 Months** | | **Safety Success 12 Months** | |
|---|---|---|---|---|---|---|
| | **Control** | **STAR** | **Control** | **STAR** | **Control** | **STAR** |
| **Age Category** | | | | | | |
| < 50 | 3 (21.4%) | 10 (47.6%) | 3 (21.4%) | 14 (56%) | 12 (85.7%) | 18 (85.7%) |
| 50 - 70 | 1 (3.6%) | 31 (41.9%) | 1 (3.6%) | 40 (53.3%) | 29 (90.6%) | 57 (79.2%) |
| > 70 | 2 (18.2%) | 22 (52.4%) | 3 (27.3%) | 30 (69.8%) | 9 (81.8%) | 34 (79.1%) |
| **BMI Category** | | | | | | |
| Normal (BMI< 25) | 2 (13.3%) | 20 (57.1%) | 3 (20.1%) | 26 (68.4%) | 13 (81.3%) | 27 (79.4%) |
| Overweight (BMI 25 - 29) | 4 (21.0%) | 21 (37.5%) | 4 (21.1%) | 30 (51.7%) | 20 (95.2%) | 43 (78.2%) |
| Obese (BMI > 30) | | 22 (47.8%) | | 28 (59.6%) | 17 (85.0%) | 39 (83%) |
| **Primary Diagnosis** | | | | | | |
| Primary Arthrosis | 1 (7.1%) | 30 (55.6%) | 2 (14.3%) | 37 (67.3%) | 14 (87.5%) | 43 (82.7%) |
| Posttraumatic Arthrosis | 3 (8.6%) | 29 (42%) | 3 (8.6%) | 37 (52.1%) | 33 (89.2%) | 55 (79.7%) |
| Rheumatoid Arthrosis | 2 (50%) | 4 (28.6%) | 2 (50%) | 10 (58.8%) | 3 (75%) | 11 (73.3%) |
| **Race** | | | | | | |
| Caucasian | 5 (10.4%) | 63 (47.4%) | 6 (12.5%) | 81 (59.1%) | 46 (88.5%) | 107 (80.5%) |
| Hispanic | | | | 1 (100%) | 2 (66.7%) | |
| African American | | | | 2 (50%) | 1 (100%) | 2 (66.7%) |
| Other | 1 (100%) | | 1 (100%) | | 1 (100%) | |
| **Gender** | | | | | | |
| Male | 2 (8.3%) | 34 (52.3%) | 2 (8.3%) | 43 (63.2%) | 24 (88.9%) | 50 (78.1%) |
| Female | 4 (13.8%) | 29 (40.3%) | 5 (17.2%) | 41 (54.7%) | 26 (86.7%) | 59 (81.9%) |
| **History of Smoking** | | | | | | |
| Yes | 4 (14.8%) | 30 (46.9%) | 4 (14.8%) | 40 (59.7%) | 27 (93.1%) | 50 (78.1%) |
| No | 2 (7.7%) | 33 (45.8%) | 3 (11.5%) | 44 (58.7%) | 23 (82.1%) | 58 (81.7%) |
| Missing | | | | | | 1 (100%) |

*Table 26A. 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 | | | | | | |

After post-hoc subgroup analysis, at the 12-month evaluation, younger STAR patients (<50 years of age ), with normal body mass (BMI < 25), with primary diagnosis of post-traumatic arthrodesis and non-smoker males appear to have somewhat better outcomes than older, heavier female patients or patients with primary diagnosis of primary or rheumatoid arthrosis.

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. In addition, heavier patients (BMI 25-29) with primary arthrosis appear to have better outcomes than lighter patients with post-traumatic arthrosis.

Please note that the success rates presented in Tables 26 and 26A were not statistically powered and are the results of post-hoc analyses. Thus, any conclusions drawn from these results will have limited utility.

### *7. Secondary Efficacy Endpoints*

The pivotal study ***secondary efficacy endpoints*** analysis consisted of the following:
a) BP subscales of function and range of motion,
b) improvement in total BP score of 40 points or more,
c) Pain Visual Analog Scale (VAS, 100 mm scale),
d) patient satisfaction (Coughlin rating four category scale: excellent, good, fair, poor),
e) quality of life (SF-36), and
f) medication usage.

a. Buechel-Pappas (BP) Subscale for Function and Range of Motion

Looking specifically at BP subscale for function, the STAR group performed better than the controls, at 24 months, in stair usage, standing and support categories and had a higher overall mean value (13.4 vs. 9.7) than the arthrodesis controls. As to range of motion subscale, the STAR group and the controls could not be compared as the intent of arthrodesis was to eliminate ankle motion. However, comparing STAR post-operative ankle ROM at 3 months with the ROM present at the 24 month follow-up, there appears to be some increase in ankle motion (mean value 2.5 at 3 months vs. 3.6 at 24 months). There was no significant difference in ankle ROM between the 12- and 24-month follow-up.

b. Improvement in Total BP Score

The STAR Ankle total BP values for the total BP score with or without use of the ROM subscale in the 'completers' and per protocol patients showed non-inferiority with the control group. Comparing the BP score sub-scores (Table 27) shows no significant improvement in stair climbing, standing, support, walking, limping and overall function in STAR patients between the 12- and 24-month evaluation periods.

*Table 27. Mean Improvement in BP Function Sub-Scores from Baseline*

| | 12 Months | | 24 Months | |
|---|---|---|---|---|
| | **Control** | **STAR** | **Control** | **STAR** |
| **Stairs (8 points)** | | | | |
| N | 52 | 143 | 48 | 142 |
| Mean (SD) | 1.2 (2.1) | 1.6 (2.1) | 0.9 (2) | 1.6 (2.1) |
| Range | -3, 6 | -6 , 6 | -6 , 5 | -6 , 6 |
| **Standing (8 points)** | | | | |
| N | 52 | 143 | 48 | 142 |
| Mean (SD) | 2.0 (2.8) | 3.5 (2.4) | 1.7 (3.3) | 3.4 (2.8) |
| Range | -6 , 8 | -3 , 8 | -6 , 8 | -3 , 8 |
| **Support (8 points)** | | | | |
| N | 51 | 143 | 47 | 142 |
| Mean (SD) | 0.7 (2.2) | 1.6 (2.5) | 0.8 (1.9) | 1.7 (2.2) |
| Range | -8 , 4 | -8 , 8 | -4 , 5 | -8 , 8 |
| **Walking (8 points)** | | | | |
| N | 52 | 143 | 48 | 142 |
| Mean (SD) | 2.2 (2.1) | 2.6 (2) | 2.7 (1.9) | 2.6 (1.9) |
| Range | -4 , 6 | -2 , 8 | -2 , 6 | -2 , 6 |
| **Limp (8 points)** | | | | |
| N | 53 | 143 | 48 | 142 |
| Mean (SD) | 3.2 (2.5) | 4.2 (2.3) | 3.4 (3.4) | 4.1 (2.2) |
| Range | -3 , 8 | -3 , 8 | -7 , 8 | -2 , 8 |
| **Function (40 points)** | | | | |
| N | 53 | 143 | 48 | 143 |
| Mean (SD) | 9.5 (8.1) | 13.6 (7.9) | 9.7 (8.7) | 13.4 (7.3) |
| Range | -22 , 28 | -15 , 32 | -9 , 28 | -16 , 30 |

c. Pain Visual Analog Scale (VAS)

Scale of 100 mm was used. Both the control and STAR group showed minimal change in pain perception at 12 and 24 months with the STAR group having higher pain VAS values than the controls (51.8 for STAR vs. 44.6 for control), as denoted in Table 28.

*Table 28. Mean Pain VAS Improvement From Baseline*

| | 12 Months | | 24 Months | |
|---|---|---|---|---|
| | **Control** | **STAR** | **Control** | **STAR** |
| N | 51 | 144 | 45 | 144 |
| Mean (SD) | 43.5 (27.0) | 51.1 (24.3) | 44.6 (27.3) | 51.8 (26.5) |
| Range | -25, 81 | -23, 100 | -35, 88 | -39, 100 |

d. Patient Satisfaction

The Coughlin rating four category scale was used with ratings of excellent, good, fair and poor. Table 29 showed no significant difference between the controls and STAR patients in combined excellent and good rating at 24 months. However, while the arthrodesis patients showed improvement between the 12 month and 24 month scores, the STAR patient excellent/good scores remained relatively unchanged. In addition, the poor rating seemed to decrease in arthrodesis group between the 12 and 24-month evaluations (5.7% at 12 months and 4.3% at 24 months), whereas the STAR patient poor rating increased during this same timeframe (0.7% at 12 months and 2.8% at 24 months).

*Table 29. Patient Satisfaction by Follow-up Visit*

| | **12 Months** | | **24 Months** | |
|---|---|---|---|---|
| | **Control** | **STAR** | **Control** | **STAR** |
| **Patient Satisfaction** | N=53 | N=141 | N=47 | N= 143 |
| Excellent | 20 (37.7%) | 69 (48.9%) | 22 (46.8%) | 67 (46.9%) |
| Good | 20 (37.7%) | 50 (35.5%) | 18 (38.3%) | 56 (39.2%) |
| Fair | 10 (18.9%) | 21 (14.9%) | 5 (10.6%) | 16 (11.2%) |
| Poor | 3 (5.7%) | 1 (0.7%) | 2 (4.3%) | 4 (2.8%) |

e. Quality of Life (SF-36)

At 24 months there was no significant difference between the control and STAR patients in the total physical score with STAR patients having a higher total mental score. The STAR patients seemed to have a slight decrease in both the physical and the mental scores between the 12 and 24 month evaluations.

f. Medication Usage

Medication use by all patients (control and STAR) did not seem to change appreciably between the pre-surgery use and at the 24 month follow-up. While some patients stopped taking previous medications, others have started new medication use.

***8. Additional Analyses***

a. Failure-free Survival

At the request of FDA, the applicant also conducted Log-rank test to compare the failure-free survival time (which is equivalent to the composite patient safety success) between the STAR Ankle patients and the arthrodesis patients in the pivotal study. All follow-up information up to the time of database closure on 12/1/2006 was included in the analysis. There was no statistically significant difference (p=0.09) between the two survival curves. The Kaplan-Meier estimates of safety success at 24 months were 85% and 74% for the arthrodesis and the STAR Ankle group, respectively. Only five (5) control patients were followed beyond 36 months, making it difficult to compare the long-term survival between the two groups.

***Note***: Overall there were only 10 safety failures for the control group, therefore there may not be enough power to detect significant overall survival difference between the two groups.

b. Complications Stratified by Bearing Thickness

On January 9, 2007, the applicant responded to additional questions posed by the FDA. The applicant was specifically requested to stratify complications by bearing size. Tables 30 and 31 show device complication by bearing size for the STAR Ankle arm of the pivotal study. It should be noted that the study was not prospectively designed to ascertain whether there were

clinical performance differences in bearing thickness. This post-hoc analysis was performed at the request of the FDA to determine whether an obvious difference in bearing thickness performance was observable. Based upon this post-hoc analysis, it does not appear that there was any direct relationship between bearing thickness and failure; however, it should be noted that these analyses were not powered.

*Table 30. Device Complications up to 24 months by Bearing Size*

| Bearing Size, mm | Number of Patients – Pivotal Study | Device Failure | Device Instability | Device Subsidence | Device Malalignment | Revision | Removal |
|---|---|---|---|---|---|---|---|
| **6** | 89 | 0 | 1 | 2 | 0 | 4 | 2 |
| **7** | 34 | 0 | 1 | 1 | 0 | 4 | 0 |
| **8** | 18 | 1 | 0 | 0 | 0 | 0 | 0 |
| **9** | 10 | 0 | 1 | 1 | 0 | 3 | 0 |
| **10** | 7 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 158 | 1 | 3 | 4 | 0 | 11 | 2 |

*Table 31. Device Complications up to 24 months for Pivotal Study*

| Bearing Size, mm | Number of Patients – Pivotal Study | Bony Changes | | | Number of patients | X-Ray Failure |
|---|---|---|---|---|---|---|
| | | Cyst | Exostosis | Osteolysis | | |
| **6** | 89 | 1 | 5 | 0 | 82 | 13 |
| **7** | 34 | 0 | 2 | 0 | 31 | 3 |
| **8** | 18 | 0 | 0 | 1 | 13 | 3 |
| **9** | 10 | 0 | 0 | 0 | 7 | 1 |
| **10** | 7 | 0 | 1 | 0 | 5 | 1 |
| **Total** | 158 | | | | 138 | 21 |

## G. Continued Access (CA) Cohort Results

### *1. Device Failures, Revisions or Removals*

A total of 448 patients received the STAR ankle in the CA group. Table 32 shows the surgically related adverse events in the CA group. The most common events continued to be bone fracture at the time of surgery with decreasing frequency within the initial 6 months after surgery (44 fractures). Also common were nerve injury (97 procedures), pain (155 procedures) and soft tissue edema and wound problems in 22 and 86 patients respectively. Infection was noted in 16 patients and ankle bony changes in 24 procedures.

*Table 32. Operative Site Adverse Events Over Time - Event Basis*

| Type | OP<br>n | DC-6 weeks<br>n | 6 weeks-3 months<br>n | 3-6 months<br>n | 6-12 months<br>n | 12-24 months<br>n | 24+ months<br>N | Total<br>n |
|---|---|---|---|---|---|---|---|---|
| **bone fracture** | 21 | 8 | 8 | 5 | 2 | . | . | 44 |
| **bony changes** | . | 2 | . | 1 | 5 | 8 | 8 | 24 |
| **decreased ROM** | . | 3 | . | . | . | . | . | 3 |
| **device failure** | . | . | . | . | 1 | . | 1 | 2 |
| **device migration** | 1 | . | . | . | . | 1 | 4 | 6 |
| **device subsidence** | . | . | . | 2 | 2 | 1 | 1 | 6 |
| **embolism** | . | 3 | . | . | . | 2 | . | 5 |
| **foot deformity** | . | . | . | . | 1 | 1 | . | 2 |
| **gait problems** | . | . | 1 | . | . | 2 | . | 3 |
| **infection** | . | 5 | 9 | . | . | 1 | 1 | 16 |
| **muscle problems** | . | 1 | 1 | . | 1 | . | . | 3 |
| **nerve injury** | 29 | 27 | 15 | 11 | 7 | 7 | 1 | 97 |
| **pain** | 13 | 13 | 21 | 46 | 36 | 17 | 9 | 155 |
| **soft tissue edema** | 1 | 1 | 9 | 4 | 3 | 4 | . | 22 |
| **tendon problem** | 1 | 1 | . | 3 | 5 | 2 | 2 | 14 |
| **wound problem** | . | 66 | 16 | 2 | . | 2 | . | 86 |

In Table 33, adverse events are compared between the CA and the pivotal groups (control and STAR).

*Table 33. Comparison of Adverse Events in Control and Pivotal Groups with Continued Access to 24 Months After Surgery*

| | **Pivotal Study** | | **Continued Access Arm*** |
|---|---|---|---|
| **Adverse Events** | **Control (N=66)** | **STAR (N=158)** | **STAR (N=352)**** |
| bone fracture | 2 (3.0%) | 28 (17.7%) | 37 (10.5%) |
| intra-operative fracture | 1 (1.5%) | 15 (9.5%) | 21 (5.0%) |
| post-operative fracture | 1 (1.5%) | 15 (9.5%) | 19 (5.4%) |
| bony changes | 0 (0%) | 12 (7.6%) | 15 (4.3%) |
| pain | 32 (48.5%) | 69 (43.7%) | 115 (32.7%) |
| nerve injury | 5 (7.6%) | 32 (20.3%) | 75 (21.3%) |
| wound problem | 4 (6.1%) | 32 (20.3%) | 65 (18.5%) |
| surgical intervention | 11 (16.7%) | 34 (21.5%) | 26 (7.4%) |
| revision or removal | 10 (15.2%) | 21 (13.3%) | 12 (3.4%) |
| other intervention | 3 (4.5%) | 19 (12.0%) | 15 (4.3%) |
| major complication | 1 (1.5%) | 14 (8.9%) | 17 (4.8%) |
| infection | 1 (1.5%) | 2 (1.3%) | 3 (0.8%) |
| bone problems | 0 (0%) | 8 (5.1%) | 10 (2.8%) |
| wound problems | 1 (1.5%) | 5 (3.2%) | 5 (1.4%) |
| wound problems and infections | 0 (0%) | 1 (0.6%) | 0 (0%) |

*The follow-up rate is lower for the continued access patients than for the pivotal study
**The adverse event rates for the CA study has only included data from 352 patients who have reached 24 months post-procedure.

At 24 months, when compared to the STAR pivotal group, the CA patients had a lower overall rate of fractures (10.5% for CA vs. 17.7% for STAR pivotal), and intra-operative and post-operative fractures (5.0% (21/424) for CA vs. 9.5% (15/158) for STAR pivotal). Also noted between the STAR CA and the pivotal groups were decreases in post-operative pain and the rate of surgical interventions and device revisions (3.4% for the CA group vs. 13.3% for the pivotal group). Major complications, which included infection, bone problems and wound problems, were also reduced in the CA group (4.8% for the STAR CA group vs. 8.9% for the STAR pivotal group).

However, comparing the pivotal study controls with the CA population, the control group has a lower bone fracture rate (3.0% vs. 10.5%), lower incidence of nerve injury (7.6% vs. 21.3%), lower incidence of wound problems (6.1% vs.18.5%), and lower rate of major complications (1.5% vs. 4.8%). Table 38 also shows a higher rate of surgical interventions and "revisions or removal" in the control population than the CA group (surgical interventions - 16.7% for pivotal controls vs. 7.4% for the CA group). Specific types of surgical interventions or revisions/removals are not provided in Table 33; however were provided by the applicant in the PMA.

### *2. Safety Analyses*

The data collected during the continued access arm is not complete. The follow up at 12 and 24 months at the time of PMA was 84% (355/424) and 66% (211/320), respectively . Thus the ability to infer the patient outcomes if all patients had complete follow-up data is diminished. The applicant has speculated that changes in the surgical techniques and instruments based upon experiences learned during the pivotal study has translated into higher safety success rates reported in the continued access study. Although there appears to be a trend to support this theory in the data presented in Table 34, only 80 continued access patients received independent radiographic reviews, which makes direct comparison to the pivotal study difficult, as radiographic failure was a component of the composite safety endpoint.

*Table 34. Patient Safety Success for the Pivotal Study and Continued Access Study*

| | Pivotal Study Control Success Rate | Pivotal Study STAR Success Rate | STAR Continued Access Success Rate[1] |
|---|---|---|---|
| Per Protocol | 33/40 (83%) | 88/126 (70%) | 186/212 (88%) |
| "Completers" | 43/52 (83%) | 101/142 (71%) | 196/225 (87%) |

1. Please note the continued access success rate may not be directly comparable to the pivotal study as only 80 continued access patients received independent radiographic reviews.

Please note the low follow-up rate in the continued access study may easily introduce bias in the patient safety success rates, if the patients were not missing completely at random.

**PANEL QUESTION: The panel will be asked to comment on whether or not the sponsor has adequately addressed the implications of modifications to the surgical technique to decrease adverse events for STAR Ankle patients based on the available data for the continued access patient cohort.**

### *3. Additional Analyses*

In Amendment 10, the applicant provided information related to complications stratified by bearing size. Tables 35 and 35A show device complications by bearing size for the STAR Ankle arm of the continued access cohort.

*Table 35. Continued Access – Device complications up to 24 months by Bearing Size*

| Bearing Size, mm | Number of Patients | Device failure | Device instability | Device subsidence | Device malalignment | Revision | Removal |
|---|---|---|---|---|---|---|---|
| **6** | 104 | 0 | 0 | 1 | 0 | 2 | 2 |
| **7** | 144 | 1 | 0 | 1 | 0 | 2 | 3 |
| **8** | 93 | 0 | 0 | 1 | 1 | 2 | 0 |
| **9** | 52 | 0 | 0 | 1 | 0 | 1 | 0 |
| **10** | 31 | 0 | 0 | 1 | 0 | 1 | 1 |
| **Total** | 424 | 1 | | 5 | 1 | 8 | 6 |

*Table 35A. Continued Access – Device complications up to 24 months by Bearing Size(continued)*

| Bearing Size, mm | Number of Patients – Continued Access | Bony Changes | | |
|---|---|---|---|---|
| | | Cyst | Exostosis | Osteolysis |
| **6** | 104 | 0 | 2 | 1 |
| **7** | 144 | 0 | 1 | 2 |
| **8** | 93 | 0 | 3 | 0 |
| **9** | 52 | 0 | 2 | 1 |
| **10** | 31 | 0 | 0 | 1 |
| **Total** | 424 | | | |

Based upon this post-hoc analysis, it does not appear that there was any direct relationship between bearing thickness and failure; however, it should be noted that these analyses were not powered to definitely support this conclusion.

## H. Bilateral Cohort Results

Data from the bilateral patients provided additional safety information for the PMA. In total, at 24 months, data from 12 ankles (12/27) was available for evaluation. Review of the available safety data did not reveal new or increase types of adverse events associated with bilateral surgery. Bone fracture (8.5%), significant pain (22.2%), and nerve injury 11.1%) were noted along with non-specific musculoskeletal and general complaints.

Two (2) patients died during the course of the bilateral study, one patient from complications related to a stroke approximately 15 months post-surgery and one from cardiac arrest 1 year post-surgery. Neither of these deaths were considered to be related to the STAR Ankle or surgery to implant the device.

## I. Learning Curve

Based on a post-hoc assessment of the adverse event data in the pivotal and continued access outcomes data, the applicant suggests that the learning curve for the STAR Ankle patients could be as low as 15 patients. Intra-operative fracture, surgical intervention and major complications (wound/infection or bony changes) of the pivotal patients were compared to the first 15 patients of the continued access (CA 1-15) and to the remaining patients (CA 16-last) from the continued access study (Table 36).

*Table 36. Rate of Intra-Operative Fracture, Surgical Intervention, and Major Complication*

| Event | Pivotal Study | Continued Access | |
|---|---|---|---|
| | | 1 – 15 patients | 16 – last patients |
| **Intra-operative Fracture** | 15/158 (9.5%) | 11/150 (7.3%) | 9/244 (3.7%) |
| **Surgical Intervention** | 13/158 (8.2%) | 7/148 (4.7%) | 3/178 (1.7%) |
| **Major Complication** | 14/158 (8.9%) | 6/148 (4.1%) | 11/178 (6.2%) |
| **Wound problem or infection** | 6/158 (3.8%) | 3/148 (2.0%) | 4/178 (2.2%) |
| **Bony changes** | 8/158 (5.1%) | 3/148 (2.0%) | 7/178 (3.9%) |

This table only includes patients with at least 24 months of follow-up.

In addition, the applicant looked at 3 investigators who only participated in the continued access study and they concluded that a 15 patient learning curve was apparent (Table 37). No statistical justification was provided for choosing a 15 patient learning curve.

*Table 37. Major complications and surgical revisions/removals up to 24 months*

| | Pivotal Study | Continued Access Study | |
|---|---|---|---|
| | Pivotal Investigators | Pivotal Investigators | New Investigators |
| **Number of Investigators** | 10 | 10 | 3 |
| **Intra-operative Fracture** | 15/158 (9.5%) | 20/394 (5.1%) | 1/26 (3.8%) |
| **Major Complication** | 14/158 (8.9%) | 17/326 (5.2%) | 0/26 (0.0%) |
| **Surgical Intervention** | 13/158(8.2%) | 10/326 (3.1%) | 1/26 (3.8%) |

**PANEL QUESTION: The panel will be asked to comment on the interpretation of the applicant's assessment of the learning curve and the aspects which may influence the learning curve, including the changes to instrumentation, training and specific surgical technique to decrease adverse events for STAR Ankle patients.**

## J. Overview of Training Program

The applicant plans to require certification for all surgeons interested in the STAR Ankle procedure. A series of courses are planned at various sites around the country. The planned courses will run 1.5 days with both lectures and a cadaveric lab. A full surgical video will also be presented and reviewed. Opportunities will exist for questions and answers. Particular attention will be paid to the initial incision, surgical lessons learned during the US IDE studies, modifications to the instruments that were implemented during those studies and the use and understanding of the trials and fin tamp. A certification test will be administered at the conclusions of the course. The applicant has provided an outline of their proposed training program in Tab 10 of the Panel Pack.

## VI. Additional Statistical Considerations

### A. Study Design and Analysis

#### *1. Nonrandomized Pivotal Study*

The pivotal study was controlled, but not randomized. Ten sites enrolled exclusively STAR Ankle patients and five sites enrolled exclusively arthrodesis patients. Such design could introduce bias for which there is no way of adjusting, because the observed treatment difference between the STAR Ankle and arthrodesis could be solely attributed to site differences.

#### *2. Site Variability*

Since each site enrolled exclusively STAR Ankle patients or arthrodesis patients in the pivotal study, site variability has to be evaluated separately for each treatment group. As seen in Table 38 below, most of the p-values for site variability for the 24-month BP score and 24-month patient success are significant or close to being significant, indicating variability exists between sites in the same treatment arm. This observation makes it more difficult to distinguish the treatment effect from the site variability. However, the applicant does make rationale that all but one STAR Ankle sites have mean BP scores higher than any of the control sites. The same rationale was provided for patient success.

*Table 38. Site Variability in STAR Ankle and Control Group in the Pivotal Study*

| | 24-Month BP (ANOVA) | | 24-Month Patient Success (Chi-square test) | |
|---|---|---|---|---|
| | STAR | Control | STAR | Control |
| Unadjusted p-value for Site Variability | 0.018 | 0.007 | 0.052 | 0.55 |
| Adjusted p-value for Site Variability | 0.023 | 0.015 | Not Conducted | Not Conducted |

#### *3. Missing Data*

In the ***pivotal*** study, 19 of the 66 enrolled arthrodesis patients (29%) had missing 24-month effectiveness primary endpoint data. Such a large number of missing arthrodesis patients reduce the power of the study and make it difficult to avoid biases in statistical analyses. At the request of FDA, the applicant compared the 6-month BP scores of patients who discontinued between 6-months and 24-months and the patients who had complete 24-month follow-up (Table 39). The data showed that arthrodesis patients with missing 24-month BP scores had lower average BP scores at 6 months than arthrodesis patients with complete 24-month BP scores, although the difference is not statistically significant. This suggests ignoring these missing control patients may bias the 24-month control BP scores upwards, making the comparison to the STAR Ankle group more conservative. However, single and multiple imputations were performed by the applicant to properly account for these missing data.

*Table 39. Comparison of 6 month BP Scores and Change from Baseline BP Scores between 24 Month Completers and Non-Completers for Arthrodesis Patients*

| | Arthrodesis Drop-outs with no 24-month Data (N=17) | Arthrodesis Patients with 24-month Data (N=45) | T-test p-value |
|---|---|---|---|
| 6-month BP Score (Std dev) | 60.1 (18.7) | 64.0 (14.3) | 0.38 |
| 6-month BP Change from Baseline (Std dev) | 17.6 (18.5) | 20.7 (15.9) | 0.52 |

## VII. Post-Approval Study

### A. Overview of Post-Approval Study Proposal

**Note: If PMA is recommended for approval with conditions with one of the conditions being to conduct a post-approval study.**

**NOTE TO PANELISTS:** ***FDA's inclusion of a section/discussion on a Post-approval study in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether or not to approve a device must be based on the pre-market data. The pre-market data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data.***

The applicant's stated objectives of the post-approval study are the following: 1) to evaluate the long-term revision or removal rate for the STAR Ankle; and 2) to assess the learning curve of physicians who are initially treating patients with the STAR Ankle after device approval. To achieve these objectives, the applicant has proposed collection of information from two-different cohorts:

- A long-term follow-up component with a rate of device revision or removal as the primary outcome, and
- A short-term physician learning curve component with a rate of major complications as the primary outcome.

#### *1. Long-term Follow-up Component*

Within this phase of the post-approval study (PAS), the applicant has proposed to recruit all surviving STAR Ankle patients from the Continued Access (CA) cohorts who have not had revision or removal and follow them for up to 8 years after the index surgery, with clinical evaluation at 6 weeks, 12, 24, 48, 72, and 96 months post-operation. This component of the post-approval study will not recruit or enroll any new STAR Ankle patients post-approval, but will only consist of eligible patients who were originally enrolled into the CA cohorts and are now willing to consent to longer-term follow-up.

Buechel-Pappas Scale score, Visual Analog Pain scale, Quality of Life and American Orthopedic Foot Ankle Society Score (AOFAS) will be measured as secondary outcomes. Clinically-indicated anterior-posterior and lateral x-ray images of the treated ankle will be obtained and interpreted by the treating surgeon to assess device breakage, tilt, migration, and subsidence as well as osteolysis, sclerosis, and heterotopic changes of the surrounding ankle. Within the current proposal, there is no indication that radiographic assessment will be mandatory or performed by an independent radiologist. Further, it is unclear whether any formal radiographic measurements will be taken by the treating surgeons. The applicant does not address whether all removed/revised device components will be sent back to the applicant for explant analyses. Furthermore, STAR Ankle patients in the CA study who have had a revision or removal before patient recruitment for the PAS begins (including those reported in the PMA) will not continue to be followed in the PAS. In addition, the study does not propose any comparisons to either historical arthrodesis controls or the pivotal study controls. Although the loss-to follow-up rate was high in the PMA study (22.6% for the arthrodesis control group at 24 months post-operation and only 66% (211/320) of STAR Ankle patients in the CA study had data at 24 months post-operation), the applicant has not provided a

comprehensive plan to control loss to follow-up within this component of the post-approval study. The applicant has proposed to evaluate without hypothesis testing, the performance of a subgroup, patients less than 50 years of age with/without a primary diagnosis of post-traumatic arthritis, within this component.

***2. Learning Curve Component***

Within this phase of the post-approval study, the applicant has proposed to include 5 new investigators and enroll 125 new STAR Ankle patients to examine the learning curve of surgeons who begin their clinical experience with the STAR Ankle after device approval. The proposal indicates that patients will be evaluated using the outcome measurements described for the long-term follow-up component, yet at shorter timepoints to include only baseline, 6 weeks, 6 months, and 12 months post-operation. This study component does not include documentation of sampling and recruitment procedures for the new investigators and new STAR Ankle patients. The proposal does not provide a justification for the proposed sample size.

**PANEL QUESTION: If the panel makes the recommendation to approve the device with a condition of approval being a post-approval study, you will be asked to address the adequacy of the applicant's proposed post-approval study plan.**

## VIII. Summary

The data provided in this PMA appears to indicate its performance is statistically non-inferior to arthrodesis controls using both the original and the modified BP scores. However, for the safety endpoint, STAR Ankle pivotal patients did not meet non-inferiority over the control arthrodesis patients when using the originally defined IDE study endpoints. Adverse events, fractures and nerve injuries appear to occur more frequently in STAR Ankle patients than in the arthrodesis patients. The applicant showed some preliminary evidence that the adverse event rates appear to be lower in the continued access patients, which the sponsor attributes to changes in surgical techniques. However, these lower adverse event rates may be confounded by the much lower follow-up rates in this cohort of patients.

In the risk/benefit analysis, while the primary efficacy endpoint in the pivotal study was met, the primary safety endpoint in the pivotal study, using the original IDE protocol, was not met.

In response to an additional information request from FDA, dated February 8, 2007, the applicant revised the radiographic success criteria outlined in the IDE as described previously. Radiographic success was part of the criterion for successfully meeting the safety endpoint. Through this re-analysis, the applicant concluded that the S.T.A.R. Ankle had met the primary safety endpoint. The post hoc change in the analysis presents a challenge to interpreting the safety and effectiveness of this device

Because total ankle preclinical testing is not standardized, questions concerning the adequacy of the applicant's functional wear testing have emerged. Typically, wear and/or fatigue testing is performed under worst-case physiological loading conditions. During normal gait, force in the ankle can reach 5.5 times body weight. Patients in the pivotal trial weighing greater than 250 lbs (1112 N) were excluded from the trial. Using this criterion, the worst-case loading condition for the STAR Ankle is a test in which load reaches 6116 N. Though the load applied in the applicant's wear testing wa[redacted]ely constant (potentially more rigorous than a true cyclic load), it was less than half [redacted] of this theoretical worst case load. Pre-clinical wear/fatigue testing is important becaus[redacted] as a surrogate long term endpoint to support the durability of the device. In the case of the first of a kind device, this type of surrogate is expected to provide some information about the long term durability of the device as longer term clinical data is collected to confirm the preclinical information.

All of the issues outlined in this Executive Summary have generated the questions for the Panel members captured in Tab 2 of this Panel Pack.