ORTHOPEDIC AND REHABILITATION DEVICES PANEL
Gaithersburg, Maryland
April 24, 2007
PMA Link STAR Ankle System

EXECUTIVE SUMMARY

Applicant and Address
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Device Description
The STAR Ankle is an unconstrained, uncemented ankle prosthesis system comprised of three functional components, and a set of accessory surgical instruments to facilitate device placement, all designed to maintain as much normal ankle motion as possible. The three principal components of the prosthesis are:

- A chromium molybdenum tibial component with titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing; and
- A chromium molybdenum talar component with titanium porous plasma spray coating.

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 arthritis, or post-traumatic arthritis. 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.

Preclinical Testing
The sponsor has conducted several types of *in vitro* testing to validate the performance of the STAR Ankle. This testing included the following assessments:

- Mechanical testing to evaluate the intrinsic stability of the device in rotation, anterior-posterior displacement, and medial-lateral displacement;
- Finite element analysis to assess the stresses within the polyethylene component of the device;
- Mechanical testing to determine the contact stresses between the principal components of the device;
- Wear characteristic testing under simulated functional use conditions; and

- An informal, post hoc explant analysis of polyethylene mobile bearing to evaluate device burnishing, abrasion, pitting, surface deformation, delamination, scratching, debris capture, and fracture.

Together, this preclinical testing demonstrates the suitability of the STAR Ankle for permanent implantation as an ankle prosthesis.

Clinical Studies

Three multicenter, prospective clinical trials were conducted to show the safety and efficacy of the STAR Ankle. The three studies are summarized below.

Table 1. US Clinical Studies

Clinical Study	Study Design	Objective	Number of Centers	Enrolled Patients
Pivotal	Non-randomized concurrent and historical control multi-center study	Evaluate the safety and efficacy of the STAR Ankle compared to ankle arthrodesis	10 STAR Ankle; 5 arthrodesis	158 STAR Ankle patients; 66 Arthrodesis patients
Bilateral	Single-arm multi-center study	Evaluate the safety of bilateral STAR Ankle implantation	6	21 Bilateral STAR Ankle patients
Continued Access	Single-arm multi-center study	Confirm the findings of the pivotal study	10	448 STAR Ankle patients

The pivotal study was a 2:1 (STAR Ankle to control) multi-center, non-randomized, concurrent control clinical trial. The study was designed as a non-inferiority trial comparing the safety and efficacy of the STAR Ankle to Arthrodesis. The control group in the STAR Ankle pivotal trial consisted of concurrently recruited Arthrodesis patients for evaluation of efficacy, with a combination of concurrent Arthrodesis patients and historical arthrodesis controls for the safety analysis. A total of 224 patients (158 STAR;66 arthrodesis) were enrolled in the study with supplemental safety data collected on an additional 413 historical arthrodesis controls.

The study's primary efficacy endpoint was the mean total Buechel-Pappas Scale score ("Buechel-Pappas score"). The safety endpoint was the composite event of absence of major complications, loosening, migration, or device failure, removal/revision for the STAR Ankle group and the absence of major complications, non-union, mal-union, delayed union, or revision for the arthrodesis group. Efficacy success was defined as a minimum 40-point increase in Buechel-Pappas score from baseline. Overall patient success was defined as success for both efficacy and safety at 12 and 24 months.

Clinical Results

Efficacy, safety and overall patient success rates at 12 and 24 months are shown in the **Table 2** below. As demonstrated in the table, significantly higher efficacy and patient success rates were shown for the STAR Ankle patients at 12 and 24 months as compared with the Arthrodesis patients. Safety success rates in the STAR continued access study were also comparable between groups at 12 and 24 months. The subset of continued access patients with independent radiographic review was used for this comparison as it allows a fair comparison of the two groups based on the same safety success criteria. (A revised analysis of safety success rates, which the sponsor believes is more clinically appropriate, is provided below in **Table 4**.)

Table 2. Success Rates at 12 and 24 Months

	Pivotal						Continued Access*		
	Control			STAR			STAR		
	n	N	%	n	N	%	n	N	%
12 Month									
Patient Success Rate	6	53	11.3%	63	137	46.0%	80	105	76.2%
Efficacy Success Rate	7	53	13.2%	84	143	58.7%	86	107	80.4%
Safety Success Rate	50	57	87.7%	109	136	80.1%	101	108	93.5%
24 Month									
Patient Success Rate	7	51	13.7%	64	142	45.1%	61	81	75.3%
Efficacy Success Rate	7	47	14.9%	83	142	58.5%	70	83	84.3%
Safety Success Rate	43	52	82.7%	101	142	71.1%	72	81	88.9%

*The subset of patients with independent radiographic review was used for comparison.

Additional analysis of patient success and efficacy success rates excluding the Buechel-Pappas range of motion (ROM) subscale, which was not part of the analysis plan in the protocol, was requested by FDA. This analysis does not capture the important fact that the ankle joint motion provided by the STAR Ankle is a key clinical benefit of the device allowing STAR patients to enjoy ankle function that is considerably closer to that of a normal ankle. Additionally, the use of the BP score without the ROM subscale has not been described in the literature. These issues notwithstanding, the STAR Ankle demonstrated higher efficacy success rates compared to Arthrodesis even with the ROM subscale removed as shown in **Table 3**.

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Table 3. Patient Success and Efficacy Success Rates at 12 and 24 Months, Excluding ROM Subscale from the Buechel-Pappas Score

	Pivotal						Continued Access*		
	Control			STAR			STAR		
	n	N	%	n	N	%	n	N	%
12 Month									
Patient Success Rate	33	53	62.3%	90	136	66.2%	88	104	84.6%
Efficacy Success Rate	34	53	64.2%	113	143	79.0%	96	107	89.7%
24 Month									
Patient Success Rate	33	51	64.7%	87	141	61.7%	68	80	85.0%
Efficacy Success Rate	34	47	72.3%	114	142	80.3%	79	82	96.3%

In consultation with its clinical experts, the company has determined that the analysis used to determine radiographic success criteria in the pivotal study was biased against the STAR Ankle and inconsistent with the radiographic success criteria as originally stated in the company's IDE study protocols. STAR Ankle patients were carried forwarded as radiographic failures even if they subsequently were judged to be successes on follow-up images. Minor, expected radiographic findings that were stable over time were also considered a radiographic failure. Both of these are clinically inappropriate for a prosthesis where bony in-growth is expected. Consequently, the radiographs originally classified as failures were reviewed and reclassified according to a clinically appropriate analysis for radiographic success. Based on this revised radiographic analysis, the primary safety comparison at 24 months between the groups was accordingly revised. As shown in **Table 4**, the safety success rates between study groups are more similar using the clinically appropriate analysis for radiographic success criteria. (Note that the STAR patient success rates shown in **Tables 2** and **3** would further increase if based on the revised radiographic analysis.)

Table 4. Safety Success Rates for Completers at 24 Months, Based on Revised Analysis for Radiographic Success

	Pivotal		Continued Access
Safety Success at 24 months	**Control**	**STAR**	**STAR**
(a) Revised, without carrying forward prior X-ray failures	43/52 (82.7%)	108/142 (76.1%)	72/81 (88.9%)
(b) Revised, clinically appropriate analysis	43/52(82.7%)	113/142 (79.6%)	73/81 (90.1%)
Components of Safety Endpoint			
No surgical intervention	47/52 (90.4%)	122/142 (81.0%)	80/85 (94.1%)
No major complication	51/52 (98.1%)	128/142 (90.1%)	82/85 (96.5%)
Fusion (union)	46/52 (88.5%)	N/A	N/A
Success on X-ray			
(a) Revised, without carrying forward prior X-ray failures	N/A	124/137 (90.5%)	76/80 (95.0%)
(b) Revised, clinically appropriate analysis	N/A	129/137 (94.2%)	77/80 (96.3%)

Furthermore, none of the above analyses incorporate potential errors in the radiographic assessment of fusion in the Arthrodesis arm of the clinical study, which was a component of radiographic success for these patients. There is reason to believe that the fusion rates in the control group reported by the study investigators were overly optimistic, given clinical data that is available for these patients. If the company were to adjust the Arthrodesis fusion success rates based on this information and correspondingly lower the Arthrodesis safety success rate, the STAR Ankle would compare even more favorably to Arthrodesis.

Primary efficacy endpoint results are shown in **Table 5**, which summarizes the mean Buechel-Pappas score at 12 and 24 months and the change in Buechel-Pappas score at 12 and 24 months from baseline. The Buechel-Pappas scores at 12 and 24 months were significantly higher in the STAR Ankle group.

Table 5. Mean-Buechel Pappas Score at 12 and 24 Months

	Pivotal Study						Continued Access Study		
	Control			STAR			STAR		
Buechel-Pappas	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
12 Month	53	65.9	17.0	143	80.7	14.3	344	83.2	12.6
Improvement at 12 Months	53	23.3	15.9	143	39.7	15.0	344	45.8	14.0
24 Month	47	69.7	16.8	142	81.6	14.0	206	84.4	11.5
Improvement at 24 Months	47	26.3	17.1	142	40.5	15.1	206	46.7	13.6

A summary of selected adverse events is presented in **Table 6**. A number of modifications to the surgical techniques were implemented prior to the initiation of the continued access study as a result of lessons learned during the pivotal study. As can be seen, rates of major complications and surgical interventions decreased substantially in the continued access study.

Table 6. Selected Adverse Events, Surgical Interventions and Major Complications at 24 Months

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	p-value (STAR vs. Control)	STAR Continued Access (N=352)*
Bone fracture	2 (3.0%)	28 (17.7%)	0.002	37 (10.5%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)	0.044	21 (5.0%)
Post-operative fracture	1 (1.5%)	14 (8.9%)	0.044	19 (5.4%)
Bony changes	0 (0%)	12 (7.6%)	0.02	15 (4.3%)
Pain	32 (48.5%)	69 (43.7%)	0.557	115 (32.7%)
Nerve injury	5 (7.6%)	32 (20.3%)	0.019	75 (21.3%)
Wound problem	4 (6.1%)	32 (20.3%)	0.009	65 (18.5%)
Surgical intervention	7 (10.6%)	26 (16.5%)	0.260	26 (7.4%)
Revision or removal	6 (9.1%)	12 (7.6%)	0.707	12 (3.4%)
Other intervention	1 (1.5%)	18 (11.4%)	0.016	15 (4.3%)
Major complication	1 (1.5%)	14 (8.9%)	0.074	17 (4.8%)
Infection	1 (1.5%)	2 (1.3%)	1	3 (0.8%)
Bone problems	0 (0%)	8 (5.1%)	0.109	10 (2.8%)
Wound problems	1 (1.5%)	5 (3.2%)	0.673	5 (1.4%)
Wound problems and infections	0 (0%)	1 (0.6%)	1	0 (0%)

*Not all 424 continued access patients had reached their 24 month follow-up as of the time of database closure on 12/1/2006. To allow a fair comparison to the pivotal study data, with the exception of intra-operative fracture, the adverse event rate for the continued access study has been calculated using data from the 352 patients who have reached 24 months post-procedure only.

Meta-Analysis

Additional safety information on Arthrodesis was obtained through a meta-analysis of reports in the literature. The historical complication rates for arthrodesis were comparable to the rates observed for Arthrodesis patients in the pivotal study. The rate was also comparable to STAR patients in the pivotal study for device failure, revision, or removal. The rate of surgical interventions due to infection, delayed wound healing, post-operative fracture of adjacent bones, or bony changes was higher in the STAR pivotal patients than those observed in the meta-analysis and the concurrent arthrodesis control patients. However, modifications to surgical technique, instruments and increased surgeon experience during the course of the pivotal study have lowered the overall rate of all surgical interventions in the continued access study to a level that is comparable to the control rate.

Learning Curve

The learning curve for a surgeon new to the STAR Ankle could be as few as 15 patients. The effect of learning curve for the STAR ankle was evaluated by comparing the rates of intra-operative fracture, major complications (wound/infection or bony changes), and surgical intervention. The rate of intra-operative fracture, the rate of surgical revision/removal, and the rate of major complications relating to wound problems and infections all showed a steady decline from earlier to later cases. The rates for intra-operative fracture and surgical revision/removal were significant lower after the first 15 cases in the continued access study than in the pivotal study. With the increased awareness and training on the anterior surgical approach occurring across the foot and ankle surgical community, new surgeons are likely to resemble the STAR investigators towards the end of their learning curve. This is confirmed by the experience of three investigators new to the STAR Ankle who performed their first cases in the course of the continued access study. The rates of intra-operative fracture, major complication and surgical revision or removal for these new investigators were substantially similar to the complication rates of other surgeons in the continued access study who had participated in the pivotal study.

Conclusions Drawn from Studies

The various clinical studies demonstrate that the STAR Ankle is safe and effective in the treatment of patients with ankle arthritis who have failed six months of conservative therapy. In the majority of efficacy parameters measured (including overall patient success, total Buechel-Pappas score, 40 point or greater improvement in Buechel-Pappas score), the STAR Ankle showed favorable results when compared to ankle arthrodesis. The primary efficacy parameter of mean total Buechel-Pappas Score was shown, not only to be non-inferior to ankle arthrodesis, but also superior to arthrodesis. The STAR Ankle demonstrates somewhat lower safety success rates at 12 and 24 months as compared to Arthrodesis patients in the pivotal study based on the original analysis for radiographic success. However, when STAR radiographic outcomes are adjusted (1) for patients inappropriately carried forward as radiographic failures, and (2) to allow patients with minor, expected imaging findings to constitute radiographic success, the STAR radiographic success rate is substantially higher than that of the control group. The safety success rate is also substantially similar to that of the control group. The lower bound of the confidence interval of the difference in the safety success rate is less than the pre-specified delta for the safety endpoint. Therefore, non-inferiority of the STAR ankle to the control group with respect to safety has been demonstrated.

Additionally, modifications to surgical technique, instruments and increased surgeon experience during the course of the pivotal study have increased the safety success rate in the continued access study to a level that is comparable to the control rate and well within the safety delta.

Post Approval Study

Link Orthopaedics will conduct a post-approval study to: (1) evaluate the long-term revision or removal rate for the STAR Ankle; and (2) assess the learning curve of physicians who are initially treating patients with the STAR Ankle. A synopsis of the company's proposed study follows.

The long-term revision and removal arm will consist of all patients from the continued access study who consent to additional follow-up, and will include patients who have been previously considered failures. The principal endpoint of this arm of the post-approval study will be STAR Ankle revisions and removals at 48 months, with confirmation at 72 and 96 months. In addition, the Kaplan-Meier method will be used to estimate the revision or removal rate over time.

A second arm of the post-approval study will assess the physician learning curve. This arm of the study will consist of 125 newly recruited patients treated by surgeons new to the STAR Ankle at 5 sites, with follow-up at 6 weeks, 6 and 12 months. Analysis in this arm will consist of comparing major complications of the first 15 patients treated by each surgeon with subsequently treated patients. Major complications are defined as: (1) revisions, removals or reoperations; (2) wound problems requiring surgical intervention; (3) infections requiring surgical intervention; and (4) and perioperative fractures that require surgical reduction and fixation.

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

Gaithersburg, Maryland

April 24, 2007

Link Scandinavian Total Ankle Replacement System

PMA P050050

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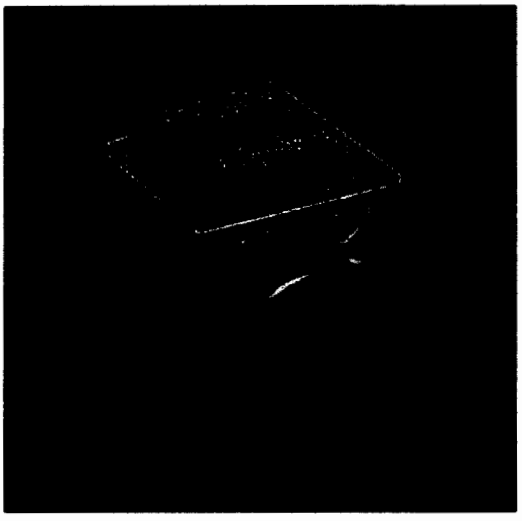
DEVICE DESCRIPTION

The Link Scandinavian Total Ankle Replacement System ("STAR Ankle") is an unconstrained, uncemented ankle prosthesis system comprised of three functional components, and a set of customized accessory surgical instruments to facilitate device placement, all designed to maintain as much normal ankle motion as possible. The three principal components of the prosthesis are:

- A chromium molybdenum tibial component with a titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing;
- A chromium molybdenum talar component with a titanium porous plasma spray coating.

An illustration of the STAR Ankle is provided in Illustration 1 below.

Illustration 1: The STAR Ankle



There are two bearing surfaces in the STAR Ankle: (1) the interface between the upper side of the UHMWPE mobile bearing and the facing surface of the tibial plate; and (2) the interface between the lower surface of the UHMWPE mobile bearing and the facing surface of the talar component. The tibial plate has one flat surface and one surface with two raised cylindrical projections oriented in the anterior/posterior direction. The flat surface of the tibial plate slides against the upper flat surface of the UHMWPE mobile bearing. The projecting cylinders serve to fix the device to bone at the distal tibia. The lower surface of the UHMWPE mobile bearing is concave, fitting against the convex upper surface of the talar component.

The mobile bearing design of the device is intended to reduce the shear and torque forces on the UHMWPE mobile bearing, which can lead to loosening of either metal component, and to decrease stress at the metal/bone interface. The sloped sides are designed to improve the weight bearing characteristics of the talar component.

INDICATIONS FOR USE / CONTRAINDICATIONS 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 arthritis, or post-traumatic arthritis. 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.

SUMMARY OF PRECLINICAL TESTING

The sponsor has conducted several types of *in vitro* testing to validate the performance of the STAR Ankle. This testing included the following assessments:

- Mechanical testing to evaluate the intrinsic stability of the device in rotation, anterior-posterior displacement, and medial-lateral displacement.
- Finite element analysis to assess the stresses within the polyethylene component of the device;
- Mechanical testing to determine the contact stresses between the principal components of the device; and
- Wear characteristic testing under simulated functional use conditions.
- An informal, post hoc explant analysis of polyethylene mobile bearing to evaluate device burnishing, abrasion, pitting, surface deformation, delamination, scratching, debris capture, and fracture.

The mechanical testing confirmed that the STAR Ankle exhibits minimal constraint in the rotational, anterior-posterior, and medial-lateral displacement modes. The minimal constraint is designed to reduce stress on the bone implant interface and the soft tissue. These characteristics are believed to provide load sharing with the adjacent soft tissues, potentially reducing the stresses that may cause implant loosening and articular wear. Results of

[redacted]

[1] Stauffer RN, Chao EYS, Brewster RC: Force and Motion Analysis of the Normal, Diseased, and Prosthetic Ankle Joint, Clinical Orthopaedics, 127:189, 1977.

In order to better understand the actual performance of the device *in vivo*, the company performed an analysis of available STAR Ankle polyethylene mobile bearings that had been explanted during the course of the pivotal and continued access studies.

only limited conclusions may be drawn from the analysis of the explanted components. Still, the overall revision or removal rate

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[2] Kobayashi A, Minoda Y, Kadoya Y, Ohashi H, Takaoka K, Saltzman CL Ankle arthroplasties generate wear particles similar to knee arthroplasties. Clin Orthop Relat Res. 2004 Jul;(424):69-72.

in the STAR Ankle pivotal study was comparable to that seen in the literature for total ankle prostheses. The revision or removal rate for the continued access study was considerably better than the rates seen in both the pivotal study and the literature, suggesting that the true results for the STAR Ankle implanted with the surgical techniques refined during the pivotal study are superior to comparable devices. Furthermore, the instances of significant wear identified in the explant analysis are likely due to factors such as thorough joint debridement, proper ankle positioning, and adequate ankle stabilization, all factors that may be addressed during initial STAR Ankle placement surgery.

CLINICAL INVESTIGATIONS

1. Overview of Clinical Safety and Effectiveness Data

The US studies of the Link Scandinavian Total Ankle Replacement System ("STAR Ankle") are summarized in **Table 1** below.

Table 1. US Clinical Studies

Clinical Study	Study Design	Objective	Number of Centers	Number Treated
Pivotal	Non-randomized 2:1 concurrent and historical control multi-center study	Evaluate the safety and efficacy of the STAR Ankle	10 STAR Ankle; 5 arthrodesis	158 STAR Ankle patients; 66 Arthrodesis patients
Bilateral	Single-arm multi-center study	Evaluate the safety of bilateral STAR Ankle implantation	6	21 Bilateral STAR Ankle patients
Continued Access	Single-arm multi-center study	Confirm the findings of the pivotal study	10	448 STAR Ankle patients

In addition to the clinical studies described above, a meta-analysis of historical arthrodesis cases described in the literature was performed to provide further comparative safety data to the STAR arm of the pivotal study.

2. Summary of Study Protocols

2.1. Pivotal Study Protocol

The following is a summary of the pivotal study protocol comparing the STAR ankle to an arthrodesis control. A copy of the complete protocol for this IDE study is also included in this panel pack under the tab labeled "Protocol".

2.1.1. Study Design and Objectives

The STAR Ankle pivotal study was a multi-center, non-randomized, concurrently controlled clinical trial with a 2:1 ratio of STAR Ankle cases to an arthrodesis control, which was conducted at 15 centers in the US. Participating centers performed either arthroplasty using the STAR Ankle (10 centers) or arthrodesis (5 centers). The target for the arthrodesis control group was 67 evaluable subjects, with 134 evaluable subjects in the STAR Ankle in the treatment arm (79 arthrodesis and 158 STAR subjects after a 15% adjustment for anticipated loss to follow-up). In addition, historical arthrodesis controls, obtained via a meta-analysis of the scholarly literature, were used to provide further comparative safety data.

The objective of this study was to evaluate the safety and efficacy of the STAR Ankle compared to ankle arthrodesis in the treatment of ankle joints with moderate or severe

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pain, loss of mobility, and loss of function due to primary arthritis, posttraumatic arthritis, or rheumatoid arthritis.

The primary efficacy endpoint was the mean total BP Scale score ("BP score") assessed at one year. A composite safety endpoint was comprised of: (i) no device failures, revisions, or removals; (ii) no radiographic failures; and (iii) no major complications (see definitions in **Section 2.1.3.4.** below). Overall patient success for an individual patient, combining safety and efficacy information, was defined as at least a 40 point increase in total BP score and a success on the composite safety endpoint.

2.1.1.1. Arthrodesis

Arthrodesis was considered to be an appropriate control for the STAR device as it is currently the standard of care for patients with arthritic ankle joints who have failed non-operative management. As described in detail in **Section 2.1.3.1.**, this procedure involves obliteration of the ankle joint with placement of cancellous screws across the former joint space to maintain alignment until bone bridging occurs.

2.1.1.2. Historical Control

To augment the arthrodesis control group, a review of the arthrodesis literature was performed so as to provide a historical comparison, particularly for complications occurring with this procedure. Given that arthrodesis was originally described in 1882 and there are a large number of articles in the scholarly literature reporting its clinical utility and complications, a historical control was felt appropriate to more completely capture the clinical experience surrounding this well-established procedure. Further reflecting the well-established nature of arthrodesis, FDA initially suggested to the company that the STAR Ankle pivotal study utilize a historical rather than a concurrent control. However, the sponsor believed that additional data from a concurrent control would be helpful in establishing the safety and effectiveness of the STAR Ankle and ultimately elected to use data from both a concurrent and a historical control.

2.1.2. Study Population

Study subjects were drawn from the practices of the clinical investigators at the 15 participating sites. All consecutive patients meeting study eligibility criteria and giving informed consent were enrolled. Ten (10) of these sites exclusively performed arthroplasty using the STAR device with 5 sites performing arthrodesis only. Study sites are listed in **Table 2**.

Table 2. Number of Patients Treated by Clinical Site

	Site	Principal Investigator	Control	STAR
MANN	Dr. Roger Mann, Inc. Oakland, California	Roger A. Mann, MD		26
USCM	University of Southern California School of Medicine, Health Research Association Los Angeles, California	David B. Thordarson, MD	8	
IOWA	University of Iowa, Orthopedic Surgery Iowa City, Iowa	Charles L. Saltzman, MD		31
F&A	Foot & Ankle, Inc. Boise, Idaho	Michael J. Coughlin, MD		15
UTMS	University of Texas Medical School Houston, Texas	Thomas Clanton, MD		6
MAYO	Mayo Clinic Jacksonville, Florida	James K. DeOrio, MD		28
HSS	Hospital for Special Surgery New York, New York	Jonathan T. Deland, MD	23	
OFAC	Orthopaedic Foot & Ankle Center Cincinnati, Ohio	Thomas H. Lee, MD		20
KUMC	Kansas University Medical Center Kansas City, Kansas	Greg Horton, MD		8
FOI	Florida Orthopaedic Institute Tampa, Florida	Arthur Walling, MD		9
BRI	Baylor Research Institute Dallas, Texas	James W. Brodsky, MD		6
DUMC	Duke University Medical Center Raleigh, North Carolina	James Nunley, MD		9
SUMC	Stanford University Medical Center San Francisco, California	Loretta Chou, MD	7	
EXO	Extreme Orthopaedics Philadelphia, Pennsylvania	Keith L. Wapner, MD	18	
MOC	Miller Orthopaedic Clinic Charlotte, North Carolina	Robert Anderson, MD	10	
	Total		**65**	**158**

2.1.2.1. Inclusion Criteria

- Moderate or severe pain, loss of mobility and function of the ankle (total BP score of less than 50 and BP pain score of 20 or less).
- Primary arthritis, posttraumatic arthritis or rheumatoid arthritis.
- At least 6 months of conservative treatment[3] for severe ankle conditions, confirmed by the patient's medical history, radiographic studies and medication record.
- Patients must fail a trial of foot and ankle orthosis and/or analgesic medication for 3 months prior to inclusion in the study.

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[3] Conservative treatments for a painful ankle included, but were not limited to, the following: foot and ankle orthosis (to support and immobilize the ankle joint), counseling on changing employment (sitting job versus manual labor) and/or activity, or planned pain or anti-inflammatory medication management (to reduce or eliminate the pain).

- Willing and able to give informed consent.

2.1.2.2. Exclusion Criteria

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

2.1.3. Description of Study Procedures, Assessments and Endpoints

2.1.3.1. Arthrodesis

Ankle arthrodesis in this study was carried out through a lateral approach to the ankle joint. The distal fibula was removed. A cut was made in the distal tibia which was perpendicular to the long axis of the tibia. Care was taken not to remove the medial malleolus. The foot was placed into a plantigrade position and a cut was made in the superior aspect of the talus that was parallel to the original cut made in the tibia. If alignment was satisfactory, two large screws were placed from the talus into the tibia for internal fixation, although other methods were employed at the surgeon's discretion. Following surgery, the leg was kept

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immobilized in a below-the-knee non-weight bearing cast for 6 weeks and then in a below-the-knee walking cast for 6 weeks. Union typically occurred in approximately 12 to 14 weeks.

2.1.3.2. STAR Arthroplasty

STAR arthroplasty was carried out through a wide anterior approach to the ankle joint. The tibial drill and saw guide were positioned over the tibia using alignment screws and wire pins. A straight 5 mm spacer was then attached to the tibial drill and saw guide before it was placed on the tibia. The distal edge of the spacer was aligned with the edge of the tibia, the saw guide was locked in position, and the alignment guide was fastened to the leg with pins to ensure that the guide remained parallel to the tibia. Using this guide, the spacer was removed, and the saw blade guide was attached. A horizontal osteotomy was then performed using an oscillating saw to remove a precise 5 mm segment of the distal tibia (the remaining articular surface at the dome of the tibial plafond). Using similar procedures, a 4 mm spacer was attached to the tibial drill and saw guide, holding the foot in a plantigrade position, to resect a precise 4 mm segment of the superior dome of the talus.[4]

Following the cuts of tibia and talus, as described above, the tibial drill and saw guide was removed and a side cutting talar saw guide was selected. These instruments were available in both left- and right-sided configurations and in a range of sizes to conform to the patient's anatomy. The talar saw guide was aligned and fixed in position, then a 2-3 mm segment was removed from the medial and lateral aspects of the talus. The talar chamfer guide was aligned, and anterior and posterior sections of the talus were resected. A milling guide was then used to create a slot in the superior aspect of the talus to receive the fixation fin of the prosthesis. The talar tamp was used after milling of the trough to verify that the trough was the proper shape to accept the keel. Talar trials were then used to allow the surgeon to observe the position that the actual keel would occupy post-implantation.

The tibial jig was then reapplied to the distal tibia, sagittal thickness was measured, and two holes were created to accommodate the cylindrical barrels of the tibial component. The drill holes in the tibia were then opened with a special gauge. The talar prosthesis of correct size was then placed onto the talus and seated onto the cut surfaces. A tibial spacer guide was inserted between the implanted talar component and the tibia. The appropriate size tibial component was selected by measuring sagittal thickness of the tibia using a depth gauge. Holding the foot at a 90° angle to the tibia, the tibial component was then inserted using an impactor. A trial spacer was placed between the tibial and talar components, and the final polyethylene mobile bearing was then selected. Proper sizing was verified by ensuring that the final implant configuration provided adequate soft tissue tension while permitting sufficient mobility.

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[4] As noted in Section 2.1.5 below, a recommendation was later provided to surgeons for the prophylactic protection against intra-operative medial malleolar fractures. This recommendation was provided as an attempt to reduce the number of intra-operative fractures that were experienced in the pivotal trial.

Following surgery, the patient was typically immobilized for a period of approximately 6 weeks. During the first two weeks, weight-bearing was minimized. From 2 to 4 weeks post-surgery, the patient was permitted to bear 50% weight in a removable cast, and at 4 weeks, the patient was permitted to bear full weight in cast. Gentle range of motion ("ROM") exercises were initiated after the fourth week. The cast was typically removed at 6 weeks unless a ligamentous reconstruction was carried out, in which case the cast was left on for a total of 8 weeks.

2.1.3.3. Follow-up Evaluations

Patients were asked to return for post-operative follow-up evaluations as summarized in **Table 3** below.

Table 3: Baseline and Follow-Up Assessments

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

2.1.3.4. Endpoint Assessment

Primary efficacy endpoint

The primary efficacy endpoint was total Buechel-Pappas ("BP") score, as measured on the BP scale at 12 months, with further confirmation at 24 months. The use of the Buechel-Pappas score was the subject of numerous discussions between the company and FDA prior to FDA approval of the IDE including the protocol describing this primary endpoint and prior to the initiation of the pivotal IDE study. The literature supporting the use of the BP score specifically described a 100-point scale consisting of subscales for pain (40 points), function (40

points), ROM (15 points), and deformity (5 points).[5] The function subscale is further divided into five 8-point questions pertaining to limp, standing, walking, stairs, and support. Importantly, the literature did not describe the use of any of the subscales on an individual basis, nor has the use of the use of the instrument with removal of one or more of the subscales been described in the literature. Notably, the use of the BP score without the ROM was specifically discussed with the agency during the process that led to approval of the IDE for the STAR Ankle pivotal study. During this pre-IDE dialogue, FDA indicated that it would not be appropriate to use the instrument in this manner, since only the utility of the total BP score was known.

At the time of the STAR Ankle protocol development, various ankle scoring systems had been developed and were being used. The earlier scoring systems for which there was the most experience and relevant scholarly literature included: (1) the BP score (1977); (2) the Mazur scoring system (1979); (3) the Kofoed scoring system (1986); (4) the Evanski scoring system (1977); and (5) the Kitaoka scoring system (1994). Levi et al. (1998) compared these five different ankle scoring systems in ankle arthroplasty.[6] This research demonstrated that these instruments yielded similar results in pre- and postoperative scoring.

Composite safety endpoint

The composite safety endpoint was defined as an individual patient meeting the following three criteria:

- No device failures, revisions, or removals; and
- Radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group); and
- No major complications, defined as:
  - No significant infection requiring surgical intervention;
  - No significant delayed wound healing, wound dehiscence, or skin necrosis requiring surgical intervention (including graft or free-flap procedures);
  - No significant postoperative fractures of adjacent bones (not caused by trauma) requiring surgical intervention; and
  - No significant bony changes of adjacent bones (cysts, osteolysis, avascular necrosis) requiring surgical intervention (including debridement or bone grafting).

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[5] Buechel FF, Pappas MJ, Iorio LJ. New Jersey Low Contact Stress Total Ankle Replacement: Biomechanical Rationale and Review of 23 Cementless Cases. *Foot & Ankle* 8(6):279-290, 1988.

[6] Levi N, Lundberg-Jensen A, Kofoed H. Comparison of Five Different Ankle Scoring Systems in Ankle Arthroplasty. *Foot & Ankle Surg* 4:167-170, 1998.

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Overall patient success

An individual patient was considered to be a success (*i.e.*, "patient success") if all of the following were met:

- ≥ 40 point improvement in total BP score;
- No device failures, revisions, or removals;
- Radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group); and
- No major complications (as defined above).

Secondary efficacy endpoints

- Buechel-Pappas subscales of function and range of motion ("ROM").
- Improvement in total BP score of 40 points or more.
- Pain Visual Analog Scale (VAS) (100mm scale).
- Patient satisfaction (Coughlin rating four category scale: excellent, good, fair, poor[7]).
- Quality of Life (SF-36).
- Medication usage.

2.1.4. Statistical Methods Planned in Protocol

The primary efficacy endpoint of mean total BP score was compared between the two treatment groups using the method of Blackwelder[8] to determine if the overall outcome in the STAR Ankle group was not inferior to that of the arthrodesis group. In addition, based on the methodology proposed by Dunnett & Gent[9] and Morikawa & Yoshida,[10] a two-sample Wilcoxon Test was performed, without adjustment for multiple comparisons, to determine if the STAR outcome was also superior to arthrodesis.

The secondary endpoints of function and ROM BP subscale scores and quality of life scores were compared between treatment groups using a two-sample t-test. The percentage of patients with a 40 point increase in total BP score and patient satisfaction were compared

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[7] Coughlin MJ. Etiology and treatment of hallux valgus: Arthrodesis of the first metatarsophalangeal joint with mini-fragment plate fixation. *Orthopedics* 13(9):1037-1044, 1990.

[8] Blackwelder WC. "Proving the Null Hypothesis" in Clinical Trials. *Controlled Clinical Trials* 3:345-353 (1982).

[9] Dunnett CW, Gent M. An alternative to the use of two-sided tests in clinical trials. *Stat Med* 15:1729-1738, 1996.

[10] Morikawa T, Yoshida M. A useful testing strategy in phase III trials: Combined test of superiority and test of equivalence. *J Biopharm Stat* 5(3):297-306, 1995.

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between treatment groups using a Chi-square test. Pain VAS was compared between groups using a two-sample Wilcoxon Test to determine whether these parameters were similar between the two groups.

Further adjustments for differences in baseline characteristics were performed using multiple linear regression techniques. Standard repeated measures analysis of variance techniques, such as Generalized Estimating Equations ("GEE"), were used to evaluate the total BP and VAS outcomes at various time points.

2.1.4.1. Determination of Sample Size

The sample size required to evaluate the primary efficacy endpoint of mean BP scores was 36 evaluable patients (24 STAR Ankle and 12 arthrodesis). This sample size was based on data collected from the BP score evaluation and assumed that the clinically insignificant difference in mean BP score ("delta") was 10 points. This choice of delta corresponds to only 10% of the total 100-point scale and is equal to the smallest width of the categories often used to classify the scale (85-100=Excellent, 75-85=Good, 65-75=Fair, etc.).

The composite safety endpoint was not characterized as a primary endpoint in the IDE protocol and accordingly no specific hypothesis was attached to this endpoint. Nevertheless, the study was sized to permit a reasonable evaluation of the composite safety endpoint. The calculated sample size of 201 evaluable patients (134 STAR Ankle and 67 Arthrodesis) assumed a success rate of 80% in both groups and was based on a non-inferiority delta of 15%. Notably, this choice of delta was discussed with the agency throughout the IDE process. There were a number of potential functional advantages of STAR arthroplasty which were not directly measured in this study, but which warranted this choice of delta, including applicability of the STAR Ankle to bilateral patients (given the mobility issues associated with bilateral arthrodesis), ability to climb hills and steps, earlier postoperative weight-bearing, improved gait pattern, reduced need for orthotic footwear, and a reduction in the rate of adjacent joint degeneration. The value of preventing such degeneration, which was theoretical at the outset of the STAR Ankle pivotal study, has now been demonstrated for the STAR Ankle and, to a certain extent, for other ankle arthroplasty devices.[11] [12]

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[11] Horton E, et al. Abstract presented at the 22nd Annual Summer Meeting of the American Foot and Ankle Society. This presentation reported no observed progression in degenerative change in 60 patients ranging from 5 ½ to 8 years status-post STAR Ankle placement.

[12] Knecht SI, Estin M, Callaghan JJ, Zimmerman MB, Alliman KJ, Alvine FG, Saltzman CL. The Agility total ankle arthroplasty. Seven to sixteen-year follow-up. *J Bone Joint Surg Am* 2004 Jun;86-A(6):1161-71.

2.1.5. Changes in the Conduct of the Study or Planned Analyses

The following protocol changes were made from July 2000 through September 2001:

- The eligibility criteria for the arthrodesis treatment group was changed to be identical with the criteria for the arthroplasty group.
- The method of measuring ROM in the BP score was changed from a radiographic means to clinical means using a goniometer, as indicated in the original article by Buechel and Pappas.

The following changes were made from October 2001 through September 2002:

- A recommendation was provided to surgeons for the prophylactic protection against intra-operative medial malleolar fractures. Specifically, in instances where there is high risk of malleolar fracture, it was recommended that two .062" 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 American Orthopaedic Foot and Ankle Society (AOFAS) scale[13] was added as an additional patient assessment for all patients who were enrolled into the arthrodesis group of the pivotal trial after April 2002.

Beyond these formal protocol changes, a number of modifications were made to the placement procedure of the STAR Ankle to address issues that were identified in the course of the pivotal study. These modifications included the following:

Changes to the Use of Instruments

- Modification of captured tibial saw alignment guides to decrease the possibility of bony nicks and notches, reducing the risk of subsequent fracture.
- Medial/lateral adjustable guide block modification to allow more precise device placement, reducing the risk of fracture and bone problems.
- Addition of talar trials and talar tamp to assist in proper device placement, reducing the risk of fracture and bone problems.

Surgical Technique Changes

- General downsizing of STAR Ankle talar components. Prior to commencement of the continued access study, the decision was made to systematically use the smaller of two metal component sizes where a patient fell between two component sizes, as opposed to using the larger component, in order to decrease the bony stress that may

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[13] Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M.Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int. 1994 Jul;15(7):349-53.

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results from use of a larger component. Use of a smaller component also permits the resection of a smaller amount of bone from the malleoli, which may also mitigate the risk of fracture.

- General use of a thicker polyethylene mobile bearing to reduce potential wear.
- General lengthening of the anterior surgical incision to permit needed retraction while minimizing the risk of tissue damage.
- Elimination of self-retaining retractors in favor of frequently repositioned hand retractors to minimize the risk of tissue trauma.
- Elimination of the use of skin staples in favor of a two-layer suture closure technique.

Changes to Patient Instructions

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

2.2. Bilateral Study

An arm of the pivotal study STAR arthroplasty treatment group was added to allow for the bilateral treatment of 21 patients. The study was a single arm multi-center clinical study conducted by the same investigators who performed the STAR Ankle arthroplasty pivotal study cases, at the same 10 clinical sites. The purpose of the study was to evaluate the safety of the STAR Ankle for patients with bilateral disease. Eligible subjects were patients with bilateral ankle disease requiring surgical intervention who had previously enrolled in either the pivotal or continued access study because of single ankle disease and who subsequently developed disease in the contralateral ankle, or who had not enrolled in either study. Other eligibility criteria were the same as for the pivotal study.

Bilateral patients were only subject to a safety analysis because the efficacy analyses used in the STAR Ankle pivotal study placed emphasis on functional status. In bilateral study patients, functional status was expected to be compromised by the disease state and subsequent surgical correction of the contralateral ankle due to the staging of the bilateral surgical procedures.

The assessments and procedures were the same as for the pivotal study, with the exception that a second arthroplasty procedure was performed on patients in the bilateral study, and since the relevant data from these patients is safety data, the BP score, Pain VAS, Coughlin Satisfaction Scale, and SF-36 were not collected in this study.

2.3. Continued Access Study

Enrollment of all planned arthroplasty patients in the pivotal trial was completed in 2001, with the last STAR Ankle pivotal patient implanted on December 10, 2001. Between 2002 and 2004, Link requested and received approval from FDA for a multi-center registry continued access study (three phases of 150 patients each). The same investigators who participated in the pivotal study also participated in the continued access study. Co-investigators

at the same sites who did not participate in the pivotal study were also permitted to perform STAR Ankle placement procedures in the continued access study.

The inclusion criteria for the continued access study were identical to those used in the pivotal study, with the exception that "primary arthritis, posttraumatic arthritis or rheumatoid arthritis" was expanded to include metabolic disorders (*e.g.,* hemochromatosis). The exclusion criteria were also the same, with the exception that "motor dysfunction due to neuromuscular impairment" was expanded to include "motor dysfunction due to neuromuscular impairment, insulin dependent diabetes, peripheral neuropathy, or Charcot changes." The STAR Ankle placement procedure used in the continued access study incorporated the modifications made during the course of the pivotal study as described above.

Each patient had a baseline evaluation to determine eligibility and establish pre-operative pain and functional status. Patients were asked to return for post-operative follow-up evaluations at 6 weeks, 6 months, 12 months, and 24 months. Assessments for the continued access study were identical to those for the pivotal study, with the addition of the AOFAS scale as an evaluation for the STAR Ankle patients.

2.3.1. Changes in the Conduct of the Continued Access Study

The protocol for the second phase of the continued access study (second 150 patients), approved in 2003, was identical to that of the first. The following changes were made to the protocol for the third phase of the continued access study, approved in 2004: (1) collection of medication information was limited to medications taken for treatment of the ankle condition; (2) at the 6-month follow-up visit, investigators collected only safety and adverse event data; and (3) adverse event information was collected only for events that occurred in the lower extremity of the side of the body implanted with the STAR Ankle. In November 2004, the follow-up schedule was modified such that after the 24-month visit, subjects were asked to return for follow-up visits every 24 months for two additional visits, at 48 and 72 months respectively.

3. Pivotal Study Results (Unilateral Patients)

3.1. Enrollment and Accountability

3.1.1. Overall Accountability

Patient enrollment in the STAR Ankle study began with full IDE approval on November 30, 2000. A total of 158 subjects were enrolled and treated in the STAR Ankle group and the remaining 66 patients were enrolled and treated in the Arthrodesis group. **Table 2** above summarizes the number of patients enrolled by study site.

While STAR Ankle patient recruitment concluded as anticipated in December 2001, recruitment into the Arthrodesis group progressed more slowly, possibly due to a reluctance on the part of surgeons and patients to participate in the control arm of a study that offered standard surgical treatment and that required extensive follow-up visits and record-keeping responsibilities.

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3.1.2. Visit Accountability

Study evaluations were performed pre-operatively, perioperatively, and postoperatively at 2 and 6 weeks, and 3, 6, 12, and 24 months. This information is summarized in **Table 3** above.

Follow-up evaluation rates of STAR patients were excellent, with follow-up visits complete for 96.7% (147/152) of expected patients at 12 months (a cumulative total of 3 patients lost to deaths, 1 to device failure, and 2 patients transferred to bilateral group) and 96.7% (145/150) of expected patients at 24 months (cumulative total of 4 patient deaths, 2 device failures, and 2 transferred to bilateral group). **Table 4** provides information on follow-up evaluations.

Table 4. Patient Accountability by Visit

	Pre-op		2 Weeks		6 Weeks		3 Months		6 Months		12 Months		24 Months		48 Months	
	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR
Theoretical	66	158	66	158	66	158	66	158	66	158	66	158	66	158	35	153
Deaths (cumulative)	0	0	0	1	0	1	0	1	0	2	0	3	1	4	1	0
Failures[1] (cumulative)	0	0	0	0	0	0	0	1	0	1	0	1	0	2	0	0
Transferred to Bilateral Arm (cumulative)	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0	2
Not Yet Overdue	0	0	0	0	0	0	0	0	0	0	1	0	3	0	11	32
Expected	66	158	66	157	66	157	66	158	66	155	65	152	62	150	23	119
Actual[2]	66	158	66	155	66	157	65	154	63	151	53	147	48	145	4	47
Actual Total BP	66	158	NA	NA	NA	NA	62	152	62	149	53	143	47	142	4	44
Actual ROM BP	66	155	NA	NA	NA	NA	63	152	62	148	53	144	48	143	4	44
Actual Function BP	66	158	NA	NA	NA	NA	63	152	62	150	53	143	48	143	4	47
Actual VAS	64	158	NA	NA	NA	NA	65	152	63	149	53	144	47	144	4	4
Actual Coughlin	NA	NA	NA	NA	NA	NA	65	152	63	149	53	141	47	143	4	46
Actual SF-36 PCS	57	147	NA	NA	NA	NA	54	144	55	130	37	127	43	128	1	44
Actual SF-36 MCS	57	152	NA	NA	NA	NA	48	147	52	136	43	129	42	125	1	42
X-ray Taken																
Independent Fusion Review[3]	NA	NA	66	NA	66	NA	65	NA	63	NA	53	NA	48	NA	4	NA
Independent X-ray Review (STAR)	NA	NA	NA	NA	NA	NA	NA	NA	NA	148	NA	134	NA	141	NA	26
Physical Exam	66	158	66	155	66	157	64	154	63	151	53	146	48	144	4	44
% Follow-up (based on Actual[2])	100.0%	100.0%	100.0%	98.7%	100.0%	100.0%	98.5%	98.7%	95.5%	97.4%	81.5%	96.7%	77.4%	96.7%	17.4%	39.5%

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

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

[3] Independent review of fusion status on a single occasion after the investigator determined identified the patient was either fused or would not heal. This review could have occurred at any time point but are considered the response for 12 and 24 months

Follow-up in the Arthrodesis group reflected good patient compliance, with 81.5% (53/65) of expected patients completing follow-up evaluations at 12 months and 77.4% (48/62) of expected patients completing evaluations at 24 months. When patients in both groups returned for follow-up visits, all evaluations required by the protocol were occasionally not completed. However, many of these incomplete evaluations involved missing SF-36 data, which was not a primary endpoint or used to evaluate patient success.

A small number of patients did not complete the study for a several of reasons. A total of 5 patient deaths (4 STAR and 1 Arthrodesis) occurred by 24 months, none of which were considered to be device-related. Additional information concerning patient deaths is provided in

Section 3.8.3. All STAR device removals are described in detail in **Section 3.8.4.**, with only 2 of these removals considered a failure for data accounting purposes. These 2 patients were not followed after the device was removed and the subject's ankle fused. Finally, 2 patients who were originally treated in the pivotal study were transferred to the bilateral study and data for these patients after the point of transfer was no longer considered part of the pivotal study database.

3.2. Study Administration Issues

Certain protocol deviations were encountered during the pivotal study and many of these deviations were minor in nature. Major protocol deviations were deemed to be those protocol deviations that could potentially impact the primary endpoint data. Other protocol deviations were classified as minor protocol deviations.

Patients were termed "Completers" if they had data necessary required to determine safety and efficacy at the 24 month time point. All patients with major deviations, patients considered as bilateral, and Non-Completers were excluded from the Per Protocol analyses but were included in the Intent-to-Treat ("ITT") analyses. Patients who were Completers with no major protocol deviations were included in both the Per Protocol and ITT analyses. Please refer to **Section 3.3.** for the definition of these analysis populations.

3.2.1. Deviations from Eligibility Criteria

Thirty-five (35) patients in the pivotal study did not explicitly meet all eligibility criteria. The majority (23/35) of these deviations were due to subjects being enrolled with a BP score of more than 50 (10 STAR and 13 Arthrodesis). Most of these 23 patients (8 STAR and 10 Arthrodesis) were enrolled with a BP score between 50 and 60, while the 5 remaining patients (2 STAR and 3 Arthrodesis) were enrolled with a BP score >60. During the post enrollment re-verification process, review of complete patient records revealed arithmetic errors that placed the true BP score $\geq$ 50 for these enrolled and treated patients. The sponsor made a considerable effort to prevent such errors once this issue was recognized. While the primary study endpoint was mean improvement in BP score, the protocol defined "patient success" criteria required an improvement in BP score of more than 40 points. Given this criteria, the sponsor, in conjunction with the study's medical monitors, decided that all patients with baseline BP scores of $\geq$ 60 would be considered to have a major protocol deviation, as it would not be possible to achieve protocol defined success. As it was possible for patients enrolled with a BP score between 50 and 60 to meet the patient success criteria, the sponsor's medical experts concluded that the 18 patients with such scores should be considered to have minor protocol deviations and be included in all analyses.

Four (4) patients (1 STAR and 3 Arthrodesis) were enrolled despite weighing greater than 250 lbs. Upon review by the company's medical experts, it was determined that a 15 lb. deviation from the inclusion weight limit would not significantly impact the performance of either the STAR Ankle or arthrodesis. Accordingly, 3 patients (1 STAR and 2 Arthrodesis) with weights between 250 and 265 lbs were deemed to have minor protocol deviations and were

included in all analyses. One (1) Arthrodesis patient, at 283 lbs., was deemed to have a major protocol deviation and excluded from the Per Protocol analysis.

One (1) STAR Ankle patient was enrolled with a history of osteoporosis of the foot. This patient was subsequently excluded from the Per Protocol analysis because the patient's poor bone stock was felt to predispose to complications such as fracture and device subsidence, both of which this patient subsequently experienced. Another patient had a history of a prior deep infection (osteomyelitis) in the subject ankle. This patient was included in the Per Protocol analysis, as the infection had resolved several years prior and this history was considered to have no impact on the patient's ability to heal.

3.2.2. Other Protocol Deviations

Three (3) Arthrodesis patients were treated with bone growth stimulation following their study surgery. All 3 patients were included in the Per Protocol analysis, as any enhanced healing made possible by bone growth stimulation would likely only bias results against the STAR Ankle group.

Two (2) STAR patients did not have their BP score formally recorded at their 24-month evaluations; these scores were later recreated either from dictated reports or memory. Given the potential impact of the post hoc scoring on the accuracy of those BP score evaluations, both patients were considered to have major protocol deviations and excluded from the Per Protocol analysis.

Missed visits at 2-3 weeks, 6 weeks, 3 months, and 6 months were considered minor deviations, as data collected at these visits were not crucial to the evaluation of study endpoints. Visits occurring within 5 months of the 12 and 24 month visits described in the protocol were considered minor deviations, and these patients were included in the 12 and 24 month Per Protocol analysis. This 5 month window was believed to be adequate to accurately capture patient data at these time points as patient results are generally believed to be stable during the 5 months before and after the 12 and 24 month visits and since these expanded windows were non-overlapping.

3.3. Analysis Populations

Analyses were performed based on the ITT patient population where that analysis population included all patients who enrolled in the study, where data were available ("Completers"). Additional analyses of the efficacy, safety and patient success rates were based on the Per Protocol population and the ITT patient population with imputations performed to account for missing data. The Per Protocol population for a particular endpoint consisted of all ITT patients who had no major protocol deviations (as described above), patients with a visit within window, and who were "Completers" (*i.e.*, patients for whom the necessary data for a particular endpoint was present at the time of database closure). Patients who had the contralateral ankle treated, either before study entry, after study treatment, or by nature of transfer to the bilateral study arm, were considered bilateral in nature and were excluded from the Per Protocol population.

Accountability for the populations used for the analysis of efficacy, safety and patient success rates at 12 and 24 months is outlined in **Table 5**. Two (2) patients transferred to the bilateral arm of the study due to a second procedure being performed on the contralateral ankle before the 24 month follow-up visit; these patients remained in the Per Protocol safety and efficacy analysis for the unilateral arm until the placement of the contralateral STAR Ankle. Following placement of the contralateral ankle, these patients were removed from both the safety and efficacy analysis for the unilateral arm and analyzed with the bilateral arm.

Table 5. Patient Populations for Endpoint Analysis

	Safety 12 Months		Efficacy 12 Months		Patient Success 12 months		Safety 24 Months		Efficacy 24 Months		Patient Success 24 months	
	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR	Control	STAR
Theoretical Patients (ITT)	66	158	66	158	66	158	66	158	66	158	66	158
Expected Patients	65	152	65	152	65	152	62	150	62	150	62	150
Missed Data[1]	9	22	13	15	13	21	14	16	19	16	15	18
All Data Available for Completers Analysis	57	136	53	143	53	137	52	142	47	142	51	142
Identification of Per Protocol Population												
Eligibility Violations	4	3	4	3	4	3	1	3	1	3	1	3
Data Excluded for Major Deviation[2]												
Missing Evaluation	0	0	0	0	0	0	0	2	0	0	0	0
Out of Window Visit	1	1	1	0	1	0	8	1	7	1	7	1
Bilateral Patients[3]												
Transferred to Bilateral Study[4]												
Contralateral Ankle Treated Prior to Treatment in Additional Database		3		3		3		3		4		3
Contralateral Ankle Treated Prior to Treatment Not in Additional Database	1	6	1	6	1	6	1	6	1	6	1	6
Contralateral Ankle Treated After Treatment[4]	1	1	1	1	1	1	2	1	2	1	2	1
Per Protocol	50	122	46	130	46	124	40	126	36	127	40	128

[1] Includes all missed data no matter the reason, i.e. death, removal from study, missed visit

[2] Subjects with Eligibility Violation and Missing Evaluation or Out of Window will be counted in this category only.

[3] Subjects with Eligibility Violation and/or have a Missing Evaluation or Out of Window that also are Bilateral Subjects will be counted in this category only.

[4] All data collected prior to contralateral ankle intervention is included in the pivotal study results.

There are different numbers of available patients in each of the three assessments of success (namely, safety, efficacy, and patient success) because of the manner in which each of the populations were determined. First, a patient was only included in the assessment of efficacy success if a valid BP score was collected. Second, a patient was included in the evaluation of safety success for three different reasons: (1) a collected visit with complete safety data; (2) a known safety failure carried forward from prior visits; or (3) known safety information at 12 months from the collection of a 24 month visit. Finally, a patient was included in the assessment of patient success if both safety and efficacy components were known or if a patient was a known to be a safety or efficacy failure.

At 12 months, there were 124 STAR and 46 Arthrodesis patients included in the Per Protocol analysis of the patient success endpoint and 137 STAR and 53 Arthrodesis patients included in the Completers analysis. Comparable figures were observed at 24 months with 128 STAR and 40 Arthrodesis patients included in the Per Protocol analysis of the patient success endpoint and 142 STAR and 51 Arthrodesis patients included in the Completers analysis. Thus,

90% of STAR patients (142/158) were available for analysis of the important success rate endpoints at 24 months.

3.4. Baseline Characteristics

3.4.1. Demographics and Selected History

Baseline demographics and selected history for the STAR and Arthrodesis groups are outlined in **Table 6**. There were no significant differences between the Arthrodesis group and the STAR group in terms of gender, race, smokers, mean height, mean weight or mean body mass index (BMI).

Table 6. Baseline Characteristics

Characteristic	Control	STAR	p-value
Gender			
Male	30 (45.5%)	78 (49.4%)	0.593
Female	36 (54.5%)	80 (50.6%)	
Race			
Caucasian	60 (90.9%)	152 (96.2%)	0.205
Hispanic	3 (4.5%)	1 (0.6%)	
African American	2 (3%)	4 (2.5%)	
Other	1 (1.5%)	1 (0.6%)	
Age			
N	66	158	0.004
Mean (SD)	57.1 (12.3)	62.7 (12.6)	
Range	24 - 79	33 - 100	
Current Smoking Status			
Yes	5 (13.9%)	15 (20%)	0.433
No	31 (86.1%)	60 (80%)	
History of Smoking			
Yes	31 (47%)	74 (47.1%)	0.982
No	35 (53%)	83 (52.9%)	
Height (inches)			
N	66	158	0.612
Mean (SD)	67.0 (4.5)	67.3 (3.7)	
Range	57.5 - 77	60 - 74	
Weight (pounds)			
N	66	158	0.378
Mean (SD)	185.6 (38.6)	180.9 (34.9)	
Range	115 - 283	110 - 253	
BMI			
N	66	158	0.409
Mean (SD)	29.1 (5.8)	28 (4.8)	
Range	21.0 - 55.3	16.0 - 43.0	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

Both groups were predominantly Caucasian, thought to at least partially reflect the pattern of patient referral to the participating orthopedic surgeons. Since patients with severe osteoporosis (which is more prevalent in Caucasians) were excluded from this study, the race of treated patients was not believed to impact the generality of study results.

There was a significant difference between groups in age, with the STAR patients being an average of 5 years older than the Arthrodesis patients (mean age of 62.7 years vs. 57.1 years, respectively). This age difference was thought to be due to the use of sites in locations with a large percentage of elderly patients. For example, the Mayo Clinic in Jacksonville,

Florida, in particular, enrolled a large percentage of elderly patients, with approximately 80% of those enrolled at this site older than the mean age of 62.7 years for STAR Ankle patients. Age was evaluated as a covariate in the analysis of patient success rates to evaluate any association of age with patient outcome.

3.4.2. Baseline Medical History by Group

Table 7 summarizes the primary diagnoses for both the STAR and Arthrodesis groups. There tended to be more patients with a diagnosis of primary arthritis and of rheumatoid arthritis in the STAR arm.

Table 7. Primary Diagnosis

	Control	STAR	p-value
Primary Diagnosis			
Primary Arthrosis	19 (28.8%)	62 (39.2%)	0.054
Post-traumatic Arthrosis	43 (65.2%)	76 (48.1%)	
Rheumatoid Arthrosis	4 (6.1%)	20 (12.7%)	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

There was no significant difference in the affected ankle (right versus left). Patients receiving the STAR Ankle and those undergoing arthrodesis underwent a wide variety of conservative treatments prior to entering into the study, none of which were believed to affect results.

3.4.3. Baseline Disease History

The majority of patients in both the STAR and Arthrodesis groups had some form of underlying baseline disease, with similar disease histories between groups, as seen in **Table 8**. The most prevalent disease was osteoarthritis, with similar percentages of patients affected in both the STAR Ankle and Arthrodesis groups (43% and 44%, respectively).

Table 8. Baseline Disease History

Disease	Control	STAR
Ankle Instability		1 (1%)
Arthritis		4 (3%)
Avascular necrosis	1 (2%)	
Osteoarthritis	29 (44%)	68 (43%)
Osteopenia	6 (9%)	7 (4%)
Osteoporosis	2 (3%)	9 (6%)
Peripheral neuropathy	2 (3%)	2 (1%)
PVNS	1 (2%)	
Pyarthrosis		1 (1%)
Rheumatoid arthritis	2 (3%)	2 (1%)

Numbers and percents based on the number of patients

3.4.4. Baseline Work Status

A significantly lower percentage of STAR Ankle patients (28.5%) were engaged in full-time employment compared to the Arthrodesis group (44.6%), reflecting the higher percentage of retired persons in the STAR group versus Arthrodesis (46.2% versus 20%). Any impact of the higher average age in the STAR group would likely bias the results against the STAR Ankle.

3.4.5. Baseline Physical Examination by Group

The general condition of patients was comparable in both groups, for the percentage of patients considered to be in either good or excellent condition (89.9% STAR, 93.9% Arthrodesis). Overall, any variability in condition was not believed to affect results.

There was no statistically significant difference between STAR Ankle and Arthrodesis groups with regard to adequate ligament support, use of a special shoe, or ability to bear weight. Almost no study patients in either group had motor, sensory or neurological deficits at baseline. There was, however, a statistically significant difference in functional difficulties between groups, with 97% (64/66) of Arthrodesis patients having functional difficulties versus 77.8% (123/158) of STAR Ankle patients. Nevertheless, the higher level of difficulties in the Arthrodesis group is not believed to have adversely impacted the outcome of arthrodesis so as to bias the comparison with arthroplasty. Complete baseline physical examination results may be found in **Table 30**.

3.4.6. Baseline Buechel-Pappas Score by Group

Table 9 describes the baseline BP subscores by study group. As demonstrated in this table, the STAR Ankle group had a higher percentage of patients with a total BP score in the poor category at baseline as well as a higher level of pain as compared to Arthrodesis. The worse pain and function BP scores in the STAR group is consistent with a poorer baseline ankle condition as compared to the Arthrodesis group. Any between group imbalance reflected in these lower BP scores would likely favor arthrodesis over the STAR Ankle. Baseline total BP score was included as a covariate in the patient success rate analysis to adjust for any baseline differences (see **Section 3.6.3.**).

Table 9. Baseline Buechel-Pappas

	Control	STAR	p-value
Deformity			
None	4 (6.1%)	18 (11.4%)	0.222
Slight	14 (21.2%)	29 (18.4%)	
Mild	27 (40.9%)	45 (28.5%)	
Moderate	15 (22.7%)	38 (24.0%)	
Significant	6 (9.1%)	23 (14.6%)	
Most Severe	0	5 (3.2%)	
Functional Limitation			
None			0.033
Mild	17 (25.8%)	18 (11.4%)	
Moderate	36 (54.6%)	90 (57.0%)	
Severe	13 (19.7%)	49 (31%)	
Disabled	0	1 (0.6%)	
Pain			
None			0.033
Slight			
Mild			
Moderate	16 (24.2%)	17 (10.8%)	
Severe	47 (71.2%)	134 (84.8%)	
Totally Disabled	3 (4.6%)	7 (4.4%)	
ROM			
Combined Motion < 5°	9 (13.6%)	10 (6.3%)	0.015
Combined Motion 5° to 14°	26 (39.4%)	35 (21.2%)	
Combined Motion 15° to 24°	12 (18.2%)	49 (31.0%)	
Combined Motion 25° to 34°	12 (18.2%)	41 (25.9%)	
Dorsiflexion 5° - Plantarflexion 30°	7 (10.6%)	18 (11.4%)	
Dorsiflexion 15° - Plantarflexion 45°		5 (3.2%)	
Total[1]			
Excellent (86 - 100)	0	0	0.068+
Good (71-85)	0	0	
Fair (55-70)	6 (9.1%)	4 (2.5%)	
Poor (< 55)	60 (90.9%)	154 (97.5%)	

[1]Score Range

+Fisher's Exact Test

All p-values are based on a chi-square test or a t-test unless otherwise noted

There was a statistically significant difference between STAR Ankle and Arthrodesis groups in the ROM subscale, with more motion seen in the STAR Ankle group. In this regard, it should be noted that the post-operative goal of arthrodesis is ankle joint immobilization.

3.4.7. Baseline Pain VAS by group

STAR patients had a somewhat higher baseline pain VAS than did the Arthrodesis patients prior to surgery. This likely reflects the older age and more debilitated state of the STAR Ankle patients and their ankles as compared to the Arthrodesis group.

3.4.8. Baseline SF-36 by Group

There was no statistically significant difference in the majority of SF-36 subscales between the STAR and Arthrodesis groups.

3.4.9. Baseline Ankle Surgeries

Table 10 demonstrates that there is no statistically significant difference in the number of prior surgeries at baseline between the STAR and Arthrodesis groups. The majority of patients in both groups had at least one prior surgery in the affected ankle.

Table 10. Baseline Previous Surgeries on Affected Ankle

	Control	STAR	p-value
Number of Previous Surgeries - Affected Ankle			
0	26 (39.4%)	65 (41.1%)	0.923
1	18 (27.3%)	47 (29.7%)	
2	11 (16.7%)	26 (16.5%)	
3	8 (12.1%)	16 (10.1%)	
4+	3 (4.6%)	4 (2.5%)	

Numbers and percents are patient based
All p-values are based on a chi-square test or a t-test unless otherwise noted

3.4.10. Baseline Radiographic Data

There was no statistically significant difference in baseline radiographic data, including tibial-talar joint space narrowing, evidence of major degenerative changes, and fusion of adjacent joints, between STAR Ankle and Arthrodesis patients.

3.5. Procedural Characteristics

3.5.1. Operative Characteristics by Group

Table 11 summarizes the operative characteristics by study group. Tourniquet time, operative time, anesthesia time, and length of stay for STAR surgeries were quite comparable to that for arthrodesis cases. Estimated mean blood loss was greater in the Arthrodesis group versus the STAR group (75.3 cc as compared to 53.1 cc). Although this was not a statistically significant difference, it may reflect the more extensive osseous resection routinely required for arthrodesis. In any event, no patient in either group required a blood transfusion as a result of their ankle surgery. More STAR patients received general anesthesia or a combination of local and general anesthesia than did Arthrodesis patients (71.4% as compared to 43.9%). This may reflect differences in institutional practices and/or surgeon preference and is not expected to impact overall efficacy or safety.

Table 11. Operative Data

	Control	STAR	p-value
Tourniquet Time (hours)			
N	64	158	
Mean (SD)	2 (0.8)	1.9 (0.5)	0.321++
Range	0.8 , 4.12	0 , 3.5	
Operative Time (hours)			
N	65	156	
Mean (SD)	2.4 (1.2)	2.2 (0.5)	0.613++
Range	0.75 , 5.68	1.08 , 3.63	
Anesthesia Time (hours)			
N	65	157	
Mean (SD)	3.2 (1.3)	3.1 (0.7)	0.784++
Range	1.38 , 6.92	1.6 , 5.62	
Anesthesia Type			
Local	37 (56.1%)	45 (28.7%)	<0.001
General	21 (31.8%)	59 (37.6%)	
Both	8 (12.1%)	53 (33.8%)	
Missing		1	
Estimated Blood Loss (cc)			
N	66	158	
Mean (SD)	75.3 (89.9)	53.1 (44.5)	0.318++
Range	0 , 300	0 , 400	
Length of Stay (days)			
N	66	158	
Mean (SD)	3 (1.3)	3.1 (1.9)	0.810++
Range	1 , 8	2 , 19	

++Wilcoxon Two-Sample Test

All p-values are based on a chi-square test or a t-test unless otherwise noted

3.5.2. Procedure Related Information

Tables 12 and **13** outline procedure related information and operative difficulties, respectively. Operative difficulties were encountered more frequently with the STAR Ankle (10.1%) than in the Arthrodesis group, which had no such events. This likely reflects the increased complexity inherent in an arthroplasty procedure involving an anterior approach as compared to arthrodesis, which is a commonly performed orthopedic surgical procedure. Intraoperative fractures are discussed in **Section 3.5.3.** In addition, the foot and ankle surgeons who performed the arthrodesis procedures in the control arm of the STAR pivotal study had extensive experience with the transmalleolar approach used for ankle fusion, making complications less likely.

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Table 12. Procedure Related Information[1]

	Control	STAR	p-value
Operative Difficulties			
Yes	0 (0%)	16 (10.1%)	0.008
No	66 (100%)	142 (89.9%)	
Missing	1		
Ligament Repair			
Yes	2 (3%)	23 (14.6%)	0.013
No	64 (97%)	135 (85.4%)	
Ligament Release			
Yes	0 (0%)	9 (5.7%)	0.048
No	66 (100%)	149 (94.3%)	
Concomitant Procedures			
Yes	32 (49.2%)	35 (22.3%)	< 0.001
Part of Procedure	26	13	
Extra Procedure	3	6	
Complication	0	15	
Part of Procedure & Extra Procedure	3	0	
Part of Procedure & Complication	0	1	
No	33 (50.8%)	122 (77.7%)	
Missing	1	1	

[1]Assessments were made by the Medical Monitors.
All p-values are based on a chi-square test or a t-test unless otherwise noted.

Table 13. STAR Operative Difficulties

Description of Operative Difficulty	# of Patients
Bone Fracture	8
Bone Injury (Non-Fracture)	1
Difficulty with Ankle Positioning	1
Difficulty with Component Placement	4
Injured Superficial Peroneal Nerve	2

Ligament repair was more frequently performed with STAR Ankle placement (14.6% versus 3.0%), likely reflecting the limited need to repair ligaments where an ankle is being fused. Similarly, ligament release was only necessary in the STAR Ankle group, reflecting the need to preserve motion.

Concomitant procedures were performed more frequently in the Arthrodesis group (50% compared to 32.3% in the STAR group). The majority of these procedures, including additional osteotomies, bone graft procedures or hardware removal, are often seen in a posttraumatic population and may be explained by the higher rate of posttraumatic arthritis seen in the Arthrodesis group. Many of the concomitant procedures in the STAR group consisted of open reduction with internal fixation required to repair intra-operative fractures. Some

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procedures in both groups were patient specific and unrelated to the particular ankle therapy provided.

As noted in **Table 13**, intraoperative bone fractures occurred in a small number of STAR patients. These fractures are discussed along with other adverse events occurring prior to discharge in the next section.

3.5.3. Adverse Events Occurring Pre-Discharge

Table 14 summarizes adverse events that occurred following surgery and prior to discharge. Adverse events referable to the operative site were more frequent with STAR Ankle patients (26.6%) than with Arthrodesis patients (6.1%). This higher rate reflects the nature of the STAR Ankle procedure, which involves an anterior approach and placement of the STAR device, as opposed to the standard lateral operative approach used in arthrodesis. Clinical investigators participating in the STAR Ankle pivotal study generally had far less experience with the anterior approach as opposed to the standard lateral approach at the beginning of the pivotal study. For example, 9 patients had nerve injury in the STAR group (5.7%) as compared to no such injuries with the Arthrodesis group. This is directly attributable to the anterior approach which may injure a superficial branch of the common peroneal nerve. Notably, the loss of sensation that results from injury to this nerve is mild, usually clinically insignificant, and in most cases, transient.

Table 14. Adverse Events Occurring Pre-Discharge

	Control	STAR
Operative Site Events		
anesthesia		1 (0.6%)
bone fracture	1 (1.5%)	15 (9.5%)
bony changes		1 (0.6%)
decreased ROM		3 (1.9%)
embolism		1 (0.6%)
gait problems	1 (1.5%)	1 (0.6%)
infection		1 (0.6%)
nerve injury		9 (5.7%)
pain	3 (4.5%)	12 (7.6%)
soft tissue edema		3 (1.9%)
wound problem		2 (1.3%)
Any Operative Site Event	4 (6.1%)	42 (26.6%)
Other Events		
cardiovascular	1 (1.5%)	4 (2.5%)
gastrointestinal	2 (3.0%)	7 (4.4%)
general	3 (4.5%)	7 (4.4%)
infection - other	2 (3.0%)	1 (0.6%)
neurologic		1 (0.6%)
pain - other		3 (1.9%)
skin		2 (1.3%)
urologic		2 (1.3%)
Any Other Event	7 (10.8%)	20 (12.7%)

Numbers and percents are patient based

It is important to note that there has been considerable change to post-graduate medical training in Orthopedic Surgery with regard to foot and ankle procedures in the last several years. Leading institutions have incorporated ankle reconstruction, including ankle arthroplasty, into their formal resident training curriculum, reflecting the increasing importance of these procedures in the care of patients with ankle joint disease.[14] Accordingly, orthopedic surgeons completing their post-graduate training now and into the future can be expected to be familiar with ankle arthroplasty techniques and the methods by which to minimize the potential complications associated with the anterior approach needed to place these devices. Further, the anterior approach to the ankle, which was uncommon at the onset of the study, is now routinely taught.

Intra-operative fractures occurred at a higher rate in the STAR patients than in Arthrodesis patients (9.5%, 15/158 versus 1.5%, 1/66). Fracture in the STAR Ankle group occurred during the placement procedure, with all but one fracture recognized and treated during surgery. The majority of these fractures did not impact patient outcome. Only one of these fractures (a medial malleolar fracture) failed to heal within 12 weeks of surgery. Moreover, in the arthrodesis group, the reporting of intraoperative fracture is likely under reported as there is no reason to record an intraoperative fracture in an ankle fusion. For example, in many arthrodesis procedures the malleolar is removed so the between group comparison of intraoperative fractures is inherently biased against the STAR group.

The incidence of intra-operative medial malleolar fractures was discussed with the company's medical monitors and the STAR Ankle surgical protocol was altered to include a recommendation to take specified protective measures to prevent intra-operative medial malleolar fractures, including use of .062" K-wires. Since the implementation of the use of the K-wires, the rate of intra-operative fractures decreased considerably. In addition to this protocol change, a number of modifications were made to the STAR Ankle placement procedure to decrease the risk of fracture, including changes to instruments and downsizing talar components. These changes are further described in **Section 2.1.5.**

Reflecting the comparable systemic risk of ankle surgery whether that surgery involved arthroplasty or arthrodesis, operative adverse events outside of the operative site were comparable between groups.

3.6. Endpoint Success Rates

Efficacy, safety and patient success results for the STAR Ankle pivotal study are provided in the following sections. All endpoint success rates are given based on the Per Protocol population, the Completers population with data available, and the ITT population.

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[14] Education website for the Department of Orthopaedics and Sports Medicine at the University of Washington http://www.uwmedicine.org/Education/ResidenciesAndFellowships/Programs/Orthopaedic+Surgery.htm (accessed January 11, 2007).

Additionally, since the missing data among patients in the ITT patient population may have an impact on results, imputation methods were performed to assess whether similar results would be observed assuming different distributions of the missing data.

The results demonstrate higher efficacy success rates for the STAR Ankle and statistical superiority for the STAR Ankle for patient success (based on both the ITT patients with data available and the per protocol population). Furthermore, as described in a subsequent section, the difference between the STAR Ankle and control groups with regard to the primary efficacy endpoint (mean improvement in BP score) at both 12 and 24 months is well within the non-inferiority margin specified within the protocol. The observed safety success rates in the STAR group were somewhat lower than in the control group, where the 15% non-inferiority delta for safety success rates was nearly met at 12 months. It is important to note that the STAR safety success rates were much improved in the continued access study, as more fully described below.

3.6.1. Efficacy Success Rates

For an individual patient, efficacy success was defined to be a 40 point or greater improvement in BP score. As shown in **Table 15**, significantly higher efficacy success rates were observed at 12 and 24 months among Completers in the STAR Ankle group compared to the Arthrodesis group (58.7% versus 13.2% at 12 months, and 58.5% versus 14.9% at 24 months). Thus, more than twice as many STAR patients had a $\geq$ 40 point improvement in BP score compared to Arthrodesis patients at both 12 and 24 months. These higher efficacy success rates reflect, in part, the increased ROM provided with the STAR Ankle as compared to Arthrodesis, and the improved gait that this ROM affords. This motion is a key clinical benefit to STAR Ankle and provides STAR patients ankle function that is far closer to normal than arthrodesis. Nevertheless, as outlined in **Section 3.7.4.** below, the benefit of the STAR Ankle largely persists even when the ROM component is removed from the calculation of the total BP score, as seen by improvements in STAR patients in other prongs of the BP score.

Table 15. Efficacy 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	10% Delta Met?
Month 12	Per Protocol	7	46	15.2%	79	130	60.8%	45.6%	34.3%	Yes
	Completers	7	53	13.2%	84	143	58.7%	45.5%	35.3%	Yes
	ITT – Single Imputation	19	66	28.8%	90	158	57.0%	28.2%	16.9%	Yes
	ITT - Worst Case Scenario	20	66	30.3%	84	158	53.2%	22.9%	11.5%	Yes
Month 24	Per Protocol	6	36	16.7%	76	127	59.8%	43.2%	30.7%	Yes
	Completers	7	47	14.9%	83	142	58.5%	43.6%	32.6%	Yes
	ITT – Single Imputation	25	66	37.9%	89	158	56.3%	18.5%	6.7%	Yes
	ITT - Worst Case Scenario	26	66	39.4%	83	158	52.5%	13.1%	1.3%	Yes

Adjusted analysis for efficacy success at 24-month.

Patient Population	Adjusted odds ratios for success (STAR/Control)	Lower Bound of 90% CI for adjusted odds ratios
Completers – propensity-score-adjusted	5.77	2.64
Completers – covariate-adjusted	7.63	3.45
Per protocol – propensity-score-adjusted	5.33	2.3
Per protocol – covariate-adjusted	7.12	3.03
GEE analysis – covariate-adjusted	8.36	4.41

Efficacy Success defined as at least a 40 point improvement in BP score.

3.6.2. Safety Success Rates

Safety success was defined as: (i) no device failures, revisions, or removals; (ii) radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; (iii) no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group); and (iv) no major complications. As shown in **Table 16**, Arthrodesis Completers had a somewhat higher safety success rates than STAR Ankle patients at 12 and 24 months (87.7% and 80.1% versus 82.7% and 71.1%, respectively).

Table 16. 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	Delta Met?
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

In reviewing the radiographic analysis originally used to determine radiographic success in the pivotal and the clinical access studies, the company discovered that this analysis was clinically inappropriate for a device for which bony in-growth is expected, such as the STAR Ankle. Using a revised, clinically appropriate analysis, which is more consistent with the radiographic success criteria contained in the study protocols, radiographic success and safety success is substantially higher than with the original, clinically inappropriate analysis. **Table 16a** summarizes the safety success rates based on the initial radiographic analysis, an analysis that does not carry forward prior X-ray failures, and on the clinically appropriate radiographic success analysis. As shown in the table, using the most clinically appropriate radiographic analysis, the safety success rate in the control group is only 3% higher than that in the STAR Ankle group. The lower bound of the confidence interval of this difference is well within the pre-specify safety delta for non-inferiority.

Table 16a. Safety success rates for completers at 24 months, based on both initial PMA analysis and revised analyses for defining radiographic success for STAR Ankle

	Control	STAR	Difference in Success Rate (STAR-Control)	Lower Bound of 90% CI for Difference
Safety Success				
a) Initial PMA analysis	43/52 (82.7%)	101/142 (71.1%)	-11.6%	-22.2%
b) Revised, without carrying forward prior X-ray failures	43/52 (82.7%)	108/142 (76.1%)	-6.6%	-17.1%
c) Revised, clinically appropriate analysis	43/52 (82.7%)	113/142 (79.6%)	-3.1%	-13.4%

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

Details of the company's revised radiographic analysis are provided below.

3.6.2.1. Origin of the Sponsor's Original Interpretation of Radiographic Success Criteria

As described in the protocol for the STAR Ankle pivotal study, radiographic success was defined as the absence of "loosening" or "migration," two characteristics that are generally accepted to be associated with the potential failure of a joint prosthesis. The clear intent of these criteria was to identify radiographic findings with a high degree of correlation to clinically significant loosening or migration. However, at the outset of the STAR Ankle pivotal study, little published information was available to aid the company in development of a radiographic analysis to evaluate these criteria for an ankle prosthesis. In the absence of this information, the company, in conjunction with its medical experts, developed a specific radiographic analysis of STAR Ankle patients. With the knowledge gained throughout the course of the STAR Ankle IDE studies, the company has determined that this original analysis over-estimated the clinical significance of these radiographic findings, and were thus inconsistent with the intent of the protocol's radiographic success criteria. The revised analysis, as outlined below, provides a more accurate radiographic assessment of STAR Ankle patients and is wholly consistent with the pivotal study's original definition of radiographic success.

3.6.2.2. Specific Issues with the Original Radiographic Interpretation in the Pivotal Study

1. Inappropriate Carrying Forward of Radiographic Information

In the initial radiographic analysis, all STAR subjects who did not meet the radiographic success criteria at 6 or 12 months were not permitted to subsequently become successes, even if they met the success criteria at 24 months. This is not appropriate for an arthroplasty device which has a dynamic interface designed specifically to achieve bone-in-growth and stabilization of radiographic parameters with increased time from implantation.

As bone in-growth and stabilization occur with the passage of time, it is more fitting to assess radiographic success based on analysis of the 24 month images and not to carry forward information based on prior x-rays. Using this revised analysis, 7 patients previously considered to be radiographic failures are now appropriately considered radiographic successes and appropriate adjustments have made to efficacy, safety and overall success rates. This approach is fully consistent with both the pivotal study protocol and current radiographic standards of practice. Moreover, this reclassification is further substantiated by the fact that none of these 7 patients had any major complications or underwent any surgical revisions, removals, or re-operations through the 24 month follow-up visit.

2. Inappropriate Interpretation of Minor, Expected Radiographic Findings as Radiographic Failures

The second issue present with the original interpretation of the STAR Ankle radiographs was the clinically inappropriate classification of several minor imaging findings observed with uneventful device placements, such as early, minor device settling, as not meeting the radiographic success criteria. At the outset of the STAR IDE clinical trials, there was essentially no guidance in the literature as to what constituted subtle radiographic evidence of device failure for an ankle prosthesis. Drawing on the existing literature for hip and knee arthroplasty devices, the company reported in the original analysis what is now recognized as an overly conservative, and clinically inconsequential radiographic success criteria

As previously noted, radiographic success in the STAR Ankle protocol required that there be no evidence of device loosening or migration. 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 interface: (1) a lucency of greater than 4 mm; (2) tilting in any direction of greater than 4 mm; or (3) migration in any direction of greater than 4 mm. Upon review of the data, the company has determined that this analysis captured findings that were clinically insignificant for a device which is placed into a surgically created osseous defect, particularly for a device like the STAR Ankle where settling is not uncommon and bone in-growth is expected. Notably, such findings could be considered clinically insignificant if early movement of the device stabilized and the implant did not demonstrate progressive changes over time. Accordingly, this original analysis

was not consistent with the pivotal study protocol, which clearly required that there be no clinically significant loosening or migration.

In the hip and knee literature, loosening as defined by lucency at the bone-prosthesis interface is generally considered to be present when that lucency is present along more than 30-40% of the implant surface.[15] This is equivalent to 3 or more radiographic zones for the STAR Ankle, whereas the original STAR radiographic analysis inappropriately assigned failure to patients with lucency in a single zone. In addition, the STAR Ankle is placed in a surgically created interface in native bone. As the patient applied his or her full weight to the prosthesis over the next 6 weeks, slight movement or angulation could occur at a likely imperfectly created surface between the STAR Ankle and bone as the device becomes fully seated. Thus, minor migration can occur with a properly placed, well-performing STAR Ankle and does not constitute radiographic failure. The company's conclusion regarding this original analysis is supported by several articles that describe clinically insignificant movement in total ankle arthroplasty devices in the months following initial device placement.[16] [17] [18]

To further confirm that such findings are de minimus, and that ultimately stable migration and/or tilt were not clinically relevant, the company reviewed the radiographic stability and clinical outcomes of all 5 patients who did not meet the radiographic success criteria based on these minor observations. All of the radiographic observations were stable with time through 48 months follow-up. Perhaps more importantly, all of these patients enjoyed good, long-term clinical results, confirming that these minor imaging findings should have been considered radiographic successes. Consequently, the company believes that it is both reasonable and appropriate to consider these patients as constituting radiograph success.

3.6.2.3. Safety and Overall Success Based on Correct Classification of Radiographic Findings

The impact of the more clinically appropriate classification of the above 12 subjects as radiographic successes is evaluated for the primary safety comparison at 24 months for both the radiographic success rate and overall safety success rate. The results are provided in **Tables 16a** and **17a**. As outlined in these tables, with the application of either of these more clinically appropriate radiographic success criterion, the STAR radiographic success rate at 24

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[15] Bloebaum RD, Bachus KN, Jensen JW, Hofmann AA. Postmortem analysis of consecutively retrieved asymmetric porous-coated tibial components. *J Arthroplasty* 1997;12(8):920.

[16] Valderrabano V, et al. Scandinavian total ankle replacement: A 3.7 year average follow-up of 65 patients. *Clinical Orthopedics and Related Research* 2004;424:47-56.

[17] Carlsson A, et al. Radiostereometric analysis of the double-coated STAR total ankle prosthesis. *Acta Orthopaedica* 2005;76:573-579.

[18] Nelissen RG, et al. Early migration of the tibial component of the Buechel-Pappas total ankle prosthesis. *Clinical Orthopaedics and Related Research* 2006;448:146-151.

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months is higher than that of the control group. **Table 16a** also shows that when both corrections (eliminating the inappropriate carrying forward of radiographic failures and considering minor findings as constituting radiographic failure) are properly made the STAR safety success rate is only 3.1% lower than that of the control group (79.6% vs 82.7%, respectively). Since the lower bound of the confidence interval of the difference is less than the pre-specified delta for the safety endpoint, non-inferiority of the STAR ankle to the control group with respect to safety has been demonstrated.

Furthermore, none of the revised analyses incorporates potential errors in the radiographic assessment of fusion in the Arthrodesis arm of the clinical study, which was a component of radiographic success for these patients. As described in **Section 3.8.6**, there is reason to believe that the fusion rates in the control group reported by the study investigators were overly optimistic, given clinical data that is available for these patients. If the company were to adjust the Arthrodesis fusion success rates based on this information and correspondingly lower the Arthrodesis safety success rate, the STAR Ankle would compare even more favorably to Arthrodesis.

3.6.3. Patient Success Rates

Table 17 provides information on "composite" patient success rates at 12 and 24 months, where individual patient success was defined as: (i) ≥40 point improvement in total BP score; (ii) no device failures, revisions, or removals; (iii) radiographic success; and (iv) no major complications. Thus, in order for an individual to be a patient success they must have positive safety and efficacy results. For most analysis populations, there is a significantly higher rate of patient success in the STAR Ankle group as compared to Arthrodesis.

Table 17. Patient 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	Delta Met?
Month 12	Per Protocol	6	46	13.0%	58	124	46.8%	33.7%	22.7%	Yes
	Completers	6	53	11.3%	63	137	46.0%	34.7%	24.6%	Yes
	ITT - Single Imputation	17	66	25.8%	71	158	44.9%	19.2%	8.2%	Yes
	ITT - Worst Case Scenario	19	66	28.8%	63	158	39.9%	11.1%	-0.1%	Yes
Month 24	Per Protocol	6	40	15.0%	59	128	46.1%	31.1%	19.3%	Yes
	Completers	7	51	13.7%	64	142	45.1%	31.3%	20.9%	Yes
	ITT - Single Imputation	17	66	25.8%	72	158	45.6%	19.8%	8.8%	Yes
	ITT - Worst Case Scenario	22	66	33.3%	64	158	40.5%	7.2%	-4.3%	Yes

Composite patient success rates for the primary comparison at 24 months are shown in **Table 17a** based on the initial radiographic analysis, an analysis that does not carry forward prior X-ray failures, and on the clinically appropriate radiographic success analysis described above. The STAR patient success rate at 24 months increased from 45.1% in the PMA analysis to 49.3%, using the clinically appropriate radiographic analysis.

Table 17a. Overall patient success rates for completers at 24 months, based on both initial PMA analysis and revised analyses for defining radiographic success for STAR Ankle

	Control	STAR	Difference in Success Rate (STAR-Control)	Lower Bound of 90% CI for Difference
Overall Patient Success				
a) Initial PMA analysis	7/51 (13.7%)	64/142 (45.1%)	31.3%	20.9%
b) Revised, without carrying forward prior X-ray failures	7/51 (13.7%)	68/142 (47.9%)	34.2%	23.7%
c) Revised, clinically appropriate analysis	7/51 (13.7%)	70/142 (49.3%)	35.6%	25.1%

Table 18 provides details on the components of this patient success rate. The higher overall patient success rates seen with the STAR Ankle are largely a result of dramatically higher, statistically significant differences in success rates in the efficacy prong (*i.e.,* 40 or more point improvement in BP score) that were observed among the STAR patients. Importantly, there was no statistically significant difference in success rates between those patients who were younger and those who were older than 50 years of age.

Table 18. Components of Composite Patient Success Rates for Completers

	12 Months						24 Months					
	Control			STAR			Control			STAR		
	n	Evaluated	%	n	Evaluated	%	n	Evaluated	%	n	Evaluated	%
Overall Patient Success	6	53	11.3%	63	137	46.0%	7	51	13.7%	64	142	45.1%
Success on B-P (≥ 40 pt Improvement)	7	53	13.2%	84	143	58.7%	7	47	14.9%	83	142	58.5%
Success on Safety Component	50	57	87.7%	109	136	80.1%	43	52	82.7%	101	142	71.1%
No Surgical Interventions	54	57	94.7%	125	136	91.9%	47	52	90.4%	122	142	81.0%
No Major Complications	56	57	98.2%	126	136	92.6%	51	52	98.1%	128	142	90.1%
Fusion (union)	51	57	89.5%	NA	NA	NA	46	52	88,5%	NA	NA	NA
Success on X-Ray	NA	NA	NA	120	131*	91.6%	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 meansures to determine x-ray success/failure for 5 patients at 12 months and 4 patients at 24 months.

Table18a below reflects the results of the clinically appropriate radiographic analysis described above. The radiographic success rate in the STAR group is higher than that in the control group based on either revised analysis.

Table 18a. Components of Safety Endpoint for completers at 24 months, based on both initial PMA analysis and revised analyses for defining radiographic success for STAR Ankle

	Control	STAR
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		
a) Initial PMA analysis	N/A	117/138 (84.8%)
b) Revised, without carrying forward prior X-ray failures	N/A	124/137* (90.5%)
c) Revised, clinically appropriate analysis	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.

Table 19 compares patient success by investigational site in the Completers population at 24 months. Notably, while there is some variability in patient success rates across sites as anticipated, a test for homogeneity across sites was not statistically significant. Given these results, and the fact that all sites utilized highly qualified investigators and an identical protocol, the results across sites are believed to be comparable. For the STAR patients, the patient success rate based on the clinically appropriate analysis resulted in one additional patient success at four sites, two additional patient successes at one site, and no change in the remaining five sites. The patient success rate based on this revised analysis ranged from 22.2% to 78.6% for the STAR sites.

Table 19. Comparison of Patient Success Rates at 24 months by Site (Completers Population)

Site	Control			STAR		
	n	N	%	n	N	%
MANN				11	23	47.8
USCM	0	7	0			
IOWA				12	27	44.4
F&A				11	14	78.6
UTMS				4	6	66.7
MAYO				12	24	50.0
HSS	4	18	22.2			
OFAC				2	16	12.5
KUMC				3	8	37.5
FOI				4	9	44.4
BRI				3	6	50.0
DUMC				2	9	22.2
SUMC	0	5	0			
EXO	2	15	13.3			
MOC	1	6	16.7			
Total	7	51	13.7	64	142	45.1

As requested by FDA, but not specified in the analysis plan of the protocol, **Table 20** provides revised patient success rates, where success is defined as a safety success and at least a 25 point improvement in BP score when the ROM component is excluded. Even under such an analysis, which is biased against the STAR group, comparable patient success rates are observed in both groups at 12 and 24 months for the Per Protocol and Completers populations.

Table 20. 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	141	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 success on the safety endpoint and at least a 25 point improvement in BP score.

3.6.4. Subgroup and Adjusted Analyses of Success Rates

Patient, efficacy and safety success rates by selected subgroups are provided in **Table 21**. Across essentially all subgroups, including age, BMI, and primary diagnosis, efficacy success and patient success rates for the STAR Ankle are greater than those for the Arthodesis group.

Table 21. Success Rates by Subgroups

Success Rates by Subgroups	Patient Success 12 Months		Efficacy Success 12 Months		Safety Success 12 Months		Patient Success 24 Months		Efficacy Success 24 Months		Safety Success 24 Months	
	Control	STAR	Control	STAR	Control	STAR	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%)	4 (30.8%)	8 (33.3%)	4 (33.3%)	11 (47.8%)	12 (85.7%)	19 (79.2%)
50 - 70	1 (3.6%)	31 (41.9%)	1 (3.6%)	40 (53.3%)	29 (90.6%)	57 (79.2%)	1 (3.6%)	33 (44%)	1 (3.8%)	44 (57.1%)	24 (85.7%)	53 (71.6%)
> 70	2 (18.2%)	22 (52.4%)	3 (27.3%)	30 (69.8%)	9 (81.8%)	34 (79.1%)	2 (20.0%)	23 (53.5%)	2 (22.2%)	28 (66.7%)	7 (70.0%)	29 (65.9%)
BMI Category												
Normal (BMI< 25)	2 (13.3%)	20 (57.1%)	3 (20.1%)	26 (68.4%)	13 (81.3%)	27 (79.4%)	3 (21.4%)	20 (52.6%)	3 (25.0%)	25 (65.8%)	11 (78.6%)	29 (78.4%)
Overweight (BMI 25 - 29)	4 (21.0%)	21 (37.5%)	4 (21.1%)	30 (51.7%)	20 (95.2%)	43 (78.2%)	3 (15.0%)	24 (40%)	3 (15.0%)	32 (53.3%)	17 (85.0%)	39 (67.2%)
Obese (BMI > 30)		22 (47.8%)		28 (59.6%)	17 (85.0%)	39 (83%)	1 (5.9%)	20 (45.5%)	1 (6.7%)	26 (59.1%)	15 (83.3%)	33 (70.2%)
Primary Diagnosis												
Primary Arthrosis	1 (7.1%)	30 (55.6%)	2 (14.3%)	37 (67.3%)	14 (87.5%)	43 (82.7%)	2 (14.3%)	32 (56.1%)	2 (15.4%)	37 (64.9%)	12 (85.7%)	39 (69.6%)
Posttraumatic Arthrosis	3 (8.6%)	29 (42%)	3 (8.6%)	37 (52.1%)	33 (89.2%)	55 (79.7%)	4 (13.8%)	25 (37.3%)	4 (13.3%)	35 (51.5%)	28 (82.4%)	49 (73.1%)
Rheumatoid Arthrosis	2 (50%)	4 (28.6%)	2 (50%)	10 (58.8%)	3 (75%)	11 (73.3%)	1 (25%)	7 (38.9%)	1 (25%)	11 (64.7%)	3 (75%)	13 (68.4%)
Race												
Caucasian	5 (10.4%)	63 (47.4%)	6 (12.5%)	81 (59.1%)	46 (88.5%)	107 (80.5%)	7 (15.2%)	63 (46%)	7 (16.3%)	81 (59.1%)	40 (85.1%)	97 (70.8%)
Hispanic				1 (100%)	2 (66.7%)			1 (100%)		1 (100%)	2 (66.7%)	1 (100%)
African American				2 (50%)	1 (100%)	2 (66.7%)				1 (33.3%)		3 (75%)
Other	1 (100%)		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%)	3 (12.5%)	36 (50.7%)	3 (13.6%)	41 (58.6%)	19 (79.2%)	50 (72.5%)
Female	4 (13.8%)	29 (40.3%)	5 (17.2%)	41 (54.7%)	26 (86.7%)	59 (81.9%)	4 (14.8%)	28 (39.4%)	4 (16.0%)	42 (58.3%)	24 (85.7%)	51 (69.9%)
History of Smoking												
Yes	4 (14.8%)	30 (46.9%)	4 (14.8%)	40 (59.7%)	27 (93.1%)	50 (78.1%)	7 (25.9%)	28 (44.4%)	7 (28%)	39 (60.9%)	23 (85.2%)	45 (70.3%)
No	2 (7.7%)	33 (45.8%)	3 (11.5%)	44 (58.7%)	23 (82.1%)	58 (81.7%)	0	36 (46.2%)	0	44 (57.1%)	20 (80.0%)	56 (72.7%)
Missing						1 (100%)						

An analysis of patient success rates adjusting for both propensity scores and covariates. The propensity score and covariate adjusted odds ratios (STAR/Control) for patient success rates at 24 months for Completers were 4.23 and 4.55, respectively. Similar odds ratios were found for the Per Protocol population and using a GEE covariate adjusted analysis. Thus, the higher STAR patient success rates are further confirmed after adjustments for propensity scores and covariates.

Patient and safety success rates at 24 months by subgroups based on the clinically appropriate radiographic success analysis are shown in **Table 21a**.

Table 21a. Patient and Safety Success Rates at 24 Months by Subgroups, Based on the Clinically Appropriate Radiographic Success Analysis

Success Rates by Subgroups	Patient Success		Safety Success	
	Control	STAR	Control	STAR
Age Category				
< 50	4 (30.8%)	9 (37.5%)	12 (85.7%)	20 (83.3%)
50 – 70	1 (3.6%)	36 (48.0%)	24 (85.7%)	58 (78.4%)
> 70	2 (20.0%)	25 (58.1%)	7 (70.0%)	35 (79.6%)
BMI Category				
Normal (BMI< 25)	3 (21.4%)	21 (55.3%)	11 (78.6%)	30 (81.1%)
Overweight (BMI 25 - 29)	3 (15.0%)	27 (45.0%)	17 (85.0%)	45 (77.6%)
Obese (BMI > 30)	1 (5.9%)	22 (50.0%)	15 (83.3%)	38 (80.9%)
Primary Diagnosis				
Primary Arthrosis	2 (14.3%)	33 (57.9%)	12 (85.7%)	43 (76.8%)
Posttraumatic Arthrosis	4 (13.8%)	28 (41.8%)	28 (82.4%)	55 (82.1%)
Rheumatoid Arthrosis	1 (25%)	9 (50.0%)	3 (75%)	15 (79.0%)
Race				
Caucasian	7 (15.2%)	69 (50.0%)	40 (85.1%)	109 (79.6%)
Hispanic		1 (100%)	2 (66.7%)	1 (100%)
African American		0		3 (75%)
Other		0	1 (100%)	
Gender				
Male	3 (12.5%)	38 (53.5%)	19 (79.2%)	55 (79.7%)
Female	4 (14.8%)	32 (45.1%)	24 (85.7%)	58 (79.5%)
History of Smoking				
Yes	7 (25.9%)	30 (47.6%)	23 (85.2%)	50 (78.1%)
No	0	40 (51.3%)	20 (80.0%)	63 (81.8%)

3.7. Additional Efficacy Results

3.7.1. Primary Efficacy Endpoint: Mean Buechel-Pappas Score

Table 22 summarizes the primary efficacy endpoint results relating to the mean BP score at 12 and 24 months, as well as the change in BP score from baseline to 12 and 24 months. At 24 months, the mean BP score for the STAR group was significantly higher than that

for the Arthrodesis control (81.6 vs. 69.7), and the mean improvement in BP score for the STAR group was also significantly higher than that for the Arthrodesis control (40.5 vs. 26.3). Not only was the 10% non-inferiority delta met for the primary efficacy endpoint, BP scores for the STAR Ankle were significantly higher for all comparisons to Arthrodesis noted in **Table 22**.

Table 22. Mean-Buechel Pappas Score at 12 and 24 Months

	Control			STAR			Wilcoxon	
Buechel-Pappas	N	Mean	Std Dev	N	Mean	Std Dev	Test Statistic	p-value
12 Month	53	65.9	17.0	143	80.7	14.3	3241	<0.001
Improvement at 12 Months	53	23.3	15.9	143	39.7	15.0	3051	<0.001
24 Month	47	69.7	16.8	142	81.6	14.0	2962	<0.001
Improvement at 24 Months	47	26.3	17.1	142	40.5	15.1	2861	<0.001

All p-values are based on a chi-squared test or a t-test unless otherwise noted

Table 23 provides the results of a further analysis of the primary endpoint for the Completers and Per Protocol populations including a covariate adjusted analysis of BP scores and change from baseline in BP scores. A 10% non-inferiority delta was met for all comparisons; additionally, the STAR group demonstrated significantly better BP results for all comparisons made. A GEE analysis was performed in order to take into account the repeated BP scores over time. These analyses further demonstrate the significant improvements in the primary endpoint of mean BP score in the STAR group over the control group at 24 months, even after covariate adjustments.

Table 23. Primary Endpoint Analysis - BP Score at 24 Months

		Control		STAR					
Patient Population	BP Score	N	Mean	N	Mean	Superiority Test Significance	Difference (STAR - Control)	Lower Bound of 90% CI for Difference	10 point Delta Met? (Non-inferiority Test)
Completers	24-month BP	47	69.7	142	81.6	Significant (t-test)	11.9	7.8	Yes
	24-month BP Change from Baseline	47	26.3	142	40.6	Significant (t-test)	14.2	9.9	Yes
	24-month Covariate* Adjusted BP	.	.	.	.	Significant (t-test)	11.7	7.5	Yes
	24-month Covariate Adjusted BP Change from Baseline	.	.	.	.	Significant (t-test)	11.7	7.5	Yes
Per Protocol	24-month BP	36	70.1	127	81.7	Significant (t-test)	11.6	7.1	Yes
	24-month BP Change from Baseline	36	28	127	40.6	Significant (t-test)	12.5	7.8	Yes
	24-month Covariate Adjusted BP	.	.	.	.	Significant (t-test)	10.6	6.1	Yes
	24-month Covariate Adjusted BP Change from Baseline	.	.	.	.	Significant (t-test)	10.6	6.1	Yes
GEE analysis	24-month Covariate Adjusted BP	.	.	.	.	Significant (Chi-square test)	15	12	Yes
	24-month Covariate Adjusted BP Change from Baseline					Significant (Chi-square test)	15	12	Yes

In order to assess the impact of missing data on the BP score, a multiple imputation was performed using SAS version 9. This analysis revealed very little variability between imputation results and the results based on Completer patients and the Per Protocol patients. Similarly, a last observation carried forward (LOCF) approach was also used to impute the missing BP data at 12 and 24 months. Again, the imputed results are consistent with the results based on Completer patients and with the multiple imputation method described above.

3.7.2. Improvement of ≥ 40 Points in Buechel-Pappas Score

Table 24 summarizes improvement in BP score from baseline to various follow-up visits in both study groups. At 12 and 24 months, 58.7% and 58.5% of STAR Ankle patients demonstrated a 40 point or greater increase in total BP score as compared to baseline. This is significantly greater than the corresponding figures for the Arthrodesis group, which were 13.2% and 14.9% at 12 and 24 months, respectively.

Table 24. Improvement of ≥ 40 Points in Total Buechel-Pappas Score by Follow-up Visit

	12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value
< 40 Point Improvement	46 (86.8%)	59 (41.3%)	<0.001	40 (85.1%)	59 (41.5%)	<0.001
≥ 40 Point improvement	7 (13.2%)	84 (58.7%)		7 (14.9%)	83 (58.5%)	

All p-values are based on a chi-square test or a t-test unless otherwise noted
Numbers based on all patients with available data

3.7.3. Buechel-Pappas Scores by Visit

Table 25 provides mean improvement in BP subscores and total BP scores from baseline to 3, 6, 12, and 24 months post procedure. At 24 months, STAR Ankle patients experienced significantly greater improvement in 3 of the 4 BP subscores compared to Arthrodesis patients (namely, deformity, function and ROM). For example, STAR patients experienced a 13.4 point improvement in the function subscore compared to 9.7 points in the Arthrodesis group (p=0.004). Confirming one of the intended benefits of the STAR Ankle, STAR patients experienced a 3.6 point *improvement* in the ROM subscore compared to a 3.7 point *worsening* in the Arthrodesis group (p<0.001) In the fourth subscore, STAR patients experienced improvement of pain at least as great as those patients who had an arthrodesis, a notable achievement for a mobile bearing ankle as compared to arthrodesis, as pain reduction is often thought to be one of the principal benefits of ankle fusion.

Table 25. Mean Improvement in Buechel-Pappas Score from Baseline

	3 Months			6 Months			12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value
Deformity												
N	62	152		62	149		53	144		48	143	
Mean (SD)	0.2 (1.1)	0.9 (1.4)	<0.001	0.4 (1.2)	1.2 (1.5)	<0.001	0.5 (1.2)	1.8 (1.3)	<0.001	0.4 (1.2)	1.9 (1.3)	<0.001
Range	-3 , 3	-3 , 4		-2 , 4	-3 , 5		-2 , 4	-1 , 5		-2 , 4	-1 , 5	
Function												
N	63	152		62	150		53	143		48	143	
Mean (SD)	-2.3 (10.6)	9.7 (7.6)	<0.001	6.6 (8.5)	12.6 (7.4)	<0.001	9.5 (8.1)	13.6 (7.9)	0.002	9.7 (8.7)	13.4 (7.3)	0.004
Range	-20 , 26	-14 , 27		-16 , 26	-12 , 32		-22 , 28	-15 , 32		-9 , 28	-16 , 30	
Pain												
N	63	152		62	150		53	143		48	143	
Mean (SD)	19.6 (8.3)	19.3 (8.9)	0.842	17.4 (9.3)	20.1 (8.1)	0.039	18.3 (9.6)	20.6 (9)	0.126	19.2 (9.4)	21.5 (9.6)	0.142
Range	0 , 30	0 , 40		0 , 30	0 , 40		0 , 35	-10 , 40		0 , 30	-10 , 40	
ROM												
N	62	152		62	149		53	144		47	143	
Mean (SD)	-4.6 (5.1)	2.5 (3.9)	<0.001	-4.5 (5)	3.4 (3.9)	<0.001	-4.9 (5.2)	3.7 (3.7)	<0.001	-3.7 (5.1)	3.6 (3.7)	<0.001
Range	-13 , 6	-8 , 15		-13 , 8	-8 , 15		-13 , 8	-4 , 15		-13 , 6	-4 , 15	
Total												
N	62	152		62	149		53	143		47	142	
Mean (SD)	12.2 (15.2)	32.4 (13.8)	<0.001	19.9 (16.6)	37.5 (13.2)	<0.001	23.3 (15.9)	39.7 (15)	<0.001	26.3 (17.1)	40.5 (15.1)	<0.001
Range	-22 , 45	-12 , 61		-18 , 55	0 , 69		-14 , 61	-18 , 70		-17 , 57	-1 , 73	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

A further analysis of the 24 month results provide in **Table 26** revealed that STAR Ankle patients had significantly greater scores as compared to the control group on 3 of the 5 BP function subscales, including stairs, standing and support. While not statistically significant, the STAR Ankle group also enjoyed a greater improvement than Arthrodesis on the limp subscale. Together, these results indicate that the STAR Ankle performs better than arthrodesis in all higher-level ambulatory functions, as well as functions that do not require motion (*i.e.*, standing and support). Thus, it is not believed that the ROM subscale of the BP score unduly biased results in favor of the STAR Ankle. Rather, the results demonstrate the importance of ankle motion preservation in activities that are not normally associated with motion at the ankle joint.

Table 26. Mean Improvement in Buechel-Pappas Function Sub-Scores from Baseline

	12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value
Stairs (8 points)						
N	52	143	0.243	48	142	0.039
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	<0.001	48	142	<0.001
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	0.020	47	142	0.016
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	0.165	48	142	0.746
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	0.007	48	142	0.114
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	0.002	48	143	0.004
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	

Function subscale scores were not available for a limited number of patients with a total Buechel-Pappas function score.
All p-values are based on a chi-square test or a t-test unless otherwise noted.

3.7.4. Buechel-Pappas Scores without ROM Subscore

The ankle joint motion provided by the STAR Ankle is a key clinical benefit of the device and allows STAR patients to enjoy ankle function that is considerably closer to that of a normal ankle as compared to patients treated with arthrodesis. This important benefit notwithstanding, FDA requested that the sponsor conduct superiority and non-inferiority tests on STAR Ankle total BP score results without the ROM subscale. This analysis was not part of the analysis plan set forth in the protocol and was requested by the agency in the course of its review of this application. Results of this analysis are provided as **Table 27**. Notably, the use of the BP score without the ROM subscale has not been described in the literature and this analysis was not prospectively defined in the pivotal study protocol. These issues notwithstanding, the STAR Ankle uniformly demonstrated non-inferiority in comparison to Arthrodesis in terms of BP score even with the ROM subscale removed.

Table 27. Primary Endpoint Analysis - BP Score (without ROM) at 24-months

		Control		STAR					
Patient Population	BP Score	N	Mean	N	Mean	Superiority Test Significance	Difference (STAR - Control)	Lower Bound of 90% CI for Difference	10 point Delta Met? (Non-inferiority Test)
Completers	24-month BP	47	86.4	142	89.2	Not Significant (t-test)	2.8	-1.2	Yes
	24-month BP Change from Baseline	47	30	142	36.9	Significant (t-test)	6.9	2.8	Yes
	24-month Covariate Adjusted BP	.	.	.	.	Not Significant (t-test)	3.6	-0.5	Yes
	24-month Covariate Adjusted BP Change from Baseline	.	.	.	.	Not Significant (t-test)	3.6	-0.5	Yes
Per Protocol	24-month BP	36	67.6	127	69.3	Not Significant (t-test)	1.6	-2.7	Yes
	24-month BP Change from Baseline	36	32.4	127	36.8	Not Significant (t-test)	4.4	-0.1	Yes
	24-month Covariate Adjusted BP	.	.	.	.	Not Significant (t-test)	1.5	-2.8	Yes
	24-month Covariate Adjusted BP Change from Baseline	.	.	.	.	Not Significant (t-test)	1.5	-2.8	Yes
GEE analysis	24-month Covariate Adjusted BP	.	.	.	.	Significant (Chi-square test)	6.3	3.5	Yes
	24-month Covariate Adjusted BP Change from Baseline					Significant (Chi-square test)	6.3	3.5	Yes

3.7.5. Pain Visual Analog Scale

As seen in **Table 28,** there was comparable improvement in pain at 24 months between the STAR Ankle and Arthrodesis groups as measured on a Visual Analog Scale (VAS) (51.8 versus 44.6 at 24 months, respectively), a notable achievement for a mobile bearing ankle compare to arthrodesis.

Table 28. Mean Pain VAS Improvement from Baseline

	12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value
N	51	144	0.118++	45	144	0.089++
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	

++Wilcoxon Two-Sample Test

3.7.6. Quality of Life (SF-36)

Table 29 summarizes mean change in SF-36 scores as compared to baseline, and reflects no consistent, statistically significant advantage to either the STAR Ankle or Arthrodesis. However, where statistically significant improvements over baseline do exist, these comparisons favor the STAR Ankle.

Table 29. Mean Change in SF-36 Scores from Baseline

	12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value
Total Physical Score						
N	33	119	0.259	35	122	0.677
Mean (SD)	10.5 (8.2)	12.6 (10.2)		11.0 (9.5)	11.3 (10.3)	
Range	-10 , 30.2	-10.9 , 38.8		-10.7 , 25.8	-17 , 35.4	
Total Mental Score						
N	36	125	0.941	38	121	0.100
Mean (SD)	7.6 (8.8)	7.8 (11.5)		3.2 (10.2)	6.6 (11.2)	
Range	-5 , 24	-19 , 41		-25 , 24	-21 , 38	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

3.7.7. Physical Examination

Table 30 summarizes physical examination findings post-procedure for both groups. The condition of STAR Ankle patients substantially improved following surgery (89.9% of patients were rated good or excellent pre-operatively, improving to 98.1% at 3 months) and remained high throughout the study (93.1% of patients rated good or excellent at 24 months), maintaining a significantly higher percentage of patients in good or excellent condition as compared to Arthrodesis patients at all but the 24-month evaluation point throughout the study.

Functional measures likewise saw a substantial improvement following surgery in both STAR Ankle and Arthrodesis groups as compared to pre-operative values, with functional difficulties in STAR patients dropping from 77.8% pre-operatively to 20.8% at 3 months. The percentage of patients with functional difficulties was significantly worse in the Arthrodesis group as compared to the STAR Ankle group at 3, 6 and 12 months, with patients in the Arthrodesis group experiencing functional difficulties approximately twice as often as STAR patients.

Almost no patients in either group experienced motor or neurological deficits. A number of patients did experience sensory deficits, with a higher percentage of sensory deficits in the STAR group but the difference in sensory deficits between the two groups was not statistically significant. This likely reflects the anterior approach used to place the STAR device and resulting damage to a superficial branch of the common peroneal nerve. Importantly, the loss of this small nerve is essentially clinically inconsequential in that it supplies sensation to only a small area on the medial side of the incision and often patients are not even aware of the fact that they have lost any sensation. Subjects reporting a sensory deficit due to this nerve injury noted only numbness or minimal decreased sensation on the dorsum of the foot or big toe. The function of these subjects was not impaired by this numbness or decreased sensation as evidenced by the lack of functional difficulties reported for nerve issues during the physical exam. It should be noted that when a total knee replacement is performed the infra-patellar branch of the saphaneus nerve is almost always transected since it passes across the surgical field. In these situations, an area of numbness is noted along the medial aspect of the knee. The patients often will notice this loss of sensation, but it does not interfere with any function of the knee or activities and, therefore, most patients do not consider it a problem. The minor nature of the nerve injury seen in STAR Ankle patients notwithstanding, the accompanying sensory deficit resolved in many subjects. Specifically, 32 STAR patients in the pivotal study had "nerve injury" reported as an adverse event. Two (2) weeks following surgery, only 21 patients had a sensory deficit present on clinically examination. At 24 months, only 14 patients (10% of study patients) reported a sensory deficit. Furthermore, the company's medical experts recognized the risk of injury to this nerve during the draft of the STAR Ankle protocol and did not believe that it constituted a meaningful clinical concern.

At 3 months post-procedure, 94.2% of STAR Ankle patients were at full weight bearing, considerably higher than the corresponding figure of 46% in the Arthrodesis group, as outlined in **Table 30**. This is believed to reflect the different post-operative regimen used with

STAR patients, together with the faster recovery made possible by the less extensive osseous resection required to implant the STAR Ankle as compared to the resection needed to accomplish Arthrodesis. Another factor is the number of control subjects that were still casted at 3 months to protect their healing fusion site. STAR patients also required specialized footwear less frequently than did Arthrodesis patients, likely representing an advantage of the retained tibiotalar joint motion made possible by the STAR Ankle.

Table 30. Physical Examination Findings by Visit

	Pre-Op			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value
General Condition																		
Poor	1 (1.5%)	1 (0.6%)					1 (1.6%)			2 (3.2%)								
Fair	3 (4.5%)	15 (9.5%)	<0.001	3 (4.5%)	5 (3.2%)	<0.001	3 (4.7%)	3 (1.9%)	<0.001	2 (3.2%)	4 (2.6%)	<0.001	2 (3.8%)	5 (3.4%)	0.001	7 (14.6%)	10 (6.9%)	0.129
Good	53 (80.3%)	75 (47.5%)		50 (75.8%)	63 (40.1%)		47 (73.4%)	58 (37.7%)		42 (66.7%)	57 (37.7%)		36 (67.9%)	57 (39%)		22 (45.8%)	57 (39.6%)	
Excellent	9 (13.6%)	67 (42.4%)		13 (19.7%)	89 (56.7%)		13 (20.3%)	93 (60.4%)		17 (27%)	90 (59.6%)		15 (28.3%)	84 (57.5%)		19 (39.6%)	77 (53.5%)	
Adequate Ligament Support																		
Yes	62 (93.9%)	151 (95.6%)			156 (99.4%)		3 (4.7%)	153 (99.4%)		4 (6.3%)	148 (98%)		2 (3.8%)	145 (99.3%)			144 (100%)	
No	2 (3%)	7 (4.4%)	0.081			<0.001		1 (0.6%)	<0.001		3 (2%)	<0.001		1 (0.7%)	<0.001			<0.001
N/A	2 (3%)			66 (100%)	1 (0.6%)		61 (95.3%)			59 (93.7%)			51 (96.2%)			48 (100%)		
Functional Difficulties																		
Yes	64 (97%)	123 (77.8%)	<0.001	36 (54.5%)	28 (17.8%)	<0.001	33 (51.6%)	32 (20.8%)	<0.001	30 (47.6%)	35 (23.2%)	<0.001	28 (52.8%)	29 (19.9%)	<0.001	20 (41.7%)	42 (29.2%)	0.109
No	2 (3%)	35 (22.2%)		30 (45.5%)	129 (82.2%)		31 (48.4%)	122 (79.2%)		33 (52.4%)	116 (76.8%)		25 (47.2%)	117 (80.1%)		28 (58.3%)	102 (70.8%)	
Leg Length Discrepancy																		
Yes	5 (7.6%)	20 (12.7%)		3 (4.5%)	16 (10.2%)		7 (10.9%)	15 (9.7%)		7 (11.1%)	14 (9.3%)		6 (11.3%)	16 (11%)		5 (10.4%)	16 (11.1%)	
No	61 (92.4%)	138 (87.3%)	0.271	63 (95.5%)	141 (89.8%)	0.168	57 (89.1%)	139 (90.3%)	0.789	56 (88.9%)	137 (90.7%)	0.680	47 (88.7%)	130 (89%)	0.943	43 (89.6%)	128 (88.9%)	0.894
Missing																		
Ligament Affected																		
Lateral	1 (50%)	7 (100%)									1 (33.3%)			1 (100%)				
Medial			0.047					1 (100%)			2 (66.7%)							
Both	1 (50%)																	
Missing	64	151		66	157		64	153		63	148		53	145		48	144	
Ligament Severity																		
Mild	1 (50%)	1 (14.3%)						1 (100%)			3 (100%)			1 (100%)				
Moderate		5 (71.4%)	0.200															
Severe	1 (50%)	1 (14.3%)																
Missing	64	151		66	157		64	153		63	148		53	145		48	144	
Motor Deficit																		
Yes	1 (1.5%)	2 (1.3%)	0.882											1 (0.7%)	0.546			
No	65 (98.5%)	156 (98.7%)		66 (100%)	157 (100%)		64 (100%)	154 (100%)		63 (100%)	151 (100%)		53 (100%)	145 (99.3%)		48 (100%)	144 (100%)	
Neurologic Deficit																		
Yes		2 (1.3%)	0.359		1 (0.6%)	0.516		1 (0.6%)	0.518					1 (0.7%)	0.546		2 (1.4%)	0.412
No	66 (100%)	156 (98.7%)		66 (100%)	156 (99.4%)		64 (100%)	153 (99.4%)		63 (100%)	151 (100%)		53 (100%)	145 (99.3%)		48 (100%)	142 (98.6%)	
Sensory Deficit																		
Yes	2 (3%)	7 (4.4%)	0.627	2 (3%)	17 (10.8%)	0.057	2 (3.1%)	17 (11%)	0.059	2 (3.2%)	17 (11.3%)	0.058	4 (7.6%)	12 (8.2%)	0.878	1 (2.1%)	14 (9.7%)	0.088
No	64 (97%)	151 (95.6%)		64 (97%)	140 (89.2%)		62 (96.9%)	137 (89%)		61 (96.8%)	134 (88.7%)		49 (92.4%)	134 (91.8%)		47 (97.9%)	130 (90.3%)	
Special Shoe																		
Yes	2 (3%)	15 (9.5%)		1 (1.5%)	4 (2.5%)		3 (4.7%)	11 (7.1%)		10 (15.9%)	17 (11.3%)		13 (24.5%)	22 (15.1%)		16 (33.3%)	25 (17.4%)	
No	60 (90.9%)	127 (80.4%)	0.132	52 (78.8%)	142 (90.4%)	0.019	56 (87.5%)	139 (90.3%)	0.179	52 (82.5%)	133 (88.1%)	0.518	39 (73.6%)	120 (82.2%)	0.294	31 (64.6%)	117 (81.3%)	0.058
N/A	4 (6.1%)	16 (10.1%)		13 (19.7%)	11 (7%)		5 (7.8%)	4 (2.6%)		1 (1.6%)	1 (0.7%)		1 (1.9%)	4 (2.7%)		1 (2.1%)	2 (1.4%)	
Weight Bearing																		
None		1 (0.6%)		49 (75.4%)	15 (9.6%)		8 (12.7%)	3 (1.9%)		1 (1.6%)	2 (1.3%)		2 (3.8%)	1 (0.7%)				
Partial	2 (3.1%)	6 (3.8%)	0.784	10 (15.4%)	64 (40.8%)	<0.001	26 (41.3%)	6 (3.9%)	<0.001			0.882	1 (1.9%)	1 (0.7%)	0.213	1 (2.1%)		0.082
Full	63 (96.9%)	151 (95.6%)		6 (9.2%)	78 (49.7%)		29 (46%)	145 (94.2%)		62 (98.4%)	149 (98.7%)		50 (94.3%)	144 (98.6%)		47 (97.9%)	144 (100%)	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

3.7.8. Work Status

STAR Ankle patients had a consistently lower percentage of full and part time employment at 3, 6, 12 and 24 months post procedure as compared to Arthrodesis patients. These differences, similar to those observed at baseline, likely reflect the older age and more debilitated baseline condition of the patients receiving the STAR Ankle (as evidenced by lower baseline BP scores and higher pain levels), and the higher percentage of retired persons in that group.

3.7.9. Patient Satisfaction (Coughlin rating scale)

As shown in **Table 31**, there was uniformly high patient satisfaction with the STAR Ankle as measured by the Coughlin rating scale. At 24 months, 86% of STAR Ankle subjects reported "excellent" or "good" patient satisfaction. There was no statistically significant difference in patient satisfaction between the STAR and Arthrodesis groups at any evaluation time point, with roughly comparable percentages at any given satisfaction level and evaluation point.

Table 31. Patient Satisfaction by Follow-up Visit

	12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value
Patient Satisfaction						
Excellent	20 (37.7%)	69 (48.9%)	0.106	22 (46.8%)	67 (46.9%)	0.968
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%)	

All p-values are based on a chi-square test or a t-test unless otherwise noted

3.7.10. Medication Usage

Table 32 summarizes the change in patient medication at 24 months as compared to baseline. At 24 months, the majority of STAR patients had no change in medication use when compared to baseline. Of those STAR patients whose medications did change, nearly a third of patients stopped taking medications directly related to their ankle condition. Moreover, many more STAR patients stopped taking medications in each of the medication categories related to ankle pain than did patients who started new use of those medications. Although medication use was unknown for a portion of control patients (due to missed visits or patients longer available for follow-up), similar trends were observed.

Table 32. Summary of Changes in Patient Medication Usage for Ankle Condition (From Baseline to 24 Months)

	No Change in Medication Usage		Stopped Taking Medication		New Usage of Medication		Unknown Usage of Medication	
	Control	STAR	Control	STAR	Control	STAR	Control	STAR
Medications Directly Related to Condition								
Nonnarcotic Analgesic	28 (43.1%)	92 (59.4%)	11 (16.9%)	33 (21.3%)	5 (7.7%)	13 (8.4%)	21 (32.3%)	17 (11.0%)
Narcotic Analgesic	33 (50.8%)	107 (69.0%)	7 (10.8%)	22 (14.2%)	4 (6.2%)	9 (5.8%)	21 (32.3%)	17 (11.0%)
NSAID	28 (43.1%)	86 (55.5%)	13 (20.0%)	39 (25.2%)	3 (4.6%)	13 (8.4%)	21 (32.3%)	17 (11.0%)
Muscle Relaxant	43 (66.2%)	137 (88.4%)	0	0	1 (1.5%)	1 (0.6%)	21 (32.3%)	17 (11.0%)
Medications Indirectly Related to Condition								
Arthritic-Rheumatic	35 (53.8%)	109 (70.3%)	7 (10.8%)	25 (16.1%)	2 (3.1%)	4 (2.6%)	21 (32.3%)	17 (11.0%)
Corticosteroid	35 (53.8%)	102 (65.8%)	9 (13.8%)	33 (21.3%)	0	3 (1.9%)	21 (32.3%)	17 (11.0%)
Other Medications for Ankle								
Antibiotic	42 (64.6%)	133 (85.8%)	0	0	2 (3.1%)	5 (3.2%)	21 (32.3%)	17 (11.0%)
Anticonvulsant	43 (66.2%)	137 (88.4%)	1 (1.5%)	0	0	1 (0.6%)	21 (32.3%)	17 (11.0%)
Antipsychotic	44 (67.7%)	138 (89.0%)	0	0	0	0	21 (32.3%)	17 (11.0%)

The relationship between medication and patient outcome was explored for both patient success and change in BP score. This information is provided in **Tables 33** and **34**. As seen in these tables, the use of medications does not substantially impact either patient success or BP score.

Table 33. Patient Success Rates by Medication

			Control			STAR		
Medication (at any timepoint)	**Use**	**Patient Success**	**n**	**N**	**%**	**n**	**N**	**%**
Muscle Relaxant, NSAID, Narcotic Analgesic and Non-Narcotic Analgesic	No	12 Months	0	2	0.0%	2	5	40.0%
	Yes	12 Months	6	51	11.8%	61	132	46.2%
	No	24 Months	0	3	0.0%	3	5	60.0%
	Yes	24 Months	7	48	14.6%	61	137	44.5%
Corticosteroids and Rheumatics	No	12 Months	3	30	10.0%	30	67	44.8%
	Yes	12 Months	3	23	13.0%	33	70	47.1%
	No	24 Months	5	29	17.2%	30	65	46.2%
	Yes	24 Months	2	22	9.1%	34	77	44.2%

Table 34. Change in BP Score by Medication Use

Medication (at any timepoint)		BP Change at 12 Months			BP Change at 24 Months		
		n	Mean	S.D.	n	Mean	S.D.
Muscle Relaxant, NSAID, Narcotic Analgesic and Non-Narcotic Analgesic	Group						
No	Control	1	23	.	1	18	.
	STAR	4	41.8	12.5	2	49.5	10.6
Yes	Control	52	23.4	16.1	46	26.5	17.3
	STAR	139	39.6	15.1	140	40.4	15.1
Corticosteroids and Rheumatics	Group						
No	Control	24	26.2	14.7	22	31.3	15.1
	STAR	61	38.9	16.6	58	39.6	16.3
Yes	Control	29	21	16.7	25	21.9	17.9
	STAR	82	40.3	13.7	84	41.2	14.2

3.8. Additional Safety Results

3.8.1. All Adverse Events

Table 35 summarizes operative site adverse events for the 158 STAR patients and 66 control patients. As anticipated with a new surgical procedure using an anterior surgical approach to implant a motion preserving prosthesis compared to standard arthrodesis, more operative site events were observed in STAR patients compared to arthrodesis patients. The incidence of intraoperative bone fracture has been previously described and the use of K-wires to prevent such fractures was implemented during the course of the study. Bony changes, while seen with the STAR Ankle, are also seen with hip and knee arthroplasty. Decreased ROM was noted in a small number of patients as an adverse event but it should be noted that patients in the Arthrodesis control group uniformly had little, if any, ROM postoperatively where the great majority of STAR patients had substantial ROM preserved. Nerve injury, wound problems, and soft tissue edema were all seen with the STAR Ankle.

Table 35. Operative Site Adverse Events - Patient Basis

Operative Site Events	Control	STAR
	n	n
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

While a higher rate of adverse events was seen with the STAR Ankle, most of these adverse events were minor and/or resolved as outlined in **Table 36** which provides information on adverse events by severity. As can be seen from this table, the majority of adverse events are mild in severity. The most frequent severe adverse event was pain, and that was observed in about 9% of patients in both groups. While there were a few life-threatening and fatal adverse events in the STAR group, these events were not related to the device (with the exception of a pulmonary embolism which occurred in one STAR patient after surgery but which was not related to the device itself).

Table 36. Adverse Events by Severity

	Mild		Moderate		Severe		Life-Threatening	Fatal	
Adverse Event	Control	STAR	Control	STAR	Control	STAR	STAR	Control	STAR
HEENT	1 (1.5%)	3 (1.9%)	3 (4.6%)	5 (3.2%)		1 (0.6%)			
anesthesia		1 (0.6%)							
ankle deformity	1 (1.5%)			2 (1.3%)					
ankle instability		4 (2.5%)		1 (0.6%)		1 (0.6%)			
ankle slippage		1 (0.6%)							
bone fracture	2 (3.1%)	22 (13.9%)	2 (3.1%)	15 (9.5%)	1 (1.5%)	3 (1.9%)			
bony changes		6 (3.8%)		7 (4.4%)		3 (1.9%)			
cardiovascular		8 (5.1%)	3 (4.6%)	9 (5.7%)		4 (2.5%)	3 (1.9%)		2 (1.3%)
decreased ROM		11 (7%)		1 (0.6%)					
device failure		1 (0.6%)	2 (3.1%)	2 (1.3%)		1 (0.6%)			
device instability				2 (1.3%)		2 (1.3%)			
device migration	1 (1.5%)	3 (1.9%)		2 (1.3%)					
device removal	1 (1.5%)			1 (0.6%)					
device subsidence		2 (1.3%)		6 (3.8%)					
embolism				1 (0.6%)		2 (1.3%)			1 (0.6%)
foot deformity				1 (0.6%)					
fusion problems	1 (1.5%)		1 (1.5%)		1 (1.5%)				
gait problems		5 (3.2%)	1 (1.5%)						
gastrointestinal	1 (1.5%)	11 (7%)	3 (4.6%)	10 (6.3%)	1 (1.5%)	1 (0.6%)			
general	7 (10.8%)	34 (21.5%)	12 (18.5%)	16 (10.1%)	2 (3.1%)	4 (2.5%)	2 (1.3%)		1 (0.6%)
hematologic		2 (1.3%)							
hematoma					1 (1.5%)				
hemorrhage		1 (0.6%)	1 (1.5%)	2 (1.3%)			1 (0.6%)		
impingement		1 (0.6%)	1 (1.5%)	1 (0.6%)					
incision		1 (0.6%)							
infection	8 (12.3%)	8 (5.1%)	4 (6.2%)	11 (7%)	1 (1.5%)	3 (1.9%)			
motor deficit		1 (0.6%)		1 (0.6%)					
muscle problems		2 (1.3%)	1 (1.5%)	1 (0.6%)		1 (0.6%)			
musculoskeletal	2 (3.1%)	17 (10.8%)	8 (12.3%)	12 (7.6%)	1 (1.5%)	3 (1.9%)			
nerve injury	5 (7.7%)	36 (22.8%)		3 (1.9%)					
neurologic	1 (1.5%)	14 (8.9%)	1 (1.5%)	9 (5.7%)		2 (1.3%)	1 (0.6%)	1 (1.5%)	
neuromuscular	4 (6.2%)	15 (9.5%)	1 (1.5%)	14 (8.9%)	3 (4.6%)	5 (3.2%)			
non-union		1 (0.6%)	1 (1.5%)	1 (0.6%)					
pain	33 (50.8%)	85 (53.8%)	37 (56.9%)	52 (32.9%)	6 (9.2%)	15 (9.5%)			
skin		17 (10.8%)		3 (1.9%)					
soft tissue edema	5 (7.7%)	20 (12.7%)		12 (7.6%)					
symptomatic hardware			2 (3.1%)	1 (0.6%)					
tendon problem		1 (0.6%)	6 (9.2%)	6 (3.8%)					
urologic	1 (1.5%)	8 (5.1%)		5 (3.2%)					
wound problem	6 (9.2%)	32 (20.3%)	1 (1.5%)	4 (2.5%)		2 (1.3%)			

Patient-based Adverse Events

In addition to the mild and transient nature of most STAR-related adverse events, the somewhat higher adverse event rate seen with the STAR Ankle is more than balanced by the substantial benefits relating to function and ROM enjoyed by STAR patients.

3.8.2. Selected Adverse Events

Rates of certain adverse events selected for special comment are provided in **Table 37**, and **Table 38** provides information on various measures of success for those selected adverse events. As may be seen from these tables, the majority of adverse events did not result

in a major complication nor adversely impact success rates. As outlined in these tables, the majority of these adverse events are minor, do not result in surgical intervention, are transient in nature, and have no impact on the overall clinical or functional result gained with the STAR Ankle.

Table 37. Adverse Events up to 24 Months

Adverse Events	Control (N=66)	STAR (N=158)
bone fracture	2 (3.0%)	28 (17.7%)
intra-operative fracture	1 (1.5%)	15 (9.5%)
post-operative fracture	1 (1.5%)	15 (9.5%)
bony changes	0 (0%)	12 (7.6%)
pain	32 (48.5%)	69 (43.7%)
nerve injury	5 (7.6%)	32 (20.3%)
wound problem	4 (6.1%)	32 (20.3%)
surgical intervention	11 (16.7%)	34 (21.5%)
revision or removal	10 (15.2%)	21 (13.3%)
other intervention	3 (4.5%)	19 (12.0%)
major complication	1 (1.5%)	14 (8.9%)
infection	1 (1.5%)	2 (1.3%)
bone problems	0 (0%)	8 (5.1%)
wound problems	1 (1.5%)	5 (3.2%)
wound problems and infections	0 (0%)	1 (0.6%)

Table 38. Adverse Events in Pivotal Study with Major Complications and Success Rates

Adverse Events	Patients[1]	Major Complication[1]	Safety Success	Efficacy Success	Patient Success
bone fracture					
intra-operative fracture					
Control (N=66)	1 (1.5%)	0	0	0	0
STAR (N=158)	11 (7.0%)	0	9	8	7
post-operative fracture					
Control (N=66)	1 (1.5%)	0	1	0	0
STAR (N=158)	13 (8.2%)	4	3	7	1
bony changes - STAR	10 (6.3%)	4	2	3	1
pain					
Control (N=66)	24 (36.3%)	0	19	2	2
STAR (N=158)	61 (38.6%)	0	35	25	16
infection					
Control (N=66)	3 (4.5%)	1	2	0	0
STAR (N=158)	5 (3.2%)	0	4	3	2
nerve injury					
Control (N=66)	3 (4.5%)	0	1	0	0
STAR (N=158)	31 (19.6%)	0	23	17	17
wound problem					
Control (N=66)	4 (6.1%)	1	3	1	1
STAR (N=158)	26 (16.5%)	4	15	17	11

[1] The patient and major complication numbers for each category are based on a patient basis for those patients that had 24 month data for safety, efficacy, and patient success.

Bone fracture, both intra-operative and post-operative, were seen in the STAR Ankle studies. Intraoperative fractures were recognized at the time of surgery, were largely stabilized with internal fixation without an additional surgical procedure, and did not result in long-term clinical impact on patients. Additionally, both the efficacy success and safety success

rates for patients with intraoperative fractures are similar to those of STAR Ankle patients overall. Notably, a number of current standard of care arthrodesis techniques, including the procedure called for in this study, require the cutting of the malleoli as part of the procedure and it is not considered a complication of arthrodesis procedures.

Post-operative fractures seen with the STAR Ankle largely fall into two distinct groups: non-displaced or displaced bone fractures within the first 6 months of surgery or stress fractures more than a year following surgery. With regard to the earlier group of fractures, approximately one third of these fractures that occurred within 6 months of surgery constituted major complications that required surgical reduction. However, the majority of these safety-failure subjects enjoyed clinically adequate fracture healing and were considered efficacy successes. The stress fractures that occurred more than a year following surgery were treated with simple immobilization and the associated pain resolved once the fracture was healed.

Bone fracture is a potential risk with ankle arthroplasty as it is in any orthopedic procedure requiring bony resection. Placement of the STAR Ankle requires resection of a portion of the distal tibia and the talar dome to allow placement of the device. It should be noted that this resection is somewhat challenging for arthroplasty due to the confined space between the malleoli. Working within this space may damage the adjacent malleoli, with the potential to predispose the patient to post-operative fracture. As described in **Section 3.5.3.**, the risk of fracture was also identified during the pivotal study, with modifications to the STAR Ankle placement technique made to minimize the possibility of this complication. Again, in this regard, it is important to note that many standard of care arthrodesis techniques, including the procedure described in the STAR Ankle pivotal protocol, require the cutting and removal of a malleolus as an integral part of the surgery.

Bony changes are another adverse event seen with the STAR Ankle and are a recognized complication of arthroplasty procedures. It is well known that arthroplasty, which by definition introduces a foreign body that undergoes motion into the patient, has a higher rate of bony changes such as cyst formation and osteolysis as compared to arthrodesis, which involves less extensive hardware and no joint movement. In the case of the STAR Ankle, bony changes involving the device may result in changes to adjacent bones, resulting in radiographic failure (and consequently patient failure). Specifically, 80% of the bony change adverse events were classified as patient failures based on the failure of the radiographic portion of the composite endpoint. However, the majority (60%) of these radiographic "failures" were minor in nature, such as a subtle, stable lucency or cyst that did not require treatment and did not qualify as a major complication. Link has recognized the potential of bony changes during the STAR Ankle pivotal study and has taken steps to minimize the occurrence of these complications as fully described in **Section 2.1.5.**

Wound problems, which consist of wound dehiscence, skin necrosis, and delayed wound healing, occurred at a higher rate for the STAR Ankle patients as compared with the Arthrodesis patients. However, less than 20% of all wound problems progressed to a major complication that required surgical intervention. Wound problems are a risk with any major surgical procedure, particularly where overlying soft tissues are thin and retraction is required.

Due to the anterior surgical approach necessary to place the STAR Ankle, the relatively thin skin anterior to the ankle and the paucity of underlying subcutaneous fat, wound complications may be more easily encountered than in arthrodesis, which utilizes a lateral surgical approach. Notably, the anterior approach to the ankle joint which is utilized for the STAR Ankle prosthesis, and most other ankle prostheses, including those recently receiving 510(k) clearances from the agency. The wound issue was recognized during the course of the pivotal study and the surgical technique modified to attempt to lessen the risk of wound-related complications. Link plans to incorporate these modifications into the device's proposed labeling. In addition, the anterior approach is now being routinely incorporated into post-graduate Orthopedic Surgery training programs, making surgeons completing their residency training both now and in the future much more familiar with the procedure and how its complications may be minimized.

Nerve injury in the STAR Ankle group is an adverse event that is also related to the anterior approach necessary to place the device. This surgical approach may result in neuropraxia of a superficial branch of the common peroneal nerve, which is responsible for sensation in a portion of the dorsum of the foot. The loss of sensation from injury to this nerve is mild, clinically insignificant and, in most cases, temporary. Supporting the minor nature of this issue, the majority of STAR patients with nerve injury were safety successes. As noted previously, when a total knee replacement is performed, the infra-patellar branch of the saphaneus nerve is almost always transected since it passes across the surgical field. In these situations, an area of numbness is noted along the medial aspect of the knee. These patients often will notice this loss of sensation, but it does not interfere with any function of the knee or activities and, therefore, most patients do not consider it a problem. This clinical situation is directly analogous to the nerve injury occasionally seen with the STAR Ankle.

In considering the anterior surgical approach used with the STAR Ankle and the wound problems and/or nerve injury that may result from this surgical procedure, it is worthwhile to note that certain 510(k) ankle arthroplasty devices (semi-constrained, cemented prostheses) recently cleared by FDA presumably use an identical anterior surgical approach and thus likely demonstrate a similar profile with respect to these complications.

3.8.3. Deaths

Five (5) patients expired in the 24 months post procedure, 4 in the STAR Ankle group and 1 Arthrodesis patient. One (1) STAR patient, [redacted], suffered a fatal pulmonary embolism 7 days after placement of the device. Pulmonary embolism is a known complication of lower extremity surgery in general and was noted as a potential complication on the study's informed consent materials. In addition, this patient had a number of underlying medical conditions (hypertension, melanoma, basal cell carcinoma, and rheumatoid arthritis), with multiple ongoing medical therapies. Accordingly, while this fatal adverse event is likely related to the patient's surgery and possibly to underlying disease, neither the STAR Ankle itself nor anything specific to the STAR surgery were believed to have been a factor.

The remainder of patient deaths were determined by both the study investigators and medical monitors not to be study-related. Patient [redacted] expired 94 weeks after surgery as a

result of an exacerbation of symptoms and side effects following a stroke (date of stroke unknown). Patient [redacted] died 13 weeks after surgery from a myocardial infarction, and had a baseline history of coronary artery disease and hypertension. Patient [redacted] was diagnosed with metastatic cancer to the lung 6 weeks following STAR Ankle surgery and died at 63 weeks following the procedure. Patient [redacted] died 49 weeks after surgery secondary to congestive heart failure and subsequent pneumonia. This patient had a history of hypertension and congestive heart failure.

Two (2) patient deaths occurred after 24 months post-procedure (patients [redacted] and [redacted]) both due to cancer.

3.8.4. Surgical Interventions

Table 39 summarizes the surgical interventions performed throughout the course of the study. Likely reflecting the more complex nature of the STAR Ankle placement procedure and the device itself, as well as the more debilitated nature of the STAR Ankle group, surgical interventions occurred slightly more frequently in the STAR group (21.5% of STAR patients vs. 16.7% of Arthrodesis). By its basic nature, the STAR Ankle is designed to preserve motion and will be in use whenever a patient ambulates or otherwise flexes or extends their foot at the tibial-talar joint. This motion in itself produces a variety of ongoing stress forces on the STAR Ankle. In contrast, success in arthrodesis eliminates all motion from the tibial-talar joint, which in turn limits the ways a fusion can fail. This advantage notwithstanding, a failed STAR Ankle may often be revised. There is also always the option of removing a STAR Ankle and performing a subsequent arthrodesis.

Table 39. Surgical Interventions - Summary of Interventions

	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%)
Reoperation	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%)	

Numbers and percents are patient based.
*Missing complications data for 2 Arthrodesis and 2 STAR patients.

Notably, a variety of minor modifications made to the STAR Ankle placement technique, increasing surgeon experience, and improved instructions to patients, as described in **Section 2.1.5.**, are all believed to have helped to substantially decrease the underlying causes of surgical intervention, and with them, the rate of surgical interventions as well.

The mean time to any surgical intervention was slightly shorter in the STAR Ankle group (68.3 weeks as compared to 75.8 weeks). The median time to any intervention was also shorter with the STAR Ankle (56.2 weeks as compared to 67.6 weeks for Arthrodesis).

Table 40 outlines surgical interventions specific to the STAR Ankle, with **Table 41** providing additional details on STAR component revisions and removals. Removal or replacement of the meniscal bearing were the most common interventions to the STAR device after placement. This reflects the standard practice of replacing, at a minimum, the ultra high molecular weight polyethylene component of an arthroplasty system (such as the STAR meniscal bearing) if surgery is performed on the treated joint for any reason. This is a straightforward procedure that involves simply removing the existing polyethylene component and inserting a replacement. Non-polyethylene components of an arthroplasty system (such as the tibial and talar components in the case of the STAR Ankle) are routinely left in place in the absence of visible abnormalities at the bone-component interface. Surgical interventions involving the revision or removal of a metallic component in conjunction with the polyethylene mobile bearing component were most often performed for persistent ligament laxity or residual/recurring deformity that resulted in high stresses at the bone-implant interface and could result in progressively unstable implants and loosening. Importantly, there was no correlation between polyethylene component thickness and surgical revision/removal rate.

Table 40. STAR Surgical Interventions Pivotal Study

	STAR (n%)
Surgical Interventions	45
Patients with Surgical Interventions	34 (21.5%)
Meniscal Bearing Removed	17 (10.8%)
Meniscal 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

Note that some patients that had a component replaced were also considered to have had that component removed. For example, 17 patients had their meniscal bearing removed and of these 17 patients, 2 had the meniscal bearing replaced (see item 3c).

Table 41. STAR Surgical Interventions

Patient Ankle Components Revised or Removed	Patients N
All Three Components[1]	6
Meniscal Component Only	8
Meniscal and Talar Components	2
Meniscal and Tibial Components	2
Other	3
Total Patients with Revision/Removal	21

Table is on a per patient basis across all surgical interventions (if more than one surgical intervention occurred).

[1] 2-016 had no information provided for the surgical intervention because a non-investigator removed the device and fused the ankle. The fact that all components have been removed was confirmed by radiographs.

Notably, the pivotal study revision/removal rate of 12.7% is comparable to the pooled estimated revision rate of 12.5% reported for total ankle replacements with a meniscal-bearing in a 2005 meta-analysis performed by Stengel, *et al.*[19] Finally, in all cases of surgical intervention where a STAR Ankle was removed and the ankle subsequently fused, that arthrodesis successfully healed. This demonstrates that STAR Ankle patients will most likely have the option of fusion, if clinically indicated.

3.8.5. Major Complications

Table 42 summarizes major complications encountered in both groups as determined by the study's medical monitors. A major complication was defined as any surgical intervention to the treated ankle that was a result of an infection, wound problem, or bone problem such as osteolysis, cyst formation, or non-traumatic fracture. Notably, this characterization of major complications is focused on the complications seen more commonly with arthroplasty devices as opposed to arthrodesis. Major complications generally occurred in a higher percentage of STAR patients than in patients undergoing arthrodesis, although the rate of major complications was low in both groups. **Table 43** provides a listing of these major complications. As shown in this table, most major complications involving STAR patients were wound or fracture related.

Table 42. Major Complications

	Patients	
	Control	STAR
Major Complication Classification		
Any Major Complication	1 (1.5%)	16 (10.1%)
Wound Problems	1 (1.5%)	5 (3.2%)
Infection	1 (1.5%)	3 (1.9%)
Bone Problems		9 (5.7%)
Wound Problems and Infection		2 (1.3%)

[19] Stengel D, *et al.* Efficacy of total ankle replacement with meniscal-bearing devices: a systematic review and meta-analysis. *Arch Orthop Trauma Surg* 2005;125:109-119.

As previously noted in **Section 3.8.2.**, the anterior approach necessary to place the STAR Ankle and all current ankle replacements more commonly results in wound problems as compared to the lateral approach used in arthrodesis. The skin anterior to the ankle joint is thinner and has less subcutaneous fat than the skin along lateral aspect of the ankle where the incision is made for arthrodesis. Compounding these physiological differences in incision sites, the lateral approach used for arthrodesis is a common technique in US surgical practice, whereas the anterior approach was not frequently used prior to the advent of total ankle arthroplasty devices. Accordingly, techniques initially employed by US surgeons followed those developed in Europe for the STAR Ankle. However, as ankle arthroplasty techniques are now routinely incorporated into US Orthopedic Surgery training programs, familiarity of US surgeons with the anterior approach may be reasonably expected to expand considerably in the near future.

Major complications involving wound problems occurred in 5 patients (3.2%) in the STAR group. In investigator meetings that occurred at least biannually, surgeons participating in the STAR pivotal study discussed the wound problem issue and together formulated the following procedural changes, all of which were informally in place by the commencement of the continued access study:

- Extension of the incision line.
- Elimination of the use of self-retaining retractors in favor of hand retraction.
- Elimination of the use of skin staples in favor of two-layer (superficial and deep) suture closure.

Together, the initiation of these trauma-minimizing techniques decreased the incidence of major complications involving wound problems in the continued access study.

Major complications involving bone problems related to post-operative fractures were seen in 5.1% of STAR patients as opposed to none in the Arthrodesis patients. As with the major complications involving wound problems, recognition of the fracture issue during the pivotal trial lead to a number of modifications of surgical technique and patient instructions to prevent fractures:

- Intra-operative use of K-wires in at-risk patients.
- General downsizing of STAR talar components.
- Addition of tibial saw containment guides.
- Addition of talar component trials and talar tamp (where these instruments assist in properly seating the STAR Ankle, which serves to mitigate stress at the bone-device interface that may result in fracture).
- Addition of a medial/lateral adjustable guide block.
- Increased emphasis on patient instructions regarding weight-bearing and activities that induce high stress forces.

The effect of this multi-faceted approach to major complications involving fractures lead to a substantial decrease in the rate of these major complications in the continued access study.

Other bone issues such as osteolysis, cyst formation, and heterotopic bone formation comprise the remainder of bone problems that resulted in major complications in STAR Ankle patients. Osteolysis and cyst formation are often the result of wear debris, sub-optimal device placement, or device loosening. Heterotopic bone formation, or the development

of osseous outgrowths from or around an operated site, is also a known complication of total joint replacement. As with the previously described major complications, a number of modifications were made to the STAR Ankle placement technique to minimize these major complications.

Overall, the major complication rate seen with the STAR Ankle is relatively low and consistent with complications expected for arthroplasty in general and ankle arthroplasty in particular. In addition, there is a consistent pattern of STAR investigators recognizing the potential causes of major complications identified in the pivotal study and adapting the original surgical technique taken from the European experience into more refined techniques with a much lower rate of major complications.

Apart from these considerations, it is important to recognize that a STAR Ankle patient with a major complication requiring revision of the arthroplasty has options that an Arthrodesis patient does not. A STAR Ankle may be revised with a further arthroplasy, or arthrodesis may be performed. Should an arthrodesis fail, the only option is a revision of that failed fusion. Furthermore, during all times that the STAR Ankle is in place, the patient can enjoy the benefits of arthroplasty, including an increased ROM and the more normal ambulation that motion provides, while not producing stresses that may lead to degenerative joint disease at adjacent joints.

3.8.6. Fusion Data Summary for Arthodesis Patients

Table 44 outlines fusion data for Arthrodesis patients. The substantial majority of patients achieved union in a timely fashion with only a small percentage of patients experiencing malunion or nonunion.

Table 44. 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%)

Notably, the guidance provided by the sponsor to its clinical investigators specified that fusion should occur within 12 weeks of treatment. Delayed union was defined as fusion that occurred between 12 weeks and 6 months following treatment, and was considered a radiographic failure. The investigators themselves were responsible for this assessment of the Arthrodesis patients. However, upon further review of the safety success data as requested by the FDA, the company has identified that a substantial number of control patients that were incorrectly classified as safety successes and should have been considered safety failures based on the company's definition of fusion.

Specifically, the radiographic success of the control group was 90.8% (59/65) based upon the investigators' classification. Although most arthrodesis patients eventually did go onto fusion, when utilizing the time to fusion and classifying fusion as occurring no later than 12 weeks following surgery as specified in the protocol, this rate is substantially lower at 53.8% (35/65). This adjusted success rate is further supported by the fact that only 46% (29/63) of the Arthrodesis patients were allowed to be 100% weight bearing after the 3 month visit, meaning that the remaining patients were in casts and thus not completely fused. Accordingly, a more accurate assessment of the radiographic success rate for the control group is much more comparable to the figures seen for the STAR Ankle.

3.8.7. Radiographic Data for STAR Patients

Table 45 summarizes radiographic data for STAR patients at 6, 12, and 24 months. There is a relatively low rate of failure, 3.4% at 6 months, 6.0% at 12 months, and 9.3% at 24 months from available radiographic data. Notably, there may not be complete correlation between the imaging findings constituting radiographic failure and actual patient clinical failure.

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Table 46. Pivotal Study STAR X-ray Data Summary

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*	Radiolucencies for Tibal Component*	Radiolucencies 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	145 (98%)	144 (97.3%)	148 (100%)	148 (100%)	145 (98%)	141 (95.3%)	36 (24.5%)	80 (54.8%)	144 (98%)	146 (100%)	143 (97.3%)	145 (98.6%)	5 (3.4%)	5
0-4 mm	1 (0.7%)	2 (1.4%)			1 (0.7%)	5 (3.4%)	111 (75.5%)	66 (45.2%)	3 (2%)		4 (2.7%)	2 (1.4%)		
> 4mm	2 (1.4%)	2 (1.4%)			2 (1.4%)	2 (1.4%)								
Missing							1	2	1	2	1	1		
12 Months														
None	132 (98.5%)	123 (91.8%)	134 (100%)	134 (100%)	132 (98.5%)	123 (91.8%)	38 (28.6%)	85 (64.4%)	132 (99.2%)	133 (100%)	120 (90.2%)	132 (99.2%)	6 (6.0%)	11
0-4 mm	1 (0.7%)	8 (6%)			1 (0.7%)	9 (6.7%)	94 (70.7%)	46 (34.8%)	1 (0.8%)		13 (9.8%)	1 (0.8%)		
> 4mm	1 (0.7%)	3 (2.2%)			1 (0.7%)	2 (1.5%)	1 (0.8%)	1 (0.8%)						
Missing							1	2	1	1	1	1		
24 Months														
None	137 (97.9%)	121 (86.4%)	139 (99.3%)	137 (99.3%)	134 (95.7%)	124 (88.6%)	71 (50.4%)	129 (91.5%)	136 (96.5%)	139 (98.6%)	129 (91.5%)	140 (100%)	13 (9.3%)	21
0-4 mm	1 (0.7%)	13 (9.3%)			4 (2.9%)	7 (5%)	68 (48.2%)	12 (8.5%)	5 (3.5%)	2 (1.4%)	12 (8.5%)			
> 4mm	2 (1.4%)	6 (4.3%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	9 (6.4%)	2 (1.4%)							
Missing	1	1	1	3	1	1						1		

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

**Percents are not given for cumulative failures since some patients have not yet reached all follow-up visits or the patient's x-rays have not been evaluated.

Data and percents based on all available data.

3.8.8. Meta-Analysis Results

As previously discussed, it was anticipated that it would be difficult to enroll patients in the control arm of the IDE study because of the disadvantages of ankle fusion (including permanent loss of ankle mobility and function, as well as degeneration of surrounding joints), the availability of an FDA-cleared ankle prosthesis and the reluctance of patients and physicians to comply with extensive clinical trial requirements given the standard nature of this procedure. Therefore, Link performed a meta-analysis of the published arthrodesis literature using established analysis methodologies to supplement pivotal study arthrodesis safety data.

Meta-analysis articles were selected on the basis of patient populations similar to the pivotal study, with similar pre-operative ankle diagnoses necessitating surgery (primary arthritis, posttraumatic arthritis, or rheumatoid arthritis). Operative techniques also were similar to those used in the pivotal study control group. However, most of the literature articles were not based on controlled, randomized trials. Since these studies were not designed to assess the specific multiple components of the safety endpoint of the STAR pivotal trial, the literature studies were most diligent in recording rates of nonunion, delayed union, malunion, but likely underreported other major complications. Additionally, the articles largely reported rates for individual complications separately, without specifying which patients experienced particular or multiple complications. Therefore, it was not possible to determine the actual number of patients who met the pivotal study definition of safety success.[20] The rates of individual events are compared to those rates observed in the pivotal study safety results in **Table 46** however, since composite rates of events were generally not reported for the historical control, these rates are not provided in the table.

Overall, the historical complication rates for Arthrodesis were comparable to the rates observed for Arthrodesis patients and STAR Ankle patients in the STAR pivotal study. The historical revision rate of 11.9% is higher than the 7.6% revision rate among the pivotal study Arthrodesis patients and comparable to the 12.7% revision rate among the pivotal study STAR Ankle patients. Surgical interventions due to infection, delayed wound healing, post-operative fracture of adjacent bones, or bony changes occurred in 2.2% of meta-analysis patients, comparable to the 1.5% rate seen in the Arthrodesis study patients while the pivotal study STAR Ankle patients' rate was higher at 10.1%. However, non-union, delayed union, or malunion was observed in 11.6% of patients in the meta-analysis and 11.5% of Arthrodesis patients in the pivotal study. Again, it should be noted that the historical control rate of major complications

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[20] To meet the pivotal study definition of safety success, an individual arthrodesis control patient must satisfy all of the following requirements: no device failure, revision, or removal; no radiographic evidence for non-union, delayed union, or malunion; and no major complications (no significant infection requiring surgical intervention or antibiotics; no significant delayed wound healing, wound dehiscence, or skin necrosis requiring surgical intervention; no significant post-operative fractures of adjacent bones (not caused by trauma) requiring surgical intervention; and no significant bony changes of adjacent bones (cysts, osteolysis, AVN) requiring surgical intervention (including debridement or bone grafting)).

may be underestimated for the reasons previous described and, thus, the above described 2.2% rate of surgical interventions for the historical control may have been an underestimate and the difference in the true surgical intervention rates may be smaller than what this comparison suggests. In addition, modifications to the use of instruments, surgical technique and patient instructions undertaken during the course of the pivotal study have lowered the overall rate of all surgical interventions in the continued access study.

Table 46. Meta Analysis Results

	Historical Control	Pivotal Study	
		Arthrodesis	STAR Ankle
Number of cases (n)	413	66	158
Surgical interventions due to infection, delayed wound healing, post-op fracture of adjacent bones, or bony changes	9 (2.2%)	1 (1.5%)	16 (10.1%)
Radiographic evidence for nonunion, delayed union, or malunion	48 (11.6%)	6 (11.5%)*	-
Device failure, revision, or removal	49 (11.9%)	5 (7.6%)	20 (12.7%)
Failures	-	9**	41**
%	-	17.3%	28.9%

**24 Month failure data available on 52 arthrodesis patients and 142 STAR Ankle patients. Includes the STAR patients failing based on x-ray. Failure rate was not calculated for the historical control based on the lack of composite event rate information.
* Based on 52 patients evaluated at 24 months.

Considering all these factors, this meta-analysis indicates that safety of the results observed in the pivotal study is representative of the historical controls. Importantly, the meta-analysis also indicates that the safety of the STAR Ankle is comparable not only to the safety of arthrodesis as observed in the pivotal study arm but also as observed in the historical control. In considering these results, it is also important to note that the safety results observed for STAR patients in the pivotal study represent a period in which the technique and procedures surrounding STAR Ankle placement were refined.

3.9. Conclusion for Pivotal Study

The valid scientific evidence presented demonstrates that the STAR Ankle is safe and effective in the treatment of ankle arthritis that has failed 6 months of conservative therapy. In all efficacy parameters measured, the STAR Ankle demonstrated either superiority or no statistically significant difference as compared to ankle arthrodesis. The STAR Ankle demonstrates superior total BP score at 12 and 24 months as compared to Arthrodesis, with a significantly higher percentage of STAR patients experiencing a $\geq$ 40 point increase in baseline BP score as compared to Arthrodesis.

Based on the original radiographic success criteria, the STAR Ankle demonstrates somewhat lower safety success rates at 12 and 24 months as compared to Arthrodesis patients in the pivotal study. However, when using the revised more clinically appropriate radiographic success analysis adjusting the STAR radiographic outcomes, the STAR radiographic success rate

is substantially higher than that of the control group. Accordingly, the safety success rate is also substantially similar to that of the control group. The lower bound of the confidence interval of the difference in the safety success rate is less than the pre-specified delta for the safety endpoint. Therefore, non-inferiority of the STAR ankle to the control group with respect to safety has been demonstrated.

Moreover, there is reason to believe that the fusion rates in the control group reported by the study investigators were overly optimistic, given clinical data that is available for these patients. If the company were to adjust the Arthrodesis fusion success rates based on this information and correspondingly lower the Arthrodesis safety success rate, the STAR Ankle would compare even more favorably to Arthrodesis.

Given all of these considerations, it is clear that the STAR Ankle meets the safety delta for the pivotal study. It is thus non-inferior to arthrodesis in terms of both efficacy and safety.

4. Bilateral Study Results

4.1. Enrollment and Accountability

Patient enrollment in the bilateral study began with FDA approval of the bilateral arm IDE on April 6, 2001. A total of 21 patients were approved to be included in this arm. As of database closure, data were available on a total of 16 of the 21 patients enrolled in the bilateral study, representing a total of 27 ankles implanted. All bilateral patients received the same investigational STAR Ankle arthroplasty device as the unilateral patients. **Table 1** summarizes enrollment data of these 16 patients.

Table 1. Patient Summary

	Patients	Ankles
Initial Bilateral Patients	9	15
Transfer from Continued Access Arm*	2	3
Transfer from Pivotal Arm*	5	9
Total	16	27

*Patients were initially enrolled in these studies but transferred to the bilateral arm due to receiving a STAR implant on their contralateral ankle.

Based on ankles and patients with data entered into the database as of 4/15/05

Table 2 provides visit accountability for patients in the bilateral arm. Based on the most current data, 12-month data has been collected on 72% (18/25 ankles) of the bilateral patients. Due to the later enrollment of many of the bilateral patients, data are currently available on 50% (12/24 ankles) of the bilateral patients at 24 months.

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Table 2. Patient Accountability by Visit*

	Pre-Op	2 Weeks	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical	37	37	36	35	32	29	29
Deaths (cumulative)						1	2
Failures[1] (cumulative)							
Not Yet Overdue	0	1	0	2	1	3	3
Expected	37	36	36	33	31	25	24
Actual[2]	27	26	26	22	23	18	12
Physical Exam	27	26	26	22	23	18	12
% Follow-up (based on Actual[2])	73%	72%	72%	67%	74%	72%	50%

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

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

* Numbers in this table represent the number of ankles treated at the time of database closure.

Two (2) patient deaths occurred by 24 months post second ankle implant. Neither of these deaths were believed to be device-related and are more fully described below.

No major protocol deviations occurred in the bilateral study.

All 16 patients and 27 ankles for which data are available were included in the following descriptive statistics for the bilateral group.

4.2. Demographics and Baseline Characteristics

4.2.1. Baseline Demographics

As with the pivotal study, males and females were equally represented. Mean age of bilateral patients was approximately 62.6 years at the time of the first implant and 65.2 years at the time of the second implant, comparable to STAR Ankle patients in the pivotal study for the first implant and slightly older for the second, as would be expected. Similar to the pivotal study, Caucasians formed the substantial majority of patients treated. A mean BMI of 29.8 and mean patient weight of 193.5 lbs. were slightly higher in the bilateral portion of the study as compared to unilateral patients in the pivotal study.

4.2.2. Baseline Medical History

Bilateral patients differed from STAR patients in the clinical trial in a number of aspects. The percentages of bilateral patients with a primary diagnosis of both primary arthritis and rheumatoid arthritis were higher than in the pivotal study (46.7% of first and 54.5% of second bilateral ankles implanted had a diagnosis of primary arthritis versus 39.2% in the pivotal study; 40% of first and 45.5% of second bilateral ankles had a diagnosis of rheumatoid arthritis versus 12.7% in the pivotal study). There was a lower percentage of patients with posttraumatic arthritis in the bilateral study (13.3% of first and no second bilateral ankles implanted were secondary to posttraumatic arthritis, as compared 48.1% of pivotal study patients).

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Types of conservative therapy received prior to STAR Ankle implantation were similar between the bilateral and STAR pivotal study patients.

4.2.3. Baseline Physical Examination

Similar to patients receiving unilateral STAR Ankles, a high percentage of bilateral patients were evaluated to be in good or excellent general condition (86.6% of patients at the time of the first bilateral ankle implant and 100% at the time of the second ankle implant, compared to 89.9% in the pivotal arm). The percentage of patients with functional difficulties at baseline was comparable in the bilateral and unilateral patients, as were the rates of motor, sensory and neurological deficits with no such events observed at baseline among the bilateral study patients. There was a lower ability to bear full weight in bilateral patients at baseline (71.4% with the first bilateral ankle, 88.9% with the second, versus 95.6% of unilateral STAR patients in the pivotal trial), possibly due to the small sample size in the bilateral study or possibly representing the higher level of rheumatoid arthritis present in the bilateral group.

4.2.4. Prior Ankle Surgeries

A higher percentage of bilateral patients did not have surgery to the affected ankle prior to STAR Ankle placement as compared to unilateral STAR patients in the pivotal study (73.3% of first ankles and 81.8% of second ankles had no prior surgery in the bilateral group, as compared to 41.1% with no prior surgery in the affected ankle in the pivotal trial). This is thought to reflect the lower percentage of bilateral patients with a primary diagnosis of posttraumatic arthritis (as compared to the pivotal study), as such patients typically have a higher rate of surgical intervention than the other primary diagnoses.

4.3. Procedural Characteristics

4.3.1. Operative Characteristics

Operative characteristics are comparable between first and second STAR Ankle placements. Anesthesia time, operative time, and tourniquet time were all comparable to unilateral STAR patients in the pivotal study. Estimated blood loss was slightly higher for the first and second ankles placed in the bilateral groups with a mean of 80.6 cc and 59.5 cc in the first and second ankles, respectively, as compared to STAR patients in the pivotal study (mean of 53.1 cc). This difference in estimated blood loss is not considered to be clinically significant. The choice of anesthesia was also generally comparable to STAR patients in the pivotal trial. Length of stay was considerably shorter in the bilateral group as compared to the pivotal study (mean length of stay of 1.9 days for the first ankle and 1.7 days for the second, versus 3.1 days in the pivotal study). This shorter length of stay may reflect improved discharged planning for these patients, who were largely treated following completion of the pivotal trial.

4.3.2. Procedural Related Information

No operative difficulties were encountered in the bilateral group. The rates of ligament repair, ligament release, and concomitant procedures were comparable to those seen in the pivotal study.

4.4. Efficacy Results

The implantation of two devices in any patient significantly compounds the difficulty of making any assessment as to the effectiveness of the STAR Ankle in bilateral patients. Accordingly, only safety endpoints were formally evaluated in the bilateral study.

4.5. Safety Results

4.5.1. All Adverse Events

Table 3 provides a listing of all observed adverse events. The most frequently seen adverse events in the bilateral study, such as pain, bone fracture, nerve injury, and wound problems, were similar to those adverse events seen in the pivotal trial. No new types of adverse events were observed in the bilateral study, with adverse events in this study clustered in the immediate post-operative period.

Table 3. Bilateral Adverse Events

	Number of Events	Number of Ankles (N=27)		Number of Patients (N=16)	
Adverse Event	n	n	%	n	%
Cardiovascular	2	2	7.40%	2	12.50%
bone fracture	5	5	18.50%	5	31.30%
bony changes	1	1	3.70%	1	6.30%
device subsidence	2	2	7.40%	2	12.50%
general	4	4	14.80%	4	25.00%
impingement	1	1	3.70%	1	6.30%
infection	2	2	7.40%	2	12.50%
infection - other	1	1	3.70%	1	6.30%
musculoskeletal	5	4	14.80%	3	18.80%
nerve injury	3	3	11.10%	3	18.80%
pain	6	6	22.20%	6	37.50%
pain - other	10	7	25.90%	7	43.80%
skin	1	1	3.70%	1	6.30%
soft tissue edema	1	1	3.70%	1	6.30%
urologic	1	1	3.70%	1	6.30%
wound problem	1	1	3.70%	1	6.30%
wound problems	3	3	11.10%	3	18.80%

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4.5.2. Deaths

Two (2) patients expired during the course of the bilateral study. One patient expired from complications related to a stroke that occurred at approximately 15 months following the second ankle surgery. A second patient expired approximately 1 year after implantation of the second STAR Ankle from a cardiac arrest and had a baseline history of hypertension. Neither of these deaths were considered to be related to either the STAR Ankle or surgery to implant the device.

4.5.3. Surgical Interventions

Table 4 summarizes the three surgical interventions performed during the course of the bilateral study. All three surgical interventions (component removal, fusion of an adjacent joint, and excision of an exostosis) were among the most frequently encountered interventions seen in the pivotal study. There was nothing in the bilateral surgical intervention data to suggest a new or increased risk as compared to patients receiving the STAR Ankle on a unilateral basis in the pivotal study.

Table 4. Surgical Interventions - Summary of Interventions

	STAR (N=3)
Time of Intervention after Initial Surgery (weeks)	
N	3
Mean (SD)	70.7 (87.8)
Median	39
Range	3 - 170
Intervention Classification	
Minor Operative Site Procedures	
Excision Exostosis	1
Major Operative Site Procedures	
Component removal	1
Fusion, adjacent joint	1

4.5.4. Major Complications

No major complications occurred in the bilateral study.

4.6. Conclusion for Bilateral Study

Data from the bilateral study suggest that there is no increased safety risk when the STAR Ankle is implanted bilaterally in patients who require treatment of ankle arthritis and who have failed 6 months of conservative therapy.

5. Continued Access Study Results

5.1. Enrollment and Accountability

A total of 448 patients received STAR Ankle devices during the continued access study. All continued access patients were treated at the same 10 clinical centers participating in the STAR Ankle arm of the pivotal study. **Table 1** summarizes enrollment of patients by site.

Table 1. Number of Patients Treated by Clinical Site

SITE	n
Mayo Clinic, Jacksonville (MAYO)	73
Dr. Roger Mann, Inc (MANN)	63
Duke U Med Ctr (DUMC)	58
Baylor Res Inst (BRI)	43
U of Texas Med Sch (UTMS)	39
Florida Ortho Inst (FOI)	38
Kansas U Med Ctr (KUMC)	48
U of Iowa, Ortho Surg (IOWA)	35
Ortho Foot & Ankle Ctr (OFAC)	33
Foot & Ankle, Inc (F&A)	18
	448

Table 2 summarizes patient accountability for the continued access study across the various study visits. Patient follow-up was approximately 84% through 12 months and approximately 66% through 24 months, noting that the continued access study did not begin until enrollment in the STAR arm of the pivotal study was complete. Notably, more patients in the continued access study now have 2 years of follow-up (211) than the total number of STAR patients enrolled in the pivotal study (158). Thus, the continued access study provides considerable additional information concerning the safety and effectiveness of the STAR Ankle.

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Table 2. Patient Accountability by Visit

	Pre-Op	6 Weeks	6 Months	12 Months	24 Months
Theoretical	448	447	441	432	355
Deaths (cumulative)			1	2	3
Failures[1] (cumulative)					
Transferred to Bilateral Arm (cumulative)	0	0	0	2	3
Not Yet Overdue	0	0	4	4	29
Expected	448	447	436	424	320
Actual[2,3]	424	410	387	355	211
Actual Total BP	424		377	345	204
Actual ROM BP	424		381	354	209
Actual Function BP	424		381	248	209
Actual AOFAS	398		369	344	203
Actual VAS	413		376	350	208
Actual Coughlin			379	351	210
Actual SF-36 PCS	394		357	322	193
Actual SF-36 MCS	391		343	318	191
X-ray Taken	424	410	392	360	215
Physical Exam	424	415	387	355	211
% Follow-up (based on Actual[2])	95%	92%	89%	84%	66%

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

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

[3] "All Data Available" as requested in the FDA Guidance "Points to Consider for Clinical Data Presentations for Orthopedic Device Applications" is presented in Table 4 in relation to primary endpoint analysis.

Three (3) patients in the continued access study received a second STAR device in their contralateral ankle and were transferred to the bilateral arm of the STAR clinical study. Data from these 3 patients before the time of the second ankle implant is presented in this section. Three (3) patients expired during the course of the study. None of these deaths were considered device-related.

Independent Radiographic Review

Following the submission of the original PMA in December 2005, FDA raised a question regarding the independent radiographic review for continued access patients. The company performed such an independent review on the patients enrolled in the first continued access study who had reported data in the PMA database and for whom images were readily available from the sites. Accountability for these continued access patients for whom independent radiographic review is available is provided in **Table 2a** below.

Table 2a: First Continued Access Study X-ray Accountability

Visit	Number of Patients with Visit in PMA	Number of Patients with X-ray Review
6 Months	144	118
12 Months	141*	111
24 Months	123*	84

*Includes one patient who did not have a 12-month visit but had X-ray data available and 2 patients who did not have a 24-month visit but had X-ray data available.

5.2. Study Administration Issues

5.2.1. Deviations from Eligibility Criteria

Major deviations from the eligibility criteria observed in the continued access study were similar to those observed in the pivotal study. These deviations included BP score ≥ 60, weight of over 265 lbs, and poor bone stock (osteoporosis or poor bone stock). Other eligibility deviations not seen in the continued access study involved the conservative care inclusion criteria. A total of 7 patients are considered to have a major protocol deviations based on the above eligibility deviations.

5.2.2. Other Study Administration Issues

Other study administration issues included incomplete evaluations and the use of bone growth stimulators. Four (4) patients are considered to have a major protocol deviation based on these other protocol deviations.

5.3. Analysis Populations

As in the pivotal study results section, all tables and analyses were performed on the "Completers" patient population, which included subjects with the necessary data to determine safety and efficacy at the 24 month time point. The ITT patient population includes all patients who enrolled in the study, including Completers and Non-Completers. Additional analyses were conducted on the efficacy, safety and patient success rates based on the Per Protocol patient population. The Per Protocol population consisted of Completers who had no major protocol deviations, and no arthrodesis or arthroplasty of the contralateral ankle either before or after study treatment.

Three (3) patients were transferred to the bilateral study due to a second procedure being performed in the contralateral ankle. These patients remained in the Per Protocol safety and efficacy analysis for the unilateral arm until the placement of the contralateral STAR Ankle. Following placement of the contralateral ankle, these patients were removed from both the safety and efficacy analysis for the continued access patients and analyzed with the bilateral patients.

Efficacy success analysis at 12 months included 344 Completers and 333 patients in the Per Protocol analysis, with corresponding figures of 206 and 194 patients, respectively, at 24 months. At 12 months, there were 360 Completers available for analysis and 348 patients available for the Per Protocol safety analysis, with 225 and 212 patients available for each analysis group, respectively, at 24 months. At 12 months, 349 Completers were available for patient success endpoint analysis, with 338 STAR patients available for the Per Protocol analysis. Corresponding figures at 24 months were 222 and 210 patients, respectively.

5.4. Demographics and Baseline Characteristics

5.4.1. Baseline Demographics

Baseline demographics of continued access patients are summarized in **Table 3**. Patient demographics for the continued access studies were largely comparable to those of STAR Ankle patients in the pivotal trial.

Table 3. Baseline Demographics

Characteristics	n (%)
Gender	
Male	172 (40.6%)
Female	252 (59.4%)
Race	
.	1
Caucasian	407 (96.2%)
Hispanic	6 (1.4%)
African American	7 (1.7%)
Other	3 (0.7%)
History of smoking	
.	4
No	241 (57.4%)
Yes	179 (42.6%)
Current smoking status	
.	136
No	187 (64.9%)
Yes	31 (10.8%)
N/A	70 (24.3%)
	424 (100%)
	Mean ±SD (N=424)
Age	62.92 ±11.57
Height (inches)	66.76 ±3.89
Weight (lbs)	180.7 ±35.3
Body Mass Index	28.44 ±4.89

5.4.2. Other Baseline Characteristics

Table 4 shows the distribution of primary diagnoses among the continued access patients. There was a higher percentage of post-traumatic arthritis in the continued access study as compared to the pivotal study (62.3% versus 48.1%) and a lower percentage of primary

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arthritis (21.0% versus 39.2%). A substantial percentage of patients with a primary diagnosis of a metabolic disorder (9.9%) were treated in the continued access, while no such patients were treated in the pivotal study since the study eligibility criteria was not expanded to include such patients until the continued access study.

Table 4. Primary Diagnosis

Primary diagnosis	n (%)
.	29
Primary arthrosis	83 (21.0%)
Post traumatic arthrosis	246 (62.3%)
Rheumatoid arthrosis	27 (6.8%)
Metabolic disorder	39 (9.9%)
	424 (100%)

The respective percentage of right and left ankles treated in the continued access study was comparable to that of the STAR patients in the pivotal study. While there were similar percentages of patients in both studies receiving conservative treatment, there were some differences as to the type of conservative therapy utilized.

Disease history by body system is comparable between patients in the pivotal and continued access studies. Baseline work status was also comparable to those of STAR Ankle patients in the pivotal study.

Overall, baseline physical exam data was comparable to STAR Ankle patients in the pivotal study. An exception was the percentage of patients with functional difficulties, which was higher in the continued access study, indicating a poorer baseline functional condition for these patients.

Table 5 summarizes baseline BP score in continued access study patients. Total BP score is comparable between continued access patients and STAR patients in the pivotal trial. However, the percentage of patients with "significant" or "moderate" deformity (12.2%) was much lower than that seen with STAR Ankle patients in the pivotal study (41.8%). As baseline deformity may impact a surgeon's ability to correctly align the ankle at the time of surgery and ultimate patient outcome, the lower degree of deformity seen with continued access patients may explain the improved outcome of these patients as compared to STAR patients in the pivotal study. It should be noted that prior to the initiation of the continued access study, investigators were cautioned that patients with a coronal deformity could be expected to do less well. The remainder of the BP score subscales were comparable to those of the STAR patients in the pivotal study.

Table 5. Baseline Buechel-Pappas

Deformity score	n (%)
Significant	12 (2.8%)
Moderate	40 (9.4%)
Mild	105 (24.8%)
Slight	149 (35.1%)
None	118 (27.8%)
Function	
Disabled	21 (5.0%)
Severe	171 (40.3%)
Moderate	220 (51.9%)
Mild	12 (2.8%)
Pain	
Totally disabled	37 (8.7%)
Severe	377 (88.9%)
Moderate	10 (2.4%)
ROM	
Dorsiflexion 15 - Plantarflexion 45	21 (5.0%)
Dorsiflexion 5 - Plantarflexion 30	59 (13.9%)
Combined Motion 25 to 34	91 (21.5%)
Combined Motion 15 to 24	124 (29.3%)
Combined Motion 5 to 14	108 (25.5%)
Combined Motion Less Than 5	21 (5.0%)

Mean baseline VAS was slightly higher than that of STAR patients in the pivotal study (mean of 76.6 versus 71.1). As with baseline physical examination and BP scores, these pain VAS values are consistent with a somewhat more debilitated population as compared to patients receiving the STAR Ankle in the pivotal study.

Both SF-36 total mental score and total physical score are comparable to baseline values seen in STAR Ankle patients in the pivotal study.

The rate of patients who had undergone prior surgery at baseline was comparable between groups, with a similar distribution of the types of surgical procedures performed.

Tibial-talar joint narrowing, major degenerative changes and evidence of adjacent joint fusion are comparable between the continued access study and STAR patients in the pivotal study.

5.5. Procedural Characteristics

5.5.1. Operative Data

Table 6 summarizes the operative characteristics of patients in the continued access study. These characteristics are largely comparable to those of the pivotal study, although there was a slightly shorter length of stay in the continued access study (mean of 2.8 days versus 3.1 days in the pivotal study).

Table 6. Operative Data

Type of anesthesia	n (%)
.	5
Local	121 (28.9%)
General	69 (16.5%)
Both	229 (54.7%)

Operative data	N	Mean ±SD
Tourniquet time (hours)	417	1.99 ±0.49
Surgery time (hours)	422	2.34 ±0.65
Anesthesia time (hours)	404	3.17 ±0.81
Estimated blood loss (c.c.)	421	52.96 ±64
Length of stay (days)	420	2.8 ±1.14

5.5.2. Procedure Related Information

Operative difficulties occurred less frequently in the continued access group as compared to STAR patients in the pivotal study (5.0% versus 10.1%), possibly changes to the procedural technique instituted in the course of the pivotal study. However, ligament repair was more frequently performed in the continued access study, possibly reflecting the more debilitated nature of these patients' ankles. Ligament release and the rate of concomitant procedures are comparable to those seen in patients receiving the STAR Ankle in the pivotal study.

Sizes of the tibial, talar and meniscal components were generally smaller in the continued access study as compared to the pivotal study. This was the result of a conscious decision to select the smallest appropriate components, in part to decrease the risk of fracture.

5.5.3. Adverse Events Occurring Pre-Discharge

Table 7 summarizes adverse events occurring pre-discharge. Operative site adverse events were lower in the continued access study (14.2% as compared to 26.6% of STAR Ankle patients in the pivotal study). Notably, the rate of intra-operative fracture in the continued access study was approximately half that seen in the pivotal study (5.0% versus 9.5%), almost certainly a result of the modified surgical technique that was adopted when the intra-operative fracture issue was recognized during the course of the pivotal trial. The use of smaller components may also have contributed to this improvement. Events beyond the operative site were comparable in both the continued access and pivotal studies.

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Table 7. Adverse Events Occurring Pre-Discharge

	STAR
Operative Site Events	
anesthesia	2 (0.5%)
bone fracture	21 (5.0%)
device migration	1 (0.2%)
nerve injury	29 (6.8%)
pain	11 (2.6%)
soft tissue edema	1 (0.2%)
tendon problem	1 (0.2%)
Any Operative Site Event	60 (14.2%)

*Percentages based on 424 patients with data available at the time of database closure

5.6. Success Rates

Table 8 summarizes patient, efficacy and safety success rates at 12 and 24 months. In general, these various success rates in the continued access study were even higher than the STAR success rates observed in the pivotal study at both time points. In evaluating these data, please note that while efficacy success criteria are identical to those applied to pivotal study patients, the criteria used for safety success and patient success were somewhat different. Specifically, independent radiographic data were not available for all continued access patients and were not evaluated where unavailable although all investigators did review radiographs for signs of failure during each study visit. Accordingly, the comparisons described for both safety success and patient success are not direct comparisons.

Table 8. Success Rates at 12 and 24 months

	n	N	%
12 month patient success rate			
Completers	245	349	70.2
Per protocol	237	338	70.1
12 month efficacy success rate			
Completers	253	344	73.6
Per protocol	245	333	73.6
12 month safety success rate			
Completers	338	360	93.9
Per protocol	327	348	94.0
24 month patient success rate			
Completers	148	222	66.7
Per protocol	142	210	67.6
24 month efficacy success rate			
Completers	156	206	75.7
Per protocol	148	194	76.3
24 month safety success rate			
Completers	196	225	87.1
Per protocol	186	212	87.7

Following the submission of the original PMA in December 2005, the company performed such a radiographic review on the patients for the first arm of the continued access

study who had reported data in the PMA database. Of the 150 patients in this arm there were 120 patients who had a 24 month follow-up visit reported in the PMA database. The independent radiographic review was performed on those patients in whom radiographic films were then available from the sites. Therefore, the independent radiographic review was performed on 85 of the patients with 24-month data.

In an attempt to compare the composite safety profile between the pivotal and continued access studies, we compared the composite safety success rate between the control patients and the subset of continued access patients who had independent radiographic results. This permits a fair comparison of the two groups based on the same safety success criteria. The results are shown in **Table 8a**. Results based on both the initial and the clinically appropriate radiographic success analysis as described in **Section 3.6.2.2.** are presented.

Table 8a. Patient success rates for completers at 24 months, based on both initial PMA analysis and revised, clinically appropriate analysis for defining radiographic success for STAR Ankle

	Control	STAR	Difference in Success Rate (STAR-Control)	Lower Bound of 90% CI for Difference
Overall Patient Success				
a) Initial PMA analysis	7/51 (13.7%)	61/81 (75.3%)	61.6%	50.4%
b) Revised, clinically appropriate analysis	7/51 (13.7%)	62/81 (76.5%)	62.8%	51.7%
Efficacy Success	7/47 (14.9%)	70/83 (84.3%)	69.4%	58.7%
Safety Success				
a) Initial PMA analysis	43/52 (82.7%)	72/81 (88.9%)	6.2%	-4.2%
b) Revised, clinically appropriate analysis	43/52 (82.7%)	73/81 (90.1%)	7.4%	-2.8%
Components of Safety Endpoint				
No surgical intervention	47/52 (90.4%)	80/85 (94.1%)		
No major complication	51/52 (98.1%)	82/85 (96.5%)		
Fusion (union)	46/52 (88.5%)	N/A		
Success on X-ray				
a) Initial PMA analysis	N/A	76/80* (95.0%)		
b) Revised, clinically appropriate analysis	N/A	77/80* (96.3%)		

*80 of the 85 patients had complete radiographic results.

Additional analysis was performed to impute the safety success rate in the Completer population in the continued access study. For patients who did not have an independent radiographic evaluation, safety success rate was imputed using radiographic success rate observed in the pivotal study (the initial and the revised clinically appropriate radiographic success analysis).[21] [22]

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[21]Based on the initial analysis, the radiographic success rate in the pivotal study patients was 84.8%. In the continued access study, 145 patients did not have radiographic reviews (76+145*84.8%≈198).

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The difference in safety success rate also meets the safety delta as specified in the protocol. The results are shown in **Table 8b**.

Table 8b. Imputed safety results: Safety success for completers at 24 months, based on both the initial PMA analysis and the revised, clinically appropriate analysis for defining radiographic success for STAR Ankle

	Control	STAR	Difference in Success Rate (STAR-Control)	Lower Bound of 90% CI for Difference
Safety Success*				
a) Initial PMA analysis[1]	43/52 (82.7%)	176/225 (78.2%)	-4.5%	-14.2%
b) Revised, clinically appropriate analysis[2]	43/52 (82.7%)	189/225 (84.0%)	1.3%	-8.2%

*Rates for STAR patients were imputed.
[1]Based on the initial analysis, the safety success rate in the pivotal study patients who did not have any major complications or surgical interventions was 87.1%. Among the continued access patients who did not have radiographic reviews, 120 of them did not have any major complications or surgical interventions (72+120*87.1%≈176).
[2]Based on the revised analysis, the safety success rate in the pivotal study patients who did not have any major complications or surgical interventions was 97.4%. Among the continued access patients who did not have radiographic reviews, 120 of them did not have any major complications or surgical interventions (73+120*97.4%≈189).

It is important to note that the result of this analysis is likely to be conservative, providing an underestimate of the true safety success rate in the continued access study. This is so since the rates of surgical intervention and major complication decreased during the continued access study compared with the pivotal study as the result of improvement in surgical technique and instrumentations, it is reasonable to expect that the radiographic failure rate in the continued access study would also be reduced as was observed in the subset of patients with radiographic reviews; nevertheless, for purposes of this analysis the higher failure rate in the pivotal STAR group was used for imputation purposes.

5.6.1. Efficacy Success Rates at 12 and 24 Months

Efficacy success at 12 and 24 months in the continued access study was higher than comparable figures seen in the pivotal study (73.6% as compared to 60.8% at 12 months, and 76.3% as compared to 59.8% at 24 months based on a Per Protocol analysis with similar results for Completers). These differences likely reflect the refinements to the surgical technique used to place the STAR Ankle. These results reinforce the efficacy success rates seen in the pivotal study.

5.6.2. Safety Success Rates at 12 and 24 Months

As with efficacy success rates, safety success rates were higher in the continued access study in comparison with the pivotal data, although direct comparison of these rates is

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[22] Based on the revised analysis, the radiographic success rate in the pivotal study patients was 94.2%. In the continued access study, 145 patients did not have radiographic reviews (77+145*94.2%≈213).

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difficult for the reasons stated above. These differences likely reflect the modification to surgical technique and procedures. In any event, the continued access safety success data support the safety of the STAR Ankle as demonstrated in the pivotal study and by comparison to the meta-analysis.

5.6.3. Patient Success at 12 and 24 Months

Per protocol patient success at both 12 and 24 months were also higher than comparable figures for STAR patients in the pivotal study (direct comparisons are again difficult) reflecting high success rates for both safety and efficacy at both time points. These results confirm and reinforce the results of the pivotal trial, and suggest that the success rates for the STAR device improve with modifications to the surgical technique.

5.7. Additional Efficacy Results

5.7.1. Mean Total Buechel-Pappas Score at 12 and 24 Months

Table 9 provides mean total BP score at 12 and 24 months, as well as the change in score as compared to baseline at both time points. As with STAR patients in the pivotal study, mean BP score demonstrates substantial improvement at 12 and 24 months as compared to baseline. Improvement in the continued access study was slightly greater than that seen in the pivotal study (45.8 versus 39.7 in the pivotal study at 12 months, and 46.7 versus 40.5 at 24 months). These results further support those of the pivotal study.

Table 9. Mean Buechel-Pappas Score at 12 and 24 months

Variable	Visit	N	Mean ±SD
BP score	12 months	344	83.16 ±12.59
BP score	24 months	206	84.4 ±11.45
Change of BP score	12 months	344	45.79 ±13.97
Change of BP score	24 months	206	46.73 ±13.64

5.7.2. Buechel-Pappas ≥ 40 Point Improvement

At 12 and 24 months, a higher percentage of continued access patients enjoyed 40 or more points of improvement in their BP score as compared to STAR Ankle patients in the pivotal study (73.6% versus 58.7%, and 75.7% versus 58.5%, at 12 and 24 months, respectively). These results further confirm and reinforce the results of the pivotal trial by demonstrating that the rate of 40 point or greater total BP improvement noted in the pivotal study can be reproduced if not exceeded and that the STAR patients had significantly higher BP scores than was observed in the Arthrodesis arm of the pivotal study.

5.7.3. Buechel-Pappas Scores by Visit

By 6 months, 77.2% of patients had a good or excellent total BP score, further demonstrating the relatively quick improvements with STAR Ankle. Patients continued to

improve after 6 months with almost all (87.4%) patients having a good or excellent total BP score by 24 months. At 6, 12, and 24 months, the percentage of continued access patients with good or excellent total BP scores is also consistently higher than STAR Ankle patients in the pivotal study. Furthermore, substantial improvements are seen relatively quickly after implantation and remain consistently high through 24 months. These data reinforce the results seen in the pivotal study by further demonstrating superior effectiveness of the STAR Ankle in improving the total BP score compared with Arthrodesis.

5.7.4. Buechel-Pappas Scores without ROM Subscore

As with the pivotal study, an analysis requested by FDA was performed of the total BP score without the ROM subscale and the results are provided in **Table 10**. The mean BP score without the ROM subscale at 24 months was comparable between the continued access study and STAR patients in the pivotal study. This analysis further confirms that there is considerable efficacy seen with the STAR Ankle even with the ROM subscale contribution removed.

Table 10. Mean Buechel-Pappas Score without ROM at 12 and 24 months

Variable	Visit	N	Mean ±SD
BP score without ROM	12 months	344	70.63 ±11.95
BP score without ROM	24 months	205	72.17 ±10.8
Change of BP score without ROM	12 months	344	41.92 ±13.33
Change of BP score without ROM	24 months	205	41.92 ±12.84

5.7.5. Mean Pain VAS Scores by Visit

Pain VAS levels for patients in the continued access study were higher than for the pivotal study patients at baseline; however, patients showed a higher level of improvement that resulted in even lower pain levels at 6, 12 and 24 months. These results provide further support of the effectiveness of the STAR Ankle in decreasing pain levels.

5.7.6. Quality of Life (SF-36)

The SF-36 total physical and total mental scores were similar to those of STAR patients in the pivotal trial at baseline. However, for both the total physical and total mental scores, greater improvements were seen among the continued access patients who resulted in higher scores at each of the 6, 12 and 24 month follow-up visits. These results provide further support of the effectiveness of the STAR Ankle in improving the quality of life of patients.

5.7.7. AOFAS

AOFAS results demonstrate a dramatic improvement in mean total AOFAS score from baseline to 6 months (28.5 to 83.3). These positive results are maintained and improved

with time, with mean total AOFAS of 84.9 at 12 months and 86.5 at 24 months. These results confirm similar improvements in total AOFAS as seen with the total BP score.

Both BP and AOFAS scores dramatically improve from baseline to 6 months and continue to improve at both 12 and 24 months. In order to assess the comparability of the AOFAS and BP scores, the correlation between the two measurements was assessed. The total BP score was found to be significantly correlated with the total AOFAS score both at baseline and at 24 month follow-up. The Spearman's correlation coefficients were 0.40 and 0.74, respectively. The similar results seen with both evaluation instruments further validate the improvements found by the BP score which was used to evaluate primary efficacy in the pivotal trial.

5.7.8. Physical Examination

As previously noted, the baseline physical exam results for general condition, adequate ligament support, leg length discrepancy, motor deficit, neurological deficit, sensory deficit and use of a special shoe were similar to those seen among STAR patients in the pivotal study. While the percentage of patients having functional difficulties at baseline was higher among the continued access patients, the percentage dropped to a similar level as seen among STAR patients in the pivotal study for the 3, 6, 12 and 24 month visits with only 16% of continued access patients reported functional difficulties at 24 months.

5.7.9. Work Status

The percentage of continued access patients engaged in full-time employment rose slightly from baseline to 24 months post-procedure (29.4% at baseline to 33.2% at 24 months). This is likely due to the increase in patient age over the study period.

5.7.10. Patient Satisfaction (Coughlin Rating Scale)

At 12 months over 90% of patients indicated good or excellent satisfaction with the STAR Ankle with 92.8% of patients indicating good or excellent satisfaction with the STAR Ankle at 24 months.

5.7.11. Medication Usage

As with STAR patients in the clinical study, there was a reduction in the number of patients taking medications directly related to their ankle condition during the 12 months following surgery (90.3% at baseline compared with 55.8% at 12 months).

5.8. Additional Safety Results

5.8.1. All Adverse Events

Table 11 provides information on adverse events at the operative site over time. **Table 12** compares adverse events at up to 24 months in the continued access study to both the

STAR and Arthrodesis arms of the pivotal study. Notably, not all continued access patients had reached their 24 month follow-up as of the time of database closure. To allow comparison to the pivotal study data, the adverse event rate for the continued access study has been calculated in two ways. In the column with "N=424," the adverse events seen up to 24 months in the continued access study were divided by the total number of treated continued access patients and reported in the database. This analysis captures these important events for almost all continued access patients. As all continued access patients have not yet reached the 24 month follow-up, these rates may underestimate the true adverse event rate seen in the continued access study. The last column provides information on the continued access adverse event rate seen to date divided by the patients who have reached 24 months post-procedure. In considering these two estimates, it is also important to note that a number of adverse events, including those related to wound problems, infection, nerve damage, and fracture (both intra- and post-operative), are generally seen within 12 months of surgery and are thus likely represented in the estimate using the entire number of continued access patients.

Table 11. Operative Site Adverse Events Over Time • Event Basis

	OP	DC-6 weeks	6 weeks-3 months	3-6 months	6-12 months	12-24 months	24+ months	Total
	n	n	n	n	n	n	n	n
TYPE								
anesthesia	2	.	.	.	.	.	.	2
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

Table 12. Adverse Events up to 24 Months in Pivotal and Continued Access Studies

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	p-value (STAR vs. Control)	STAR Continued Access (N=424)	STAR Continued Access (N=352)*
bone fracture	2 (3.0%)	28 (17.7%)	0.002	42 (9.9%)	37 (10.5%)
intra-operative fracture	1 (1.5%)	15 (9.5%)	0.044	21 (5.0%)	21 (5.0%)
post-operative fracture	1 (1.5%)	14 (8.9%)	0.044	22 (5.2%)	19 (5.4%)
bony changes	0 (0%)	12 (7.6%)	0.02	15 (3.5%)	15 (4.3%)
pain	32 (48.5%)	69 (43.7%)	0.557	123 (29.0%)	115 (32.7%)
nerve injury	5 (7.6%)	32 (20.3%)	0.019	90 (21.2%)	75 (21.3%)
wound problem	4 (6.1%)	32 (20.3%)	0.009	76 (17.9%)	65 (18.5%)
surgical intervention	7 (10.6)	26 (16.5%)	0.26	31 (7.3%)	26 (7.4%)
revision or removal	6 (9.1%)	12 (7.6%)	0.707	13 (3.1%)	12 (3.4%)
other intervention	1 (1.5%)	18 (11.4%)	0.016	20 (4.7%)	15 (4.3%)
major complication	1 (1.5%)	14 (8.9%)	0.074	18 (4.2%)	17 (4.8%)
infection	1 (1.5%)	2 (1.3%)	1	3 (0.7%)	3 (0.8%)
bone problems	0 (0%)	8 (5.1%)	0.109	10 (2.4%)	10 (2.8%)
wound problems	1 (1.5%)	5 (3.2%)	0.673	6 (1.4%)	5 (1.4%)
wound problems and infections	0 (0%)	1 (0.6%)	1	0 (0%)	0 (0%)

*Analysis limited to patients who had surgery performed at least 24 months prior to database closure on 12/01/2006.

*Not all continued access patients had reached their 24 month follow-up as of the time of database closure on 12/1/2006. To allow comparison to the pivotal study data, the adverse event rate for the continued access study has been calculated in two ways. In the column with "N=424," the adverse events seen up to 24 months in the continued access study were divided by the total number of treated continued access patients and reported in the database. These rates may underestimate the true adverse event rate seen in the continued access study. The last column with "N=352," provides information on the continued access adverse event rate up to 24 months divided by the patients who have reached 24 months post-procedure, with the exception of intra-operative fracture.

Like STAR patients in the pivotal study, operative site adverse events encountered by continued access patients included pain, bone fracture, bony changes, nerve injury, infection, device subsidence, soft tissue edema, and wound problems. The rates of some of these adverse events were substantially lower in the continued access study than for STAR patients in the pivotal study. For example, the rate of intraoperative fractures was nearly cut in half between the pivotal and continued access study. The rates of all types of surgical interventions also decreased dramatically in the continued access study. Moreover, the rate of major complications was also substantially reduced in the continued access study. This lower rate of adverse events and surgical interventions is believed to represent the refinements to surgical technique and procedures. The lowered rate of adverse events confirms the overall safety of the STAR Ankle as seen in the pivotal study and demonstrates that substantial improvements in adverse event rates may be realized with relatively minor modifications to surgical technique and procedures. Given the nature of the anterior surgical procedure and approach generally, and due to the presence of a prosthesis, which permits continued flexibility of the ankle joint, certain adverse events such as wound problems and nerve injury remained relatively consistent in the continued access study compared to the pivotal study.

5.8.2. Deaths

Three (3) patients expired in the 24 months following the implantation procedure in the continued access study. One patient died of pancreatic cancer approximately 18 months following STAR Ankle surgery. Another patient expired from metastatic lung cancer about 8 months following surgery. The third patient expired from atherosclerotic coronary artery disease 3 months after STAR Ankle surgery. None of the 3 deaths is believed to be related to either the STAR Ankle or its surgical placement. One additional death after 24 months was due to a cardiac cause unrelated to the STAR Ankle.

5.8.3. Surgical Interventions

Surgical interventions in the continued access study occurred at a substantially lower rate than for STAR patients in the pivotal trial, with component revision the most common underlying reason for intervention in both groups. The lower rate of surgical intervention in the continued access study likely reflects the modifications and refinements to surgical techniques and procedures developed during the pivotal study.

Like the pivotal study, removal or replacement of the meniscal bearing were the most common interventions specific to the STAR device in the continued access study. The relative frequency of interventions other than the removal or replacement of the meniscal bearing were also comparable to those seen in the pivotal study.

A single patient [redacted] suffered a series of adverse events following STAR Ankle placement, including avascular necrosis of the talus and wound problems, and eventually underwent a below-the-knee amputation. This was the only instance of amputation during all STAR Ankle placements described in this PMA and was reported to FDA at the time of the event. As described at the time of that report, it is believed that the use of talar trials and the talar tamp will lower the risk of the reoccurrence of the undetected talar fracture that likely led to this adverse event.

5.8.4. Major Complications

Table 13 provides a listing of major complications. The definition used was identical to that used in the pivotal study.

Major complications in the continued access study occurred at a much lower rate than seen with STAR patients in the pivotal study. As with improvement in the rate of adverse events, this is believed to reflect the improvements in surgical methods and technique undertaken during the pivotal study.

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5.9. Conclusion for Continued Access Study

The continued access study provides confirmation of both the safety and efficacy data obtained in the pivotal study with regard to the STAR Ankle. Furthermore, given the prolonged nature of enrolled in the Arthrodesis arm of the pivotal study, the STAR clinical data gathered in the continued access study provides a reasonable and very favorable concurrent comparison to the Arthrodesis arm of the pivotal study.

With regard to efficacy, the continued access study confirms the pivotal study findings with regard to improvement in total BP score at 12 and 24 months, and the pivotal study findings with regard to the percentage of patients experiencing a $\geq$ 40 point increase in baseline BP score. The continued access study suggests that efficacy results with the STAR Ankle improve with refinement of surgical technique and methods.

The continued access study confirms the safety of the STAR Ankle as demonstrated in the pivotal study and provides no indication of adverse events other than those seen in the pivotal study. This study demonstrates that refinements to surgical technique and methods were successful in decreasing the rates of certain important adverse events and surgical interventions. It also confirms that the majority of adverse events experienced by STAR Ankle patients are minor and resolve without long-term clinical consequences.

6. Risk-Benefit Analysis

As with any surgical treatment for ankle joints with moderate or severe pain, loss of mobility, and loss of function due to primary arthritis, posttraumatic arthritis, or rheumatoid arthritis, there are risks associated with the STAR Ankle. In assessing the level of these risks, as well as the risks associated with Arthrodesis, it is important to focus on the clinical impact of any adverse events that contribute to those risks and to balance those risks against the real benefits that the STAR Ankle provides patients.

An appropriate measure of the clinical risks associated with the STAR Ankle and Arthrodesis are the prospectively defined safety success criteria used in the pivotal study. These criteria include: (i) no device failures, revisions, or removals; (ii) radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group); and (iii) no major complications.

While data from the pivotal clinical study suggests a somewhat higher rate of certain adverse events for the STAR Ankle, the majority of these adverse events were minor and resolved without long-term consequences for STAR patients. Moreover, the decreasing rate of adverse events in STAR patients seen from the pivotal study to the continued access study suggests that the adverse event rates decrease with the refinement of surgical technique, including the use of new and modified surgical instruments. These include the modification of the captured tibial saw alignment guide, and the addition of talar trials and a talar tamp. The risk of intra-operative fracture was mitigated by a change in surgical technique undertaken during the

pivotal trial when this fracture risk was identified, which involved the placement of two K-wires in the malleolus for the duration of surgery. In addition, the continued access study used smaller components to further reduce fracture risk. Furthermore, when assessing the significance of intra-operative fractures in the STAR group, it is important to note that a deliberate fracture or osteotomy is required for all patients undergoing an ankle arthrodesis. In fact, the safety success rates of the continued access group, in which these modifications were implemented, were non-inferior to the control group.

Following any ankle surgery, there are known adverse events which include bone fracture, bone changes, infection, nerve injury, pain, soft tissue edema, and wound problems. There may also be loosening, instability, or failure of any surgical hardware involved, whether those devices consist of surgical screws or a complex arthroplasty device such as the STAR Ankle. Additional surgery may be necessary to correct some of these problems. Results from the pivotal study demonstrate a somewhat higher rate of certain post-discharge adverse events in the STAR Ankle group as compared to Arthrodesis, likely reflecting the anterior surgical approach used with the STAR Ankle and the relative complexity of the device as compared to simple fusion.

Both ankle arthrodesis and arthroplasty with the STAR Ankle carry with them clinically comparable and acceptable risks. However, there are a number of important benefits of the STAR Ankle that outweigh these risks. Successful arthrodesis or arthroplasty using the STAR Ankle can both substantially reduce patient symptoms, particularly the ankle joint pain that can impact virtually any patient ambulatory activity. However, the STAR Ankle provides significant treatment advantages by preserving ankle joint motion.

A key advantage of the STAR's mobility is that it allows more normal patient ambulation, an attribute frequently cited by surgeons involved in the STAR studies. This permits STAR patients to climb hills and stairs without difficulty, activities that are considerably more difficult with the fused tibial-talar joint inherent in arthrodesis. Simply put, the STAR Ankle allows patients requiring surgical treatment of their ankle condition a considerably more normal life than is possible with arthrodesis.

The improved mobility afforded by the STAR Ankle has increasing benefits with passing time. It is well-established that arthrodesis increases the motion in the adjacent joints of the hindfoot, over time leading to arthritis and the pain that accompanies this degenerative change.[23] There is evidence that maintaining motion at the tibial-talar joint prevents this secondary hindfoot arthritis, giving patients a considerably better long-term result as compared to arthrodesis.[24] This decreased rate of secondary arthritis and the improved ability to ambulate are important to patients of all ages. In the rheumatoid patient with multiple joint involvement, preserving ankle mobility can make the difference between allowing some of those patients to

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[23] Coester LM, et al. Long-term results following ankle arthrodesis for post-traumatic arthrosis. *J Bone Joint Surg* 200; 83:219.

ambulate as opposed to being wheelchair bound. The patient with bilateral arthritis will be significantly more functional with ankle motion than with bilateral ankle fusions.

Both of these considerations are reflected in the higher overall patient success rates seen at both 12 and 24 months in comparison with arthrodesis in the pivotal trial. Similarly, STAR patients enjoyed significantly greater improvements in their total BP scores at 12 and 24 months as compared to Arthrodesis patients. Data from the continued access study reinforces the substantial improvement in total BP score seen in the pivotal study. These substantial clinical benefits clearly outweigh the risks to patients seen with the STAR Ankle, particularly given that these risks are clinically comparable to arthrodesis, a surgical therapy that offers considerably less patient benefit.

Beyond the clear benefits provided by the STAR Ankle, there is little clinical downside to surgical treatment of ankle joint disease with the STAR Ankle. The amount of bone resection necessary to place the STAR Ankle leaves sufficient bone in place to allow a patient who has failed therapy with a STAR Ankle to go on to arthrodesis, if needed. This means that the present standard of care, arthrodesis, is always an option for STAR Ankle patients.

7. Learning Curve Analysis

It is well accepted that surgical outcomes improve after an initial learning curve period of time. The effect of learning curve for the STAR Ankle was evaluated by comparing the rates of intra-operative fracture, major complications (wound/infection or bony changes), and surgical intervention in the pivotal study, the first 15 patients in the continued access study, and later continued access cases. Only patients with at least 24 months of follow-up were included in the analysis of the rate of surgical intervention or major complication.

As shown in **Table 17**, both the rate of intra-operative fracture and the rate of surgical revision/removal showed a downward trend in later patients. Specifically, following the first 15 patients, the rates of intra-operative fracture and surgical revisions/removals were significantly lower as compared to the pivotal study (9.5% vs. 3.7%; p=0.02 and 8.2% vs. 1.7%; p=0.005, respectively). The rate of major complications was also lower in the continued access study versus the pivotal study. While both wound problems and infections decreased, there was no corresponding steady decline between the initial 15 patients and later patients in the continued access study for major complications related to bony changes rather than wound problems or infection. This likely reflects that wound problems and infection may be affected by surgical technique and thus are subject to a learning curve. However, bony changes are often related to patient non-compliance with various activity restrictions and the individual's response to the implant materials, and are not impacted by the surgeon's learning curve.

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[24] Knecht SI, et al. The Agility total ankle: seven to sixteen year follow-up. *J Bone Joint Surg Am* 2004; 86-A(6):1161-71.

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Table 17. 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%)

With the increased awareness and training on the anterior surgical approach in US practice, the company believes that surgeons recently trained on the implantation of the STAR Ankle are likely to resemble the original STAR investigators towards the end of their learning curve. To evaluate this observation, the sponsor reviewed the results of the three investigator who were new to the STAR Ankle and treated their first STAR Ankle patients in the continued access study. The results for these investigators, as shown in **Table 18**, demonstrated that the rates of intra-operative fracture, major complication and surgical revision or removal were similar to rates seen for the experienced STAR investigators late in the continued access study.

For these three new investigators, there was only one intra-operative fracture and one surgical revision/removal, the latter involving replacement of the device STAR due to malalignment. Both adverse events occurred among the 12 patients treated by one of the three new investigators. The surgical revision/removal occurred in the first patient that investigator treated and the intra-operative fracture in the seventh patient. The other two investigators treated 5 and 9 patients, respectively, with no major complications.

These findings suggest that the modified STAR Ankle placement technique and instruments has largely eliminated the learning curve. Even in instances where surgeons did not have the benefit of this postgraduate training (as with the original STAR investigators), data from the pivotal and continued access studies suggest that the learning curve for the STAR Ankle could be as few as 15 patients. We expect the learning curve to be even smaller as most surgeons recently completing their residency and fellowship are now trained during their post-graduate education in the anterior surgical approach to the ankle.

Table 18. 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%)

8. Post Approval Study

The Sponsor proposes a post approval study and the primary objectives of this post-approval study are: (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.

The study will be a multi-center study consisting of two arms, one arm for assessment of long-term revisions and removals, and a second arm to examine the physician learning curve. The patient population for the long-term revision and removal arm will potentially include all patients who have previously enrolled in the continued access study. In addition to including all patients who have previously been reported as failures, the company will attempt to recruit into the long-term revision or removal arm all living patients who participated in the continued access study and have not had a revision or removal. The learning curve arm will consist of 125 newly-recruited patients at 5 sites who will undergo STAR Ankle placements with surgeons who did not participate in the STAR Ankle IDE studies. For both arms of the post-approval study, all consecutive subjects meeting the eligibility criteria and giving informed consent will be entered into the study. Subjects will be recruited from among patients in the practices of the investigators.

Following a baseline evaluation, patients in the long-term revision and removal arm will be asked to return for postoperative follow-up evaluations at 6 weeks, 12 months, 24 months, 48 months, 72 months and 96 months post STAR Ankle placement surgery. The follow-up evaluations will include assessment of complications, administration of the Buechel-Pappas Ankle Scale, Pain VAS, AOFAS, and SF-36. Patients in the physician learning curve arm of the study will undergo a baseline evaluation and follow-up evaluations at 6 weeks, 6 and 12 months. Link Orthopaedics will take all reasonable efforts to ensure that patients are not lost to follow-up in both arms of the post-approval study. A complete copy of the proposed post approval study protocol is located under the tab entitled "Proposed Post Approval Study Protocol."

9. Overall Conclusions

The data from the various STAR clinical studies presented in this PMA convincingly demonstrate that the STAR Ankle is safe and effective in the treatment of rheumatoid arthritis, primary arthritis, or post-traumatic arthritis in patients who have failed six months of conservative therapy.

With respect to efficacy, the STAR Ankle was clearly non-inferior to arthrodesis in all respects and the primary endpoint of the study was met. Moreover, in the majority of efficacy parameters measured, the STAR Ankle was superior to ankle arthrodesis. With regard to specific efficacy measures in the pivotal study, the STAR Ankle demonstrated substantial improvement in total BP score at 12 and 24 months as compared to Arthrodesis, with more than twice the percentage of patients enjoying a $\geq$ 40 point increase in baseline BP score as compared to Arthrodesis. These results were even further improved upon in the continued access study, reflecting the impact of minor refinements to surgical technique, modified instruments and increased surgeon experience.

The STAR Ankle demonstrates somewhat lower safety success rates at 12 and 24 months as compared to Arthrodesis patients in the pivotal study based on the original

radiographic success analysis. However, when using the most clinically appropriate radiographic success analysis adjusting the STAR radiographic outcomes (1) to allow patients who were radiographic successes at 24 months but who had not met the radiographic success analysis at an earlier time point to be considered as overall radiographic successes, and (2) for inappropriately considering patients with minor imaging findings as not meeting the definition of radiographic success, the STAR radiographic success rate is substantially higher than that of the control group. The safety success rate is also substantially similar to that of the control group. The lower bound of the confidence interval of the difference in the safety success rate is less than the pre-specified delta for the safety endpoint. Therefore, non-inferiority of the STAR ankle to the control group with respect to safety has been demonstrated.

The continued access study confirmed the safety profile of the STAR Ankle. More importantly, the improved safety results seen in the continued access study are believed to better represent the true safety profile of the STAR Ankle, given the modifications to surgical and instrumentation, as well as increasing surgeon experience. In the continued access study, rates of major complications and surgical interventions all decreased when compared to those rates in the pivotal study. Furthermore, the continued access study demonstrates comparable safety success rates of the STAR Ankle to Arthrodesis patients (when either considering the safety success rates based on those continued access patients with independent radiographic review or when imputing the radiographic failure rate from the pivotal study for those continued access patients without such radiographic review).

Further reinforcing the safety of the STAR Ankle as compared to arthrodesis is the data presented in the company's meta-analysis. These data, which summarized the historical safety profile of the arthrodesis, are comparable to safety profile demonstrated with the STAR Ankle.

Finally, the STAR group showed significantly higher rates of overall patient success in both the pivotal and continued access study, where overall patient success is a composite variable combining both individual patient safety and efficacy.

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Investigational Device Exemption

for

Link Orthopaedics, Inc.

Scandinavian Total Ankle Replacement (S.T.A.R. Ankle)

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3.0 Investigational Plan

3.0 INVESTIGATIONAL PLAN

3.1 INTRODUCTION

Severe ankle pain due to arthrosis (primary degenerative or rheumatoid) or trauma injury is not uncommon. Surgical reconstruction of the ankle is often necessary in order to eliminate pain and instability. This can be achieved either by arthrodesing the ankle bones together leading to a fusion or by performing joint arthroplasty.

Arthrodesis of the ankle was described by Albert in 1882 [9] and is achieved by removing the cartilage until bleeding bone is observed. An autogenous bone graft may be placed between the joint surfaces. To better achieve fusion, the joint is mechanically secured with bone screws and/or pins. The ankle is immobilized throughout the bone fusing process to prevent micromotion. As reported in the literature, arthrodesis can have an early complication rate of between 10 - 40% due to infection, nonunion and malunion [10]. Arthrodesis often eliminates pain but results in loss of ankle mobility for the patient. Long term results (greater than 5 years) demonstrate arthrosis of the joints distal to the ankle joint secondary to the increased stress brought about by the arthrodesis [11]. This

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[9] Einige faire kunstilcher anklyosen: Bidung an paralytischen gliemassen. *Wein Med Pross* 23:726-728, 1882

[10] Frey C, Halikus NM, Vu-Rose T, Ebramzadeh E. A review of ankle arthrodesis: predisposing factors to nonunion. *Foot Ankle Int* 15(11):581-584, 1994

[11] Mann RA, Rongstad KM. Arthrodesis of the ankle: A critical analysis. *Foot & Ankle Int* 19(1):3-9, 1998.

condition may require extension of the arthrodesis into the foot, which may create even greater stiffness.

Arthroplasty of the ankle has been performed since 1970 [12] and has been used as an alternative to arthrodesis of the ankle. Like hip and knee arthroplasty, ankle designs have evolved over the years. Three different basic types of articulation geometry have been used: (1) roller and trough (*e.g.*, Smith, Beech-Steffee, ICLH, and Mayo constrained ankles and the semi-constrained Alvine ankle); (2) unconstrained, hemispherical Bath & Wessex design; and (3) tri-compartmental design (*e.g.*, S.T.A.R. and New Jersey LCS).

Another evolution has been the change from cemented to non-cemented device designs. This change is largely due to the difficulty of using conventional cementing techniques in the limited space within the ankle mortise. The oblique angle of the tibia [13] and the dense structure of the talus bone also contribute to the difficulty. Several authors have shown clinically equivalent results with the non-cemented ankle devices. These ankle designs have been used on both male and female patients who are skeletally mature (ages 22 to 84 years) and on patients with both rheumatoid and osteoarthritis. Postoperative surgical complications are similar to that of arthrodesis patients but postoperative rehabilitation is faster . Arthrodesis requires a minimum of 12 weeks of

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[12] Lord G, Marotte JH. Arthroplastie totale de cheville. Experience sur 10 ans. A propos de 25 observations personnelles. *Revue de Chirurgie Orthopedique* 66:527-530, 1980.

[13] Carlson AS, Henricson A, Linder L, et al, . Medium term results in rheumatoid arthritis with the Bath & Wessex ankle prosthesis. in *Current status of ankle arthroplasty, p 86-89.* Published by Springer 1998.

immobilization (which may require the patient to be wheelchair bound), half of which is allowed to be weight bearing, whereas after S.T.A.R. ankle arthroplasty, the patient is allowed to bear some weight immediately and is out of all immobilization in 4-6 weeks. Some of the modern ankle designs like the S.T.A.R. also have the advantage that they only require removal of a minimum amount of bone in the ankle joint, providing an opportunity to revise the surgery to an arthrodesis, if necessary, without significantly compromising the patient's leg length.

3.2 PURPOSE, OBJECTIVES, AND ENDPOINTS

The purpose of this study is to evaluate the safety and efficacy of the S.T.A.R. device, as compared to patients undergoing ankle arthrodesis. The specific objectives are to show that S.T.A.R. ankle patients experience equivalent pain relief, range of motion, related function, and complications, as compared to arthrodesis patients.

The primary efficacy endpoint to be measured is:

- Total Buechel-Pappas Scale score [14]

Other efficacy outcomes to be measured include:

- Buechel-Pappas range of motion and function subscale scores
- Increase in Buechel-Pappas Scale of 40 points
- Pain Visual Analog Scale (VAS) (100mm scale)

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[14] Buechel FF, Pappas MJ, Iorio LJ. New Jersey Low Contact Stress Total Ankle Replacement: Biomechanical Rationale and Review of 23 Cementless Cases. *Foot & Ankle* 8(6):279-290, 1988.

- Patient satisfaction (Coughlin rating scale [15])
- Quality of Life (SF-36)
- Medication usage

Safety endpoints to be measured are:

- Device failure, device removal/revision, or arthrodesis (S.T.A.R. ankle group only)
- Radiographically confirmed loosening and migration (S.T.A.R. ankle group only)
- Non-union, mal-union, delayed union, or revision (Arthrodesis group only)
- Complications (see Section 1.7)

Overall patient success will be defined as a 40-point increase in Buechel-Pappas score and no device failures or major complications as defined above. It is expected that patient success will be equivalent between the two groups.

3.3 STUDY DESIGN

The study will be a multicenter clinical trial with concurrent non-randomized controls. The control group will consist of 79 patients undergoing arthrodesis and the experimental group will consist of 158 patients undergoing total ankle arthroplasty using the S.T.A.R. device. Approximately 12-16 sites will participate in the investigation, with 6-8 sites performing only arthrodesis and 6-8 sites performing only S.T.A.R. ankle arthroplasty. The duration of the study is

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15 Coughlin MJ. Etiology and treatment of hallux valgus: Arthrodesis of the first metatarsophalangeal joint with mini-fragment plate fixation. *Orthopedics* 13(9):1037-1044, 1990.

expected to be 3-4 years, with 1-2 years of recruitment and 2 years of follow-up for all patients.

A chart indicating the schedule of assessments and procedures for each visit is given in **Appendix 3.1** to this section. Each subject will undergo a baseline evaluation to determine eligibility and to establish the patient's preoperative pain and functional status. Patients who agree to participate in the study and give informed consent will be enrolled in the study and scheduled for surgery. Patients will undergo a postoperative evaluation and follow-up evaluations at 3, 6, 12, and 24 months.

3.4 STUDY POPULATION

3.4.1 Subject Recruitment

All consecutive subjects meeting the eligibility criteria and giving informed consent will be entered into the study. Subjects will be recruited from among patients in the practices of the investigators.

3.4.2 Inclusion Criteria

Subjects will be included in the study only if they meet all of the following criteria:

- Moderate or severe pain, loss of mobility and function of the ankle (Buechel-Pappas Scale total score of less than 50 and Buechel-Pappas pain score of 20 or less)
- Primary arthrosis, post traumatic arthrosis or rheumatoid arthrosis

- At least six months of conservative treatment [16] for severe ankle conditions, confirmed by the patient medical history, radiograph studies and medication record
- Patients must fail a trial of foot and ankle orthosis and/or analgesic medication for 3 months prior to inclusion in the study
- Willing and able to give informed consent

3.4.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- Patients who have not reached skeletal maturity
- Active or prior deep infection in the ankle joint or adjacent bones
- Prior arthrodesis at the involved site
- History of prior mental illness or patient demonstrates that their mental capacity may interfere with their ability to follow the study protocol
- Obesity (weight greater than 250 lbs)
- History of current or prior drug abuse or alcoholism
- Any physical condition precluding major surgery
- Hindfoot malpositioned by more than 35 degrees or forefoot malalignment which would preclude a plantigrade foot

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[16] Conservative treatments for a painful ankle include, but are not be limited to, the following: foot and ankle orthosis (to support and immobilize the ankle joint), counseling on changing employment (sitting job versus manual labor) and/or activity, or planned pain or anti-inflammatory medication management (to reduce or eliminate the pain)

- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Avascular necrosis of the talus
- Inadequate skin coverage about the ankle joint
- Severe deformity that would not normally be eligible for ankle arthroplasty
- Prior surgery and/or injury that has adversely affected the ankle bone stock
- Severe osteoporotic or osteopenic condition or other conditions that may lead to inadequate implant fixation in the bone
- Insufficient ligament support
- Motor dysfunction due to neuromuscular impairment
- Under the age of 35 and unwilling or unable to accept the physical limitations imposed by ankle arthroplasty, including limitation on certain vigorous physical activities and on manual labor.
- Juvenile-onset Type I diabetes. Patients with adult-onset Type II diabetes will be excluded only if they have neuropathic changes or if they have a history of infection in either foot.
- Pregnancy, avascular necrosis of the tibia, and significant bone tumor of the foot or ankle.

Note that arthrodesis patients meeting any of the above criteria are not expected to have poorer outcomes than those that do not. Thus, inclusion of patients meeting

any of the above criteria in the arthrodesis group is not expected to bias the comparison between arthrodesis and arthroplasty in favor of arthroplasty.

3.5 STUDY EVALUATIONS, PROCEDURES AND ASSESSMENTS

3.5.1 Baseline Evaluation

To determine eligibility for the study, subjects will undergo a complete medical history and physical examination. The medical history will include administration of the Buechel-Pappas Ankle Scale (see **Appendix 3.2** to this section) and Pain VAS. Patients who meet all eligibility criteria will be asked to give informed consent. Patients who give consent will be enrolled into the study and scheduled for surgery.

3.5.2 Arthrodesis

Ankle arthrodesis is carried out through a lateral approach to the ankle joint. The distal fibula is removed. A cut is made in the distal tibia which is perpendicular to the long axis of the tibia. Care is taken not to remove the medial malleolus. The foot is placed into a plantigrade position and a cut is made in the superior aspect of the talus that is parallel to the original cut made in the tibia. The alignment of the foot is then checked and, if satisfactory, one may proceed with internal fixation. Two large screws placed from the talus into the tibia may be utilized for fixation, although other methods can be employed at the surgeon's discretion.

Following surgery, the leg is kept immobilized in a below-knee non-weight bearing cast for six weeks and then in a below-knee walking cast for six

weeks. As a general rule, union will occur in approximately twelve to fourteen weeks. There is about a 10-15% non-union rate.

3.5.3 S.T.A.R. Arthroplasty

The S.T.A.R. arthroplasty [17] is carried out through an anterior approach to the ankle joint. A wide approach is made to the joint. An alignment block is utilized to remove the distal 5 mm of the tibia in such a way as to just skim off the remaining articular surface at the dome of the tibial plafond. Utilizing another portion of the tibial jig, a 4 mm block is utilized to remove the superior dome of the talus while the foot is held in a plantigrade position.

Following this, the tibial jig is removed and a side cutting talar guide is applied and the medial and lateral 2-3 mm of talus are removed. The second chamfer guide is applied to the talus and the anterior and posterior portions of the talus are removed, creating a surface for the talar component. A slot is made in the superior aspect of the talus to receive the fin of the prosthesis. The talar prothesis of correct size is then placed onto the talus and seated onto the cut surfaces.

Returning now to the distal tibia, the tibial jig is reapplied and two holes are then placed into the distal tibia to accommodate the barrels of the tibial component. The tibial component is then inserted. A polyethylene trial spacer is placed between the tibial and talar components and a permanent spacer is then selected.

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[17] LINK S.T.A.R.. Totale Sprunggelenksprothese. Broschure zur Operationstechnik 7:96.

The patient is immobilized for a period of six weeks following the arthroplasty. The first two weeks weight-bearing is minimized, at two weeks the patient is permitted to bear 50% weight in their cast, at four weeks the patient is permitted to bear full weight. The cast is removed at six weeks unless a ligamentous reconstruction was carried out, in which case the cast is left on for a total of eight weeks. Gentle range of motion exercises are begun after the fourth week.

3.5.4 Follow-up Evaluation

Patients will be asked to return for postoperative follow-up evaluations at 2-3 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months. The follow-up evaluations will include assessment of complications (see Section 3.7), medication history, radiographic evaluation (see **Appendix 3.4** to this section), administration of the Buechel-Pappas Ankle Scale, Pain VAS, Coughlin Satisfaction Scale (See **Appendix 3.3** to this section), and SF-36. See **Appendix 3.1** to this section for a list of assessments to be performed at each visit. The radiographic evaluation for the experimental group will focus on the incidence, zone, size and progression of radiolucencies and osteolysis around the implant components, which may indicate loosening. The amount of varus or valgus as well as plantar and dorsiflexion alignment will be recorded and migration of either the tibia or talar component will be assessed.

3.6 STATISTICAL CONSIDERATIONS

3.6.1 Endpoints

The primary efficacy endpoint is mean total Buechel-Pappas score assessed at one year. The Buechel-Pappas Scale is a 100-point scale (See **Appendix 3.2** to this section) consisting of subscales for pain (40 points), function (40 points), range of motion (15 points), and deformity (5 points). The function subscale is further divided into five 8-point questions pertaining to limp, standing, walking, stairs, and support. The Buechel-Pappas Scale is one of several similar published instruments for evaluating ankle arthroplasty. Each of the published scales include, to varying degrees, pain, function and range of motion components, and each gives similar total scores when administered to the same group of patients[18]. The Buechel-Pappas Scale was determined to be the most appropriate instrument for this clinical trial because of its low discontinuity error and its balanced coverage of the different components. Other instruments such as the AOFAS and the Ankle Osteoarthritis Scale were evaluated but not chosen because they do not focus on the ankle (AOFAS) or because they have not been used to evaluate arthroplasty (AOS).

Secondary efficacy endpoints include Buechel-Pappas subscales of function and range of motion, 40-point improvement in Buechel-Pappas total score, pain VAS, patient satisfaction and quality of life. Pain is evaluated using VAS

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18 Levi N, Lundberg-Jensen A, Kofoed H. Comparison of five different ankle scoring systems in ankle arthroplasty. *Foot & Ankle Surg* 4:167-170, 1998.

instead of the Buechel-Pappas pain subscale since it provides a more precise and objective measure of pain. Patient satisfaction will be measured using rating proposed by Coughlin, which is a four category scale (excellent, good, fair, poor), relating satisfaction with pain and function (See **Appendix 3.3** to this section). Quality of life will be measured using the SF-36, a validated and widely used measure of health status.

The safety endpoint for the S.T.A.R. group is absence of major complications, loosening, subsidence, migration, or device removal/revision. The safety endpoint for the arthrodesis group is absence of major complications, non-union, delayed union, mal-union, or revision.

Overall patient success is defined as a 40-point increase in Buechel-Pappas score between baseline and one year, with no device failures, device removal/revision, device migration/subsidence/loosening, or major complications. While it is expected that the patient success rate will be equivalent between the two treatment groups, no formal statistical hypothesis testing will be done, since patient success criteria for ankle arthroplasty/arthrodesis are not widely agreed upon.

3.6.2 Statistical Analysis

The primary efficacy endpoint of mean total Buechel-Pappas score will be compared between the two treatment groups using the method of Blackwelder [19], to determine if the overall outcome is equivalent between the two groups. In

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[19] Blackwelder WC. "Proving the Null Hypothesis" in Clinical Trials. *Controlled Clinical Trials* 3:345-353 (1982).

addition, based on the methodology proposed by Dunnett & Gent[20] and Morikawa & Yoshida[21], a two-sample t-test can also be performed, without adjustment for multiple comparisons, to determine if the S.T.A.R. outcome is also superior to arthrodesis.

The secondary endpoints of function and range of motion subscale scores will be compared between treatment groups using a two-sample t-test, to determine if function and range of motion with the S.T.A.R. is superior to that of arthrodesis. The percent of patients with a 40-point increase in total Buechel-Pappas score will be compared between groups using a chi-square test. Pain VAS, patient satisfaction and quality of life will be compared between treatment groups using a two-sample t-test, to determine whether these parameters are similar between the two groups.

The primary comparison will be at one year, with further confirmation at the two year time point [22]. Further adjustments for differences in baseline characteristics will be done using multiple linear regression techniques. Standard repeated measures analysis of variance techniques, such as Generalized Estimating Equations (GEE), will be used to evaluate the outcomes at each time point simultaneously.

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20 Dunnett CW, Gent M. An alternative to the use of two-sided tests in clinical trials. *Stat Med* 15:1729-1738, 1996.

21 Morikawa T, Yoshida M. A useful testing strategy in phase III trials: Combined test of superiority and test of equivalence. *J Biopharm Stat* 5(3):297-306, 1995.

22 Accordingly, the company will provide primarily one-year results in the PMA submission, and provide complete two-year results as part of its post-market studies.

Kaplan-Meier survival analysis will be used to calculate the probability of device failure (removal or revision) for the S.T.A.R. ankle treatment group and the probability of non-union or surgical revision in the arthrodesis control group.

The percentage of subjects experiencing adverse events will be calculated and compared using chi-square tests or Fisher's exact test as appropriate.

3.6.3 Sample Size

As shown in **Appendix 3.5** to this section, the sample size required to evaluate the primary efficacy endpoint of equivalent Buechel-Pappas score is 36 (12 arthrodesis and 24 S.T.A.R. ankle). This sample size is based on data collected by Buechel & Pappas and assumes that the clinically insignificant difference in mean Buechel-Pappas score ("delta") is 10 points. This choice of delta is appropriate, since it is only 10% of the total 100-point scale, and it is also equal to the smallest width of the categories used to classify the scale (85-100=Excellent, 75-85=Good, 65-75=Fair, etc.).

The sample size required to evaluate the safety endpoint is 201 (67 arthrodesis and 134 S.T.A.R. ankle). This sample size assumes a success rate of 80% in both groups and a delta of 15%. Based on the safety profile of the S.T.A.R. device observed to date and the lack of viable alternatives for ankle arthroplasty (particular non-constrained), the company's medical advisors consider this to be a reasonable delta. Additionally, there are a number of potential functional advantages of S.T.A.R. arthroplasty which will not be directly measured in this

study, but which warrant a delta of this size, including applicability to bilateral patients, ability to climb hills and steps, earlier post-operative weight bearing, better gait pattern, and reduced need for orthotic footwear. It is expected that the success rate for the S.T.A.R. will actually exceed that of arthrodesis, so that the confidence limits for the observed difference between group will likely be considerably less than 15%.

Since the sample size required to evaluate the primary efficacy endpoint is only 36, the sample size for the safety endpoint (201) will be considered as well, even though it is not a primary endpoint. Thus, the sample size required to evaluate both the primary efficacy endpoint and the safety endpoints in this study is 201. Allowing for 15% loss to follow-up over the two year duration of the study, the sample size required to obtain 201 evaluable patients at two years is 237 (79 arthrodesis and 158 S.T.A.R. ankle).

3.7 COMPLICATIONS AND ADVERSE EVENTS

European surgeons having experience with the S.T.A.R. device have been queried regarding complications which have occurred with the S.T.A.R. ankle device. European clinical reports concerning the S.T.A.R. have also been reviewed.

There has only been one reported device failure, that of a failed UHMWPE bearing. (This case was due to surgeon error, in which too large a bearing was used, resulting in the patient requiring a revision).

Few complications or adverse events were reported in the published European studies. Most complications were due to operative technique, especially

early in the surgeon's experience. Other complications included deep infection, prosthetic subsidence, retraction lesion of the posterior tibial nerve behind the medial malleolus, meniscal breakage, and skin necrosis.

Review of published literature of implant devices has identified the following adverse effects associated with total joint replacement and arthrodesis surgeries. Potential complications occurring with the S.T.A.R. ankle prosthesis should be similar to those of current total ankle implant designs and arthrodesis surgeries. The following is a list of complications that could arise from the ankle surgery.

OPERATIVE COMPLICATIONS	POSTOPERATIVE COMPLICATIONS
Hemorrhage/Bleeding	Additional Stabilization Required
Instrument Malfunction	Device Migration (no re-operation)
Improper Device Placement	Device Migration (with re-operation)
Vessel Damage	Device Breakage
Ligament Damage	Arthrodesis or Surgical Intervention
Fracture of the Bone(s)	Ankle Pain
Nerve Damage	Similar Pain as Preoperative
Tendon Damage	Persistent Nerve Damage
	Ligament Instability
	Thrombophlebitis
	Embolism
	Soft Tissue Edema

Wound Infection (superficial or deep)

Wound Dehiscence

Skin slough or breakdown

Death (unrelated)

Death Related to the Procedure

3.8 RISK/BENEFIT ANALYSIS

The indications for any surgical procedure require the careful consideration of the goals, benefits and risks of the surgery and postoperative care.

The device goals should include the reduction of pain, restored function and activity. The potential risks of the procedure include infection, failure of the device, persistent pain, malalignment, and/or instability of the joint.

3.8.1 Risks

The risk of complications is dependent on many factors including: the device design, method of fixation, condition of the patient's bone, patient's age, and the surgical technique. The risks that are of concern are:

- Deep and superficial wound infections
- Fracture of the bones supporting the device
- Vascular and nerve damage
- Migration or subsidence of the device or failure of any of the individual implant components
- Skin sloughing

3.8.2 Potential Benefits

There are several significant benefits of total ankle arthroplasty:

- Significant pain relief
- Shorter postoperative rehabilitation period than for arthrodesis: some weight bearing possible immediately after surgery and full weight bearing within 4-6 weeks
- Patient can return to more normal activities (stairs, walking, sports, etc.) than with arthrodesis
- More normal gait pattern than with arthrodesis
- Since device permits motion to occur at the ankle joint, there is little or no abnormal stress placed on the subtalar or transverse tarsal joint, diminishing the possibility of arthrosis at these joints (seen in about 30% of arthrodesis patients at five years)[22]

Weighing the risks and benefits of total ankle arthroplasty and arthrodesis, it would appear that the risk of failure is similar in both and that there are several significant advantages of the total ankle that outweigh any unique risks. In addition, risks involved in the total ankle arthroplasty will be minimized by excluding from the study patients who are at increased likelihood of complications due to conditions such as osteoporosis, history of infection, vascular insufficiency, obesity, severe deformity, and avascular necrosis of the talus.

3.9 STUDY MONITORING

Link Orthopaedics will arrange for investigational site monitoring to ensure that all investigators are in compliance with the protocol and the Investigator Agreement. Link Orthopaedics, or designated CRO, will monitor the sites to ensure the information documented on the completed case report forms match the medical records, and resolve any differences. The monitor will also identify any instances in which the investigator deviates from the clinical protocol. If an investigator does not comply with the provisions of the Investigator Agreement, the clinical protocol, or applicable FDA regulations, Link Orthopaedics will take whatever action necessary to secure compliance, and retains the right to remove either the investigator or the investigational site from the study.

Link Orthopaedics will review significant new information, including unanticipated adverse device effects and ensure that such information is provided to all reviewing IRBs, regulatory authorities and investigators.

APPENDIX 3.1

EVALUATION SCHEDULE

		Follow-up					
Assessment	**Baseline**	**2-3 Weeks**	**6 Weeks**	**3 month**	**6 month**	**12 month**	**24 month**
Eligibility Assessment	X						
Medical History	X						
Physical Examination	X	X	X	X	X	X	X
Medication History	X	X	X	X	X	X	X
Complication Report		X	X	X	X	X	X
X-Ray evaluation	X	X	X	X	X	X	X
Buechel-Pappas Scale	X			X	X	X	X
Pain VAS	X			X	X	X	X

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APPENDIX 3.2

BUECHEL-PAPPAS SCALE (*Foot & Ankle* 8(6):279-290, 1988)

I. PAIN	(MAX. 40 POINTS)
None	40 points
Slight	35 points
Mild	30 points
Moderate	20 points
Severe	10 points
Totally Disabled	0 points
II. FUNCTION	(MAX. 40 POINTS)
LIMP	
None	8 points
Mild	6 points
Moderate	3 points
Severe	1 point
Unable to walk	0 points
STANDING	
No support for ¾ hour	8 points
No support for ½ hour	6 points
No support for ¼ hour	3 points
Unable to stand without support	0 points
WALKING	
Unlimited	8 points
6 blocks	6 points
2-3 blocks	4 points
Indoors only	2 points
Bed & chair	0 points
STAIRS	
Normally without banister	8 points
Normally with banister	6 points
External support and banister	3 points
Not able	0 points
SUPPORT	
None	8 points
Single cane for long walks	6 points
Single cane most of the time	4 points
1 crutch most of the time	3 points
2 canes most of the time	2 points
2 crutches/walker most of the time	0 points

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III. **RANGE OF MOTION** (Radiographic)		(MAX. 15 POINTS)
	(SPECIFY: ___ ° TO ___ °)	
	Dorsiflexion 15 ° – Plantarflexion 45 ° or equal to unaffected contralateral ankle	15 points
	Dorsiflexion 5 ° – Plantarflexion 30 °	13 points
	Combined motion 25 ° to 34 °	11 points
	Combined motion 15 ° to 24 °	9 points
	Combined motion 5 ° to 14 °	5 points
	Combined motion less than 5 °	0 points
IV. **DEFORMITY**		(MAX. 5 POINTS)
	(CHECK ALL THAT APPLY)	
	Heel varus ☐ valgus ☐ If less than 6 °	1 point
	Equinus, dorsiflexes to neutral	1 point
	Calcaneus, plantarflexes to 20 °	1 point
	Limb-length discrepancy less than 1.5 cm	1 point
	Swelling, less than 1+ edema	1 point

APPENDIX 3.3

COUGHLIN SATISFACTION SCALE (*Orthopedics* 13(9):1037-1044, 1990)

Rating	Description
Excellent	Without problems, very satisfied, mild or no pain, walks without difficulty
Good	A few problems, satisfied, mild pain, walks without difficulty or with mild difficulty, would still have surgery
Fair	Moderate pain, some difficulty with walking, reservations about success of surgery
Poor	Continued pain, little improvement in walking, regrets surgery

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APPENDIX 3.4

Regular x-rays under fluoroscopy of the patient's ankle will be taken prior to or during the office visits as part of the study evaluation.

A. PREOPERATIVELY - Weight bearing A/P and lateral views of the foot and ankle are taken to assess the degree of arthrosis. Narrowing or collapse of the patient's joint space should observed, and the physician should verify the absence of avascular necrosis. An MRI will be done if avascular necrosis is suspected.

B. POSTOPERATIVELY - Weight bearing radiographs should be taken from the A/P and lateral aspects of the ankle. From these x-rays, measurements, and observations of the implant fixation, the device's position and orientation are assessed..

C. RADIOLUCENCIES - Verification and progress of any radiolucencies of the bone will be observed and quantified measuring the amount in millimeters. Three specific categories of radiolucencies will be charted:

Tibia	Talar		
☐	☐	None	(no radiolucencies of components noted)
☐	☐	0 to 4mm	(radiolucencies up to 4mm noted)
☐	☐	>4mm	(radiolucencies greater than 4mm noted)

(Changes of < 4 mm cannot be reliably detected.)

D. MIGRATION - Postoperative x-ray films will be taken at regular intervals, on or during the office visits. Migration of the tibia or talar components will be measured using a scale and the amount in millimeters

noted. Three specific categories of migration will be charted for the tibia and talar components:

Tibia	Talar		
☐	☐	None	(no migration of components noted)
☐	☐	0 to 4mm	(migration of up to 4mm noted)
☐	☐	>4mm	(migration greater than 4mm noted)

Migration of >4mm or more of either tibia or talar component should be considered a failure. The tibia and talar components are to be scored as individual components.

E. <u>TILTING</u>

Tilting of the prosthesis is expressed in terms of direction (varus-valgus or plantiflexion-dorsiflexion) and amount of tilt (in mm) in comparison with the position in the first postoperative x-ray.

VARUS-VALGUS		PLANTIFLEXION-DORSIFLEXION		
Tibia	Talar	Tibia	Talar	
☐	☐	☐	☐	None
☐	☐	☐	☐	0 to 4 mm
☐	☐	☐	☐	>4 mm

APPENDIX 3.5

Sample Size Justification

Safety Endpoint

Definitions

Success (S.T.A.R. Ankle group): No major complication, device removal/revision, loosening, subsidence, migration, and plantigrade foot.
Success (Arthrodesis group): No major complication, non-union, delayed union, mal-union, revision, and plantigrade foot.

π_e: Proportion of successes in the Experimental treatment (S.T.A.R. Ankle) group
π_c: Proportion of successes in the Control treatment (Ankle Arthrodesis) group

Hypotheses (method of Blackwelder [23]):

$$H_0: \pi_c \geq \pi_e + \delta$$

$$H_1: \pi_c < \pi_e + \delta$$

Type I error: the difference $\pi_c - \pi_e$ is less than δ when in fact the difference is greater than or equal to δ, *i.e.,* we choose the experimental treatment when the control treatment is actually substantially better.

Type II error: the difference is greater than or equal to δ when it is actually less than δ *i.e.,* we chose the control treatment when the experimental treatment is essentially just as good.

Assumptions and Calculations

$\alpha = 0.05$	(Probability of Type I error)
$\beta = 0.20$	(Probability of Type II error; power = $1 - \beta$)
$\pi_c = \pi_e = 0.80$	(Estimated success rate for control and treatment groups)
$\delta = 0.15$	(Difference that can be considered clinically insignificant: $\pi_c - \pi_e < \delta$)

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23 *Supra* note 11.

$\lambda = 1.5$ (For 2:1 experimental:control ratio)

Sample size (when $\pi = \pi_c = \pi_e$)

$$N = \frac{\lambda(Z_{1-\alpha} + Z_{1-\beta})^2\, \pi(1-\pi)}{\delta^2} = 67 \text{ Arthrodesis} \rightarrow 134 \text{ S.T.A.R. ankle}$$

Primary Efficacy Endpoint: Total Buechel-Pappas Scale score

Definitions

μ_e: Mean Total Buechel-Pappas Score in the Experimental treatment (S.T.A.R. Ankle) group
μ_c: Mean Total Buechel-Pappas Score in the Control treatment (Ankle Arthrodesis) group

Hypotheses:

$$H_0: \mu_e \geq \mu_c + \delta$$

$$H_1: \mu_e < \mu_c + \delta$$

Type I error: the difference $\pi_e - \pi_c$ is less than δ when in fact the difference is greater than or equal to δ, *i.e.*, we choose the experimental treatment when the control treatment is actually substantially better.

Type II error: the difference is greater than or equal to δ when it is actually less than δ, *i.e.*, we chose the control treatment when the experimental treatment is essentially just as good.

Assumptions and Calculations

$\alpha = 0.05$	(Probability of Type I error, one sided)
$\beta = 0.20$	(Probability of Type II error; power = 1 - β)
$\sigma = 11.3$	(Population standard deviation, from New Jersey LCS paper [24])
$\delta = 10.0$	(Difference that can be considered clinically significant)
$\lambda = 1.5$	(For 2:1 experimental:control ratio)

Sample size

$$N = \frac{\lambda(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = 12 \text{ Arthrodesis} \rightarrow 24 \text{ S.T.A.R. Ankle}$$

[24] *Supra* note 6.

3 SUMMARY OF SAFETY AND EFFECTIVENESS (3/12/07 REV)

3.1 GENERAL INFORMATION

Device Generic Name: Total Ankle Prosthesis

Device Trade Name: Scandinavian Total Ankle Replacement (STAR)

Applicant's Name: Link America, Inc. DBA Link Orthopaedics
300 Roundhill Drive
Rockaway, NJ 07866

PMA Number: P050050

Date of Panel Recommendation: TBD

Date of Notice of Approval to the Applicant: TBD

3.2 INDICATIONS FOR USE

Link Orthopaedics' ("Link") Scandinavian Total Ankle Replacement ("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 arthritis, or post-traumatic arthritis. 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.

3.3 CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications:

- Active or prior deep infection in the ankle joint or adjacent bones.
- Prior arthrodesis at the ankle joint.
- Hindfoot or forefoot malalignment precluding plantigrade foot.
- Severe deformity that would not normally be eligible for ankle arthroplasty.
- Avascular necrosis of the talus.
- Charcot joint.
- Severe osteoporotic or osteopenic condition or other conditions resulting in poor bone quality that may result in inadequate bony fixation.

- Prior surgery and/or injury that has adversely affected ankle bone quality.
- Insufficient ligament support that cannot be repaired with soft tissue stabilization.
- Skeletal maturity not yet reached.
- Obesity (weight greater than 250 lbs).
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure.
- Poor skin and soft tissue quality about the surgical site.
- Neuromuscular disease resulting in lack of normal muscle function about the affected ankle.
- Psychiatric problems that hinder adequate cooperation during perioperative period.
- Significant malalignment of the knee joint.
- Peripheral neuropathy that may lead to Charcot joint of the affected ankle.

Warnings/Precautions:

- Only implant the STAR Ankle after adequate training and familiarity with the surgical technique manual, to avoid increased risk of device failure due to improper surgical technique.

- Do not use STAR Ankle components in combination with prosthesis components made by other manufacturers, because design, material, or tolerance differences may lead to premature device and/or functional failure. Components of the system have been specifically designed to work together.

- Always determine that the patient does not have a possible allergy to the implant/prosthesis material before selecting the STAR implant, to minimize the risk of an allergic response.

- Discard all damaged or mishandled implants. Do not reuse implants and components. Although the implant may appear undamaged, it may have small defects and internal stress patterns which may lead to early failure of the device.

- Do not resterilize. Do not use implants or components if the package is open or damaged.

- Always exercise care in selecting the proper type and size of implant. Size and shape of the human bone place restrictions on the size and shape of the implant, thus limiting its weight-bearing capabilities.

- Proper use of the talar bone tamper and talar trials provided in the STAR Ankle instrument set is necessary to minimize the risk of undetected talar fracture.

- Do not contour or bend an implant because it may reduce its fatigue strength and cause failure under load. Correct handling of the implant is extremely important.

- Caution the patient that the STAR implant can be expected to withstand only limited stress until the supporting bones are completely healed, and that the load-bearing capability of implants cannot be compared to that of a healthy bone. Premature and/or excessive loading of the implant may result in device failure.

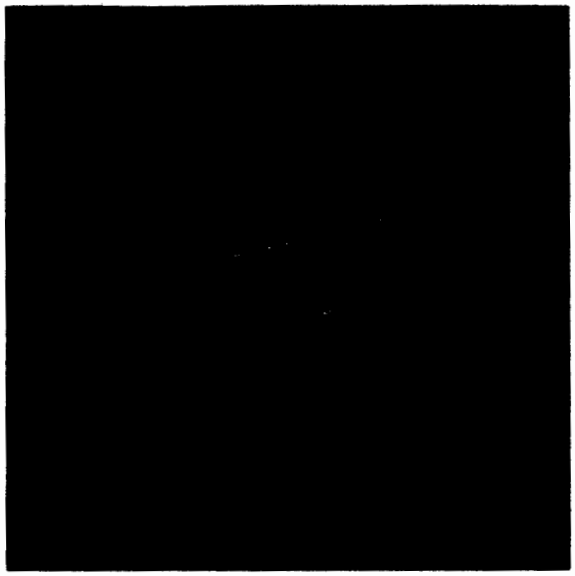
3.4 DEVICE DESCRIPTION

3.4.1 Overview

The STAR Ankle system comprises the ankle prosthesis itself, which includes three functional components, and a set of customized accessory instruments that are used in the surgical procedure. The three principal components of the prosthesis are:

- A metal tibial component with titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing; and
- A metal talar component with titanium porous plasma spray coating.

The intermediate UHMWPE mobile bearing articulates on the tibial and talar metal implant surfaces, as shown in the photograph of the three components of the STAR Ankle system below:



The STAR Ankle is designed to replace a portion of the tibial and talar components of the normal ankle joint, while preserving range of motion as much as possible. As illustrated in **Table 1** below, the design characteristics of the STAR Ankle correspond closely to the normal ankle joint.

Table 1: Comparison of Design Characteristics of the STAR Ankle to the Normal Ankle Joint

Design Feature	Normal Ankle	STAR Ankle Prosthesis
Congruency	96%	100%
Rotation	12-15° talus rotation	12-15° talus rotation plus tibial-meniscal rotation
Extension/flexion (radiographic)	10/30°	7/20°

There are two bearing surfaces in the STAR Ankle: (1) the interface between the upper side of the UHMWPE mobile bearing and the facing surface of the tibial plate, and (2) the interface between the lower surface of the UHMWPE mobile bearing and the facing surface of the talar component. The tibial plate has one flat surface and one surface with two raised cylindrical barrels oriented in the anterior/posterior direction. The upper flat surface of the UHMWPE mobile bearing slides against the flat surface of the tibial plate. The projecting cylinders of the tibial plate serve to fix the device to bone at the distal tibia. The lower surface of the UHMWPE mobile bearing is concave, fitting against the convex upper surface of the talar component.

The mobile bearing design of the device is intended to reduce the shear and torque forces on the UHMWPE mobile bearing, which can lead to loosening of either metal component, and to decrease stress at the metal/bone interface. The sloped sides are designed to improve the weight bearing characteristics of the talar component.

3.4.2 Components

3.4.2.1 Tibial Plate

When viewed from the top, the tibial plate has a trapezoidal shape with rounded corners. This component is manufactured from cobalt chromium molybdenum (CoCrMo) per ASTM F-75. The smaller end of the wedge is oriented towards the posterior aspect of the ankle joint. This wedge is shaped to conform to the existing anatomy and, thereby, reduces the need to remove excess bone from inside the joint. On the proximal surface of the tibial plate, two parallel cylindrical barrels are positioned equidistant from the center of the plate running anterior to posterior for bone fixation. These cylinders must be inserted into hard subchondral bone.

[redacted]

Tibial plates are available in five sizes with varying widths and lengths: extra-small (30mm x 30mm), small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm). Tibial plates for revision procedures are available in small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm) sizes. The [redacted]

The tibial plate is coated on the bone-opposing surfaces with a titanium plasma spray porous coating. The tibial plate is intended to be press-fit without the use of cement, and should rest on anterior and posterior cortical bone. The stemmed tibial components are uncoated and have a matte finish where they interface with bone.

3.4.2.2 UHMWPE Mobile Bearing

The polyethylene mobile bearing is manufactured from Ultra High Molecular Weight Polyethylene ("UHMWPE"), which is machined from medical grade extruded plate stock and conforms to ASTM F-648. [redacted]

[redacted] Revision mobile bearings are available in sizes of 11mm, 12mm, 13mm, and 14mm.

3.4.2.3 Talar Component

The talar component is designed as an anatomical prosthesis to cover the talar dome, anterior, posterior, and medial and lateral facets. Like the tibial plate, this component is manufactured from CoCrMo. The talar component is designed to minimize the amount of bone that must be removed. From the apex of the dome, the walls slope outwards to conform to the normal bone anatomy. The component is offered in five sizes: extra-extra-small (28mm x 29 mm), extra-small (30mm x 31mm), small (34mm x 35mm), medium (36mm x 35mm), and large (38mm x 35mm), and in both left- and right-sided configurations.

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

As with the tibial plate, the talar component is also provided with a titanium plasma spray porous coating.

3.5 ALTERNATIVE PRACTICES AND PROCEDURES

Treatments for degenerative ankle disease range from conservative methods, such as rest, heat, electrotherapy, physical therapy, bracing, and pain medication to surgery. When conservative therapy fails to relieve patient symptoms, surgical intervention may be recommended. Some surgeons recommend ankle fusion surgery, in which the lower leg bone is fused to the foot. Some surgeons recommend total ankle replacement, in which the ankle joint is replaced by a prosthetic device which attempts to mimic the movement of the ankle. Currently, there are a limited number of semi-constrained prosthesis available in the United States.

3.6 MARKETING HISTORY

The STAR Ankle has been marketed in Europe since 1990. The STAR Ankle received a CE Mark in January of 1996. It has not been withdrawn from the market in any country for reasons related to safety or efficacy.

3.7 ADVERSE EFFECTS OF THE DEVICE ON HEALTH

An Investigational Device Exemption ("IDE") study of the STAR Ankle was conducted (G000140). A total of 158 STAR Ankle patients and 66 arthrodesis control patients were enrolled in the pivotal multicenter clinical study. An additional continued access study was conducted with adverse event data available, at the time of database closure, on 424 patients. See **Table 2** below for a summary of rates of adverse events observed at the operative site for the pivotal and continued access studies.

Table 2. Summary of Adverse Events, Surgical Interventions and Major Complications at 24 Months[1]

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	p-value (STAR vs. Control)	STAR Continued Access (N=352)
Bone fracture	2 (3.0%)	28 (17.7%)	0.002	37 (10.5%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)	0.044	21 (5.0%)
Post-operative fracture	1 (1.5%)	14 (8.9%)	0.044	19 (5.4%)
Bony changes	0 (0%)	12 (7.6%)	0.02	15 (4.3%)
Pain	32 (48.5%)	69 (43.7%)	0.557	115 (32.7%)
Nerve injury	5 (7.6%)	32 (20.3%)	0.019	75 (21.3%)
Wound problem	4 (6.1%)	32 (20.3%)	0.009	65 (18.5%)
Surgical intervention	7 (10.6%)	26 (16.5%)	0.260	26 (7.4%)
Revision or removal	6 (9.1%)	12 (7.6%)	0.707	12 (3.4%)
Other intervention	1 (1.5%)	18 (11.4%)	0.016	15 (4.3%)
Major complication	1 (1.5%)	14 (8.9%)	0.074	17 (4.8%)
Infection	1 (1.5%)	2 (1.3%)	1	3 (0.8%)
Bone problems	0 (0%)	8 (5.1%)	0.109	10 (2.8%)
Wound problems	1 (1.5%)	5 (3.2%)	0.673	5 (1.4%)
Wound problems and infections	0 (0%)	1 (0.6%)	1	0 (0%)

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1 Not all 424 continued access patients had reached their 24 month follow-up as of the time of database closure on 12/1/2006. To permit a reasonable comparison to the pivotal study data, with the exception of intra-operative fracture, the adverse event rate for the continued access study has been calculated using data from the 352 patients who have reached 24 months post-procedure only. For the comparison of intra-operative fracture rate, all 424 continued access patients were analyzed.

In the STAR Ankle group, the most common adverse events were ankle and/or other pain, fracture, soft tissue edema, nerve injury, and skin necrosis.

3.8 POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There are no reasonably foreseeable adverse events that have not been observed in the STAR pivotal, bilateral and continued access studies.

3.9 NON-CLINICAL STUDIES

3.9.1 Biocompatibility

The biocompatibility of the STAR Ankle is demonstrated by the safe use of the patient contacting materials, CoCrMo, titanium plasma spray, UHMWPE, and stainless steel, in other legally marketed devices and, the company certifies to the biocompatibility of each of these materials.

3.9.2 Mechanical Testing

The company has conducted the following types of mechanical testing to validate the performance of the STAR Ankle: testing to evaluate the intrinsic stability of the device in rotation, anterior-posterior displacement, and medial-lateral displacement; finite element analysis to assess the stresses within the polyethylene component of the device; and wear testing. The results of these mechanical tests are summarized briefly below.

3.9.2.1 Intrinsic Stability Testing

Testing by an independent laboratory was conducted to measure the degree of constraint imposed by the ankle prosthesis in rotation, anterior-posterior, and medial-lateral directions. The degree of [redacted] results demonstrate that the STAR Ankle exhibits minimal constraint in the anterior-posterior, medial-lateral, and rotational modes. This low-constraint feature is considered favorable because it will provide load sharing with the soft tissues, thereby potentially reducing the stresses that may cause implant loosening and articular wear.

3.9.2.2 Finite Element Modeling

Finite element analysis of the STAR Ankle was performed to assess the internal and surface pressure distributions in the polyethylene component. Simulations were performed under several sets of conditions, [redacted]

3.9.2.3 Wear Testing

[redacted] The observed amount of wear was consistent with expectations based on published wear rates for hip prostheses and knee prostheses composed of similar materials. Even under these loading conditions, the prosthesis remained capable of proper articulation, with no functional failures. Particle analysis of the test fluid obtained during the simulator testing was performed to examine debris from each sample. [redacted] This result is consistent with a reduction in wear mechanisms. In all cases, the proportion of submicron particles was quite small.

3.10 CLINICAL STUDIES

3.10.1 European Clinical Studies

Between 1996 and 2004, at least 15 published articles have reported clinical results with the STAR Ankle. Several of these publications are larger series of 50 to 280 STAR Ankle replacements, with mean follow-up periods in the range of 3 to 6 years. All of the STAR Ankle studies reported good pain relief and improvement in symptoms, as well as improvements in range of motion and stability. Few device failures were reported in the first 2 years after implantation and failure rates after 5 years ranged from 5-15%, with a 200-case series demonstrating a cumulative 5-year survival rate of 92.7%.[2]

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[2] Wood PLR, Deakin S. Total ankle replacement: The results in 200 ankles. *JBJS (Br.)* 85B:334-341 (2003).

3.10.2 U.S. Clinical Studies (IDE G000140)

3.10.2.1 Introduction

Three multicenter, prospective clinical trials were conducted to evaluate the safety and efficacy of the STAR Ankle and are summarized in **Table 3** below.

Table 3. U.S. Clinical Studies

Clinical Study	Study Design	Objective	Number of Centers	Enrolled Patients
Pivotal	Non-randomized concurrent and historical control multicenter study	Evaluate the safety and efficacy of the STAR Ankle	10 STAR Ankle; 5 arthrodesis	158 STAR Ankle patients; 66 Arthrodesis patients
Bilateral	Single-arm multicenter study	Evaluate the safety of bilateral STAR Ankle implantation	6	21 Bilateral STAR Ankle patients
Continued Access	Single-arm multicenter study	Confirm the findings of the pivotal study	10	448 STAR Ankle patients

3.10.2.2 Pivotal Study

The pivotal study was a 2:1 (STAR Ankle to Control) multicenter, non-randomized, concurrent control clinical trial. The study was designed as a non-inferiority trial comparing the safety and efficacy of the STAR Ankle to Arthrodesis. The control group in the STAR Ankle pivotal trial consisted of concurrently recruited Arthrodesis patients for evaluation of efficacy, with a combination of concurrent Arthrodesis patients and historical Arthrodesis controls for the safety analysis. Efficacy measures collected consisted of the Buechel-Pappas Scale score ("Buechel-Pappas score"), ankle pain VAS, patient satisfaction (Coughlin rating scale), physical exam, and the SF-36. Safety was assessed based on adverse events and radiographic evaluations.

Eligibility Criteria

Subjects were considered for inclusion in the study if they met all of the following key criteria:

- Moderate or severe pain, loss of mobility and function of the ankle (total BP score of less than 50 and BP pain score of 20 or less).
- Primary arthritis, posttraumatic arthritis or rheumatoid arthritis.

- At least 6 months of conservative treatment[3] for severe ankle conditions, confirmed by the patient's medical history, radiographic studies and medication record.
- Patients must fail a trial of foot and ankle orthosis and/or analgesic medication for 3 months prior to inclusion in the study.
- Willing and able to give informed consent.

Subjects meeting any of the following criteria were excluded from the study:

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

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[3] Conservative treatments for a painful ankle included, but are limited to, the following: foot and ankle orthosis (to support and immobilize the ankle joint), counseling on changing employment (sitting job versus manual labor) and/or activity, or planned pain or anti-inflammatory medication management (to reduce or eliminate the pain).

- Pregnancy, avascular necrosis of the tibia, and significant bone tumor of the foot or ankle.

Description of Study Evaluations, Procedures and Assessments

Following surgery, the patient was typically immobilized for a period of approximately 6 weeks. During the first two weeks, weight-bearing was minimized. From 2 to 4 weeks post-surgery, the patient was permitted to bear 50% weight (in a removable cast), and at 4 weeks, the patient was permitted to bear full weight in cast. Gentle range of motion exercises were initiated after the fourth week. The cast was typically removed at 6 weeks unless a ligamentous reconstruction was carried out, in which case the cast was left on for a total of 8 weeks. Patients were asked to return for postoperative follow-up evaluations at 2-3 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months.

Endpoints

The primary efficacy endpoint was:

- Total Buechel-Pappas score[4] assessed at 1 year, with further confirmation at 2 years.

Secondary efficacy endpoints included:

- Buechel-Pappas subscales of function and range of motion
- Improvement in total Buechel-Pappas Scale of 40-points
- Pain Visual Analog Scale (VAS) (100mm scale)
- Patient satisfaction (Coughlin rating scale[5])
- Quality of Life (SF-36)
- Medication usage

Overall patient success was defined as an individual patient meeting the following four prongs of this composite endpoint:

- $\geq$ 40 point improvement in total Buechel-Pappas Scale score
- No device failures, revisions, or removals

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4 Buechel FF, Pappas MJ, Iorio LJ. New Jersey Low Contact Stress Total Ankle Replacement: Biomechanical Rationale and Review of 23 Cementless Cases. *Foot & Ankle* 8(6):279-290, 1988.

5 Coughlin MJ. Etiology and treatment of hallux valgus: Arthrodesis of the first metatarsophalangeal joint with mini-fragment plate fixation. *Orthopedics* 13(9):1037-1044, 1990.

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- Radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group)
- No major complications, defined as:
    - No significant infection requiring surgical intervention
    - No significant delayed wound healing, wound dehiscence, or skin necrosis requiring surgical intervention (including graft or free-flap procedures)
    - No significant postoperative fractures of adjacent bones (not caused by trauma) requiring surgical intervention, and
    - No significant bony changes of adjacent bones (cysts, osteolysis, avascular necrosis) requiring surgical intervention (including debridement or bone grafting).

The safety endpoint was defined as an individual patient meeting the following three prongs:

- No device failures, revisions, or removals
- Radiographic success (no radiographic evidence of loosening or migration in the STAR Ankle group; no radiographic evidence of non-union, delayed union, or malunion in the control arthrodesis group)
- No major complications (as defined above)

Statistical Analysis

The primary efficacy endpoint of mean total Buechel-Pappas score was compared between the two treatment groups using the method of Blackwelder[6] to determine if the overall outcome in the STAR Ankle group was not inferior to that of the arthrodesis group. In addition, based on the methodology proposed by Dunnett & Gent[7] and Morikawa & Yoshida,[8] a two-sample t-test was performed, without adjustment for multiple comparisons, to determine if the STAR outcome was also superior to arthrodesis.

The secondary endpoints of function and range of motion subscale scores were compared between treatment groups using a two-sample t-test to determine if function and range of motion with the STAR Ankle were superior to function and range of motion with arthrodesis. The percentage of

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6 Blackwelder WC. "Proving the Null Hypothesis" in Clinical Trials. *Controlled Clinical Trials* 3:345-353, 1982.

7 Dunnett CW, Gent M. An alternative to the use of two-sided tests in clinical trials. *Stat Med* 15:1729-1738, 1996.

8 Morikawa T, Yoshida M. A useful testing strategy in phase III trials: Combined test of superiority and test of equivalence. *J Biopharm Stat* 5(3):297-306, 1995.

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patients with a 40-point increase in total Buechel-Pappas score was compared between treatment groups using a Chi-square test. Pain VAS, patient satisfaction, and quality of life were compared between the groups using a two-sample t-test to determine whether these parameters were similar between the two groups.

The primary comparison was at 1 year, with further confirmation at the 2 year time point. Patient success was further evaluated with adjustments for differences in baseline characteristics performed using logistic regression techniques and propensity scores. Standard repeated measures analysis of variance techniques, such as Generalized Estimating Equations ("GEE"), were used to evaluate the outcomes at each time point simultaneously.

3.10.2.3 Bilateral Study

An arm of the pivotal study STAR arthroplasty treatment group was added to allow for the bilateral treatment of 21 patients. These patients were enrolled either from the original pivotal study or the continue access study after developing arthritis in the contralateral ankle, or directly into the bilateral study. The purpose of the study was to evaluate the safety of the STAR Ankle for patients with bilateral disease.

Study Population

Eligible subjects were patients with bilateral ankle disease requiring surgical intervention:

- Who had previously enrolled in the pivotal or continued access study because of single ankle disease and who subsequently developed disease in the contralateral ankle; or
- Who had not previously enrolled in the pivotal study.

Other eligibility criteria were the same as for the pivotal study.

Study Evaluations, Procedures, and Assessments

The assessments and procedures were the same as for the pivotal study, with the exception that a second arthroplasty procedure was performed on patients in the bilateral study, and certain efficacy measures were not collected in this study. Patients originally enrolled in the pivotal study were transferred to the bilateral study as of the time of implantation of the second STAR Ankle.

3.10.2.4 Continued Access Study

Enrollment of all planned arthroplasty patients in the pivotal trial was completed in 2001. Between 2002 and 2004, additional STAR Ankle patients were enrolled in the continued access study to be

conducted by investigators participating in the ongoing STAR Ankle arthroplasty pivotal study. The continued access study was approved for a total enrollment of 450 patients. The purpose of the continued access study was to evaluate the safety and efficacy of the STAR Ankle.

Study Population

The inclusion criteria for the continued access study were identical to those used in the pivotal study, with the exception that "Primary arthritis, posttraumatic arthritis or rheumatoid arthritis" was expanded to include metabolic disorders (*e.g.*, hemochromatosis). The exclusion criteria were also the same, with the exception that "Motor dysfunction due to neuromuscular impairment" was expanded to include "Motor dysfunction due to neuromuscular impairment, insulin dependent diabetes, peripheral neuropathy, or Charcot changes."

Study Evaluations, Procedures, and Assessments

Each patient underwent a baseline evaluation to determine eligibility and establish preoperative pain and functional status. Patients were asked to return for postoperative follow-up evaluations at 6 weeks, 6 months, 12 months, and 24 months.

The surgical technique was modified where it was recommended that two 0.062" K-wires be inserted into the malleolus prior to the tibial cut to prevent risk of intraoperative malleolar fracture in certain patients.

The assessments for the continued access study were identical to those for the pivotal study, with the addition of the AOFAS scale, which was included as an assessment tool at all follow-up visits in which the Buechel-Pappas score also was to be administered.

Endpoints

The endpoints for the continued access study were identical to those for the pivotal study, with the addition of the AOFAS score, which was included among the secondary efficacy endpoints.

3.10.2.5 Pivotal Study Results

As of the database closure, a total of 224 patients were enrolled in the pivotal study. Of these patients, 158 subjects were enrolled and treated in the arthroplasty group (or the STAR Ankle group) and the remaining 66 patients were enrolled and treated in the Arthrodesis group. The number of patients with 12 and 24 month data available, at the time of database closure, for each of these study follow-up evaluations is summarized in **Table 4**.

Table 4. Pivotal Study: Accountability by Visit

	Pre-op		2 Weeks		6 Weeks		3 Months		6 Months		12 Months		24 Months	
	C	S	C	S	C	S	C	S	C	S	C	S	C	S
Theoretical	66	158	66	158	66	158	66	158	66	158	66	158	66	158
Deaths (cumulative)	0	0	0	1	0	1	0	1	0	2	0	3	1	4
Failures[1] (cumulative)	0	0	0	0	0	0	0	1	0	1	0	1	0	2
Transferred to Bilateral Arm (cumulative)	0	0	0	0	0	0	0	0	0	0	0	2	0	2
Not Yet Overdue	0	0	0	0	0	0	0	0	0	0	1	0	3	0
Expected	66	158	66	157	66	157	66	156	66	155	65	152	62	150
Actual[2]	66	158	66	155	66	157	65	154	63	151	53	147	48	145
% Follow-up (based on Actual)	100%	100%	100%	98.7%	100%	100%	98.5%	98.7%	95.5%	97.4%	81.5%	96.7%	77.4%	96.7%

C=Control; S=STAR Ankle

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

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

Follow-up evaluations for STAR patients were completed for 96.7% (147/152) of expected patients at 12 months (cumulatively 3 deaths, 1 device failure, and 2 patients transferred to the bilateral group) and 96.6% (145/150) of expected patients at 24 months. Follow-up evaluations in the Arthrodesis group were completed for 81.5% (53/65) of the expected patients completing follow-up evaluations at 12 months and 77.4% (48/62) of expected patients completing evaluations at 24 months.

Study Administration Issues

Some patients were identified as having a major protocol deviation and were excluded from the per protocol analyses. The major protocol deviations were related to eligibility criteria (7 patients) and evaluation deviations (2 patients).

Analyses were based on the intent-to-treat ("ITT") patient population where that analysis population included all patients who enrolled in the study, where data were available. Additional analyses of the efficacy, safety and patient success rates were based on the Per Protocol population and the ITT

patient population. The Per Protocol population for a particular endpoint consisted of all ITT patients who had no major protocol deviations (as described above), patients with a visit within window, and who were "Completers" (*i.e.*, patients for whom the necessary data for a particular endpoint was present at the time of database closure). Patients who had the contralateral ankle treated, either before study entry, after study treatment, or by nature of transfer to the bilateral study arm, were considered bilateral in nature and were excluded from the Per Protocol population. The patient populations used for the analysis of efficacy, safety and patient success rates at 12 and 24 months are outlined in **Table 5**.

Table 5. Pivotal Study: Patient Populations for Endpoint Analysis

	12 Months						24 Months					
	Safety		Efficacy		Patient		Safety		Efficacy		Patient	
	C	S	C	S	C	S	C	S	C	S	C	S
All Data Available for Completers Analysis[1]	57	136	53	143	53	137	52	142	47	142	51	142
Per Protocol	50	122	46	130	46	124	40	126	36	127	40	128

[1]All Data Available for primary endpoint analysis only

Two patients were transferred to the bilateral group when a second procedure was performed on their contralateral ankle. These patients remained in the Per Protocol safety and efficacy analysis for the unilateral arm until the placement of the contralateral STAR Ankle. Following placement of the contralateral ankle, these patients were placed with the bilateral arm.

Baseline Demographics

Baseline demographics for both the STAR and Arthrodesis groups are outlined in **Table 6**. The average age of patients in the study was approximately 60 years, >90% were Caucasian, the average body mass index ("BMI") was approximately 28, and males and females were nearly equally represented. There was no significant difference ($p<0.05$) between study groups in the distribution of gender, smoking status, height, weight or BMI. There was a significant difference between groups in age, with the Arthrodesis patients being an average of 5 years younger than the STAR patients.

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Table 6. Pivotal Study: Baseline Demographics

	Control	STAR
Gender		
Male	30 (45.5%)	78 (49.4%)
Female	36 (54.5%)	80 (50.6%)
Race		
Caucasian	60 (90.9%)	152 (96.2%)
Hispanic	3 (4.5%)	1 (0.6%)
African American	2 (3%)	4 (2.5%)
Other	1 (1.5%)	1 (0.6%)
Current Smoker	5 (13.9%)	15 (20%)
History of Smoking	31 (47%)	74 (47.1%)
	Mean (sd)	**Mean (sd)**
Age (years)	57.1 (12.3)	62.7 (12.6)
Height (inches)	67.0 (4.5)	67.3 (3.7)
Weight (pounds)	185.6 (38.6)	180.9 (34.9)
BMI	29.1 (5.8)	28 (4.8)

Table 7 summarizes the primary diagnoses for both the STAR and Arthrodesis groups. There was no significant difference between groups with regard to primary diagnosis, with posttraumatic arthritis being the leading primary diagnosis for both groups.

Table 7. Pivotal Study: Primary Diagnosis

Primary Diagnosis	Control	STAR
Primary Arthritis	19 (28.8%)	62 (39.2%)
Post Traumatic Arthritis	43 (65.2%)	76 (48.1%)
Rheumatoid Arthritis	4 (6.1%)	20 (12.7%)

Based on the physical exam, the general condition of patients was comparable in both groups, with a high percentage considered to be in either good or excellent condition, as seen in **Table 8**. A high percentage of patients in both groups had either severe or totally disabling pain, with a significant

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difference in pain categories between groups. STAR Ankle patients had higher, but not statistically significant, baseline pain VAS than did the Arthrodesis patients prior to surgery. There were no significant differences in baseline total physical or mental SF-36 Scale scores.

Table 8. Pivotal Study: Baseline Evaluations

Physical Exam	**Control**	**STAR**
General Condition	**n (%)**	**n (%)**
Poor	1 (1.5%)	1 (0.6%)
Fair	3 (4.5%)	15 (9.5%)
Good	53 (80.3%)	75 (47.5%)
Excellent	9 (13.6%)	67 (42.4%)
Buechel-Pappas[1]		
Excellent (86-100)	0	0
Good (71-85)	0	0
Fair (55-70)	6 (9.1%)	4 (2.5%)
Poor (< 55)	60 (90.9%)	154 (97.5%)
	Mean (sd)	**Mean (sd)**
VAS	66.3 (18.9)	71.1 (16.7)
SF-36		
Total Physical Score	45.2 (8.6)	44.1 (6.9)
Total Mental Score	48.2 (11.1)	46.7 (10.8)

[1]Score Range

Tables 9A and 9B summarize previous surgeries to the affected ankle and baseline radiographic data in study patients. No statistical significance between group differences were found for the number of prior procedures or for baseline radiographic data.

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Table 9A. Pivotal Study: Baseline Previous Surgeries on Affected Ankle

	Control	STAR
Previous Surgeries - Affected Ankle		
0	26 (39.4%)	65 (41.1%)
1	18 (27.3%)	47 (29.7%)
2	11 (16.7%)	26 (16.5%)
3	8 (12.1%)	16 (10.1%)
4+	3 (4.6%)	4 (2.5%)

Table 9B. Pivotal Study: Baseline Radiographic Data

	Control	STAR	p-value
Tibial Malleolar Joint Appearance - Decreased Joint Space			
Yes	61 (92.4%)	152 (96.2%)	0.308
No	5 (7.6%)	6 (3.8%)	
Major Degenerative Changes - Osteophytes/Bone Spurs			
Yes	62 (93.9%)	154 (97.5%)	0.239
No	4 (6.1%)	4 (2.5%)	
Radiographic Evidence of Adjacent Joint Fusion			
Yes	3 (4.5%)	17 (10.8%)	0.198
No	63 (95.5%)	141 (89.2%)	

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Efficacy Results

Overall patient, efficacy and safety success rates at 24 months are summarized in **Table 10**.

Table 10. Pivotal Study: Success Rates by Treatment Group[9]

24 Month Success Rates	Control			STAR			Difference in Success Rates
	N	N	%	n	N	%	
Patient Success Rates							
Per Protocol	6	40	15.0%	64	128	50.0%	35.0%
Completers	7	51	13.7%	70	142	49.3%	35.6%
Efficacy Success Rates							
Per Protocol	6	36	16.7%	76	127	59.8%	43.2%
Completers	7	47	14.9%	83	142	58.5%	43.6%
Safety Success Rates							
Per Protocol	33	40	82.5%	99	126	78.6%	-3.9%
Completers	43	52	82.7%	113	142	79.6%	-3.1%

At 24 months, overall patient success was statistically significantly higher ($p<0.001$) in STAR Ankle patients as compared to Arthrodesis for all analysis populations (50% versus 15% based on the Per Protocol population). The odds ratio for patient success when adjusted for age, baseline Buechel-Pappas score, and primary diagnosis for the STAR Ankle versus control was 5.2 in favor of the STAR Ankle with a 90% confidence interval of (2.3, 11.8).

As shown in **Table 10**, significantly higher efficacy success rates ($p<0.001$), based on a 40 point improvement in Buechel-Pappas Scale score, were observed at 24 months among the STAR Ankle patients compared with the Arthrodesis patients for both the Completers and for the Per Protocol population (59.8% versus 16.7% based on the Per Protocol population).

Arthrodesis Completers had somewhat higher safety success rates than STAR Ankle patients at 24 months (82.7% and 79.6%). It is important to note that the rates of important adverse events in the STAR only continued access study were substantially improved over the pivotal study, including

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9 "Completers" analysis examines patients with the data necessary to determine safety and efficacy at each respective evaluation time point.

rates of surgical interventions and major complications, which are important in the assessment of STAR Ankle safety success rates.

Primary Efficacy Endpoint: Total Buechel-Pappas Score

Table 11 shows the primary efficacy endpoint results. **Table 11** summarizes the mean Buechel-Pappas score at 24 months and the change in Buechel-Pappas score at 24 months from baseline. Comparisons between groups were made using the Wilcoxon Test, due to the non-normality of the Buechel-Pappas score distribution. All comparisons showed a significantly higher Buechel-Pappas score in the STAR Ankle group when compared with the Arthrodesis group with $p<0.001$. The Buechel-Pappas score at 24 months remained significantly higher in the STAR Ankle group when using various imputation methods to account for missing data including: a multiple imputation method and a last observation carried forward method.

Table 11. Pivotal Study: Mean Buechel-Pappas Score at 24 Months

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

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Efficacy Evaluations by Visit

Table 12 summarizes mean improvement in Buechel-Pappas score from baseline at 3, 6, 12 and 24 months post procedure.

Table 12. Mean Improvement in Buechel-Pappas Score from Baseline

	3 Months			6 Months			12 Months			24 Months		
	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value	Control	STAR	p-value
Deformity												
N	62	152	<0.001	62	149	<0.001	53	144	<0.001	48	143	<0.001
Mean (SD)	0.2 (1.1)	0.9 (1.4)		0.4 (1.2)	1.2 (1.5)		0.5 (1.2)	1.8 (1.3)		0.4 (1.2)	1.9 (1.3)	
Range	-3 , 3	-3 , 4		-2 , 4	-3 , 5		-2 , 4	-1 , 5		-2 , 4	-1 , 5	
Function												
N	63	152	<0.001	62	150	<0.001	53	143	0.002	48	143	0.004
Mean (SD)	-2.3 (10.6)	9.7 (7.6)		6.6 (8.5)	12.6 (7.4)		9.5 (8.1)	13.6 (7.9)		9.7 (8.7)	13.4 (7.3)	
Range	-20 , 26	-14 , 27		-16 , 26	-12 , 32		-22 , 28	-15 , 32		-9 , 28	-16 , 30	
Pain												
N	63	152	0.842	62	150	0.039	53	143	0.126	48	143	0.142
Mean (SD)	19.6 (8.3)	19.3 (8.9)		17.4 (9.3)	20.1 (8.1)		18.3 (9.6)	20.6 (9)		19.2 (9.4)	21.5 (9.6)	
Range	0 , 30	0 , 40		0 , 30	0 , 40		0 , 35	-10 , 40		0 , 30	-10 , 40	
ROM												
N	62	152	<0.001	62	149	<0.001	53	144	<0.001	47	143	<0.001
Mean (SD)	-4.6 (5.1)	2.5 (3.9)		-4.5 (5)	3.4 (3.9)		-4.9 (5.2)	3.7 (3.7)		-3.7 (5.1)	3.6 (3.7)	
Range	-13 , 6	-8 , 15		-13 , 8	-8 , 15		-13 , 8	-4 , 15		-13 , 6	-4 , 15	
Total												
N	62	152	<0.001	62	149	<0.001	53	143	<0.001	47	142	<0.001
Mean (SD)	12.2 (15.2)	32.4 (13.8)		19.9 (16.6)	37.5 (13.2)		23.3 (15.9)	39.7 (15)		26.3 (17.1)	40.5 (15.1)	
Range	-22 , 45	-12 , 61		-18 , 55	0 , 69		-14 , 61	-18 , 70		-17 , 57	-1 , 73	

All p-values are based on a chi-square test or a t-test unless otherwise noted.

Table 13 summarizes pain Visual Analog Scale (VAS), SF-36, physical exam results and patient satisfaction. Prior to surgery, STAR Ankle patients had a higher level of pain (mean of 71.1) than did Arthrodesis patients (mean of 66.3). At all follow-up evaluations, pain levels in both groups dropped substantially. There was a larger improvement in mean STAR Ankle patient VAS scores over the course of the study as opposed to Arthrodesis patients (STAR Ankle patient mean improvement of 51 ± 24.3 versus 43.5 ± 27.0 for Arthrodesis patients at 12 months).

Based on the SF-36, there was no consistent difference between the STAR Ankle or Arthrodesis groups in quality of life that persists throughout the study. Patients' general condition continued to be significantly better in the STAR Ankle group at all follow-up visits from 3 to 12 months. The condition of STAR Ankle patients substantially improved in the 3 months following surgery (89.9% of patients were rated good or excellent preoperatively, improving to 98.1% at 3 months) and remained high throughout the study, maintaining a significantly higher percentage of patients in good or excellent condition as compared to Arthrodesis patients.

Table 13. Pivotal Study: Mean Pain VAS Improvement from Baseline; Mean Change in SF-36 from Baseline; Physical Exam Results; and Patient Satisfaction at 12 and 24 Months

	12 Months		24 Months	
	Control	**STAR**	**Control**	**STAR**
VAS	43.5 (27.0)	51.1 (24.3)	44.6 (27.3)	51.8 (26.5)
SF-36				
Total Physical Score	10.5 (8.2)	12.6 (10.2)	11.0 (9.5)	11.3 (10.3)
Total Mental Score	7.8 (6.8)	7.8 (11.5)	3.2 (10.2)	6.6 (11.2)
Physical Exam				
General Condition				
Poor				
Fair	2 (3.8%)	5 (3.4%)	7 (14.6%)	10 (6.9%)
Good	36 (67.9%)	57 (39%)	22 (45.8%)	57 (39.6%)
Excellent	15 (28.3%)	84 (57.5%)	19 (39.6%)	77 (53.5%)
Patient Satisfaction				
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%)

Safety Results

Table 14 summarizes adverse events at the operative site up to 24 months. Fractures occurred in 17.7% of the STAR patients and in 3.0% of the Arthrodesis patients. The majority of these fractures did not impact patient outcome. Only one of these fractures (a medial malleolar fracture) failed to heal within 12 weeks of surgery. Due to the incidence of intraoperative medial malleolar fractures,

the STAR Ankle surgical protocol was altered to include a recommendation to take specified protective measures to prevent intraoperative medial malleolar fractures, including use of 0.062" K-wires.

Table 14. Adverse Events up to 24 Months

Adverse Events	Control (N=66)	STAR Pivotal (N=158)
Bone fracture	2 (3.0%)	28 (17.7%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)
Post-operative fracture	1 (1.5%)	14 (8.9%)
Bony changes	0 (0%)	12 (7.6%)
Pain	32 (48.5%)	69 (43.7%)
Nerve injury	5 (7.6%)	32 (20.3%)
Wound problem	4 (6.1%)	32 (20.3%)
Surgical intervention	7 (10.6%)	26 (16.5%)
Revision or removal	6 (9.1%)	12 (7.6%)
Other intervention	1 (1.5%)	18 (11.4%)
Major complication	1 (1.5%)	14 (8.9%)
Infection	1 (1.5%)	2 (1.3%)
Bone problems	0 (0%)	8 (5.1%)
Wound problems	1 (1.5%)	5 (3.2%)
Wound problems and infections	0 (0%)	1 0.6%)

Adverse events referable to the operative site occurred in 26.6% (42/158) of STAR Ankle patients and 6.2% (4/66) of Arthrodesis patients. The majority of adverse events resolved either without or with treatment.

Five (5) patients expired during the first 24 months of follow-up, 4 in the STAR Ankle group and 1 Arthrodesis patient. One (1) STAR patient suffered a fatal pulmonary embolism 7 days after placement of the device. Pulmonary embolism is a known complication of lower extremity surgery in general, the STAR Ankle itself nor anything specific to the STAR surgery were not believed to have been a factor. The remaining 4 patient deaths were determined by the study investigators and medical monitors not to be study-related. One (!) patient expired 94 weeks after surgery as a result of an exacerbation of symptoms and side effects following a stroke. One (1) patient who had a history of coronary artery disease and hypertension died 13 weeks after surgery from a myocardial infarction. One (!) patient was diagnosed with metastatic cancer to the lung 6 weeks following surgery to place the STAR device, and subsequently succumbed to this disease. One patient died 49 weeks after surgery secondary to congestive heart failure and subsequent pneumonia, where this patient had a history of hypertension and congestive heart failure.

Surgical Interventions

Table 15 summarizes the surgical interventions performed up to 24 months of follow-up. Among the 26 STAR patients that had surgical interventions, there were 2 patients that had a device removal, 11 patients that had a revision, 8 patients that had a reoperation and 10 that had other interventions performed. In the Arthrodesis group, the majority of the surgical interventions were related to hardware removal, although not all hardware removed was directly related to this fusion procedure.

Table 15. Surgical Interventions - Summary of Interventions

	Control	STAR
Surgical Interventions	**9**	**33**
Patients with Surgical Interventions	**7 (10.6%)**	**26 (16.5%)**
Intervention Type		
Revision	3 (4.5%)	11 (7.0%)
Removal	4 (6.1%)	2 (1.3%)
Reoperation	0	8 (5.1%)
Other Intervention	1 (1.5%)	10 (6.3%)
Intervention Class by Subgroup		
Minor Operative Site Procedures	4 (6.1%)	9 (5.7%)
Hardware Removal	4 (6.1%)	1 (0.6%)
Excision Exostosis		5 (3.2%)
Minor wound problem		3 (1.9%)
Synovectomy		0
Major Operative Site Procedures	3 (4.5%)	19 (12.0%)
Component removal		10 (6.3%)
Infection	1 (1.5%)	1 (0.6%)
Bone graft for osteolysis		0
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	2 (3.0%)	3 (1.9%)
None		3 (1.9%)
Hardware removal	1 (1.5%)	0
Fusion, adjacent joint	1 (1.5%)	

Numbers and percents are patient based.

*Missing complications data for 2 Arthrodesis and 2 STAR patients.

Table 16 summarizes major complications, which were defined as any surgical intervention to the treated ankle that was a result of an infection, wound problem, or bone problem such as osteolysis,

cyst formation, or non-traumatic fracture up to 24 months follow-up. Major complications occurred in a higher percentage of STAR patients than in study patients undergoing arthrodesis, although the rate of major complications was low in both groups. Most major complications involving STAR patients were wound or fracture related. The anterior approach necessary to place the STAR Ankle more commonly results in wound problems as compared to the lateral approach used in arthrodesis. Infection is more commonly encountered where the integrity of the skin is compromised, such as is the case with the wound problems encountered with the STAR Ankle. Osteolysis and cyst formation are known complications of joint prostheses, and have been observed in other weight-bearing total joint prostheses.

Table 16. Pivotal Study: Major Complications

	Patients	
	Control	**STAR**
Major Complication Classification		
Any Major Complication	1 (1.5%)	14 (8.9%)
Wound Problems	1 (1.5%)	5 (3.2%)
Infection	1 (1.5%)	2 (1.3%)
Bone Problems		8 (5.1%)
Wound Problems and Infection		1 (0.6%)

The overwhelming majority of Arthrodesis patients eventually achieved union (93.3%) with only a small percentage of patients reported by study investigators as having delayed union (3.8%), malunion (1.6%) or nonunion (2.2%). Nevertheless, only 46% of the patients were at full weight bearing within three months. For the STAR Ankle patients, the percentage of patients considered to be failures on radiographic data at 24 months was 5.8%.

Meta-Analysis Results

A meta-analysis of the published arthrodesis literature was conducted to supplement pivotal study arthrodesis safety data. The meta-analysis articles were selected on the basis of patient populations similar to the pivotal study, with similar preoperative ankle diagnoses necessitating surgery (primary arthritis, posttraumatic arthritis, or rheumatoid arthritis).

Overall, the historical complication rates for Arthrodesis were comparable to the rates observed for Arthrodesis patients and STAR Ankle patients in the STAR pivotal study. This meta-analysis

indicates that safety of the results observed among in the pivotal study is representative of the historical controls.

3.10.2.6 Bilateral Study Results

Patient enrollment in the bilateral study began with FDA approval of the bilateral arm IDE on April 6, 2001. As of database closure, data was available on a total of 16 patients in the bilateral study and a total of 27 ankles. All patients received bilateral STAR Ankle arthroplasty devices. Four (4) of the 16 patients reported in this section were originally enrolled in the pivotal study but were transferred to the bilateral arm upon placement of a second STAR Ankle.

Two (2) patient deaths occurred by 24 months. Neither of these deaths were believed to be device-related.

Most patient demographics and baseline medical history were similar to those in the pivotal study. However, there was a lower percentage of patients with posttraumatic arthritis in the bilateral study (13.3% of first and no second bilateral ankles implanted were secondary to posttraumatic arthritis, as compared 48.1% of pivotal study patients) and a lower percentage of bilateral patients that had surgery to the affected ankle prior to STAR placement.

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

A total of 3 surgical interventions occurred during the course of the bilateral study. These surgical interventions (component removal, fusion of an adjacent joint, and excision of an exostosis) were among the most frequently encountered interventions seen in the pivotal study. No major complications occurred in the bilateral study.

Data from the bilateral study suggest that there is no increased safety risk when the STAR Ankle is implanted bilaterally in patients requiring treatment of ankle arthritis that has failed six months of conservative therapy.

3.10.2.7 Continued Access Study Results

Accountability

At the time of database closure, information was available on 424 patients who had been implanted with the STAR ankle. All continued access patients were treated at the same 10 clinical centers participating in the STAR Ankle arm of the pivotal study.

Patient follow-up was approximately 84% through 12 months and approximately 66% through 24 months. There were only 5 patient withdrawals from the study. Three (3) patients received a second STAR device in their contralateral ankle and were transferred to the bilateral arm of the STAR clinical study. Data from these 3 patients before the time of the second ankle implant is presented in this section. Three patients expired during the course of the study, with none of these deaths considered device-related.

Patient demographics and baseline disease history for the continued access studies were largely comparable to those of STAR Ankle patients in the pivotal trial. Some differences in primary diagnoses were noted with a higher percentage of posttraumatic arthritis in the continued access study as compared to the pivotal study (62.3% versus 48.1%) and a lower percentage of primary arthritis (21.0% versus 39.2%). Patients with a primary diagnosis of a metabolic disorder (9.9%) were also treated in the continued access study.

There were no notable differences in baseline evaluations or operative procedures for the continued access patients as compared to the pivotal study.

Endpoint Success Rate Results

The safety profile at 24 months was obtained by comparing the composite safety success rate between the control patients and the subset of STAR continued access patients who had independent radiographic results. (Independent radiographic reviews were performed for the 150 patients in the first arm of the continued access study only, and of these 150 patients, 85 had 24-month independent radiographic data available.) This allowed a fair comparison of the two groups based on the same safety success criteria. In this comparison, the safety success rate was higher in the STAR continued access group (for those subjects with completed independent radiographic review) than that in the pivotal study control group (90.1% and. 82.7%, respectively). The results are shown in **Table 18**.

Table 18. Success Rates at 24 months

	Control			STAR			Difference in Success Rates
	N	N	%	n	N	%	
	Control			STAR			Difference in Success Rates
24 Month Success Rates	N	N	%	n	N	%	
24 Month Patient Success Rates							
Per Protocol	6	40	15.0%	60	78	76.9%	61.9%
Completers	7	51	13.7%	62	81	76.5%	62.8%
24 Month Efficacy Success Rates							
Per Protocol	6	36	16.7%	67	80	83.8%	67.1%
Completers	7	47	14.9%	70	83	84.3%	69.4%
24 Month Safety Success Rates							
Per Protocol	33	40	82.5%	70	77	90.9%	8.4%
Completers	43	52	82.7%	73	81	90.1%	7.4%

Additionally, when compared with STAR patients in the pivotal study, patient success at 24 months in the continued access study was substantially higher than comparable figures for STAR patients in the pivotal study (76.9% versus 50%, with a Per Protocol analysis). Efficacy success at 24 months in the continued access study was substantially higher than comparable figures seen in the pivotal study (83.8% as compared to 59.8% at 24 months, with a Per Protocol analysis). As with efficacy success rates, safety success rates were substantially higher in the continued access study in comparison with the pivotal data (90.9% versus 78.6% at 24 months, with a Per Protocol analysis). The improvement in the safety success rate in the continued access study may be, in part, attributed to minor refinements to the STAR surgical technique that grew out of experience in the pivotal study and that were implemented prior to initiation of the continued access study.

As with STAR patients in the pivotal study, mean Buechel-Pappas score demonstrates substantial improvement at 12 and 24 months as compared to baseline. Improvement in the continued access study was greater than that seen in the pivotal study (45.8 versus 39.7 in the pivotal study at 12 months, and 46.7 versus 40.5 at 24 months). These results support those of the pivotal study.

Safety Results

Like STAR patients in the pivotal study, adverse events most commonly encountered by continued access patients included bone fracture, bony changes, nerve injury, infection, device subsidence, soft tissue edema, and wound problems. **Table 19** summarizes adverse events in the pivotal and continued access studies up to 24 months follow-up. As outlined below, most adverse events were substantially lower in the continued access study as compared to STAR Ankle patient in the pivotal study.

Table 19. Adverse Events up to 24 Months in Pivotal and Continued Access Studies[10]

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	p-value (STAR vs. Control)	STAR Continued Access (N=352)
Bone fracture	2 (3.0%)	28 (17.7%)	0.002	37 (10.5%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)	0.044	21 (5.0%)
Post-operative fracture	1 (1.5%)	14 (8.9%)	0.044	19 (5.4%)
Bony changes	0 (0%)	12 (7.6%)	0.02	15 (4.3%)
Pain	32 (48.5%)	69 (43.7%)	0.557	115 (32.7%)
Nerve injury	5 (7.6%)	32 (20.3%)	0.019	75 (21.3%)
Wound problem	4 (6.1%)	32 (20.3%)	0.009	65 (18.5%)
Surgical intervention	7 (10.6%)	26 (16.5%)	0.260	26 (7.4%)
Revision or removal	6 (9.1%)	12 (7.6%)	0.707	12 (3.4%)
Other intervention	1 (1.5%)	18 (11.4%)	0.016	15 (4.3%)
Major complication	1 (1.5%)	14 (8.9%)	0.074	17 (4.8%)
Infection	1 (1.5%)	2 (1.3%)	1	3 (0.8%)
Bone problems	0 (0%)	8 (5.1%)	0.109	10 (2.8%)
Wound problems	1 (1.5%)	5 (3.2%)	0.673	5 (1.4%)
Wound problems and infections	0 (0%)	1 (0.6%)	1	0 (0%)

10 Not all 424 continued access patients had reached their 24 month follow-up as of the time of database closure on 12/1/2006. To permit a reasonable comparison to the pivotal study data, with the exception of intra-operative fracture, the adverse event rate for the continued access study has been calculated using data from the 352 patients who have reached 24 months post-procedure only. For the comparison of intra-operative fracture rate, all 424 continued access patients were analyzed.

Surgical Interventions

Surgical interventions were performed in 39 patients (9.2% of the 424 patients with data available) throughout the course of the continued access study. The surgical interventions consisted of 12 patients with revisions, 9 patients with removals, 10 patients with re-operation and 15 patients with other interventions. The rate of surgical interventions decreased in the continued access study, when compared to the pivotal study.

Major Complications

Major complications in the continued access study occurred at a lower rate than seen with STAR patients in the pivotal study with a total of 28 events, for a rate of 6.6%, occurring in 22 patients (5.2% of the 424 patients with data available) throughout the course of the continued access study. The major complications were due to wound problems (6 patients), infection (4 patients) and bone problems (13 patients), these are the same complications seen in the pivotal study, but the rate of major complications was lower in the continued access study.

3.10.2.8 Conclusions

Safety success rates were similar between the pivotal STAR Ankle and Arthrodesis with all available data. At 24 months, safety success rates in the pivotal study were 79.6% and 82.7% for the STAR Ankle and Arthrodesis, respectively.

Following any ankle surgery, there are known adverse events which include bone fracture, bone changes, infection, nerve injury, pain, soft tissue edema, and wound problems. There may also be loosening, instability, or failure of any surgical hardware involved, whether those devices consist of surgical screws or a complex arthroplasty device such as the STAR Ankle. Additional surgery may be necessary to correct some of these problems. While data from the clinical studies suggest a somewhat higher rate of certain adverse events for the STAR Ankle, the majority of these adverse events were minor and resolved without long-term consequences for STAR patients.

The risk of intraoperative fracture was mitigated by a change in surgical technique undertaken during the pivotal trial when this fracture risk was identified, which involved the placement of two K-wires in the malleolus for the duration of surgery in patients at risk for fracture. In addition, the continued access study used new and modified surgical instruments, as well as generally smaller STAR components to further reduce fracture risk. Moreover, the decreasing rate of adverse events in STAR patients seen from the pivotal study to the continued access study suggests that the adverse event rates decrease with increasing surgeon experience and refinement of surgical technique.

The improved mobility afforded by the STAR Ankle has increasing benefits with passing time. The benefits of the STAR Ankle are supported by the significantly higher overall patient success rates seen at 24 months in comparison with arthrodesis in the pivotal trial (50% versus 15% at 24 months, per protocol analysis). Similarly, STAR patients showed significantly greater improvements in their total Buechel-Pappas scores at 12 and 24 months as compared to Arthrodesis patients at 12 and 24 months. Data from the continued access study reinforces the substantial improvement in total Buechel-Pappas score seen in the pivotal study. These substantial clinical benefits clearly outweigh the risks to patients seen with the STAR Ankle, particularly given that these risks are clinically comparable to arthrodesis, a surgical therapy that offers considerably less patient benefit.

Learning Curve

The learning curve for a surgeon new to the STAR Ankle could be as few as 15 patients. The effect of the learning curve for the STAR ankle was evaluated by comparing the rates of intra-operative fracture, major complications (wound/infection or bony changes), and surgical intervention. The rate of intra-operative fracture, the rate of surgical revision/removal, and the rate of major complications relating to wound problems and infections all showed a steady decline from earlier to later cases. The rates for intra-operative fracture and surgical revision/removal were significantly lower after the first 15 cases in the continued access study than in the pivotal study. With the increased awareness and training on the anterior surgical approach occurring across the foot and ankle surgical community, new surgeons are likely to resemble the STAR investigators towards the end of their learning curve. This is confirmed by the experience of three investigators new to the STAR Ankle who performed their first cases in the course of the continued access study. The rates of intra-operative fracture, major complication and surgical revision or removal for these new investigators were substantially similar to the complication rates of other surgeons in the continued access study who had participated in the pivotal study.

Overall Conclusions

The valid scientific evidence presented in this PMA demonstrates that the STAR Ankle is safe and effective in the treatment of ankle arthritis that has failed six months of conservative therapy. In the majority of efficacy parameters measured (including overall patient success, total Buechel-Pappas score, 40 point or greater improvement in Buechel-Pappas Score), the STAR Ankle showed favorable results when compared to ankle arthrodesis. The primary efficacy parameter of mean total Buechel-Pappas Score was shown, not only to be non-inferior to ankle arthrodesis, but also superior to arthrodesis. The data further demonstrates that the safety of the STAR Ankle is comparable to that of Arthrodesis patients. Data from the continued access study confirms the favorable efficacy performance of the STAR Ankle and demonstrates an improvement in the rate of adverse events, surgical interventions and major complications as compared to STAR patients in the pivotal study.

This improved safety profile suggests that modifications to surgical techniques and procedures undertaken during the course of the pivotal study were successful in addressing potential safety issues with the STAR Ankle.

3.11 PANEL RECOMMENDATIONS

[TBD]

3.12 CDRH DECISION

[TBD]

3.13 APPROVAL SPECIFICATIONS

[TBD]

LINK

S.T.A.R.
Scandinavian Total Ankle Replacement

Surgical Technique

Rx Only

Surgical Technique Manual

The Surgical Technique manual that follows contains the materials provided to the STAR Ankle investigators during all IDE-covered clinical trials. However, this manual does not fully incorporate all modifications to the surgical technique and procedures described in company's PMA filing as amended and Section 2.1.5 of the Clinical Summary of this Panel Pack. Link Orthopaedics intends to fully integrate these modifications in an updated Surgical Technique manual which will be provided to FDA at a later date.

Changes in surgical technique include:

- General downsizing of STAR Ankle talar components. Prior to commencement of the continued access study, the decision was made to systematically use the smaller of two metal component sizes where a patient fell between two component sizes, as opposed to using the larger component, in order to decrease the bony stress that may results from use of a larger component. Use of a smaller component also permits the resection of a smaller amount of bone from the malleoli, which may also mitigate the risk of fracture.
- General use of a thicker polyethylene mobile bearing to reduce potential wear.
- General lengthening of the anterior surgical incision to permit needed retraction while minimizing the risk of tissue damage.
- Elimination of self-retaining retractors in favor of frequently repositioned hand retractors to minimize the risk of tissue trauma.
- Elimination of the use of skin staples in favor of a two-layer suture closure technique.
- A recommendation was provided to surgeons for the prophylactic protection against intra-operative medial malleolar fractures. Specifically, in instances where there is high risk of malleolar fracture, it was recommended that two .062" 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.
- Modification of captured tibial saw alignment guides to decrease the possibility of bony nicks and notches, reducing the risk of subsequent fracture.
- Medial/lateral adjustable guide block modification to allow more precise device placement, reducing the risk of fracture and bone problems.
- Addition of talar trials and talar tamp to assist in proper device placement, reducing the risk of fracture and bone problems.

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LINK® S.T.A.R. Scandinavian Total Ankle Replacement

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Description

Overview

The STAR Ankle system comprises the ankle prosthesis itself, which includes three functional components, and a set of customized accessory instruments that are used in the surgical procedure. The three principal components of the prosthesis are:

- A metal tibial component with titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing; and
- A metal talar component with titanium porous plasma spray coating.

The intermediate UHMWPE mobile bearing articulates on the tibial and talar metal implant surfaces, as shown in the photograph of the three components of the STAR Ankle system below:

The STAR Ankle is designed to replace a portion of the tibial and talar components of the normal ankle joint, while preserving range of motion as much as possible. As illustrated in **Table 1** below, the design characteristics of the STAR Ankle correspond closely to the normal ankle joint.

Table 1: Comparison of Design Characteristics of the STAR Ankle to the Normal Ankle Joint

Design Feature	Normal Ankle	STAR Ankle Prosthesis
Congruency	96%	100%
Rotation	12-15° talus rotation	12-15° talus rotation plus tibial-meniscal rotation
Extension/flexion (radiographic)	10/30°	7/20°

There are two bearing surfaces in the STAR Ankle: (1) the interface between the upper side of the UHMWPE mobile bearing and the facing surface of the tibial plate, and (2) the interface between the lower surface of the UHMWPE mobile bearing and the facing surface of the talar component. The tibial plate has one flat surface and one surface with two raised cylindrical barrels oriented in the anterior/posterior direction. The upper flat surface of the UHMWPE mobile bearing slides against the flat surface of the tibial plate. The projecting cylinders of the tibial plate serve to fix the device to bone at the distal tibia. The lower surface of the UHMWPE mobile bearing is concave, fitting against the convex upper surface of the talar component.

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Description

The mobile bearing design of the device is intended to reduce the shear and torque forces on the UHMWPE mobile bearing, which can lead to loosening of either metal component, and to decrease stress at the metal/bone interface. The sloped sides are designed to improve the weight bearing characteristics of the talar component.

Components

Tibial Plate

When viewed from the top, the tibial plate has a trapezoidal shape with rounded corners. This component is manufactured from cobalt chromium molybdenum (CoCrMo) per ASTM F-75. The smaller end of the wedge is oriented towards the posterior aspect of the ankle joint. This wedge is shaped to conform to the existing anatomy and, thereby, reduces the need to remove excess bone from inside the joint. On the proximal surface of the tibial plate, two parallel cylindrical barrels are positioned equidistant from the center of the plate running anterior to posterior for bone fixation. These cylinders must be inserted into hard subchondral bone.

[redacted]

Tibial plates are available in five sizes with varying widths and lengths: extra-small (30mm x 30mm), small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm). Tibial plates for revision procedures are available in small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm) sizes. The [redacted]

The tibial plate is coated on the bone-opposing surfaces with a titanium plasma spray porous coating. The tibial plate is intended to be press-fit without the use of cement, and should rest on anterior and posterior cortical bone. The stemmed tibial components are uncoated and have a matte finish where they interface with bone.

UHMWPE Mobile Bearing

The polyethylene mobile bearing is manufactured from Ultra High Molecular Weight Polyethylene ("UHMWPE"), which is machined from medical grade extruded plate stock and conforms to ASTM F-648. [redacted] Revision mobile bearings are available in sizes of 11mm, 12mm, 13mm, and 14mm.

Description

Talar Component

The talar component is designed as an anatomical prosthesis to cover the talar dome, anterior, posterior, and medial and lateral facets. Like the tibial plate, this component is manufactured from CoCrMo. The talar component is designed to minimize the amount of bone that must be removed. From the apex of the dome, the walls slope outwards to conform to the normal bone anatomy. The component is offered in five sizes: extra-extra-small (28mm x 29 mm), extra-small (30mm x 31mm), small (34mm x 35mm), medium (36mm x 35mm), and large (38mm x 35mm), and in both left- and right-sided configurations.

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

As with the tibial plate, the talar component is also provided with a titanium plasma spray porous coating.

Indications and Contraindications

INDICATIONS FOR USE

Link Orthopaedics' ("Link") Scandinavian Total Ankle Replacement ("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 arthritis, or post-traumatic arthritis. 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, WARNINGS, and PRECAUTIONS

Contraindications:

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

Warnings/Precautions:

- Only implant the STAR Ankle after adequate training and familiarity with the surgical technique manual, to avoid increased risk of device failure due to improper surgical technique.

- Do not use STAR Ankle components in combination with prosthesis components made by other manufacturers, because design, material, or tolerance differences may lead to premature device and/or functional failure. Components of the system have been specifically designed to work together.

- Always determine that the patient does not have a possible allergy to the implant/prosthesis material before selecting the STAR implant, to minimize the risk of an allergic response.

- Discard all damaged or mishandled implants. Do not reuse implants and components. Although the implant may appear undamaged, it may have small defects and internal stress patterns which may lead to early failure of the device.

- Do not resterilize. Do not use implants or components if the package is open or damaged.

Indications and Contraindications

- Always exercise care in selecting the proper type and size of implant. Size and shape of the human bone place restrictions on the size and shape of the implant, thus limiting its weight-bearing capabilities.

- Proper use of the talar bone tamper and talar trials provided in the STAR Ankle instrument set is necessary to minimize the risk of undetected talar fracture.

- Do not contour or bend an implant because it may reduce its fatigue strength and cause failure under load. Correct handling of the implant is extremely important.

- Caution the patient that the STAR implant can be expected to withstand only limited stress until the supporting bones are completely healed, and that the load-bearing capability of implants cannot be compared to that of a healthy bone. Premature and/or excessive loading of the implant may result in device failure.

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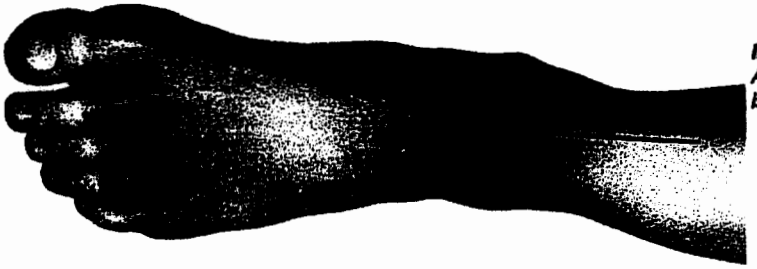
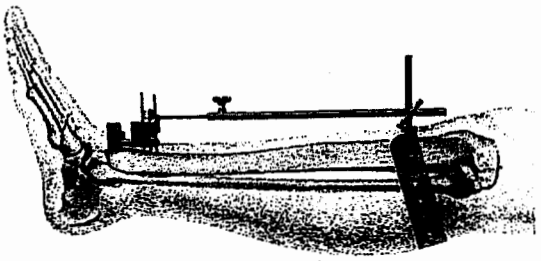
Surgical Technique

This manual is provided for informational purposes only. Proper surgical technique is the responsibility of the medical professional.

*For **preoperative planning**, new AP and lateral X-rays must be taken. New X-rays of the subtalar joints are likewise needed to estimate the extent of subtalar degeneration.*

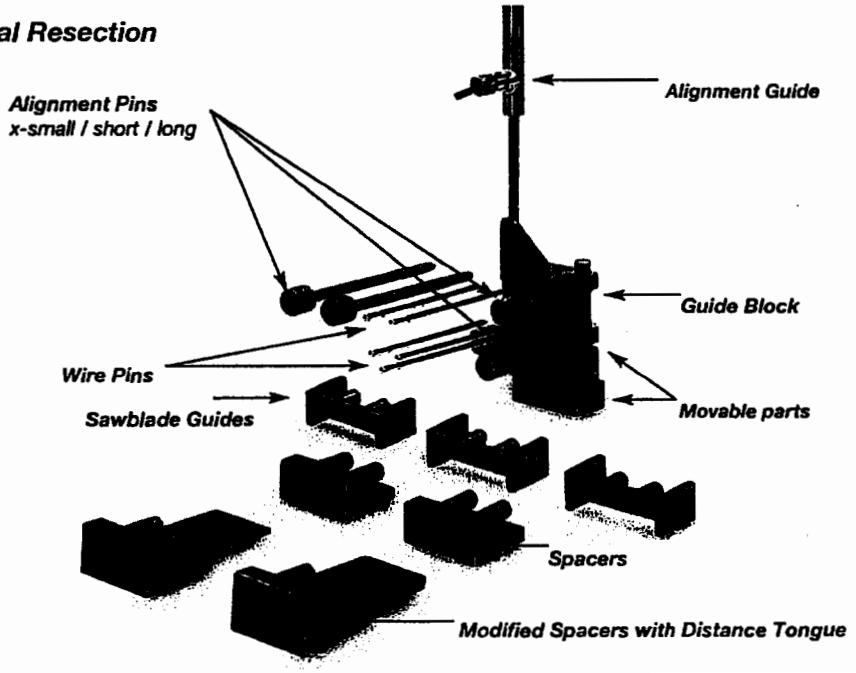


***Incision** to open the ankle joint. A wide, anterior approach is made to the joint*



*The two-part **Alignment Guide** is fastened to the leg with a **Plastic Connector** and should be aligned parallel to the axis of the tibia in the A/P and lateral planes.*

Instruments for Tibial Resection

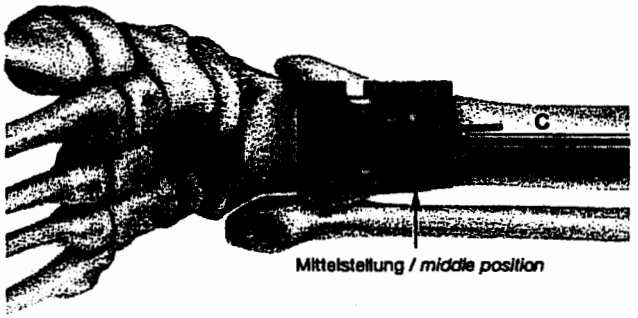


Surgical Technique

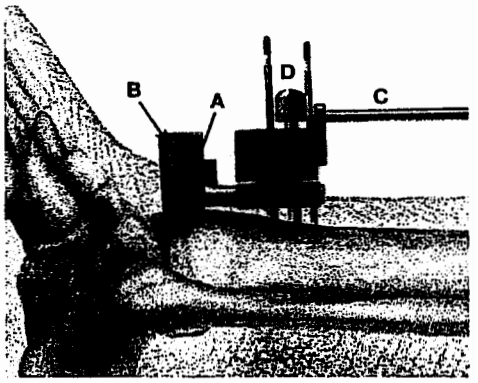
Placing of the Tibial Drill and Saw Guide

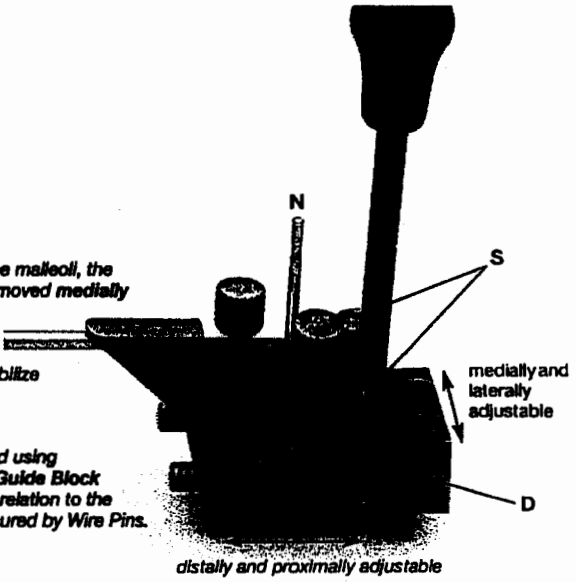
*Before the **Tibial Drill and Saw Guide** is placed, the **movable part A** of the Guide Block, which is adjustable in the longitudinal axis, is locked in the middle position, so that it can be moved **distally** or proximally if necessary. The 5 mm **Spacer B** is introduced into the movable **part A** and moved forward until its anterior edge is flush with the anterior edge of the tibial joint surface. When spacer B is removed, it will enable the surgeon to make a 5mm resection of the distal tibia.*

*The **Alignment Screw D** is used to find the horizontal plane, to compensate for the normal medial-to-lateral slope of the distal tibia. When this correction has been obtained, the Guide Block can be fixed with Wire Pins. The **Alignment Guide C** is fixed to the upper end of the tibia with a plastic connector.**



Mittelstellung / *middle position*





distally and proximally adjustable

Tibial Drill and Saw Guide (not shown in the surgical illustrations)

1. *To allow optimal positioning of the Saw Guide between the malleoli, the front part D of the Guide Block is adjustable and can be moved **medially and laterally using a Screwdriver.***
2. *Two **additional Alignment Pins "S"** help to align and stabilize the Guide distally.*
3. ***After initial alignment, the Drill and Saw Guide can be fixed using a Wire Pin "N" through an additional bore hole in the Guide Block** and be twisted around its axis into the desired position in relation to the tibial joint surface. Only then is the Guide Block finally secured by Wire Pins.*

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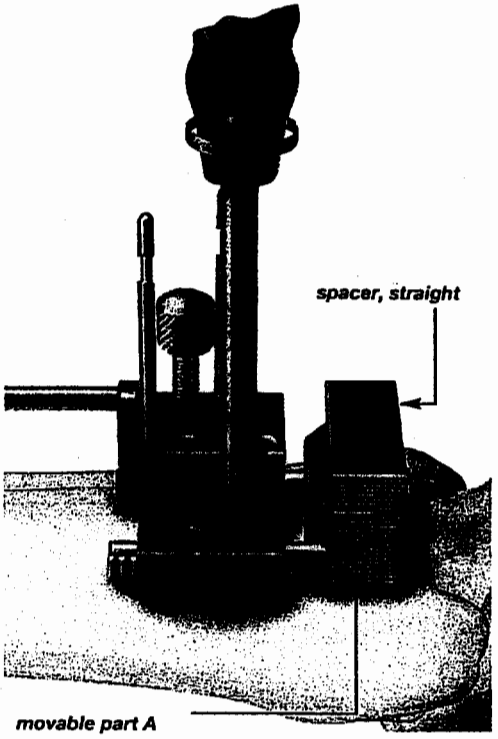
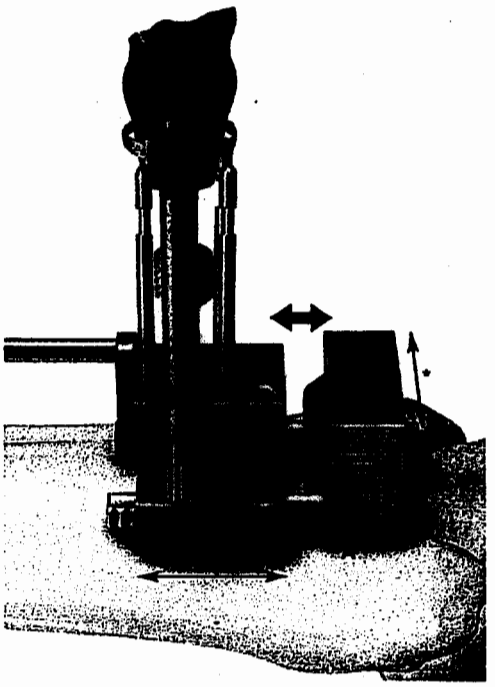
Surgical Technique

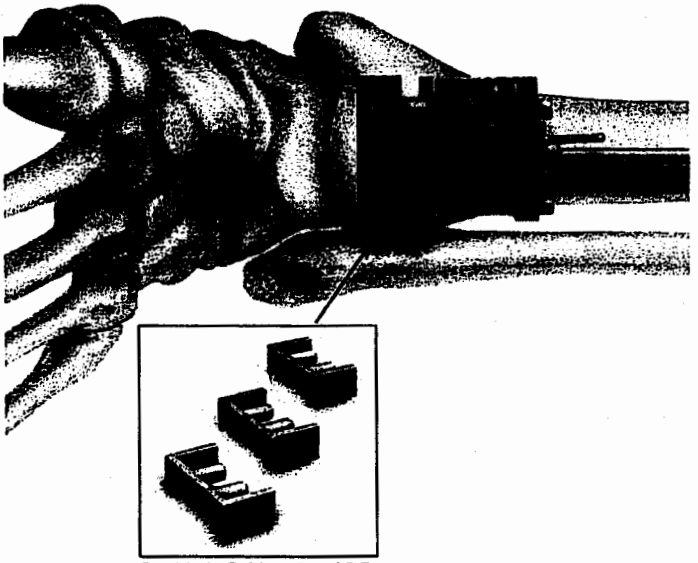


*If necessary, the **adjustment mechanism** of the **Tibial Drill and Saw Guide** allows part A to be moved both distally and proximally as necessary – even if the Guide has been secured.*
*Movable part A is locked using a **Gear Key** (upper figure); once unlocked, the same key is used to move the block in either direction (lower figure).*



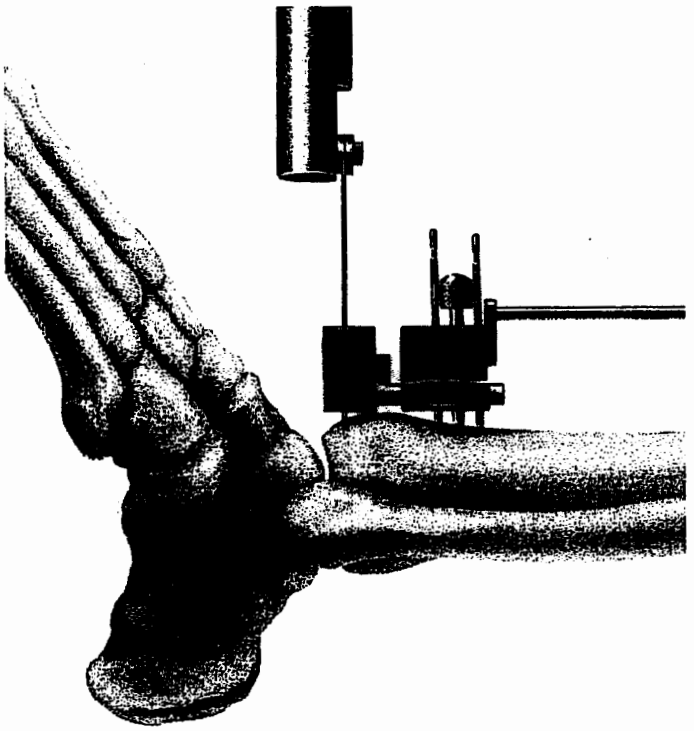
* *The laterally adjustable Saw Guide on page 4 and 5 allows also for medial or lateral shifting of the Guide Block (not shown in the surgical illustrations).*

Surgical Technique



Sawblade Guide 6.0 and 6.5 mm

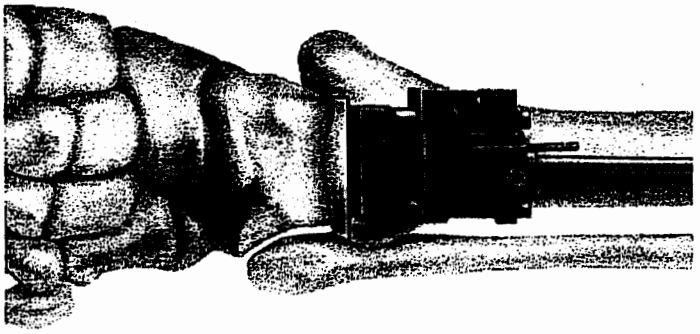
*The **Spacer** is removed and the **Sawblade Guide** mounted to prevent damage to the malleoli during resection of the distal tibia.*



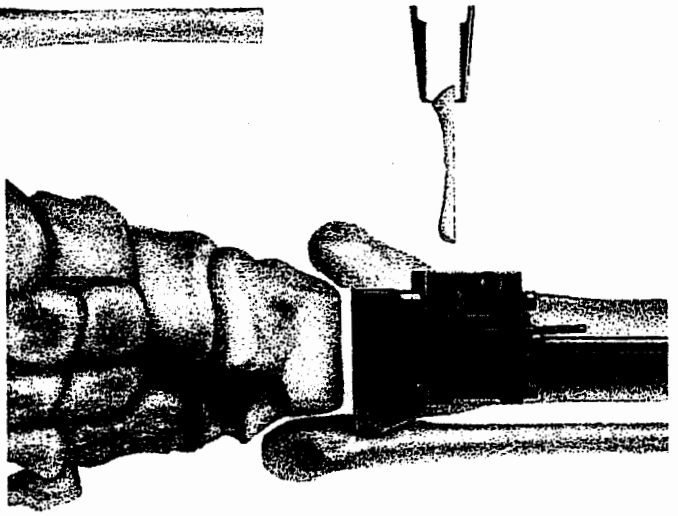
*During the distal tibial resection using an Oscillating Saw, the **Sawblade** must be held plane on the surface of the movable part of the **Guide Block**.**

**In cutting the rear part of the joint, the saw blade should be directed towards the middle of the joint to avoid damaging the malleoli.*

Surgical Technique



Surgical site after completion of the osteotomy and removal of the Sawblade Guide.

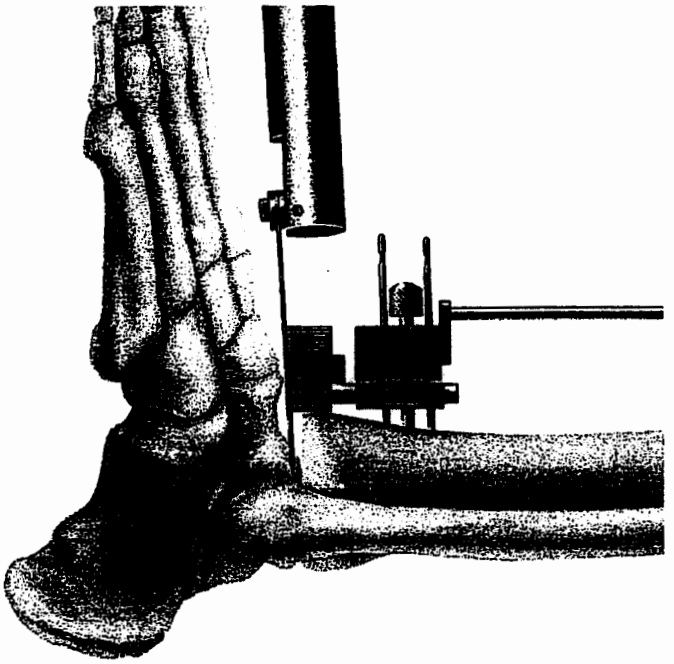


Surgical site after removal of the resected tibial bone.

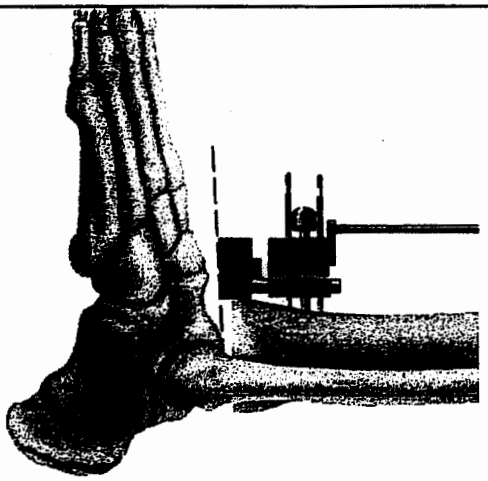
*The 4 mm oblique **Spacer** is attached to the **Tibial Drill and Saw Guide.** The foot is held at a 90° angle and firmly pressed against the resection surface of the tibia. In cases in which there is a high risk for fracturing a malleolus, it is recommended that two 0.62" K-wires be inserted into the malleolus prior to the tibial cut. In resecting the superiour aspect of the talar dome, the Sawblade is guided along the surface of the Spacer.*

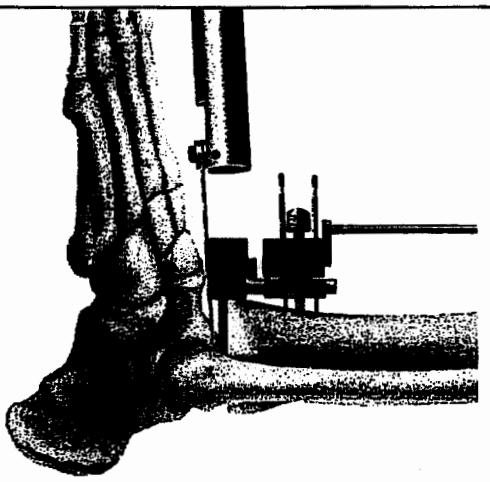
If the talus cannot be pressed up against the tibia, there are two options:

1. *Making sagittal cuts of 1 mm in the medial and lateral facets of the talus, or,*
2. *Using a modified Spacer with a Distance Tongue (see next page)*



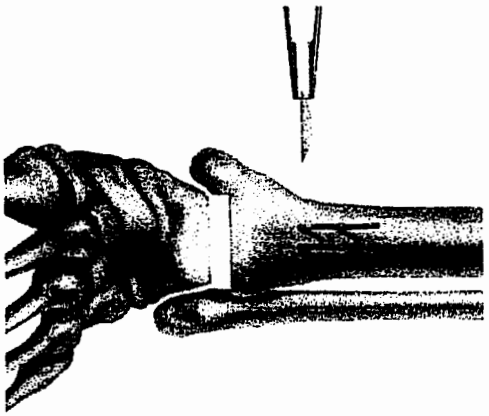
Surgical Techniques



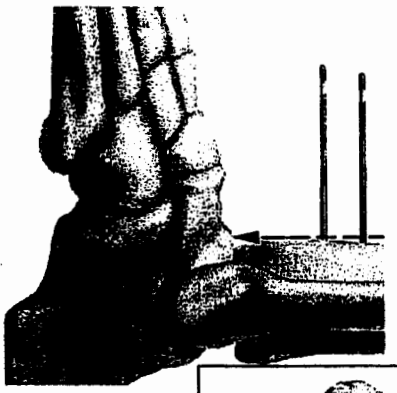


Where the ankle mortise is narrow
*The **Spacer** must be removed and replaced with a **Modified Spacer** (see figure on right).*

The foot is now held at a 90° angle and firmly pressed against the distal surface of the Modified Spacer. The superior aspect of the talar dome is resected along the surface of the Spacer.



*Surgical site after removal of the **resected talar.***

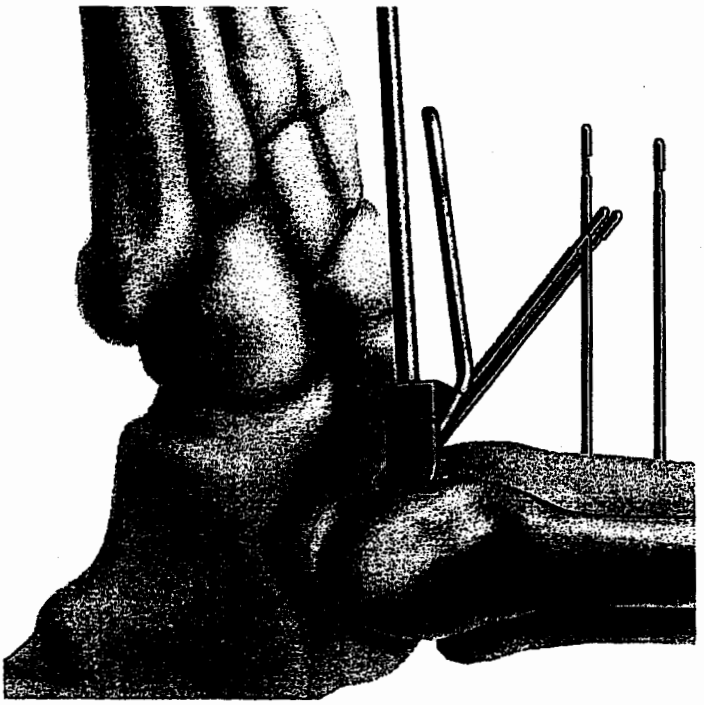


A

B

*To determine the position of the **Talus Drill and Saw Guide** the foot is brought into the 90° position. Using a **marker** (Fig. A), a **line** (Fig. B) is drawn down the anterior border of the tibia to the resected talus dome. This line indicates the junction between the talar neck and head.*

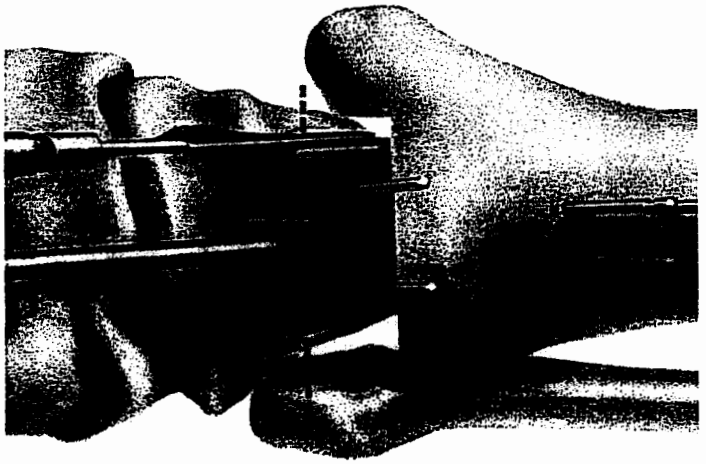
Surgical Technique



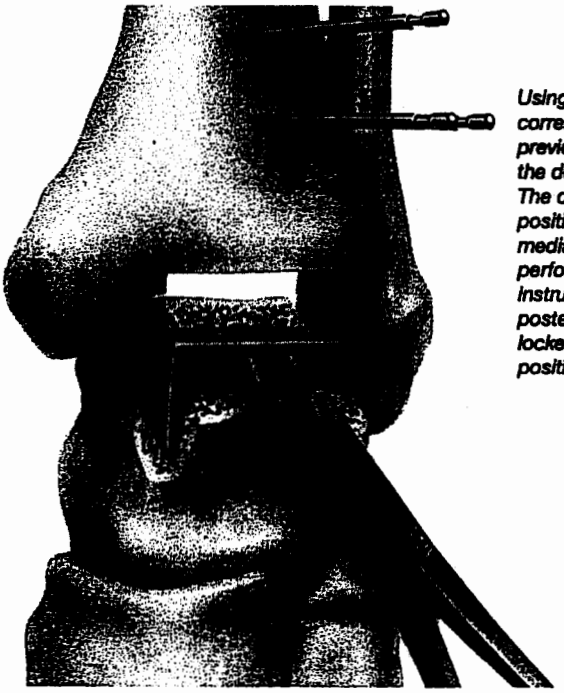
*The **Talus Drill and Saw Guide** of the correct size is positioned flat on the resected surface of the talar head, such that the apexes of its arch-shaped recesses align with the line previously drawn (see lower figure).*

*The Talus Drill and Saw Guide is fixed with **two Wire Pins.** The Guide can be additionally secured by the **curved Fixation Pin** if an extra hole is drilled. The bilateral resection is then performed along the Guide using a reciprocating saw, taking off slices of approx. 2 mm - 3 mm laterally and medially. The cut should go down about 10 mm on the medial side and about 17 mm on the lateral side.*

Note: The Saw Guide induces an oblique direction of cut.

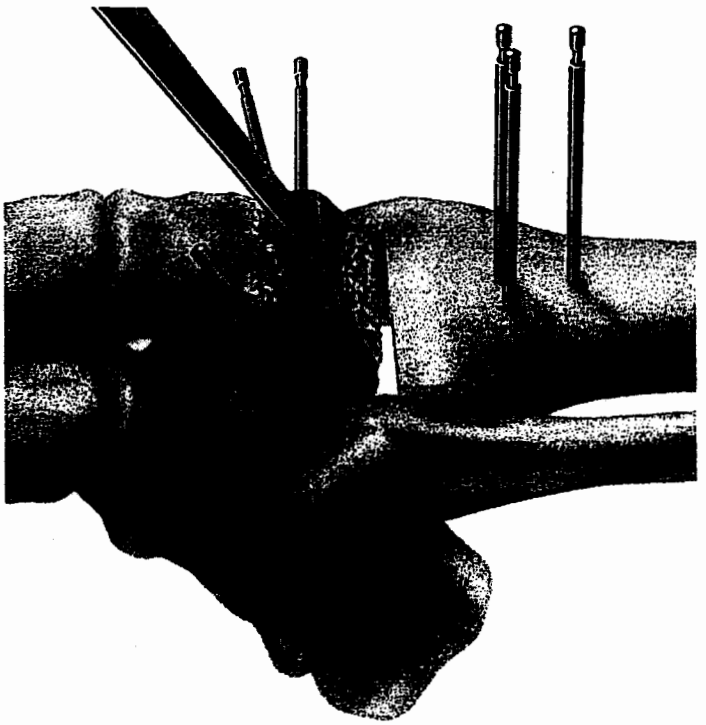


Surgical Technique



*Using the **Insertion Forceps**, the **Talar Saw Guide** corresponding in size to the Talar Drill and Saw Guide previously used is mounted on the talus to carry out the dorsal and frontal chamfered resection.*
The crossbar of the Talar Saw Guide must be positioned in the middle of the resected talus. If the medial and lateral resections have been correctly performed, this position is achieved by placing the instrument flat on the resected talar surface posteriorly and sliding it anteriorly until it is tightly locked. The Talar Saw Guide is then fixed in this position with Wire Pins (see figure below).

*The **dorsal resection** is performed using a **straight Sawblade** held flat against the face of the Saw Guide.*



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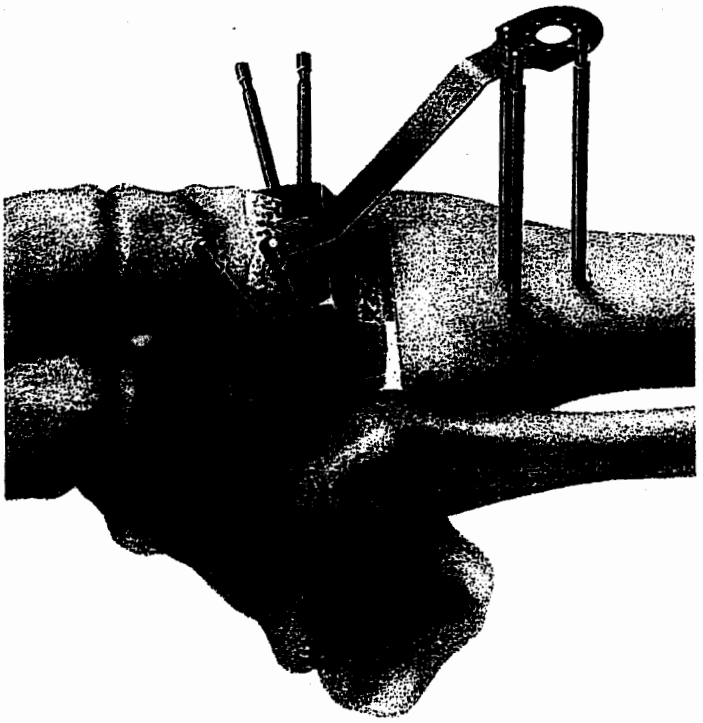
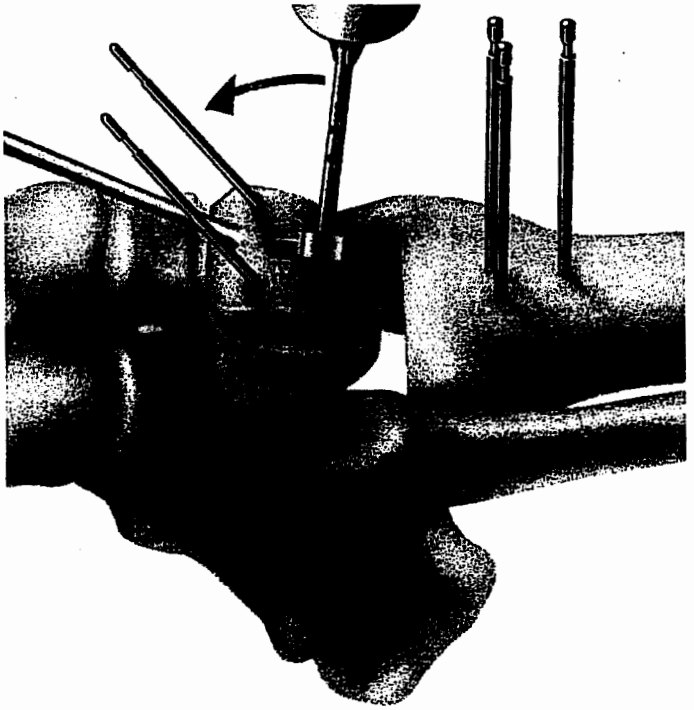
Surgical Technique

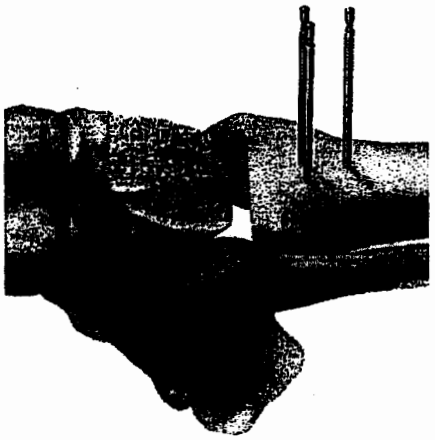


*The instrumentation includes a specially designed **double-angled Sawblade** for performing the frontal resection. In some cases, the **frontal resection** may have to be performed with a thin osteotome.*

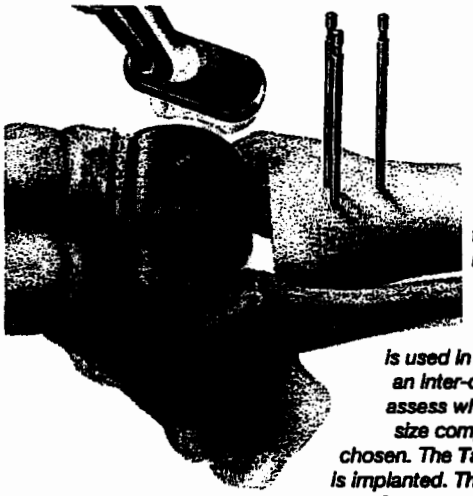
*The appropriate-sized **Talar Milling Guide** is placed on the talus and fixed with **Wire Pins**. This Milling Guide is used to ream the groove for the fixation fin of the Talar Component. Using a 3 **mm Twist Drill with stop**, holes are drilled in the talus at both ends of the slot in the Talar Milling Guide. The remaining bony bridge is then reamed away using the drill bit through the slot. The groove created should only reach as far as the back edge of the upper talar resection, but no further. Additionally, the **bone - tamper for talar** fin may be used to ensure proper fit of the talar component.*



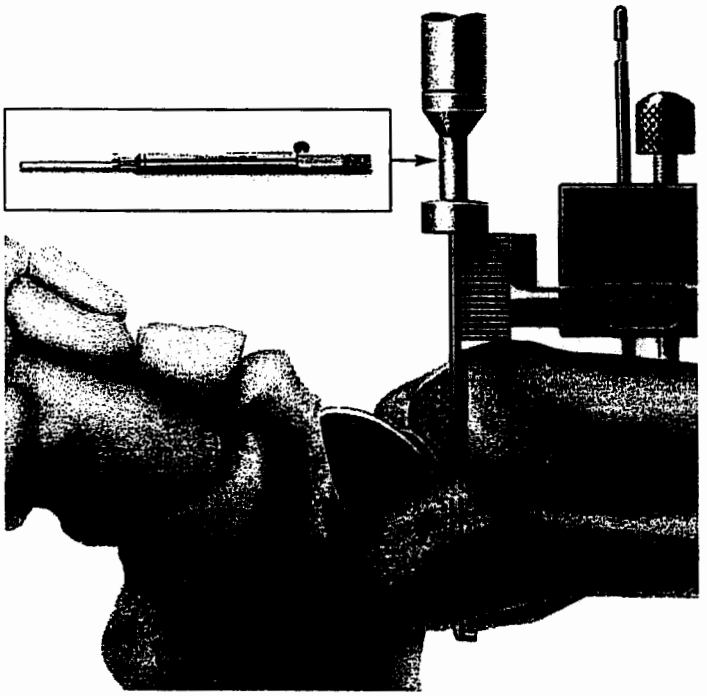
Surgical Technique



Prepared surface of the talus.

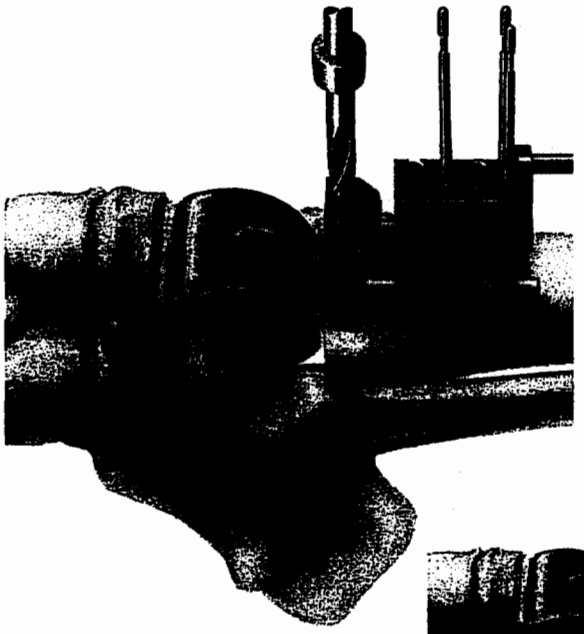


*Prior to implanting the talar component, it is recommended that the appropriate sized talar trial is used in conjunction with an inter-operative x-ray to assess whether the proper size component has been chosen. The **Talar Component** is implanted. The fin of the Talus Component is placed in the groove. The Talar Component is then tapped backwards (dorsally) with light blows (e.g., using the Tibial Spacer Guide or similar instrument) against its front edge. **Then, and only then,** the Talar Component can be driven home using the **Impactor.***

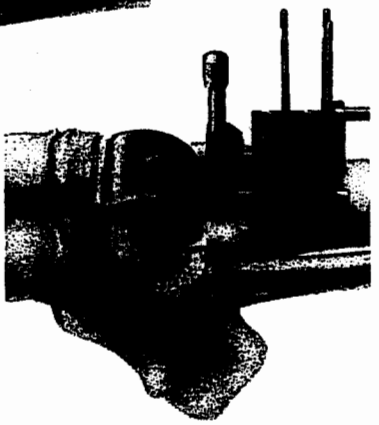


*The **Tibial Drill and Saw Guide** is once again mounted on the **Wire Pins** that have remained in the tibia. The sagittal thickness of the tibia is measured using the **Depth Gauge** and the stop on the **Twist Drill** adjusted accordingly (the stop plate on the Twist Drill is adjusted with its **Hex Key**). To avoid penetration of the posterior cortex, 5 mm is deducted from the measured distance.*

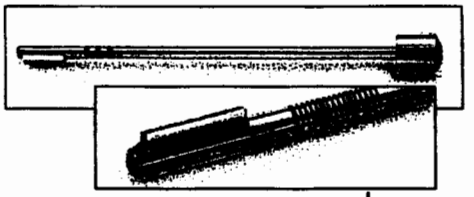
Surgical Technique

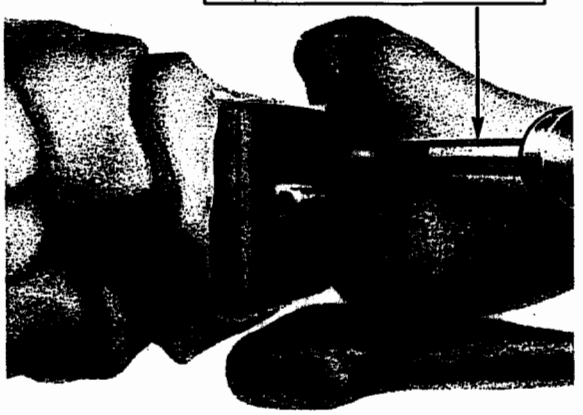


*The holes in the tibia for the cylindrical fixation bars of the Tibial Component are drilled through the holes of the Drill Guide down to the depth set on the stop of the **6 mm or 6.5 mm diameter Twist Drill.** Care must be taken to keep the Twist Drill **straight** when drilling through the Drill Guide, to prevent the tip of the drill from migrating towards the prepared resection surface of the tibia.*



To keep the same distance between the two drill holes, it is advisable to insert a Fixation Pin into the first hole before drilling the second hole.

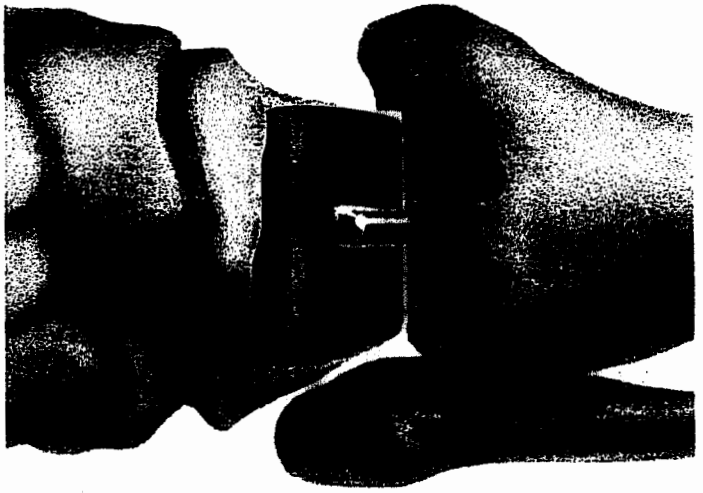




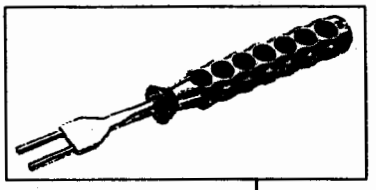
The drill holes in the tibia are now opened anteriorly with a **Special 6.0 mm or 6.5 mm Gouge.** *To avoid an uncontrolled bone defect in the osteotomy plane, care must be taken to keep the Gouge parallel to the drill hole in the tibia as it enters the hole.*

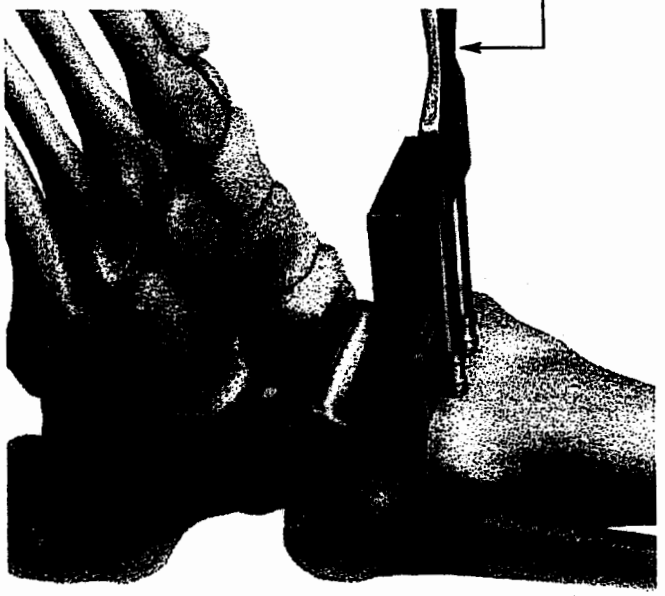
To check that the alignment is correct, a 6 mm or 6.5 mm Twist Drill with stop may be alternately inserted into the hole opposite the Gouge.

Surgical Technique



Finished tibial implant site

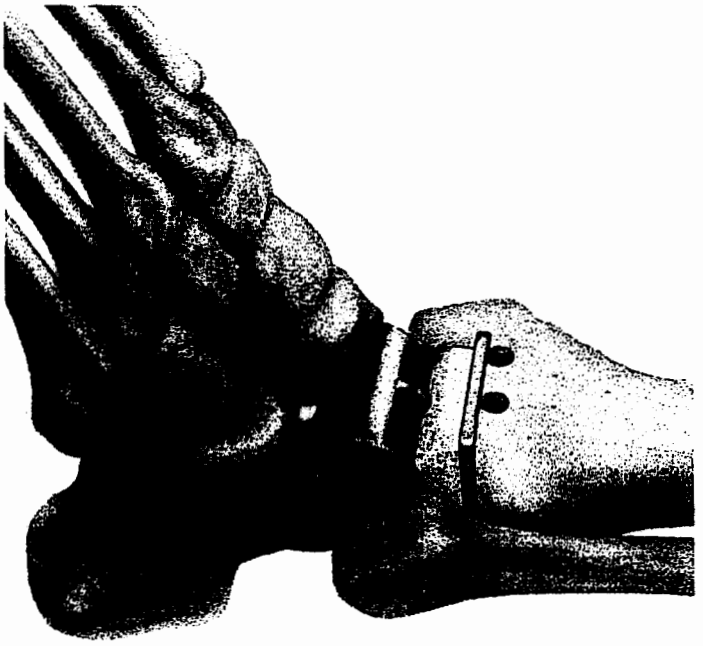




*The foot is brought at a 90°-angle to the tibia. The appropriate **Tibial Spacer Guide** is placed between the implanted Talar Component and the prepared tibial resection surface. Using the **Impactor**, the Tibial Component – the size of which is determined by measuring the sagittal length of the tibia with the Depth Gauge – is then carefully impacted until its anterior edge is flush with the anterior cortex on the lateral side, which is usually 2–3 mm lower than the medial cortex.*

Surgical Technique

*With the Talar and Tibial Components in position. The correct thickness of the **UHMWPE Sliding Core** is determined by inserting **Tibial Trial Implants** (available in nine sizes). Care should be taken to ensure both adequate soft tissue tension in the joint and the necessary mobility. If the talus tilts against the UHMWPE Sliding Core, lateral stabilization is needed.*



*The **LINK S.T.A.R.® Total Ankle Replacement** in situ. The holes in the distal tibia are filled with bone chips.*

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Postoperative Treatment

The operative leg is elevated for 2-3 days. Walking for a maximum of 10 min. at a time with full body weight on the leg is indicated. The operative leg should be alternately loaded and rested.

The ankle region operated on may be swollen for 3–6 months. During this time, it is common for the patient to experience pain after exercises or in the evening. The use of elastic support stockings and elevation of the leg operated on is advisable.

Obtaining X-rays

Suggestions for obtaining X-rays for patient follow-up

All X-rays should be taken using image intensification to provide straight frontal and lateral views. In the frontal views, the cylindrical anchoring segments of the Tibial Glide Plate must show as circular dots. The X-ray marking wire in the Sliding Core must form a straight horizontal line parallel to the Tibial Component. The Talar Component with its lateral wings appears as a rectangle where both the medial and the lateral part of the joint can be seen into. In the lateral projection, the Tibial Component should render the distal plateau as a straight line. The Talar Component shows only a straight view of one side wing of the Talar Cap.

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Literature

LINK® S.T.A.R. SCANDINAVIAN TOTAL ANKLE REPLACEMENT

Video or CD of the LINK® Scandinavian Total Ankle Replacement available on request.

Catalog 811 d-en "Implants and Instruments" available on request.

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Orthopaedic Implants

More detailed information about our implants can be supplied upon request.

Materials used for our orthopaedic implants:

- *CoCrMo alloy, ISO 5832-4/ASTM F75 or ISO 5832-12*
- *TiAl6V4 alloy, ISO 5832-3/ASTM F136 or ASTM F1108*
- *Unalloyed titanium, ISO 5832-2/ASTM F67*
- *Stainless steel, ISO 5832-1/ASTM F138 / ASTM F139*
- *CoCrNiMoFe, ISO 5832-7/ASTM F1058*
- *Al203 (aluminium oxide ceramic), ISO 6474*
- *UHMWPE, ISO 5834-2/ASTM F648*
- *Calcium phosphate coating, ASTM F1609*

WALDEMAR LINK GmbH & Co. KG, Hamburg

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S.T.A.R.
Scandinavian Total Ankle Replacement

Implants and Instruments

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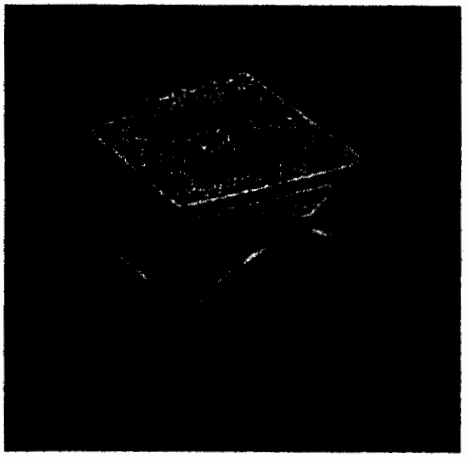
Overview

The STAR Ankle system comprises the ankle prosthesis itself, which includes three functional components, and a set of customized accessory instruments that are used in the surgical procedure. The three principal components of the prosthesis are:

- A metal tibial component with titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing; and
- A metal talar component with titanium porous plasma spray coating.

The intermediate UHMWPE mobile bearing articulates on the tibial and talar metal implant surfaces, as shown in the photograph of the three components of the STAR Ankle system below:



The STAR Ankle is designed to replace a portion of the tibial and talar components of the normal ankle joint, while preserving range of motion as much as possible. As illustrated in **Table 1** below, the design characteristics of the STAR Ankle correspond closely to the normal ankle joint.

Table 1: Comparison of Design Characteristics of the STAR Ankle to the Normal Ankle Joint

Design Feature	Normal Ankle	STAR Ankle Prosthesis
Congruency	96%	100%
Rotation	12-15° talus rotation	12-15° talus rotation plus tibial-meniscal rotation
Extension/flexion (radiographic)	10/30°	7/20°

There are two bearing surfaces in the STAR Ankle: (1) the interface between the upper side of the UHMWPE mobile bearing and the facing surface of the tibial plate, and (2) the interface between the lower surface of the UHMWPE mobile bearing and the facing surface of the talar component. The tibial plate has one flat surface and one surface with two raised cylindrical barrels oriented in the anterior/posterior direction. The upper flat surface of the UHMWPE mobile bearing slides against the flat surface of the tibial plate. The projecting cylinders of the tibial plate serve to fix the device to bone at the distal tibia. The lower surface of the UHMWPE mobile bearing is concave, fitting against the convex upper surface of the talar component.

Description

The mobile bearing design of the device is intended to reduce the shear and torque forces on the UHMWPE mobile bearing, which can lead to loosening of either metal component, and to decrease stress at the metal/bone interface. The sloped sides are designed to improve the weight bearing characteristics of the talar component.

Components

Tibial Plate

When viewed from the top, the tibial plate has a trapezoidal shape with rounded corners. This component is manufactured from cobalt chromium molybdenum (CoCrMo) per ASTM F-75. The smaller end of the wedge is oriented towards the posterior aspect of the ankle joint. This wedge is shaped to conform to the existing anatomy and, thereby, reduces the need to remove excess bone from inside the joint. On the proximal surface of the tibial plate, two parallel cylindrical barrels are positioned equidistant from the center of the plate running anterior to posterior for bone fixation. These cylinders must be inserted into hard subchondral bone.

[redacted]

Tibial plates are available in five sizes with varying widths and lengths: extra-small (30mm x 30mm), small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm). Tibial plates for revision procedures are available in small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm) sizes. The [redacted]

The tibial plate is coated on the bone-opposing surfaces with a titanium plasma spray porous coating. The tibial plate is intended to be press-fit without the use of cement, and should rest on anterior and posterior cortical bone. The stemmed tibial components are uncoated and have a matte finish where they interface with bone.

UHMWPE Mobile Bearing

The polyethylene mobile bearing is manufactured from Ultra High Molecular Weight Polyethylene ("UHMWPE"), which is machined from medical grade extruded plate stock and conforms to ASTM F-648. [redacted] Revision mobile bearings are available in sizes of 11mm, 12mm, 13mm, and 14mm.

LINK®

Description

Talar Component

The talar component is designed as an anatomical prosthesis to cover the talar dome, anterior, posterior, and medial and lateral facets. Like the tibial plate, this component is manufactured from CoCrMo. The talar component is designed to minimize the amount of bone that must be removed. From the apex of the dome, the walls slope outwards to conform to the normal bone anatomy. The component is offered in five sizes: extra-extra-small (28mm x 29 mm), extra-small (30mm x 31mm), small (34mm x 35mm), medium (36mm x 35mm), and large (38mm x 35mm), and in both left- and right-sided configurations.

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

As with the tibial plate, the talar component is also provided with a titanium plasma spray porous coating.

Indications and Contraindications

INDICATIONS FOR USE

Link Orthopaedics' ("Link") Scandinavian Total Ankle Replacement ("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 arthritis, or post-traumatic arthritis. 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, WARNINGS, and PRECAUTIONS

Contraindications:

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

Warnings/Precautions:

- Only implant the STAR Ankle after adequate training and familiarity with the surgical technique manual, to avoid increased risk of device failure due to improper surgical technique.

- Do not use STAR Ankle components in combination with prosthesis components made by other manufacturers, because design, material, or tolerance differences may lead to premature device and/or functional failure. Components of the system have been specifically designed to work together.

- Always determine that the patient does not have a possible allergy to the implant/prosthesis material before selecting the STAR implant, to minimize the risk of an allergic response.

- Discard all damaged or mishandled implants. Do not reuse implants and components. Although the implant may appear undamaged, it may have small defects and internal stress patterns which may lead to early failure of the device.

- Do not resterilize. Do not use implants or components if the package is open or damaged.

Indications and Contraindications

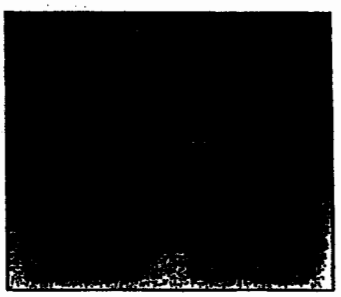
- Always exercise care in selecting the proper type and size of implant. Size and shape of the human bone place restrictions on the size and shape of the implant, thus limiting its weight-bearing capabilities.

- Proper use of the talar bone tamper and talar trials provided in the STAR Ankle instrument set is necessary to minimize the risk of undetected talar fracture.

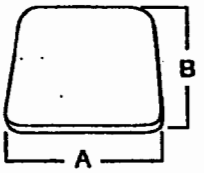
- Do not contour or bend an implant because it may reduce its fatigue strength and cause failure under load. Correct handling of the implant is extremely important.

- Caution the patient that the STAR implant can be expected to withstand only limited stress until the supporting bones are completely healed, and that the load-bearing capability of implants cannot be compared to that of a healthy bone. Premature and/or excessive loading of the implant may result in device failure.

Implants

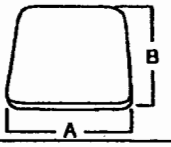


Tibial Components Material: CoCrMo Alloy			
Item No. cementless	Size	A mm	B mm
400-260	x-small	30	30
400-261	small	32	30
400-262	medium	32,5	35
400-263	large	33	40
400-264	x-large	33,5	45



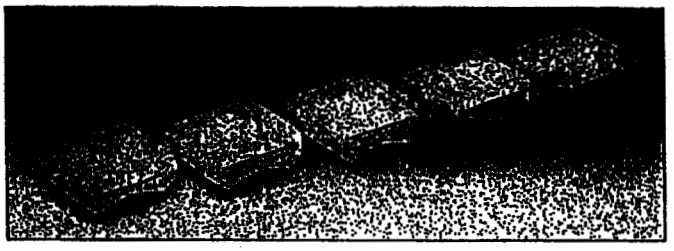
Revision Implants:

Revision Tibial Components Material: CoCrMo Alloy			
Item No.	Size	A mm	B mm
400-302	small	32	30
400-304	medium	32,5	35
400-306	large	33	40
400-307	x-large	33,5	45



LINK®

Implants



UHMWPE Sliding Cores Material: UHMWPE Stainless Steel	
Art.-Nr. / Item No.	Höhe / Height mm
400-140	6
400-141	7
400-142	8
400-143	9
400-144	10
99-0028/11	11
99-0028/12	12
99-0028/13	13
99-0028/14	14

Talar Components Material: CoCrMo Alloy		
Item No.	Size	Version
400-250	xx-small	right
400-251	xx-small	left
400-252	x-small	right
400-253	x-small	left
400-254	small	right
400-255	small	left
400-256	medium	right
400-257	medium	left
400-258	large	right
400-259	large	large

LINK®

Instruments

405-100/01 ***Instrument Set complete for LINK S.T.A.R.® Ankle Replacement***
in N21 Standard Container, on two Trays with product illustrations and storage inserts

consisting of:
N21 Standard Container
05-2002/03
575 x 275 x 130 mm — 1 ea.

Upper Tray only
405-101/01
with solid handle, with product illustrations perforated stainless steel
550 x 265 x 50 mm — 1 ea.

Lower Tray only
405-101/02
with solid handle, with product illustrations perforated stainless steel
550 x 265 x 50 mm — 1 ea.

Hex Key
405-108
for Twist Drill 405-107/01 or 405-107/01W — 1 ea.

Gear Key
405-144
For Longitudinal Adjustment of the Tibial Guide Block (405-145/11) — 1 ea.

Special Gouge
405-110/01 *Ø 6.0 mm, 175 mm*
or
405-110/01W *Ø 6.5 mm, 175 mm* — 1 ea.

Twist Drill with stop
405-107/01 *Ø 6.0 mm, 145 mm*
or
405-107/01W *Ø 6.5 mm, 145 mm* — 1 ea.

Fixation Pin
For use with Tibial Guide Block (405-145/11)
405-150 *62 mm, Ø 6.0 mm*
or
405-150W *62 mm, Ø 6.5 mm* — 1 ea.

LINK®

Instruments

405-146/11	***Tibial Drill and Saw Guide***	***1 Set***
	consisting of:	
	Ø 6.0 mm	
	Guide Block, *laterally adjustable*	*1 ea.*
405-145 TO4887	*Ø 6.5 mm*	
	Alignment Pins	
405-146/35	*x-short, 35 mm*	*2 ea.*
405-146/45	*short, 45 mm*	*2 ea.*
405-146/85	*long, 85 mm*	*2 ea.*

405-136	***Alignment Guide (2 parts)*** *250 mm*	*1 ea.*
405-137	***Plastic Connector*** *for Alignment Guide 405-136*	*1 ea.*

Spacers for Tibia Drill and Saw Guide

405-104	*angled, 4 mm For Talar Dome Resection*	*1 ea.*
405-105	*straight, 5 mm For Tibial Resection*	*1 ea.*

Modified Spacers with Distance Tongue

405-138/02	2 mm	1 ea.
405-138/04	4 mm	1 ea.

Sawblade Guide

405-147/30 or 147/30W	*x-small, 30 mm*	*Ø 6.0 mm* *Ø 6.5 mm*	1 ea.
405-147/32 or 147/32W	*small, 32 mm*	*Ø 6.0 mm* *Ø 6.5 mm*	1 ea.
405-147/33 or 147/33W	*medium/large, 33 mm*	*Ø 6.0 mm* *Ø 6.5 mm*	1 ea.

405-139/01	***Talar Drill and Saw Guide***	***1 Set***
	consisting of:	
405-139/02	*right, xx-small*	1 ea.
405-139/03	*left, xx-small*	1 ea.
405-139/04	*right, x-small*	1 ea.
405-139/05	*left, x-small*	1 ea.
405-139/06	*right, small*	1 ea.
405-139/07	*left, small*	1 ea.
405-139/08	*right, medium*	1 ea.
405-139/09	*left, medium*	1 ea.
405-139/10	*right, large*	1 ea.
405-139/11	*left, large*	1 ea.

405-140/01	***Talar Saw Guides***	***1 Set***
	consisting of:	
405-140/02	*right, xx-small*	1 ea.
405-140/03	*left, xx-small*	1 ea.
405-140/04	*right, x-small*	1 ea.
405-140/05	*left, x-small*	1 ea.
405-140/06	*right, small*	1 ea.
405-140/07	*left, small*	1 ea.
405-140/08	*right, medium*	1 ea.
405-140/09	*left, medium*	1 ea.
405-140/10	*right, large*	1 ea.
405-140/11	*left, large*	1 ea.

405-113	***Fixation Pin,*** *curved For Talar Drill and Saw Guides (405-139/02 through 405-139/11)*	1 ea.
405-115	***Twist Drill,*** *Ø 3 mm For Talar Drill and Sawguide (405-139/02 through 405-139/11) Fitting: Jacobs Chuck*	1 ea.

405-141/01	***Talar Milling Guides***	***1 Set***
	consisting of:	
405-141/02	*right, xx-small*	1 ea.
405-141/03	*left, xx-small*	1 ea.
405-141/04	*right, x-small*	1 ea.
405-141/05	*left, x-small*	1 ea.
405-141/06	*right, small*	1 ea.
405-141/07	*left, small*	1 ea.
405-141/08	*right, medium*	1 ea.
405-141/09	*left, medium*	1 ea.
405-141/10	*right, large*	1 ea.
405-141/11	*left, large*	1 ea.

405-142	***Twist Drill with stop*** *For Talar Milling Guides (405-401/02 through 405-141/11) Ø 3 mm, 75 mm*	1 ea.
405-143	***Driver and Extraction Forceps*** *210 mm*	1 ea.
405-124	**Mobile Bearing Trials,** *Set of five 6 mm - 10 mm*	*1 Set*

Additional Sizes: 99-0028/31 = 11mm
99-0028/32 = 12mm
99-0028/33 = 13mm
99-0028/34 = 14mm

Tibial Spacer Guides

405-125	*small, 24 mm wide*	1 ea.
405-128	*wide, 30 mm wide*	1 ea.
405-126	***Depth Gauge,*** 235 mm *0 mm - 80 mm*	1 ea.
405-127	***Insertion Forceps*** *For Tibial Trial Implants (405-124)*	1 ea.

Sawblade for Tibial and Talar resections

Double angled

405-130/01	***Fitting A***	1 ea.
	optional:	
405-130/02	*Fitting B*	
405-130/03	*Fitting C*	
405-130/04	*Fitting D*	

straight

405-131/01	***Fitting A***	1 ea.
	optional:	
405-131/02	*Fitting B*	
405-131/03	*Fitting C*	
405-131/ 04	Fitting D	

LINK®

Instruments

405-132	Impactor for Talar Components, 135mm
405-134/01	Impactor for Tibial Components with exchangeable tips, 220mm
405-134/02	Replacement Tips (CoCrMo Alloy) for Impactor 405-134/01, non-sterile, 1 pair

Talar Trials without lateral flanges

405-148/01	***Set of 10 ea.***

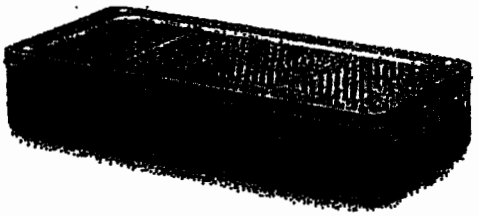
consisting of:

Item No.	*Size*	*Version*
405-148/11	*xx-small*	*right*
405-148/12	*xx-small*	*left*
405-148/13	*x-small*	*right*
405-148/14	*x-small*	*left*
405-148/15	*small*	*right*
405-148/16	*small*	*left*
405-148/17	*medium*	*right*
405-148/18	*medium*	*left*
405-148/19	*large*	*right*
405-148/20	*large*	*left*

Fixation Pins

405-106	2.4mm x 80mm
405-106/02	2.4mm x 65mm
99-0028/18	2.5mm x 120mm
99-0028/17	2.5mm x 100mm

405-149	Bone-Tamp for Talar Fin
99-0028/98	Alignment Device for Tibial Drill & Saw Guide Block (405-145/11)
405-150W	Fixation Pin for Tibial Drill & Saw Guide Block (405-145/11), 6.5 x 62mm

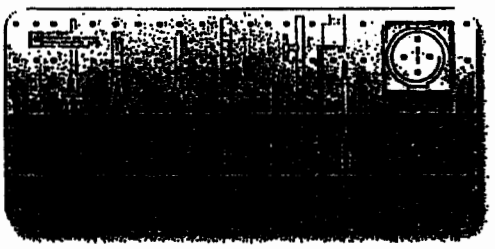


05-2002/03

N21 Standard Container
575 x 275 x 130 mm
Base (closed) and lid made of aluminium
incl. pack of 5 disposable filters and
10 disposable plastic seals

405-101/01

Upper Tray with product illustrations, only
perforated stainless steel with storage inserts and
solid handles, 550 x 265 x 50 mm

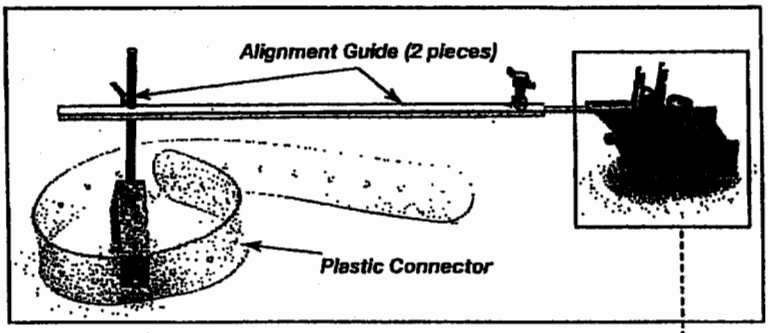


405-101/02

Lower Tray with product illustrations, only
perforated stainless steel with storage inserts and
solid handles 550 x 265 x 50 mm

LINK®

Instruments

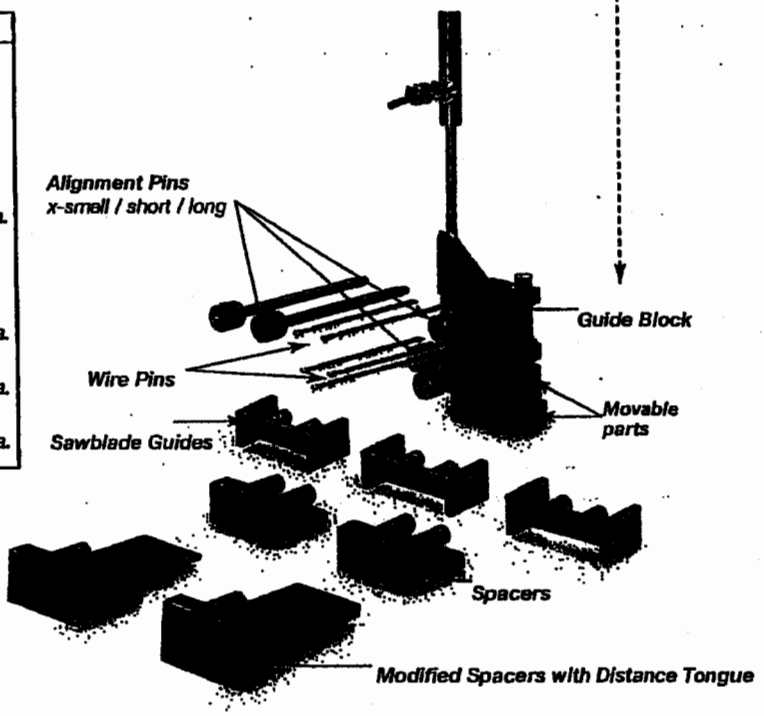


405-145/11W Set

Tibial Drill and Saw Guide
consisting of:

405-145 TO4887	Ø 6.0 mm **Guide Block, laterally adjustable** Ø 6.5 mm	1 ea.
	Alignment Pins	
405-146/35	*x-short,* 35 mm	2 ea.
405-146/45	*short,* 45 mm	2 ea.
405-146/65	*long,* 65 mm	2 ea.

Alignment Pins are used alternatively.



405-136
Alignment Guide (2 parts)

405-137
Plastic Connector

Spacers
405-104 *angled*
405-105 *straight*

Modified Spacers with Distance Tongue
405-138/02 2 mm
405-138/04 4 mm

405-106/02
Wire Pins
Ø 2.4 mm, 65 mm

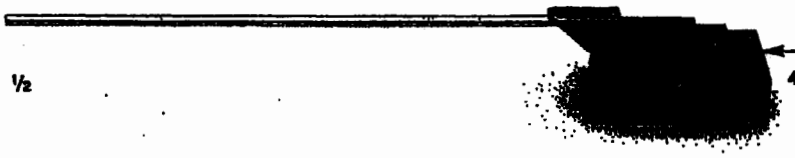
Sawblade Guides

405-147/30 *x-small, 30 mm Ø 6.0 mm*
or
147/30W *Ø 6.5 mm*

405-147/32 *small, 32 mm Ø 6.0 mm*
or
147/32W *Ø 6.5 mm*

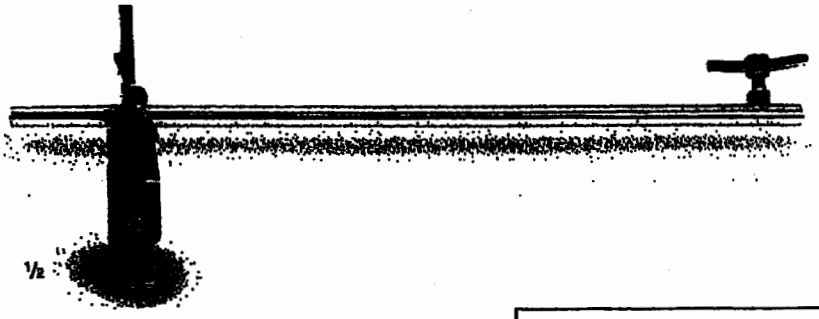
405-147/33 *medium and large, 33 mm Ø 6.0 mm*
or
147/33W *Ø 6.5 mm*

Instruments

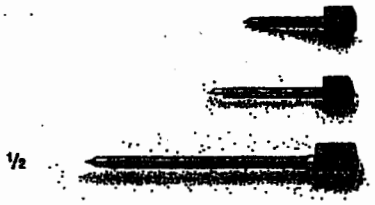


405-145/11W Ø 6.0 mm
or
405-145 Ø 6.5 mm
TO4887

Guide Block
laterally adjustable *240 mm*

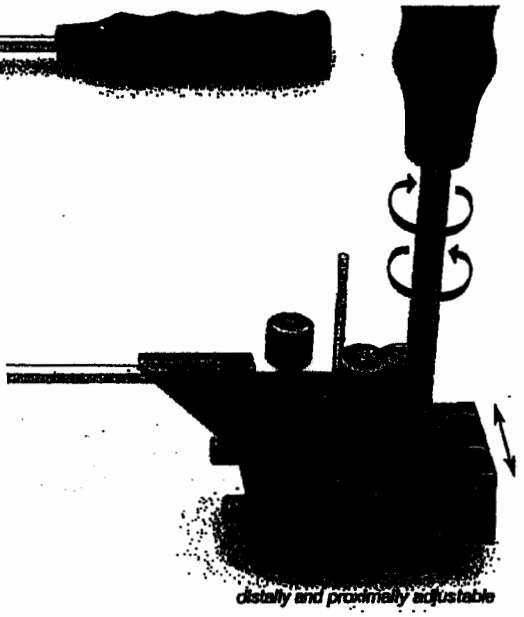


405-136
Alignment Guide (2 pieces)
250 mm



Alignment Pins		
Item No.	*Version*	*Length*
405-146/35	*x-short*	35 mm
405-146/45	*short*	45 mm
405-146/85	*long*	85 mm

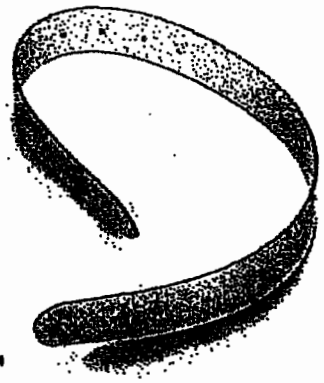
405-144
Gear Key
for longitudinal adjustment of Tibial Drill and Saw Guide
250 mm



LINK®

LINK®

Instruments

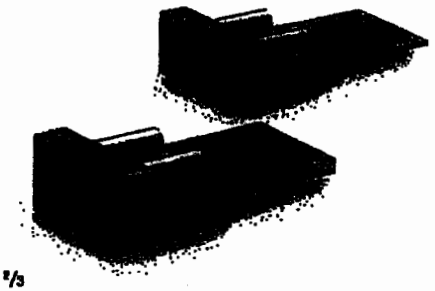


1/4

405-137
Plastic Connector
for Alignment Guide 405-136, 495 mm

2/3

Spacers for Tibial Drill and Saw Guide		
Item No.	*Version*	*for*
405-104	*angled, 4 mm*	*Resection of talar dome*
405-105	*straight, 5 mm*	*Tibial Resection*



2/3

Modified Spacers with Distance Tongue		
Item No.	*Version*	*for*
405-138/02	2 mm	*Talar Resection*
405-138/04	4 mm	

1/1

405-106/02
Wire Pin for fixation of Tibial Drill and Saw Guide
Ø 2.4 mm, 65 mm

Instruments

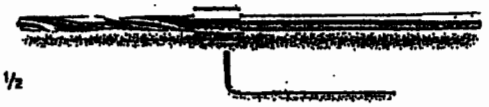
2/3

Sawblade Guides for distal tibial resection			
Item No.	Size	Version	
405-147/30 or 147/30W	x-small	30 mm	Ø 6.0 mm Ø 6.5 mm
405-147/32 or 147/32W	small	32 mm	Ø 6.0 mm Ø 6.5 mm
405-147/33 or 147/33W	medium and large	33 mm	Ø 6.0 mm Ø 6.5 mm

1/2

405-150 or 405-150W

Fixation Pin, 62 mm, Ø 6.0 mm
Ø 6.5 mm



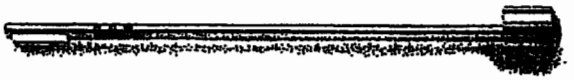
1/2

405-107/01 or 405-107/01W

Twist Drill with stop, Ø 6.0 mm, 145 mm
Ø 6.5 mm

405-108

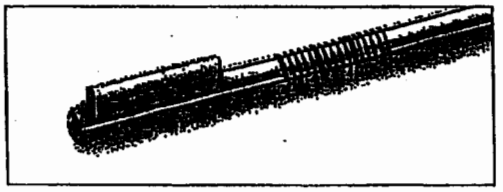
Hex Key for Twist Drill with stop 405-107/01, 50 mm
405-107/01W



1/2

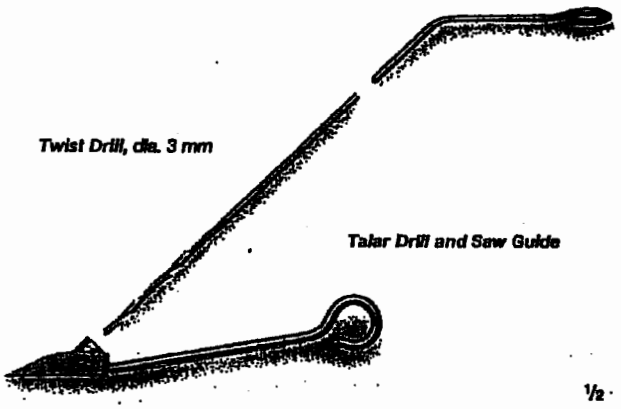
405-110/01 or 405-110/01W

Special Gouge, calibrated, 175 mm, Ø 6.0 mm
Ø 6.5 mm



LINK®

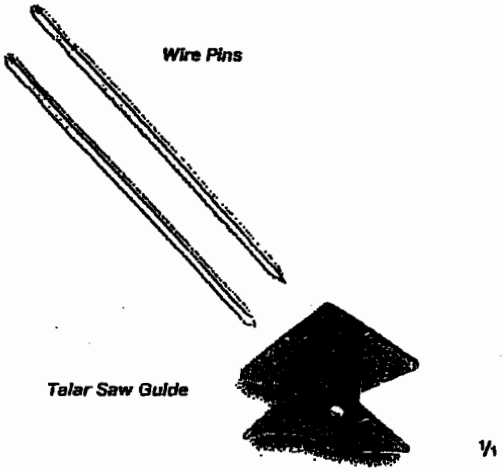
Instruments



405-113
Fixation Pin, *curved, for Talar Drill- and Saw Guides 405-139/01*

405-115
Twist Drill, *Ø 3 mm, for Talar Drill- and Saw Guides 405-139/02-/11*

405-106/02
Wire Pins *for fixation of Talar Drill- and Saw Guide and Talar Saw Guide, Ø 2.4 mm, 65 mm*



Talar Drill and Saw Guides, *115 mm*

405-139/01	Set of 10 ea.

consisting of:

Item No.	Site	Size
405-139/02	right	xx-small
405-139/03	left	xx-small
405-139/04	right	x-small
405-139/05	left	x-small
405-139/06	right	small
405-139/07	left	small
405-139/08	right	medium
405-139/09	left	medium
405-139/10	right	large
405-139/11	left	large

Talar Saw Guides

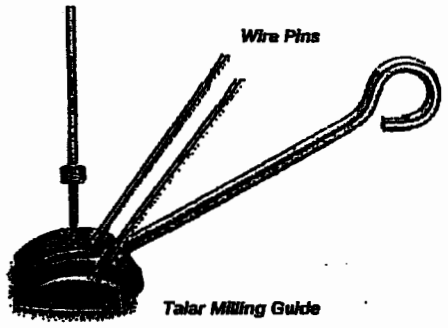
405-140/01	Set of 10 ea.

consisting of:

Item No.	Site	Size
405-140/02	right	xx-small
405-140/03	left	xx-small
405-140/04	right	x-small
405-140/05	left	x-small
405-140/06	right	small
405-140/07	left	small
405-140/08	right	medium
405-140/09	left	medium
405-140/10	right	large
405-140/11	left	large

Instruments

Twist Drill with stop



1/2

Talar Milling Guides, 110 mm

405-141/01	Set of 10 ea.

consisting of:

Item No.	Site	Size
405-141/02	right	xx-small
405-141/03	left	xx-small
405-141/04	right	x-small
405-141/05	left	x-small
405-141/06	right	small
405-141/07	left	small
405-141/08	right	medium
405-141/09	left	medium
405-141/10	right	large
405-141/11	left	large

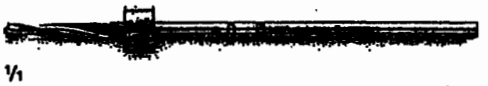
405-106/02

Wire Pin for fixation of Talar Drill and Saw Guide Talar Saw Guides and Talar Drill Guides
Ø 2.4 mm, 65 mm

1/1

405-142

Twist Drill with stop, Ø 3 mm, 75 mm



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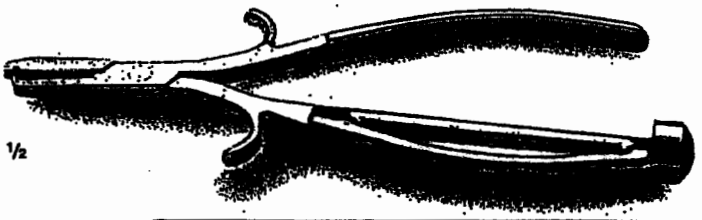

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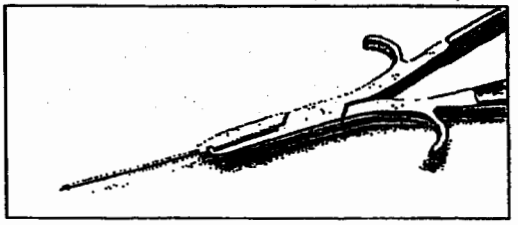


405-143

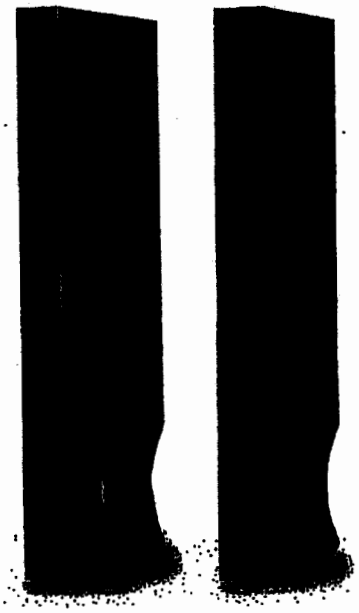
Driver and Extraction Forceps for Wire Pins, 210 mm

LINK®

Instruments

1/3

405-124
Mobile Bearing Trials
Set of 5 (6 to 10 mm)
Additional Sizes:
99-0028/31=11 mm
99-0028/32=12 mm
99-0028/33=13 mm
99-0028/34=14 mm

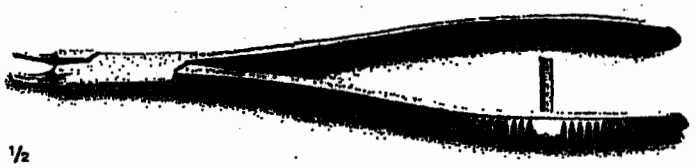


1/1

1/2

405-128
Depth Gauge (0 to 80 mm), 235 mm

Mobile Bearing Spacer Guides		
Item No.	*Version*	*Width*
405-125	*small*	24 mm
405-128	*wide*	30 mm



1/2

405-127
Insertion Forceps for Mobile Bearing Trials
405-140/01–/11, 215 mm

Instruments

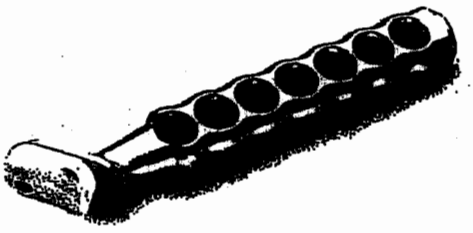
1/2

Sawblade, double angled for frontal resection (Please specify power tool)	
Item No.	*Fitting*
optional:	
405-130/01	A
405-130/02	B
405-130/03	C
405-130/04	D
99-0653/02	Stryker Fitting
99-0653/04	Zimmer Fitting
99-0653/ 06	Stryker 2000 Fitting

1/2

Sawblade, straight for dorsal resection (Please specify power tool)	
Item No.	*Fitting*
optional:	
405-131/01	A
405-131/02	B
405-131/03	C
405-131/04	D
99-0651/02	Stryker Fitting
99-0651/06	Stryker 2000 Fitting

Sawblades for single use only.

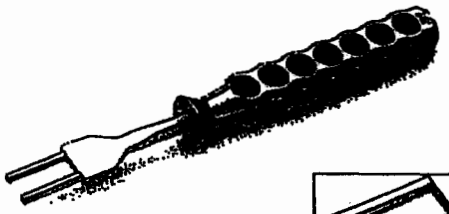


1/2

405-132
Impactor for Talar Components, 135 mm

LINK®

Instruments



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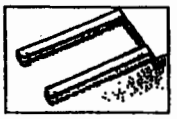


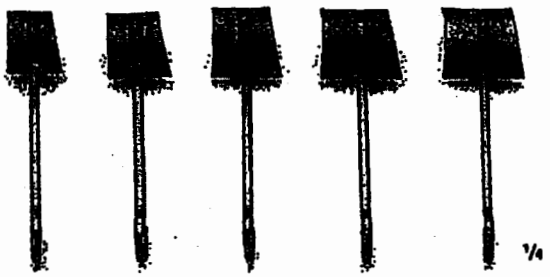
405-134/01

Impactor for Tibial Components with exchangeable tips, 220 mm

1/1

405-134/02

Replacement Tips (CoCrMo Alloy) for Impactor 405-134/01, non-sterile, 1 pair



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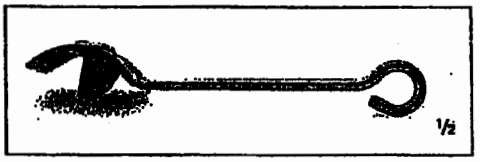


1/2

Fixation Pins

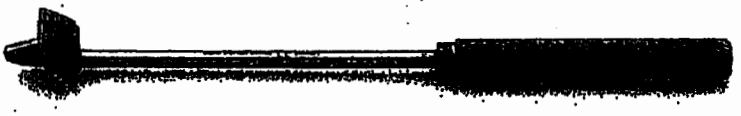
405-106	2.4mm x 80mm
405-106/02	2.4mm x 65mm
99-0028/18	2.5mm x 120mm
99-0028/17	2.5mm x 100mm

Talar Trials without lateral flanges

405-148/01	Set of 10 ea.

consisting of:

Item No.	Size	Version
405-148/11	xx-small	right
405-148/12	xx-small	left
405-148/13	x-small	right
405-148/14	x-small	left
405-148/15	small	right
405-148/16	small	left
405-148/17	medium	right
405-148/18	medium	left
405-148/19	large	right
405-148/20	large	left



1/2

405-149
Bone-Tamp for Talar Fin

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Barkhausenweg 10 · D-22839 Hamburg
Postfach 63 05 52 · D-22315 Hamburg
Telefon: +49 (0) 40 5 39 95-0
Fax: +49 (0) 40 5 38 69 29
e-mail: info@link-hh.de
Internet: www.link-hh.de

LINK

STAR Training Course Outline

Introduction

Link America 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 cadavaric lab. A full surgical video will also be presented and reviewed. Extensive 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 trails and fin tamp. A certification test will be administered at the conclusion of the course.

Course Outline

Didactic Lecture Outline (approximately 2 hours)

History of Total Ankle Replacements

Early attempts and results
Two-part ankles and their results
Three-part ankles and STAR Ankle
STAR Ankle history and IDE results

Question and Answer Opportunity

STAR Ankle Device Description and Design Rational

Tibial Component
Talar Component
Mobile Bearing

STAR Indications and Contra-Indications: How to Select the Right Patient

Warnings, Precautions and Surgical Pitfalls

Adverse Events, How to Avoid and Manage

Question and Answer Opportunity

Recent Changes to the Use of Instruments and Their Rationale

The STAR Surgical Procedure Video Review (approximately 1 hour)

Review of Clinical Procedure Video with Questions and Answers

The STAR Surgical Procedure Cadaver Lab (approximately 4.5 hours)

A hands-on cadaver workshop with three surgeons to a table. All tables will be fully equipped with X-ray equipment. Each surgeon will assist in two procedures and perform one, as they are observed intermittently by an instructor. The full procedure will be performed with special emphasis on pearls and pitfalls learned during the U.S. clinical trial.

Question and Answer Opportunity

Closing Lecture (approximately 1.5 hours)

Patient Instructions and Post Surgery Follow-Up Regime

Revision and Reoperation Strategies When Necessary

Question and Answer Opportunity

Certification Testing

Test Question and Answer Review and Re-test, if Necessary

Each certified surgeon will leave with a surgical video, procedure manual, implants and instrument manual, and contact information for the company and at least one of the instructors.

LINK® Orthopaedics

Scandinavian Total Ankle Replacement (STAR)

Information for Prescribers

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN

rev. 3-12-07 (draft)

DEVICE DESCRIPTION

The LINK® Scandinavian Total Ankle Replacement ("STAR Ankle") includes three functional components and a set of customized accessory instruments that are used in the surgical procedure. The three principal components of the prosthesis are:

- A metal tibial plate with titanium porous plasma spray coating;
- An ultra high molecular weight polyethylene ("UHMWPE") mobile bearing; and
- A metal talar component with titanium porous plasma spray coating.

The intermediate UHMWPE mobile bearing articulates on the tibial and talar metal implant surfaces. The STAR Ankle is designed to replace portions of the tibia and the talus that help constitute the normal ankle joint, while preserving range of motion as much as possible. The design characteristics of the STAR Ankle correspond closely to the normal ankle joint.

There are two bearing surfaces in the STAR Ankle: (1) the interface between the upper side of the UHMWPE mobile bearing and the facing surface of the tibial plate, and (2) the interface between the lower surface of the UHMWPE mobile bearing and the facing surface of the talar component. The tibial plate has one flat surface and one surface with two raised cylindrical projections oriented in the anterior/posterior direction. The upper flat surface of the UHMWPE mobile bearing slides against the flat surface of the tibial plate. The projecting cylinders serve to fix the device to bone at the distal tibia. The lower surface of the UHMWPE mobile bearing is concave, fitting against the convex upper surface of the talar component.

[redacted]

Tibial Plate

Viewed from the top, the tibial plate has a trapezoidal shape with rounded corners. This component is manufactured from cobalt chromium molybdenum (CoCrMo) per ASTM F-75. The smaller end of the wedge is oriented towards the posterior aspect of the ankle joint. On the proximal surface of the tibial plate, two parallel cylindrical barrels are positioned equidistant from the center of the plate running anterior to posterior for bone fixation. These cylinders must be inserted into hard subchondral bone. [redacted]

Tibial plates are available in four sizes with varying widths and lengths: extra-small (30mm x 30mm), small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra-large (33.5mm x 45mm). Stemmed tibial plates for revision procedures are available in small (32mm x 30mm), medium (32.5mm x 35mm), large (33mm x 40mm), and extra large (33.5mm x 45mm) sizes. The stem [redacted]

The tibial plate is coated on the bone-opposing surfaces with a titanium plasma spray porous coating. The tibial plate is intended to be press-fit without the use of cement, and should rest on anterior and posterior cortical bone. The stemmed tibias are not coated and have a matte finish.

Polyethylene Mobile Bearing

The polyethylene mobile bearing is manufactured from Ultra High Molecular Weight Polyethylene ("UHMWPE"), machined from medical grade extruded plate stock and conforms to ASTM F-648. The proximal surface of the mobile bearing is flat. The distal or talar surface is concave with a central radial groove running from anterior to posterior. [redacted] Revision mobile bearings are available in sizes of 11mm, 12mm, 13mm, and 14mm.

Talar Component

The talar component is designed as an anatomical prosthesis to cover the talar dome, anterior, posterior, and medial and lateral facets. This component is manufactured from CoCrMo. From the apex of the dome, the walls slope outwards to conform to the normal bone anatomy. The component is offered in five sizes: extra-extra-small (28mm x 29 mm), extra-small (30mm x 31mm), small (34mm x

35mm), medium (36mm x 35mm), and large (38mm x 35mm), and in both left- and right-sided configurations.

Viewed from the side, the proximal surface of the talar component is dome-shaped to conform to the talar dome of the normal ankle. A small, raised half-cylindrical ridge runs from anterior to posterior in the medial-lateral center of the dome to constrain the medial/lateral motion of the core.

The bone interface surfaces of the talar component are provided with a titanium plasma spray porous coating.

Refer to the STAR Ankle Implants and Instruments Manual for a complete listing of the customized accessory instruments used in the surgical procedure.

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 arthritis, or post-traumatic arthritis. 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, WARNINGS and PRECAUTIONS

Contraindications:

- Active or prior deep infection in the ankle joint or adjacent bones
- Prior arthrodesis at the ankle joint
- Hindfoot or forefoot malalignment precluding plantigrade foot
- Severe deformity that would not normally be eligible for ankle arthroplasty
- Avascular necrosis of the talus
- Charcot joint
- Severe osteoporotic or osteopenic condition or other conditions resulting in poor bone quality that may result in inadequate bony fixation
- Prior surgery and/or injury that has adversely affected ankle bone quality

- Insufficient ligament support that cannot be repaired with soft tissue stabilization
- Skeletal maturity not yet reached
- Obesity (weight greater than 250 lbs)
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Poor skin and soft tissue quality about the surgical site
- Neuromuscular disease resulting in lack of normal muscle function about the affected ankle
- Psychiatric problems that hinder adequate cooperation during perioperative period
- Significant malalignment of the knee joint
- Peripheral neuropathy that may lead to Charcot joint of the affected ankle

Warnings/Precautions:

- Only implant the STAR Ankle after adequate training and familiarity with the surgical technique manual, to avoid increased risk of device failure due to improper surgical technique.

- Do not use STAR Ankle components in combination with prosthesis components made by other manufacturers, because design, material, or tolerance differences may lead to premature device and/or functional failure. Components of the system have been specifically designed to work together.

- Always determine that the patient does not have a possible allergy to the implant/prosthesis material before selecting the STAR implant, to minimize the risk of an allergic response.

- Discard all damaged or mishandled implants. Do not reuse implants and components. Although the implant may appear undamaged, it may have small defects and internal stress patterns which may lead to early failure of the device.

- Do not resterilize. Do not use implants or components if the package is open or damaged.

- Always exercise care in selecting the proper type and size of implant. Size and shape of the human bone place restrictions on the size and shape of the implant, thus limiting its weight-bearing capabilities.

- Proper use of the talar bone tamp and talar trials provided in the STAR Ankle instrument set is necessary to minimize the risk of undetected talar fracture.

- Do not contour or bend an implant because it may reduce its fatigue strength and cause failure under load. Correct handling of the implant is extremely important.

- Caution the patient that the STAR implant can be expected to withstand only limited stress until the supporting bones are completely healed, and that the load-bearing capability of implants cannot be compared to that of a healthy bone. Premature and/or excessive loading of the implant may result in device failure.

Refer to the <u>STAR Ankle Surgical Technique Manual</u> for a complete description of the surgical procedure to be used for implantation.

ADVERSE EFFECTS

The following complications are associated with use of the device.

Operative Complications:

- Hemorrhage/Bleeding
- Instrument Malfunction
- Improper Device Placement
- Vessel Damage
- Ligament Damage
- Fracture of the Bone(s)
- Nerve Damage
- Tendon Damage

Postoperative Complications:

- Additional Stabilization Required
- Device Subsidence or Migration (no re-operation)
- Device Subsidence or Migration (with re-operation)
- Device Breakage
- Arthrodesis or Surgical Intervention
- Ankle Pain

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- Similar Pain as Preoperative
- Persistent Nerve Damage
- Ligament Instability
- Thrombophlebitis
- Embolism
- Soft Tissue Edema
- Wound Infection (superficial or deep)
- Wound Dehiscence
- Skin slough or breakdown
- Death

HOW SUPPLIED

The implant is supplied sterile using gamma irradiation to achieve a SAL of 10^{-6} and are intended for single use only.

STORAGE AND HANDLING OF IMPLANT

- The implant is shipped in sterile packaging. The implant may be stored for up to 5 years from the date of its original packaging The implant is sterile until the expiration date printed on the package and must be used before this date.

- The implant should be stored in its original, sealed packaging in clean, dry conditions. Avoid extreme or sudden changes in temperature. The recommended storage temperature is 18-20° C with 50-70% humidity. Avoid exposure to direct sunlight or dampness.

- Before removing the implants, make sure that the protective packaging is unopened and undamaged. If the packaging is damaged, the implants should be considered UNSTERILE and should not be used.

- Upon removal from the package, compare the descriptions on the package with the package contents (product number and size).

- Take particular care that aseptic integrity is assured during removal of the implant from the last packaging.

- Select suitable measures so that the implant does not come into contact with objects that could damage or otherwise affect its surface. Damaged implants are no longer functionally reliable.

- Attention must be paid to the correct and stable assembly of the prosthesis components.

- Assure that all necessary implant components are available intact.

- Assure that all instruments necessary for the implantation procedure are available intact.

STERILIZATION/RESTERILIZATION OF INSTRUMENTS

Implantation instruments are provided nonsterile for sterilization by the user. Instruments can be steam sterilized (autoclaved) using the following validated procedure: recommended temperature of 132°-135° C, with a maximum temperature of 137° C, and an exposure time of 4 minutes. Prior to sterilization, as an essential pre-requisite to ensure effective sterilization, surgical instruments must be cleaned, disinfected, and inspected using a validated procedure after every use. The following validated cleaning/disinfecting procedure is recommended:

- Dry clean-up in the operating room and removal of all visible contamination from the instruments immediately after use;
- Manual pre-cleaning (brushing or ultrasonic) with cold water without any chemical additives;
- Disassembly whenever possible;
- Machine cleaning, consisting of:
    - Cleaning at 50° C to 60° C, using demineralized water and a highly alkaline cleaning agent;
    - Rinse with water without chemical additives;
    - Acidic neutralization;
    - Rinse with dematerialized water without chemical additives;
    - Thermal disinfection at 93° C for a minimum of 3 minutes, using dematerialized water and adding a rinsing agent;
    - Drying;
    - Assembly and inspection/performance test of the instruments.

CLINICAL STUDIES

Three multicenter, prospective clinical trials were conducted to show the safety and efficacy of the STAR Ankle. The three studies are summarized in **Table 1** below.

Table 1. U.S. Clinical Studies

Clinical Study	Study Design	Objective	Number of Centers	Enrolled Patients
Pivotal	Non-randomized concurrent and historical control multi-center study	Evaluate the safety and efficacy of the STAR Ankle compared to ankle arthrodesis	10 STAR Ankle; 5 arthrodesis	158 STAR Ankle patients; 66 Arthrodesis patients
Bilateral	Single-arm multi-center study	Evaluate the safety of bilateral STAR Ankle implantation	6	21 Bilateral STAR Ankle patients
Continued Access	Single-arm multi-center study	Confirm the findings of the pivotal study	10	448 STAR Ankle patients

Pivotal Study

The pivotal study was a 2:1 (STAR Ankle to Control) multi-center, non-randomized, concurrent control clinical trial. The study was designed as a non-inferiority trial comparing the safety and efficacy of the STAR Ankle to Arthrodesis. The control group in the STAR Ankle pivotal trial consisted of concurrently recruited arthrodesis patients for evaluation of efficacy, with a combination of concurrent arthrodesis patients and historical arthrodesis controls for the safety analysis. A total of 224 patients (66 arthrodesis; 158 STAR) were enrolled in the study with supplemental safety data collected on an additional 413 historical arthrodesis controls.

Patients with moderate or severe ankle pain and loss of mobility from primary arthritis, post-traumatic arthritis, or rheumatoid arthritis who had failed at least 6 months of conservative treatment were eligible for the pivotal study. Those patients who were skeletally immature, had active or prior deep infection to the ankle, or had prior arthrodesis of the subject ankle were excluded from the study, as were patients with poor bone stock, severe hindfoot deformity, inadequate skin coverage about the ankle, or obesity.

The study's primary efficacy endpoint was the mean total Buechel-Pappas Scale score ("Buechel-Pappas score"). The safety endpoint was the composite event of absence of major complications, loosening, migration, or device failure, removal/revision for the STAR Ankle group and the absence of major complications, non-union, mal-union, delayed union, or revision for the arthrodesis group. Efficacy success was defined as a minimum 40-point increase in Buechel-Pappas score from baseline. Overall patient success was defined as success for both efficacy and safety at 24 months.

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Bilateral and Continued Access Studies

These studies were designed as multicenter single-arm registry studies to support the safety of the STAR Ankle in patients with bilateral implants (bilateral study) and to provide additional support for both the safety and efficacy of the STAR Ankle in unilateral patients (Continued Access study). The protocols and patient demographics for the bilateral and continued access studies were substantially similar to the pivotal trial. At the time of database closure, data was available on 16 bilateral patients and 424 continued access patients.

Endpoint Success Rates

Efficacy, safety and overall patient success rates based on all data available at 24 months ("Completers") are shown in **Table 2**. As demonstrated in the table, significantly higher efficacy and patient success rates were shown for the STAR Ankle patients at 24 months as compared with the Arthrodesis patients.

Table 2. Success Rates at 24 Months

24 Month Success Rates	Pivotal						Continued Access*		
	Control			STAR			STAR		
	n	N	%	n	N	%	n	N	%
Patient Success Rate	7	51	13.7%	70	142	49.3%	62	81	76.5%
Efficacy Success Rate	7	47	14.9%	83	142	58.5%	70	83	84.3%
Safety Success Rate	43	52	82.7%	113	142	79.6%	73	81	90.1%

*Only the subset of continued access patients with independent radiographic review were include in this comparison so that the same safety success criteria as used in the pivotal study could be applied.

The odds ratio for patient success when adjusted for age, baseline Buechel-Pappas score, and primary diagnosis for the STAR Ankle (pivotal study) versus control was 5.2 in favor of the STAR Ankle with a 90% confidence interval of (2.3, 11.8).

As shown in **Table 2**, Arthrodesis Completers had somewhat higher safety success rates than STAR Ankle pivotal patients at 24 months (82.7% and 79.6%, respectively). However, the difference is small (3%) and the confidence intervals for the difference is well within the pre-specified safety margin for non-inferiority.

The success rates in the subset of continued access patients with radiographic review showed substantial improvement over both the STAR Ankle group and the control group in the pivotal study. It is important to note that the rates of important adverse events in the STAR only continued access study as a whole were substantially improved over the pivotal study, including rates of surgical

interventions and major complications which are important in the assessment of STAR Ankle safety success rates (**Table 4**).

Primary Efficacy Endpoint: Total Buechel-Pappas Score

Table 3 shows the primary efficacy endpoint results. **Table 3** summarizes the mean Buechel-Pappas score at 12 and 24 months and the change in Buechel-Pappas score at 12 and 24 months from baseline. Comparisons between groups were made using the Wilcoxon Test, due to the non-normality of the Buechel-Pappas score distribution. All comparisons showed a significantly higher score in the STAR Ankle group when compared with the Arthrodesis group with $p<0.001$. The Buechel-Pappas score at 12 and 24 months remained significantly higher in the STAR Ankle group when using various imputation methods to account for missing data including a multiple imputation method and a last observation carried forward method.

Table 3. Mean-Buechel Pappas Score at 12 and 24 Months

	Pivotal						Continued Access		
	Control			STAR			STAR		
Buechel-Pappas Score	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev
12 Month	53	65.9	17.0	143	80.7	14.3	344	83.2	12.6
Improvement at 12 Months	53	23.3	15.9	143	39.7	15.0	344	45.8	14.0
24 Month	47	69.7	16.8	142	81.6	14.0	206	84.4	11.5
Improvement at 24 Months	47	26.3	17.1	142	40.5	15.1	206	46.7	13.6

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

Based on the SF-36, there was no consistent persistent difference between the STAR Ankle or Arthrodesis groups in quality of life. Patient general condition continued to be significantly better in the STAR Ankle group at all follow-up visits from 3 to 12 months. The condition of STAR Ankle patients substantially improved in the 3 months following surgery (89.9% of patients were rated good or excellent preoperatively, improving to 98.1% at 3 months) and remained high throughout the study, maintaining a significantly higher percentage of patients in good or excellent condition as compared to Arthrodesis patients.

Overall Safety

Adverse events occurring at 24 months at the operative site for both the pivotal and continued access studies are provided in **Table 4**.

Table 4. Summary of Adverse Events, Surgical Interventions and Major Complications at 24 Months[1]

Adverse Events	Control (N=66)	STAR Pivotal (N=158)	p-value (STAR vs. Control)	STAR Continued Access (N=352)
Bone fracture	2 (3.0%)	28 (17.7%)	0.002	37 (10.5%)
Intra-operative fracture	1 (1.5%)	15 (9.5%)	0.044	21 (5.0%)
Post-operative fracture	1 (1.5%)	14 (8.9%)	0.044	19 (5.4%)
Bony changes	0 (0%)	12 (7.6%)	0.02	15 (4.3%)
Pain	32 (48.5%)	69 (43.7%)	0.557	115 (32.7%)
Nerve injury	5 (7.6%)	32 (20.3%)	0.019	75 (21.3%)
Wound problem	4 (6.1%)	32 (20.3%)	0.009	65 (18.5%)
Surgical intervention	7 (10.6%)	26 (16.5%)	0.260	26 (7.4%)
Revision or removal	6 (9.1%)	12 (7.6%)	0.707	12 (3.4%)
Other intervention	1 (1.5%)	18 (11.4%)	0.016	15 (4.3%)
Major complication	1 (1.5%)	14 (8.9%)	0.074	17 (4.8%)
Infection	1 (1.5%)	2 (1.3%)	1	3 (0.8%)
Bone problems	0 (0%)	8 (5.1%)	0.109	10 (2.8%)
Wound problems	1 (1.5%)	5 (3.2%)	0.673	5 (1.4%)
Wound problems and infections	0 (0%)	1 (0.6%)	1	0 (0%)

The majority of adverse events resolved either without or with treatment.

Five patients expired during the first 24 months of follow-up, 4 in the STAR Ankle group and 1 Arthrodesis patient. One STAR patient suffered a fatal pulmonary embolism 7 days after placement of the device. Pulmonary embolism is known complication of lower extremity surgery in general, the STAR Ankle itself nor anything specific to the STAR surgery were not believed to have been a factor. The remaining four patient deaths were determined by the study investigators and medical monitors not to be study-related.

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1 Not all 424 continued access patients had reached their 24 month follow-up as of the time of database closure on 12/1/2006. To permit a reasonable comparison to the pivotal study data, with the exception of intra-operative fracture, the adverse event rate for the continued access study has been calculated using data from the 352 patients who have reached 24 months post-procedure only. For the comparison of intra-operative fracture rate, all 424 continued access patients were analyzed.

Fractures occurred in 17.7% of the STAR patients, many of which were intraoperative and in 3.0% of the arthrodesis patients. The majority of these fractures did not impact patient outcome. Only one of these fractures (a medial malleolar fracture) failed to heal within 12 weeks of surgery. Due to the incidence of intraoperative medial malleolar fractures, the STAR Ankle surgical protocol was altered to include a recommendation to take specified protective measures to prevent intraoperative medial malleolar fractures, including use of 0.062" K-wires.

Surgical interventions and major complications (defined as any surgical intervention to the treated ankle that was a result of an infection, wound problem, or bone problem such as osteolysis, cyst formation, or non-traumatic fracture) occurred in a higher percentage of STAR patients than in study patients undergoing arthrodesis, although the rates were low in both groups. The continued access study further demonstrates that refinements to surgical technique and methods were largely successful in decreasing the rates of adverse events, surgical interventions and major complications. **Table 4** shows that while the rate of surgical interventions was slightly higher in the STAR group than in the Arthrodesis group in the pivotal study (16.5% vs. 10.6%), the rate of interventions in the continued access arm was lower than that in the Arthrodesis arm.

The same types of adverse events as seen in the pivotal and continued access studies were observed among the 16 bilateral patients for whom data was available at the time of database closure. Thus, no new safety issues arose from the bilateral study.

Conclusions Drawn from Studies

The various clinical studies demonstrate that the STAR Ankle is safe and effective in the treatment of patients with ankle arthritis who have failed six months of conservative therapy. In the majority of efficacy parameters measured (including overall patient success, total Buechel-Pappas score, 40 point or greater improvement in Buechel-Pappas score), the STAR Ankle showed favorable results when compared to ankle arthrodesis. The primary efficacy parameter of mean total Buechel-Pappas Score was shown, not only to be non-inferior to ankle arthrodesis, but also superior to arthrodesis. The pivotal study data further demonstrates that the safety of the STAR Ankle is comparable to that of Arthrodesis patients. Data from the continue access study reinforces the favorable efficacy results seen in the pivotal study and demonstrates lower rates of adverse events, surgical interventions and major complications as compared to STAR Ankle patients in the pivotal study.

Patient Information

The LINK® Scandinavian Total Ankle Replacement (S.T.A.R.)

About Ankle Replacement

Replacement of the ankle joint with an artificial implant is designed to treat painful conditions of the ankle, such as arthritis. Arthritis is a condition that can take many forms, and your doctor may have used a different name to describe it. Regardless of the name, at this time, your ankle does not work properly and is causing you pain when you walk. Sometimes, arthritis can be treated without surgery, for example by taking anti-inflammatory medication and using a brace. However, if these types of treatments do not relieve your pain, surgical treatments may be an option. Your orthopedic surgeon has asked you to consider the replacement of your ankle with an artificial implant called the "S.T.A.R.® Ankle." S.T.A.R.® stands for "Scandinavian Total Ankle Replacement." A surgeon in Scandinavia designed this device. "Total" means that your entire ankle joint will be replaced. The purpose of total ankle replacement surgery is to relieve the pain in your ankle, while still allowing you to move your ankle.

Another method for relieving your ankle pain is to stop the movement of your ankle by fusing the ankle bones together. This surgery is referred to as "ankle fusion" or "arthrodesis." There are different methods that can be used for ankle fusion. These methods involve using screws or other "hardware" to hold the ankle still until the bones around the joint grow together. Unfortunately, once an ankle is fused, it generally never moves again.

The S.T.A.R.® Ankle Method

Dr. Hakon Kofoed, a leading orthopaedic surgeon from Denmark, invented the S.T.A.R.® Ankle. The current version of the product has been in use by Dr. Kofoed and many other surgeons around the world since 1991.

The S.T.A.R.® Ankle is made up of three parts. The first part covers the dome at the top of your foot. The second part covers the very bottom of your tibia bone. Both of these parts are made of a metal called cobalt chromium alloy. These parts are also coated with pure titanium in the places where they actually touch your bone. The third part of the S.T.A.R.® Ankle is placed in between the two metal parts. This middle piece is made out of polyethylene plastic. The plastic piece is designed to move in between the metal parts as you move your ankle. The materials that the S.T.A.R.® Ankle is made of have been used in artificial hips and knees for many years and have shown to be extremely well tolerated by the body.

The surgical procedure for the S.T.A.R.® Ankle calls for the surgeon to use an anterior (front) approach and remove about 3/8" of bone. The surgeon then shapes the bones of your ankle so the ankle replacement will fit in place.

Your Decision

You should discuss total ankle replacement using the S.T.A.R.® Ankle with your physician. You should also discuss other methods, such as fusion surgery, for treating your ankle pain. Please ask your doctor any questions you have so that you will make the decision that is best for you. It is important to fully understand the risks and benefits of each type of surgery before you make your decision.

Questions and Answers about the S.T.A.R.® Ankle

Q: How long will I be in the hospital after surgery?

A: Most patients are hospitalized for 2 or 3 days, although some patients have shorter hospitalizations. However, a small number of patients may have a stay longer than 5 days.

Q: Will my activity be restricted after surgery?
A: Normally, you will use crutches or a walker for two weeks after surgery before putting weight on your ankle. You can put full weight on your ankle at about four weeks after the operation. In most cases, the cast comes off after about six weeks.

Q: Have the materials in the S.T.A.R.® Ankle been used in the human body before?

A: Yes, the S.T.A.R.® Ankle device uses the same materials, cobalt chromium alloy, titanium, and ultra high molecular weight polyethylene, that have been used for the last 30 years in artificial hip and knee prostheses.

Q: What will I be permitted to do after I have recovered from the ankle surgery?
A: Most people return to full activity, except for high impact sports like jogging and basketball. Activities such as walking, hiking, and golf are encouraged.

Q: What is the advantage of the S.T.A.R.® Ankle over ankle fusion?
A: By keeping your ankle's motion, you should have a more normal ability to walk. Also, climbing hills or stairs should be much easier with the S.T.A.R.® Ankle than if your ankle is fused.

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN

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DRAFT POST-APPROVAL STUDY PROTOCOL: LINK SCANDINAVIAN TOTAL ANKLE REPLACEMENT SYSTEM ("STAR ANKLE")

1 INTRODUCTION

Severe ankle pain due to arthrosis (primary degenerative or rheumatoid) or trauma injury is not uncommon. Surgical reconstruction of the ankle is often necessary in order to eliminate pain and instability. This can be achieved either by arthrodesing the ankle bones together leading to a fusion or by performing joint arthroplasty.

Arthrodesis of the ankle was described by Albert in 1882[1] and is achieved by removing the cartilage until bleeding bone is observed. An autogenous bone graft may be placed between the joint surfaces. To better achieve fusion, the joint is mechanically secured with bone screws and/or pins. The ankle is immobilized throughout the bone fusing process to prevent micromotion. As reported in the literature, arthrodesis can have an early complication rate of between 10 - 40% due to infection, nonunion and malunion.[2] Arthrodesis often eliminates pain but results in loss of ankle mobility for the patient. Long-term results (greater than 5 years) demonstrate arthrosis of the joints distal to the ankle joint secondary to the increased stress brought about by the arthrodesis.[3] This condition may require extension of the arthrodesis into the foot, which may create even greater stiffness.

Arthroplasty of the ankle has been performed since 1970[4] and has been used as an alternative to arthrodesis of the ankle. Like hip and knee arthroplasty, ankle designs have evolved over the years. Three different basic types of articulation geometry have been used: (1) roller and trough (*e.g.*, Smith, Beech-Steffee, ICLH, and Mayo constrained ankles and the semi-constrained Alvine ankle); (2) unconstrained, hemispherical Bath & Wessex design; and (3) tri-compartmental design (*e.g.*, Scandinavian Total Ankle Replacement System ("STAR Ankle") and New Jersey LCS).

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1 Einige faire kunstilcher anklyosen: Bidung an paralytischen gliemassen. *Wein Med Pross* 23:726-728, 1882.

2 Frey C, Halikus NM, Vu-Rose T, Ebramzadeh E. A review of ankle arthrodesis: Predisposing factors to nonunion. *Foot Ankle Int* 15(11):581-584, 1994.

3 Mann RA, Rongstad KM. Arthrodesis of the ankle: A critical analysis. *Foot & Ankle Int* 19(1):3-9, 1998.

4 Lord G, Marotte JH. Arthroplastie totale de cheville. Experience sur 10 ans. A propos de 25 observations personnelles. *Revue de Chirurgie Orthopedique* 66:527-530, 1980.

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Another evolution has been the change from cemented to non-cemented device designs. This change is largely due to the difficulty of using conventional cementing techniques in the limited space within the ankle mortise. The oblique angle of the tibia[5] and the dense structure of the talus bone also contribute to the difficulty. Several authors have shown clinically equivalent results with the non-cemented ankle devices. These ankle designs have been used on both male and female patients who are skeletally mature (ages 22 to 84 years) and on patients with both rheumatoid and osteoarthritis. Postoperative surgical complications are similar to that of arthrodesis patients but postoperative rehabilitation is faster. Arthrodesis requires a minimum of 12 weeks of immobilization (which may require the patient to be wheelchair bound), and the patient is not allowed to be weight bearing for half of this period. After STAR Ankle arthroplasty, the patient is allowed to bear some weight immediately and is out of all immobilization in 4-6 weeks. Some of the modern ankle designs like the STAR also have the advantage over other marketed devices in that they only require removal of a minimum amount of bone in the ankle joint, providing an opportunity to revise the surgery to an arthrodesis, if necessary, without significantly compromising the patient's leg length.

2 PURPOSE, OBJECTIVES, AND ENDPOINTS

[redacted]

5 Carlson AS, Henricson A, Linder L, et al. Medium term results in rheumatoid arthritis with the Bath & Wessex ankle prosthesis. in *Current status of ankle arthroplasty*, p 86-89. Published by Springer 1998.

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